THE NEUROBIOLOGY OF EMOTION-COGNITION INTERACTIONS

EDITED BY: Hadas Okon-Singer, Talma Hendler, Luiz Pessoa, and Alexander J. Shackman

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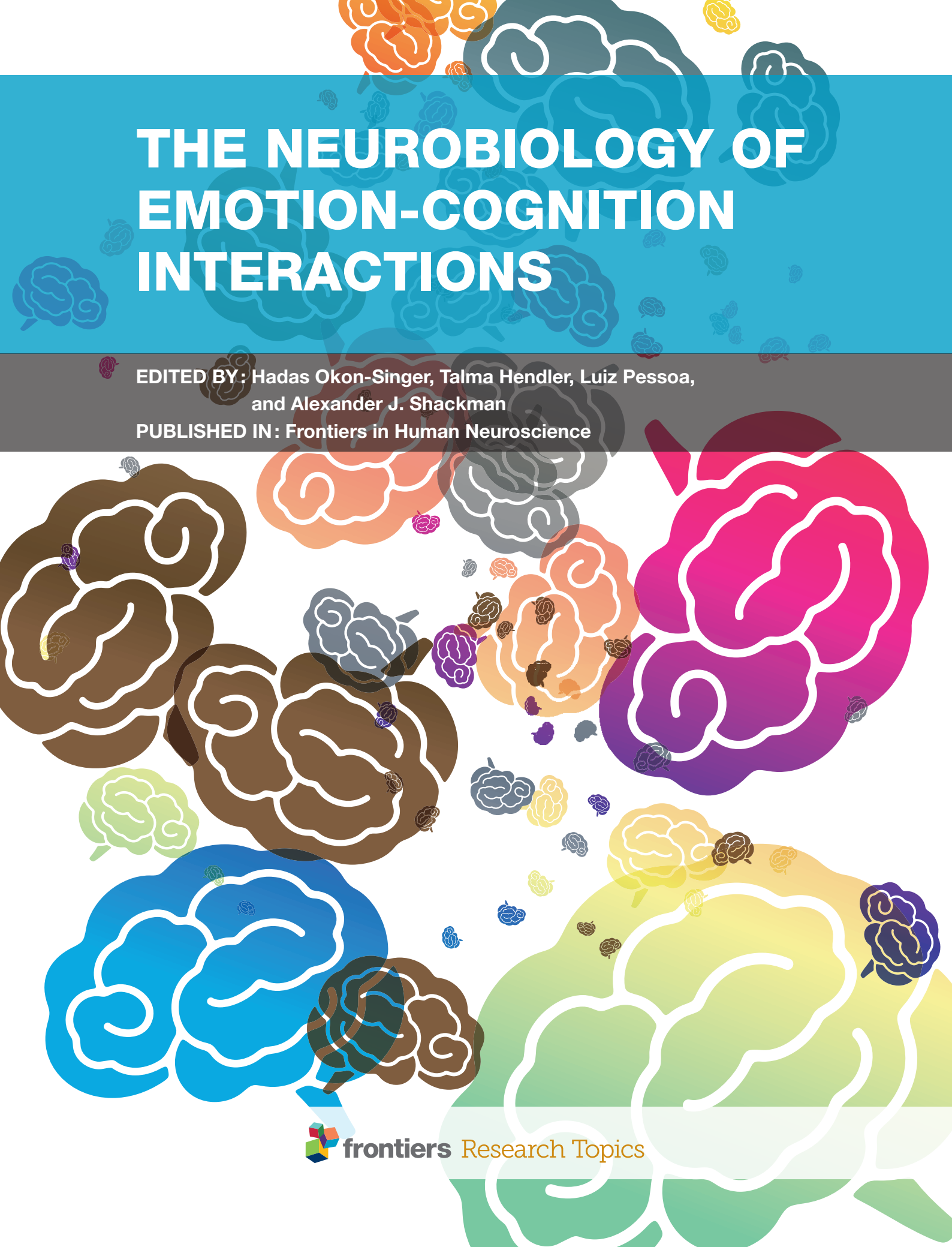

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THE NEUROBIOLOGY OF EMOTION-COGNITION INTERACTIONS

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There is increasing interest in understanding the interplay of emotional and cognitive processes. The objective of the Research Topic was to provide an interdisciplinary survey of cutting-edge neuroscientific research on the interaction and integration of emotion and cognition in the brain. The following original empirical reports, commentaries and theoretical reviews provide a comprehensive survey on recent advances in understanding how emotional and cognitive processes interact, how they are integrated in the brain, and what their implications for understanding the mind and its disorders are. These works encompasses a broad spectrum of populations and showcases a wide variety of paradigms, measures, analytic strategies, and conceptual approaches.

The aim of the Topic was to begin to address several key questions about the interplay of cognitive and emotional processes in the brain, including: what is the impact of emotional states, anxiety and stress on various cognitive functions? How are emotion and cognition integrated in the brain? Do individual differences in affective dimensions of temperament and personality alter cognitive performance, and how is this realized in the brain? Are there individual differences that increase vulnerability to the impact of affect on cognition—who is vulnerable, and who resilient? How plastic is the interplay of cognition and emotion?

Taken together, these works demonstrate that emotion and cognition are deeply interwoven in the fabric of the brain, suggesting that widely held beliefs about the key constituents of 'the emotional brain' and 'the cognitive brain' are fundamentally flawed. Developing a deeper understanding of the emotional-cognitive brain is important, not just for understanding the mind but also for elucidating the root causes of its many debilitating disorders.

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EDITORIAL
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Introduction to the special research topic on the neurobiology of emotion-cognition interactions

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Keywords: ACC, amygdala, anxiety, attention, depression, PFC, working memory

Recent years have witnessed an explosion of interest focused on the interplay of emotion and cognition (Pessoa, 2013; Braver et al., 2014; Dolcos and Denkova, 2014). The goal of our Special Research Topic was to survey recent advances in understanding how emotional and cognitive processes interact, how they are integrated in the brain, and the implications for understanding the mind and its disorders. Investigators from across North America, Israel, and Europe contributed 19 original empirical reports as well as 15 commentaries and theoretical reviews. Their work encompasses a broad spectrum of populations and showcases a wide variety of paradigms, measures, analytic strategies, and conceptual approaches. Already (August 2014), the 34 contributions to this Special Topic have been viewed on the *Frontiers* website more than 70,000 times, shared or posted to social media networks more than 16,000 times, and cited nearly 90 times. While reading, posting, sharing, and citing are undoubtedly helpful, active debate provides a more direct means of sharpening constructs, clarifying boundary conditions, articulating unspoken assumptions, identifying soft spots in the evidentiary record, and refining models. We agree with Kenrick and Funder's suggestion that, "science best progresses through multiple and mutually critical attempts to understand the same problem. When camps with…opposing sets of biases manage to come to some level of agreement, we may be more confident of the validity of the conclusions that are agreed upon" (Kenrick and Funder, 1988, p. 32). In this regard, we were pleased to see Proudfit (Proudfit et al., 2013) and Moser (Moser et al., 2013) vigorously debate the integration of anxiety and cognitive control.

The research embodied in this Special Research Topic underscores the tremendous progress made in our understanding of emotion-cognition interactions. In particular, this work demonstrates that emotional cues and states can profoundly influence key elements of cognition, including attention (Holtmann et al., 2013; Kessel et al., 2013; Mchugo et al., 2013; Mohanty and Sussman, 2013; Morriss et al., 2013; Peers et al., 2013; Stollstorff et al., 2013), working memory (Clarke and Johnstone, 2013; Iordan et al., 2013; Robinson et al., 2013b; Stout et al., 2013; Vytal et al., 2013), cognitive control (Kalanthroff et al., 2013; Proudfit et al., 2013; Robinson et al., 2013a), reinforcement learning (Berghorst et al., 2013), and various kinds of mood-congruent information processing (van Dessel and Vogt, 2012; Harle et al., 2013; Schick et al., 2013). Several contributors provided evidence that mood can have enduring consequences for cognition (Morriss et al., 2013; Vaisvaser et al., 2013), perhaps reflecting the comparatively slow dynamics of catecholamine and hormonal neurochemistry (Sacher et al., 2013; Shansky and Lipps, 2013). These and other molecular pathways may also help to explain the impact of emotional traits on cognition (Berggren et al., 2013; Kessel et al., 2013; Moser et al., 2013; Proudfit et al., 2013).

A number of contributors provided exciting new evidence that circuits involved in attention, executive control, and working memory play a central role in emotion and emotion regulation (Aue et al., 2013; Clarke and Johnstone, 2013; Iordan et al., 2013; Peers et al., 2013; Rolls, 2013; Sheppes and Levin, 2013; Stollstorff et al., 2013). Several contributors provided evidence that putatively emotional and cognitive regions can influence one another via complex webs of connections in ways that jointly contribute to adaptive and maladaptive behavior (John et al., 2013; Morrison et al., 2013; Rolls, 2013). Taken together, this research suggests that emotion and cognition are deeply interwoven in the fabric of the brain (Dreisbach and Fischer, 2012; Crocker et al., 2013; Mcdermott et al., 2013; Moser et al., 2013; Proudfit et al., 2013; Warren et al., 2013).

Despite this progress, a number of important challenges remain. We address these challenges in more detail in the accompanying review (Okon-Singer et al., 2015). Future work aimed at developing a deeper understanding of the interplay of emotion and cognition is a matter of practical as well as theoretical importance. Many of the most common, costly, and challenging to treat neuropsychiatric disorders—anxiety, depression, schizophrenia, substance abuse, chronic pain, autism, and so on—involve prominent disturbances of both cognition *and* emotion (Millan, 2013), suggesting that they can be conceptualized as disorders of the emotional-cognitive brain (Shackman et al., in press). These disorders impose a larger burden on public health and the global economy than either cancer or cardiovascular disease (Collins et al., 2011; Diluca and Olesen, 2014; Whiteford, 2014), underscoring the importance of accelerating efforts to understand the neural systems underlying the interaction and the integration of emotion and cognition.

AUTHOR CONTRIBUTIONS

All the authors contributed to co-editing the Special Research Topic. Hadas Okon-Singer and Alexander J. Shackman wrote the paper. All the authors edited and revised the paper.

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Facets and mechanisms of adaptive pain behavior: predictive regulation and action

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Neural mechanisms underlying nociception and pain perception are considered to serve the ultimate goal of limiting tissue damage. However, since pain usually occurs in complex environments and situations that call for elaborate control over behavior, simple avoidance is insufficient to explain a range of mammalian pain responses, especially in the presence of competing goals. In this integrative review we propose a Predictive Regulation and Action (PRA) model of acute pain processing. It emphasizes evidence that the nervous system is organized to anticipate potential pain and to adjust behavior before the risk of tissue damage becomes critical. Regulatory processes occur on many levels, and can be dynamically influenced by local interactions or by modulation from other brain areas in the network. The PRA model centers on neural substrates supporting the predictive nature of pain processing, as well as on finely-calibrated yet versatile regulatory processes that ultimately affect behavior. We outline several operational categories of pain behavior, from spinally-mediated reflexes to adaptive voluntary action, situated at various neural levels. An implication is that neural processes that track potential tissue damage in terms of behavioral consequences are an integral part of pain perception.

Keywords: nociception, pain, action, allostasis, predictive regulation

> *"...we need to re-examine whether pain signals the presence of a stimulus, or whether it signals a stage reached in a series of possible actions."*
>
> *Patrick Wall, 1999 (p 155)*

INTRODUCTION

Even at the earliest stages of cortical processing, it is difficult to view pain processing as a strictly sensory description of a stimulus. Rather, the processing of nociceptive information in the spinal cord, brainstem, and subcortical pathways convey to the cortex a history of multiple sensorimotor transformations, ranging from reflex action to modulatory feedback. By the time a pain-relevant signal reaches the cortex, if not before, the terms of "nociceptive processing" become inadequate to describe pain representation, just as the terms of "auditory processing" become inadequate to describe music. Evidence from many strands of current pain research suggest that from the very outset, pain processing deals with complex, nested representations of relationships between stimulus and action.

In this review we consider pain not primarily as a sensation, but as an action problem. In this perspective, a nociceptive signal travelling from the periphery via the spinal cord presents the brain with the question "what is to be done?" We propose a Predictive Regulation and Action (PRA) model of pain, which incorporates evidence that the organization of pain system is inherently action-centered, at levels from the spinal cord to the cortex. In this model, an emphasis on pain as a sensory signal is relieved, in favor of an emphasis on dynamic sensorimotor transformations among multiple interacting systems, each jostling to offer solutions to the problem of "what is to be done" when potential injury looms.

PREDICTIVE REGULATION AND ACTION (PRA) MODEL OF PAIN

As the name suggests, the PRA model of pain seeks to capture several key aspects of pain processing: prediction, regulation, and action. The prediction component brings out the idea that neural subsystems operate not just on the basis of actual signals from communicating subsystems, but on their dynamic predictions of such signals in hierarchically-organized networks (Clark, 2013). Such cascades of multiple predictions introduce the need for regulatory processes, both local and supervening, which handle error signals, assign signal weights, as well as influencing gain-modulation in other parts of the system, in pursuit of stable and energy-efficient processing. Finally, the PRA model considers pain processing as ultimately geared towards behavior. In particular, much of cortical pain processing reflects the modulation of voluntary actions in response to pain, within systems that take into account multidimensional information such as context, memory, rule-based contingencies, and even efference from past spinal reflex actions.

The PRA model synthesizes theoretical and computational ideas from the domains of action and regulatory control. Core elements of these models will be covered in more detail in later sections, and we direct the interested reader to the cited papers for formalizations of these ideas (especially Sterling, 1988; Koechlin and Summerfield, 2007; Clark, 2013; Shenhav et al., 2013). For our present purposes, we first highlight several common themes that emerge from them.

The first is *prediction*, which has become a central concept in many current models of action, cognition, and emotion. Predictive coding also has important implications for the way *error* signals are handled in the system. Regulatory processing that generates and handles such prediction and error information in turn invokes the idea of *energy-efficiency*, in which the dynamics of a neural system tend to stabilize around operations that utilize available metabolic energy with as little waste as possible. Towards that end, adaptive *tradeoffs* may occur within the system. These tradeoffs are at least partly constrained by processes predicting likely *costs and benefits*. The bottom line of predictive regulation is *behavior*. The synthesis of these ideas in the PRA model is intended to capture numerous features of the nervous system's organization that allow the anticipation of potential pain, adaptive adjustment of behavior, and the management of energetic costs—all before the risk of tissue damage becomes critical.

WITHDRAWAL REFLEX ACTION AND PREDICTIVE ADJUSTMENT OF BEHAVIOR

Withdrawal is probably the action type most frequently associated with the acute pain of injury. Such rapid, involuntary limb withdrawal actions are supported by spinal reflexes, which are in turn triggered by nociceptor activation. In the laboratory, standard tests involve measuring the latency of an animal's limb withdrawal from a hot (Hargreaves et al., 1988) or cold (Jasmin et al., 1998; Allchorne et al., 2005) plate at or above-threshold intensity (usually in rats or mice). The formalin test, which involves chemically injuring tissue by formalin injection, is another standard protocol for probing withdrawal and protective behaviors (Dubuisson and Dennis, 1977).

Heat, cold, and mechanical stimuli elicit withdrawal or flexion reflexes in both awake (Chaplan et al., 1994; McMullan et al., 2004; Dunham et al., 2010) and anesthetized animals (Bessou et al., 1971; Yeomans et al., 1996). C heat fibers (including polymodal C fibers) and Aδ fibers underlie the initial encoding of a noxious heat stimulus (Dunham et al., 2010), and Aδ fibers also signal noxious skin deformations from mechanical stimuli (Bessou et al., 1971; Lewin and Moshourab, 2004). In contrast to heat- or mechanically-mediated withdrawal behavior, cold-mediated withdrawal may be more dependent upon differing activity in multiple populations of afferents (Campero et al., 1996; Simone and Kajander, 1996, 1997). To our knowledge, electrophysiological data more definitively linking particular nociceptor populations to withdrawal to cold temperatures is lacking (for cold withdrawal behavior see Dunham and Donaldson, 2007).

Yet the relationship between tissue damage and nociceptor activation is not straightforward. Nociceptor activation does not necessarily signal tissue damage—rather, it signals a *risk* of tissue damage. This is partly owing to a gap between the point at which nociceptor classes in the skin reach their firing threshold, which is relatively invariant (for example, around 38°–42°C for heat nociceptors), and the point at which actual tissue damage occurs (for example, denaturation of tissue proteins starts at about 45°C). This liberal setting of nociceptor thresholds effectively exaggerates an input signal in order to provoke pre-emptive behavioral responses (Raja et al., 1999). The system is biased to react as if injury has actually occurred, because non-damaging degrees of stimulation in this range reliably and probabilistically predict actual tissue damage. So starting at the first stage of sensory response, at the afferent nerve level, nociception already reflects a predictive, probabilistic risk assessment. Thus, reflexes elicited by nociceptor activation are frequently protective. In this sense they are comparable to representations of metabolic need, in which hunger feelings and motivation to eat precede critical metabolic deficiency in the body's tissues.

Such protective withdrawal reflex actions are mainly supported by neurons in the spinal cord that receive signals from nociceptors. "Nociceptive withdrawal reflex" (NWR) neurons mediating muscle activations have been identified in the dorsal horn of the spinal cord (Levinsson et al., 2002). One might expect that these spinal NWR circuits are organized with respect to a somatosensory map of the incoming sensory afferent sources, but evidence indicates that they are not organized in this sensory-afferent-based manner. Instead, they are mapped with respect to the target muscle (Schouenborg and Weng, 1994; Sonnenborg et al., 2000; Levinsson et al., 2002; Schouenborg, 2003). This musculatopic mapping implies that NWR circuits are tuned to optimize sensorimotor transformations of incoming nociceptive information in the *efferent* direction, in terms of their influence on the specific muscles they innervate. Encoding of nociceptive signals is thus action-based from a very early stage.

Non-nociceptive tactile information may also be utilized in circuits that control pain-withdrawal behaviors. Most NWRs are wide-dynamic range neurons (WDRs) in the dorsal horn of the spinal cord. WDRs receive input from a variety of tactile afferents, both nociceptive and non-nociceptive. Such neurons in NWR circuits may weight tactile afferent input from the receptive field alongside nociceptive input, suggesting that non-nociceptive tactile information is taken into account in reflexive withdrawal action (Petersson et al., 2003). It is currently unclear whether non-nociceptive tactile information influences the production of a given instance of reflex withdrawal, but work with rats and cats indicates that input from non-nociceptive tactile afferents may be crucial in setting the gain on NWR circuits in the spinal cord (Holmberg and Schouenborg, 1996). Specifically, spontaneous muscle twitches during sleep (when the sensory background is otherwise relatively quiet) result in tactile signals from the skin to the NWR spinal reflex circuit (Holmberg and Schouenborg, 1996; Petersson et al., 2003; Waldenstrom et al., 2003). The NWR may apply these signals to tune the efficacy of muscle action with respect to skin sensation. In other words, feedback from low-threshold tactile mechanoreceptors can help NWR circuits encode how effectively a particular muscle contraction can "unload" an offensive stimulus from the tactile receptive field. This process

has been named "somatosensory imprinting" (Holmberg and Schouenborg, 1996; Waldenstrom et al., 2003).

Somatosensory imprinting can be considered a gain-modulating mechanism influencing the efficiency of efferent output to the muscle, in essence putting innocuous tactile information to use in order to fine-tune reflex actions. Non-nociceptive tactile afferent input may be sufficient to activate NWR units to produce behavioral adjustments in the *absence* of nociceptor input, as suggested by inhibition of the RIII withdrawal reflex by innocuous electrical stimulation of skin over the specific nerve pathway (Danziger et al., 1998). But it is possible that pain-processing systems are open to coding non-nociceptive information in pain-related terms, if it predicts a probable ramp-up to nociceptor activation. In rats, gradually decreasing cold stimulation has been observed to provoke a flick response on the stimulated foot—but at temperatures insufficiently cool to excite large numbers of cold-sensitive nociceptors (Dunham and Donaldson, 2007). Following injury, innocuous stimulation around the injury site can also produce unpleasant or painful sensations (Chaplan et al., 1994), which may in part arise from sensitization of afferent neural populations in the spinal cord (Liljencrantz et al., 2013).

We coin the term "protonoxial adjustment" for non-injury-related behavioral adjustments that occur in the presence of innocuous stimuli which are not sufficiently strong in themselves to surpass nociceptor thresholds. For example, holding a cool drink in one hand might cause enough discomfort for you to change hands after a while, despite not being cold enough to evoke a nociceptor response. Such protonoxial adjustment behaviors may partly rely on mechanisms in the central nervous system which predict somaesthetic perturbations by innocuous stimuli on the basis of previous experience (such as the eventual local numbness from holding a cold drink for too long). However, this remains to be experimentally addressed.

COMPLEX NOCIFENSIVE BEHAVIOR

Spinally-mediated and autonomic reflexes (such as withdrawal and startle, respectively) go far in accounting for the first wave of bodily defense and action readiness in the face of potential pain. However, mammalian cortex supports complex mechanisms for further flexibility and refinement of action, integrating reflex responses with higher-level spatial, temporal, and sensory information. Once again, these processes often occur in a predictive manner.

Nocifensive actions, such as swatting at a particular location with an arm using a particular force, require visuotactile and spatiotemporal integration of pain-related information as well as its sensorimotor transformation. Neural populations in primate posterior parietal cortex perform sensorimotor transformations of threat-relevant visual stimuli (Rizzolatti et al., 1997; Buneo et al., 2002; Calton et al., 2002; Fogassi and Luppino, 2005). This can occur because many neurons in these populations are "bimodal", responding to both tactile and visual stimuli in a common receptive field, for example on the cheek skin and the area of space near the cheek. In ventral intraparietal sulcus (VIP), part of the frontoparietal action circuit, microstimulation produces appropriate eye, lip, and arm movements similar to those elicited by an aversive airpuff into the eyes (Cooke and Graziano, 2003). Human parietal cortex may similarly encode aversive visual events within peripersonal hand space (Lloyd et al., 2006), indicating a role for the VIP in the orchestration of aversive movements that require integration of visuotactile information into an egocentric coordinate frame (Graziano and Cooke, 2006). Importantly, coding of a stimulus in the space *near* the face in the same terms as one actually *touching* the face can be seen as a predictive mechanism which treats spatial information on a par with tactile information. These parietal populations have anatomical connections to posterior cingulate cortex (PCC), which plays a central role in orienting the eyes and body towards threatening stimuli (Vogt et al., 2006).

Among populations in nearby parietal area 7b (macaque homologue of human area PF) are also pain-related sensory neurons that also show visual response properties, which fire both when a part of the skin on the face is stimulated with noxious heat, and when the monkey views a threatening stimulus coming towards or hovering near that part of the skin (Dong et al., 1994). In humans, meta-analysis of fMRI studies has shown that PF and surrounding inferior parietal cortex are commonly activated by painful stimuli and action execution tasks (Morrison et al., 2013), including facial expression (Budell et al., 2010), consistent with a close yoking of pain information with action planning and execution. Predicting the probable sensory consequences of an action may thus be part of the package of action planning, for example, in reaching and grasp formation (Morrison et al., 2013).

The human hand-blink reflex (HBR) illustrates the complex interaction between nocifensive responses and the spatial representation of the envelope of peripersonal space surrounding the body. If the arm's median nerve is stimulated as the hand is brought rapidly towards the face, this elicits an eyeblink reflex (Sambo et al., 2012a). The coordination of hand stimulation with a trigeminally (i.e., facial nerve) mediated eyeblink response reflects the integration of proprioceptive information (here, from the hand) with the coding of peripersonal space (here, around the face). An electromyographic (EMG) study has shown that the HBR is enhanced most when the hand is within peripersonal space and nearest the face (Sambo et al., 2012b). It is also specific to the relevant hand and dependent on cognitive expectations (Sambo et al., 2012b). This brainstem-level coding of "defensive" peripersonal space is dynamic and facilitates appropriate nocifensive action before an actual injury occurs (Sambo et al., 2012a). Further, transcranial magnetic stimulation (TMS) of motor cortex has revealed evidence of complex interactions among arm and hand muscles during pain, with reduced muscle-evoked potentials (MEPs) in distal (hand) muscles alongside a slight facilitation of proximal (upper arm) muscles, which likely reflect enhanced arm retraction simultaneously with prehension interruption (Leis et al., 2000; Le Pera et al., 2001).

PREDICTIVE CODING AND WEIGHTING OF RISK ESTIMATES

Predictive coding in the nervous system can take many forms. Since nociceptor activation has reliably predicted tissue damage during phylogenetic history, it can be considered a signal of

tissue damage risk. In the nocifensive action circuits just discussed, temporal and spatial information about events around and within the body envelope predict potential threat, and reflect complex sensorimotor integration of such predictions. Multiple neural connections bear such sensory-based signals forward among the intricately nested hierarchy of systems involved in pain processing.

Yet crucially, pain processing is not a feedforward affair. Especially in the cortex, "backward" connections can operate on incoming signals to modulate their strength or salience. For example, descending modulation can attenuate the incoming nociceptive signal from the spinal cord (Fields et al., 1977; Calejesan et al., 2000), effectively skewing the input range away from higher stimulus extremes. Pain behavior thresholds of laboratory animals can be influenced by contextual factors, such as the identity of the experimenter handling them (Chesler et al., 2002). In humans, voluntary attentional focus (Ploghaus et al., 1999; Kulkarni et al., 2005), expectation (Wiech et al., 2008), and contextual factors (Rudy et al., 2004; Jepma and Wager, 2013), and social factors (Krahé et al., 2013) can bias cortical pain processing. Spinal-level effects of descending modulation of pain by attention (Sprenger et al., 2012) and by negative emotion (Rhudy et al., 2013) have recently been demonstrated in humans.

In the PRA model, such back-modulating regulatory processes pivot on local predictions about the incoming signal. If an incoming signal to a given neural population deviates from the predicted input signal, this generates a further, information-rich signal reflecting the residual error of the prediction. In turn, this gives rise to processes that seek to account for sources of the error within the system or network. This type of "dynamic predictive coding" model (Clark, 2013) has been fruitfully applied to perception-action systems (Grush, 2004; Friston, 2005) as well as interoceptive systems (Paulus and Stein, 2010; Seth et al., 2012).

One major implication is that the sensory-based stimulus information feeding such processes consists mostly of the forward propagation of informative *error* (rather than "sensory") signals, while constantly-adjusted predictions propagate backwards and influence the forward flow of information. Rather than simply transducing the nociceptive signal, then, cortical pain networks mainly conduct their trading in the less expensive currency of error signals. In applying these ideas to pain, the PRA model implies that subjective pain experience involves the perception of this dance of prediction and error, rather than being a "direct perception" of nociceptive signaling.

The relative weighting of signals propagating through the network provides an estimate of risk, in that strongly-weighted nociceptive-based signals convey a higher likelihood of cost in terms of tissue damage. A high risk weighting also implies a high benefit of behavioral response. However, estimates may differ among different nodes of the system as to just how large a risk a given stimulus poses. For example, nociceptive signals from the spinal cord synapse in brainstem and thalamic nuclei before reaching the cortex, with information coded at each synapse along the way. Yet this forward chain of synapses probably over-estimates risk in order to guard against the perils of under-reaction. Recall the wide margin for nociceptor activation mentioned earlier: the signal is inherently exaggerated, with the needle swinging from "some likelihood of tissue damage" to "an actual injury has occurred" (even when none has). From an injury-avoidance perspective, this operational collapse of "potential" with "actual" injury is smart. From an energetic resource perspective, however, it is a recipe for unwarranted waste, since it sets up a costly false positive bias, perhaps all the way up to the thalamic level.

Allostatic models (Sterling, 1988; Schulkin, 2011) emphasize this kind of tension between ranges of prediction and energy-efficiency. For example, Sterling's general allostatic model (Sterling, 1988) posits that stable dynamics reflect energy efficiency among multiple interacting systems, not necessarily defense against deviations from a given set point (in contrast to a more literal "homeostatic" model, see e.g., Schulkin, 2011). Like dynamic predictive coding models, allostatic models highlight the role of prior experience and prediction in the system's maintenance of a stable dynamic. In these senses, an allostatic view is well-equipped to describe important features of the complex, multivariate mechanisms of regulation among the multiple interacting systems involved in pain processing (such as inflammation and stress; see also Maleki et al. (2012) for an application to migraine pain). Thus, risk weighting may provide a spur to action to other parts of the system, but other parts of the system can also play a role in deciding how seriously to take the risk estimate when the error signal is large. This dynamic should converge on energy-efficient interactions within the system, ultimately influencing the deployment of behavior in response to the nociceptive signal.

At the cortical level, incoming overestimations of risk would result in high error signals, leading to re-estimates of risk in the face of experience and other supervening contextual information, as well as re-weighting of signals to reflect error correction. The backward flow of regulatory influence can be understood in terms of gain modulation. Increasing the gain on an incoming risk estimate signal may effectively heighten the signal's salience with respect to ongoing action priorities and behavior. Likewise, lowering the gain through regulatory re-weighting can adjust its salience with respect to high-level factors, particularly where action is potentially costly. This relationship between prediction and regulation holds not only for ongoing stimulus processing but also affects predictions for future situations.

Figure 1 presents a schematic illustration of predictive coding and error-based regulation in a simplified system. A cortical area receives signals (S) from multiple input sources, for example from different thalamic nuclei. Predictions (PS) in the form of particular neural configurations await the signal, sketching out the expected input values. The differential between S and PS generates an error signal (E). Depending on the information to which the network has access, the signal variance is partially explained and therefore reduced, with a corrected prediction (PScorr) feeding back to previous stages or even to the signal sources themselves. As a whole, this process is regulatory and effectively gain-modulating, for example re-weighting the risk estimate reflected by S. Importantly, cortical populations integrate information, so higher-order predictions are likely to take multiple signal sources into account, e.g., $P(S_1, S_2)$. This also means that backward-propagating regulatory information is comparatively refined with

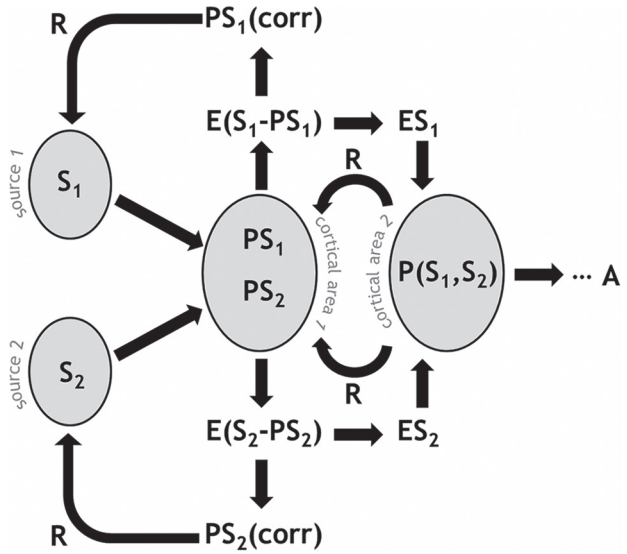

FIGURE 1 | Schematic illustration of predictive coding and error-based regulation in the PRA model of pain processing. A given cortical area receives signals (S) from multiple input sources. Predictions (PS) in the neural population represent the expected input values. An error signal (E) arises from the disparity between S and PS. A PScorr feeds back to previous stages. Higher-order predictions are likely to take multiple signal sources into account, e.g., $P(S_1, S_2)$. Ultimately, this process results in a behavioral response or action (A).

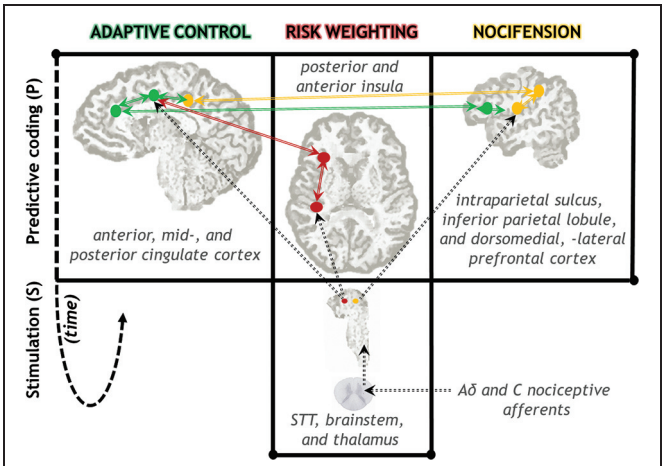

FIGURE 2 | Neuroanatomical diagram of key neural circuits in the PRA model of pain processing. Signals from nociceptive afferents arrive in cortex via STT, brainstem, and thalamic nuclei. The insula plays a central role in comparing these signals to predictions, as well as regulatory feedback processes that gain-modulate incoming signal weights (red; see also Figure 1). Spatiotemporal and proprioceptive information is integrated with pain information in parietal-centered circuits supporting nocifensive behavior (yellow). Voluntary actions in the face of actual or potential injury are supported by prefrontal regions, in particular anterior and mid-cingulate cortex (green). Action selection is likely to be influenced by risk-relevant information from the insula. Solid arrows indicate anatomical connectivity among highlighted regions. Dotted lines indicate selected major anatomical projections from the STT via thalamus. The time arrow (dotted fish-hook) indicates both the predictive (pre-stimulus) nature of these representations as well as the reiterative nature of the regulatory gain-setting processes. (Note: this schematic does not show all nociceptive-relevant regions and projections.)

respect to multiple signal sources. Ultimately, this process results in a behavioral response or action (A).

In the PRA model, the posterior insula is a main hub (Pessoa, 2008) not only for receiving nociceptive-based signals from thalamus (**Figure 2**), but integrating this information into subjective (Craig, 2003a,b; Paulus, 2007) and autonomic efferent terms (Damasio, 2000; Critchley et al., 2004; Gianaros et al., 2012). Most nociceptive afferents from the skin follow the spinothalamic tract (STT) to the cortex. Evidence from nonhuman primates suggests that posterior insula is one of the major projection sites of the STT, via thalamic nuclei containing nociceptive neurons (Craig and Zhang, 2006; Dum et al., 2009). Intriguingly, this is the only pain-related cortical region that produces subjective sensations of pain when directly electrically stimulated (Bancaud et al., 1976).

The anterior insula is also likely to be a closely-related partner in these cortical re-weighting processes, handling error signals based on thalamocortical inputs (for a similar idea see Refs. Damasio, 2000 and Craig, 2009). Processes of integrating and re-evaluating risk estimates may follow a caudo-rostral "gradient" in the insula, reaching a high degree of integration at the anterior insula (Craig, 2009). This gradient shows corresponding gradual caudo-rostral shifts in terms of connectivity with other cortical networks (Cerliani et al., 2012). Recent human neuroimaging evidence suggests that anterior insula activity predicts whether a subject will classify a stimulus as painful, biasing "perceptual decisions" about pain even before the stimulus occurs (Wiech et al., 2010). Importantly, this suggests a predictive relationship among nociceptive signals and insula processing, rather than a feedforward sequence of information handling. Patients with insular lesions evaluate pain as more intense on their affected side, suggesting that weighting is altered when insula is damaged, and show a greater recruitment of somatosensory cortices contralateral to the lesion, suggesting less efficient modulatory dynamics in these processes (Starr et al., 2009). Gain-modulation mechanisms in insula may contribute to pain's subjectively "hot" stamp by influencing signal salience (Mouraux et al., 2011).

Anterior insula has at least two subdivisions, a ventral, agranular region associated with affective processing and interconnected with many classical limbic structures such as the amygdala; and a dorsal, dysgranular region showing anatomical and functional connections with parietal and cingulate networks (Kurth et al., 2010; Wiech et al., 2010; Touroutoglou et al., 2012). Interestingly, there is also a degree of overlap between these two areas in terms of their intrinsic (resting state) connectivity (Kurth et al., 2010), suggesting scope for close functional communication between these insular subregions and their associated networks. In the rat (unlike in humans), rostral agranular insular cortex receives direct input from nociceptive neurons in medial thalamic nuclei. Specific gain-setting mechanisms of the pain signal may operate here, with gamma-aminobutyric acid (GABA) dynamically modulating neural thresholds to dampen or heighten pain behavior (Jasmin et al., 2003). Although the rat's gross neuroanatomy differs from

the human's in agranular anterior insula, the neurotransmitter mechanisms mediating gain-setting of pain signals may be similar.

The PRA model accommodates an important aspect of allostatic regulation within predictive coding networks: uncertainty. In normal acute pain, high S and high P produce low error signals and low modulatory regulation, passing a relatively unfiltered high risk estimate on through the system with high certainty. When there is no tissue damage risk at all, error and regulation are low, passing on a relatively unfiltered low risk estimate with high certainty. However, mismatches between S and P can produce high error and high uncertainty, if the system is unable to "explain away" much of the error residual.

High uncertainty alongside appropriate regulation might bootstrap learning in some circumstances, for example during the acquisition of conditioned pain responses (e.g., Rudy et al., 2004) or the reversal of such conditioning (e.g., Schiller and Delgado, 2010). Some pain syndromes and pathological pain conditions may involve high Ps in the face of relatively low weightings of S, thus overestimating risk (e.g., nocebo hyperalgesia, Colloca and Benedetti, 2007). Hypoalgesia or attenuated pain behavior may involve low Ps in the face of high weightings of S. All of these processes also have a vital temporal dimension, with failure to regulate in the right way at the right time leading to potential dysfuntion. In this perspective, anticipation of pain and pain anxiety are outcomes of high Ps, which may or may not be appropriately corrected either by bottom-up Ss (such as nociceptor activation or afferent sensitization at the spinal level) or by top-down regulatory P (corr) processes (as in descending modulation or episodic learning). Such processes could be involved in complex pain-emotion relationships like fear conditioning and the extinction and regulation of fear responses in the face of pain (Colloca and Benedetti, 2007; Schiller and Delgado, 2010; Rhudy et al., 2013).

ADAPTIVE CONTROL PROCESSES IN THE CORTEX

Strongly-weighted pain signals in the cortex can very effectively disrupt existing goals and override their associated behaviors. Yet no matter how strongly a given risk signal is estimated in the system, simple avoidance action is insufficient to explain all pain behavior. In many circumstances, pain's ultimate function of limiting tissue damage (e.g., Merskey and Bogduk, 1994) becomes complicated by the need to balance incoming nociceptive-based information with current goals and states. Sometimes the conflict is easy to resolve. For example, extreme heat on unprotected skin represents such an immediate tissue damage threat that it elicits spinal reflex action when you grasp a hot pan. But when tissue damage is more a vivid prospect than a reality, the relative weighting of sensations and goals is more difficult to resolve and requires more finely-calibrated control of behavioral outcomes.

Cortical pain representation may get a boost from the action-based pre-packaging of the incoming signal discussed earlier, in which nociceptive information is coded in sensorimotor terms even at the spinal level. But why should there be a need for further control? Frequently, there isn't. Often the sensorimotor information is sufficient for producing an appropriate action, and many risk-weighted events lead to straightforward avoidance or protective behavior. In other words, predictive coding explains and gain-modulates input signals so well that little residual error remains to propagate through the system. However, cortical representations of nociceptive signals arrive on a scene that is already bustling with various goals and motivational states—which may or may not have bearing on the question of how to act on the pain (see Chaplan et al., 1994 for an exploration of this idea with respect to opioid modulation; see also Fields, 2007). Generally speaking, the role of the cortex is to handle additional levels of conditional information that may be relevant to action selection in the face of pain. The high degree of flexibility which these processes confer arises from what Shackman and colleagues (Shackman et al., 2011) have termed "adaptive control" mechanisms in the cortex.

Such systems can be formally characterized as executive systems. The conditional information that cortical executive systems handle can be viewed as a hierarchically organized "cascade" of tightly interlinked levels (Fuster, 1991). In Koechlin and Summerfield's influential model of premotor executive control (Koechlin and Summerfield, 2007), the action information that comes bundled with the stimulus information occupies a basic level in the hierarchy, in which there is negligible residual between predicted sensory and motor signals. A further level of control subsumes both immediate context and episodic memory of past events. A still further level incorporates any relevant rule-based or otherwise contingent (e.g., "if-then") information that entails entertaining many possible action outcomes simultaneously. Applying this to the PRA framework, the greater the amount of additional information needed to select an appropriate action in the face of pain—or the greater the error—the greater the demand for higher-order levels of executive control.

A recent activation-likelihood-estimate (ALE) meta-analysis of fMRI studies showed that the anterior cingulate cortex (ACC) is the region most likely to be activated by acute pain (Duerden and Albanese, 2013). Although the cingulate cortex is often regarded as a key area in a "pain neuromatrix", a specific role in pain is unlikely, since it is also implicated in a range of non-pain-related functions (Mouraux and Iannetti, 2009). At the cortical level, even somatosensory contribution to pain processing may be small, and nociceptive-specific contribution even smaller, compared to multimodal processing in networks throughout the brain (Mouraux and Iannetti, 2009; Mouraux et al., 2011; **Figure 3**).

We consider the involvement of medial areas such as mid-cingulate cortex (MCC) far more likely to involve the adaptive control of action during pain (Shackman et al., 2011; Perini et al., 2013). Primate medial wall cortical areas including the ACC and MCC contain premotor fields (cingulate motor zones) which have both output to and input from cervical segments of the spinal cord where motoneurons are located (Picard and Strick, 1996; Koski and Paus, 2000; Dum et al., 2009), suggesting that these areas play a role in the generation and control of movements (Matelli et al., 1986; Picard and Strick, 1996; Koski and Paus, 2000; Dum et al., 2009; Perini et al., 2013). Like the posterior insula, they receive projections from the STT (Dum and Strick, 1996). But unlike posterior insula, intracranial microstimulation of human ACC does *not* result in pain sensations, but in reported feelings of urgency (Bancaud et al., 1976; Hsieh et al., 1994). Indeed, as the duration of a painful thermal stimulus increases, so do subjects'

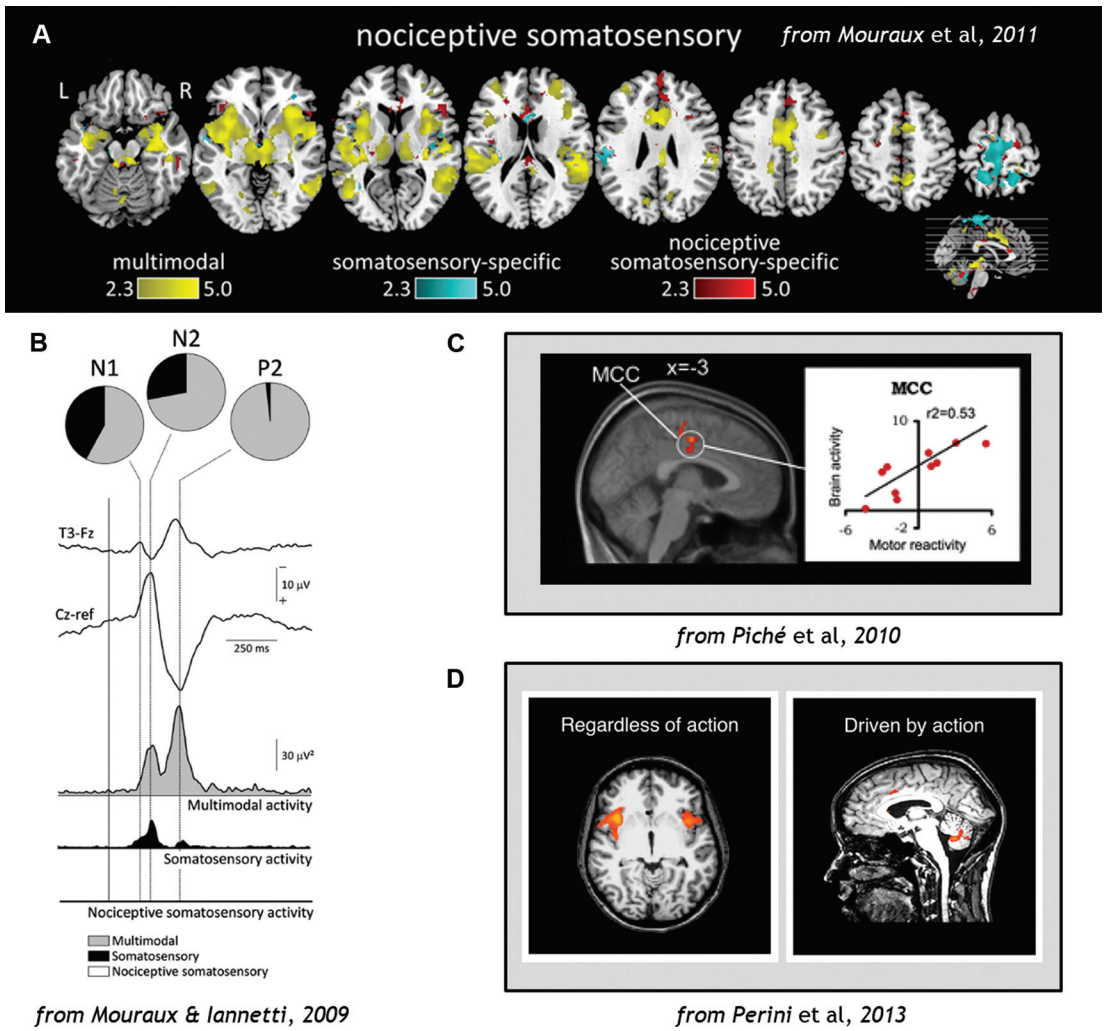

FIGURE 3 | (A) Analysis of fMRI data comparing blood-oxygen-level-dependent (BOLD) responses to stimulation across sensory domains (vision, audition, somatosensation, and pain), indicating that multimodal activity accounts for most of the cortical network activation during pain (Wiech et al., 2010). **(B)** EEG results demonstrating that cortical responses to Aδ and C nociceptor activation by laser-evoked potential (LEP) stimulation reflects predominantly multimodal and to some extent somatosensory–specific activity, but limited nociceptive-specific activity (Fuster, 1991). **(C)** fMRI evidence demonstrating correlations in regions of midcingulate cortex (MCC) with individual motor reactivity in the spinal RIII reflex (top) and variance in autonomic arousal (bottom) during electrical pain stimulation (Bancaud et al., 1976). **(D)** fMRI evidence demonstrates that midcingulate but not anterior insula activations during pain are contingent on motor processing (Duerden and Albanese, 2013). Figures reproduced with permission.

ratings of their urge to move away from the stimulus (Perini et al., 2013).

Regions of ACC and MCC have also been implicated in individual variance in motor reactivity, with nearby areas tracking autonomic variance (Piché et al., 2010; **Figure 3**). ACC responses to noxious thermal stimuli in the macaque monkey have shown increased activity during voluntary escape responses (in which monkeys could push a button to end the painful stimulation without performing the rewarded detection task; Iwata et al., 2005). However, these neurons showed decreased activity to the same stimulation during illumination and temperature change-detection tasks which required suppression of any immediate motor responses to the pain (Iwata et al., 2005). This indicates that the same region of the brain can mediate facilitory or inhibitory control over motor responses during pain. Recent human neuroimaging evidence indicates that voluntary motor-related processing can account for MCC and ACC activation during pain, particularly in the caudal cingulate motor zone (CCZ; Perini et al., 2013; **Figure 3**).

Kochelin and Summerfield's model of executive control can be applied to the medial prefrontal networks in which ACC and MCC are central hubs (Kouneiher et al., 2009). The ACC in particular has been extensively implicated in control-related processing across a range of contexts (Shenhav et al., 2013). The cingulate cortex is therefore a major site of executive control processes underlying adaptive control of pain behavior

(Shackman et al., 2011; Duerden and Albanese, 2013). These often display a caudal-rostral gradient (as do premotor executive control processes elsewhere in cortex), indicating that ACC and MCC subregions work together to integrate stimulus content and current task demands to produce appropriate and timely responses (Vogt, 2005; Kouneiher et al., 2009). Its role in such functions is partly owing to processes that link predicted value comparisons with action choices (Rushworth et al., 2012; Demanet et al., 2013). In this sense it is likely to be heavily involved in dynamic predictive representation of pain-relevant information.

Most caudally, the dorsal posterior cingulate cortex (dPCC) receives inputs from dorsal-stream parietal areas implicated in nocifensive behavior (Graziano and Cooke, 2006) and is also involved in orienting to and organizing motor responses to pain (Vogt et al., 2006). The motor fields of MCC probably contribute heavily to mobilizing context-appropriate skeletomotor responses to pain, with hemodynamic responses in the CCZ correlating with reaction times to pain (Perini et al., 2013). This region is also related to the regulation of facial expression displays during pain (Kunz et al., 2011). Importantly, neuroimaging analysis incorporating reflex variance indicates that it also receives its own "copy" of spinal reflex efference. The human RIII reflex is involved in limb withdrawal following nociceptive input to the spinal cord, and is measured by EMG activity from the muscle. Within-subject variability in human RIII reflex thresholds during painful electrical stimulation were associated with BOLD modulation of the MCC and ACC (Piché et al., 2010; see also **Figure 3**). These regions also get their own "copy" of the nociceptive signal from the STT from the same thalamic populations that project to posterior insula (Dum et al., 2009; **Figure 2**). They are also associated with the affective dimension of pain (Rainville et al., 1997).

Most rostrally, the rostral cingulate motor zone (RCZ) may be enlisted when the situation involves more complex conditional information, such as increased task complexity or dimensionality (Kouneiher et al., 2009). Processing in ACC may encode current and alternative courses of action, privileging some options in a manner closely linked to motivated choice and exploration behavior (Bancaud et al., 1976). Rostral ACC regions are particularly densely interconnected with dorsomedial and dorsolateral prefrontal networks also implicated in executive processing and action selection. These areas may contribute to a ranking of choices in both current and prospective temporal windows, perhaps even interacting in a competitive manner (Rushworth et al., 2012; Demanet et al., 2013). In the PRA model perspective, such action-based predictions might even stand in for sensory information under certain circumstances. Indeed, human psychophysical evidence suggests that, with practice, motor-based coding can improve sensory acuity without any changes in the sensory input (Saig et al., 2012).

Both adaptive control and risk-estimate-reweighting are interacting regulatory processes constrained by factors impinging on energy efficiency (Sengupta et al., 2013). Often, this involves weighing costs and benefits. Predictive systems can "look ahead" and project potential costs and benefits of outputs (ultimately, behavior) with respect to the signals from a variety of domains, including pain. For example, a rat may continue to forage for food in subzero temperatures, because the expected metabolic benefit of eating probably outweighs the current risk of tissue damage from the cold (Cabanac and Johnson, 1983; Boorman et al., 2013). Evidence from human behavior suggests that the magnitude and probability of painful stimulation can guide human behavior in a relatively direct manner (Kurniawan et al., 2010). But these mechanisms can also show complex sensitivity to previous experience, as well as any "market forces" that assign a reward value to pain tolerance (Vlaev et al., 2009), or by other outcomes which offset threat aversiveness (Hu et al., 2013). Under certain circumstances, the nociceptive route to cortex might even bypass somatosensory cortices, as suggested by a novel analysis (Liang et al., 2013), raising the possibility that sometimes even detailed somatosensory processing of a nociceptive signal can carry a prohibitively high cost. Such evidence for cost-benefit analyses with respect to pain behavior is consistent with allostatic and adaptive control processes that allow simple avoidance behavior to be circumvented in favor of expected benefits, especially those involving goals from other domains or the higher-order prospective goals we humans specialize in.

It is important to emphasize that we do not consider adaptive control processes as divorced from pain perception or its subjective nature. On the contrary, the PRA model postulates that adaptive action control processes are partly *constitutive* of subjective acute pain experience (Perini et al., 2013). We speculate that whereas predictive, regulatory processes producing risk estimate signals (as in the insula, **Figure 2**) probably make a large contribution to acute pain perception, so do movement urges arising from the action control hierarchies that both utilize and gain-set those risk signals (as in the cingulate, **Figure 2**). The interacting cingulate subsystems recruited by pain, for example, are both goal-directed and "energized" by risk and error signals originating in insula, among other places (for a detailed neurocomputational view see Holroyd and Yeung, 2012; Rushworth et al., 2012).

CONCLUSION

The PRA model of acute pain processing is an action-centered pain model that takes into account predictive coding, handling of error signals, local and supervening regulation, and dynamic interactions among the myriad hierarchical systems involved in processing acute nociceptive signals from the periphery. It also delineates operational categories of pain behavior. On the cortical level, the model focuses on the roles of the insula and the cingulate in gain-setting and action selection processes during pain. The insula may be involved in re-weighting the tissue-damage-risk estimates carried by thalamic nociceptive signals, possibly by dynamically setting the gain on nociceptive signal processing. Voluntary actions in the face of actual or potential injury are supported predominantly by MCC and ACC. The PRA model's description of neuroanatomical systems is not exhaustive, but can serve as a backbone for the mapping of pain-related processes in the nervous system as a whole. It incorporates elements from dynamic predictive coding, allostatic, and executive control models which capture the predictive and dynamic nature of these processes.

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Anxiety and error monitoring: the importance of motivation and emotion

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INTRODUCTION

Moser et al. (2013) report a novel meta-analysis across 37 studies demonstrating a small-to-medium association between the error-related negativity (ERN) and self-report measures of anxiety ($r = -0.25$); the meta-analysis further indicates a stronger relationship between the ERN and anxious apprehension ($r = -0.35$) than anxious arousal ($r = -0.09$). Based on these results, Moser et al. articulate their *compensatory error monitoring hypothesis (CEMH)*. In brief, the CEMH proposes that the relationship between anxious apprehension and an increased ERN is due to the distracting effects of worry: worrisome thoughts make it more difficult for anxious individuals to maintain task-related goals; as a result, increased effort must be employed. The CEMH suggests that an increased ERN reflects the transient increase in effort to compensate for the distracting effects of worry. Though we agree with many aspects of the CEMH (e.g., the importance of apprehensive anxiety; the potential impact of worry on the ERN), we believe that motivation and emotion are central constructs to understanding both within- and between-subjects variation in the ERN.

ERRORS ARE AVERSIVE (ESPECIALLY FOR ANXIOUS PEOPLE)

Threat has traditionally been conceptualized in terms of external stimuli—things with the capacity or intention to harm an individual. We hypothesized that the commission of errors might similarly be threatening (Hajcak and Foti, 2008; Hajcak, 2012): making mistakes place an individual in unknown danger. In support of this view, errors are experienced as distressing (Spunt et al., 2012) and are associated with a host of physiological changes consistent with defensive mobilization: following errors, the startle reflex is increased (Hajcak and Foti, 2008; Riesel et al., 2013), heart rate decelerates (Hajcak et al., 2003, 2004), the pupil dilates (Critchley et al., 2005), the corrugator (i.e., frowning) muscle contracts (Lindstrom et al., 2013), and a sympathetic nervous system response is evident in skin conductance changes (Hajcak et al., 2003, 2004). Moreover, there is increasing behavioral evidence that errors and other variants of response conflict are aversive (Botvinick, 2007; Dreisbach and Fischer, 2012; Schouppe et al., 2012). Indeed, errors activate many of the same neural circuits associated with the experience of negative affect (Shackman et al., 2011).

Previously we used the term *defensive motivation* in discussing both state and trait effects (Hajcak, 2012; Weinberg et al., 2012b); to avoid potential confusion here, we use the term *threat sensitivity* to refer to trait-like individual differences which we contrast with *defensive motivation*, which reflects a transient response to threat. Thus, we view errors as unpredictable threats that prompt an immediate defensive motivational response. Further, we believe that variation in the ERN reflects a *trait* difference in early *threat sensitivity* that drives vigilance and increased defensive motivational responses. This view is consonant with theories of early-emerging and stable individual differences in temperamental styles such as behavioral inhibition (Fox et al., 2005) and related forms of dispositional anxiety (Fox et al., 2008; Shankman et al., 2013). High behavioral inhibition describes increased sensitivity to environmental cues of punishment, novelty, and threat (Gray and McNaughton, 2000); dispositional anxiety refers to a tendency to respond excessively in the face of potential or *uncertain* threats (Barlow, 2002; Grupe and Nitschke, 2013; see also Hirsh and Inzlicht, 2008).

In this context, we argue that the increased ERN characteristic of anxious individuals reflects the disposition to respond more strongly to uncertain threat (Hajcak, 2012; Weinberg et al., 2012b). Moser et al. suggest that there is no evidence that anxious individuals are characterized by a greater defensive response to errors. However, in one study, participants scoring high in trait negative emotionality demonstrated larger increases in skin conductance after making errors (Hajcak et al., 2004). Moreover, anxious people report excessive concern about their mistakes. We would similarly predict larger startle responses after errors among more anxious individuals, and would encourage additional studies in which variability in the ERN is examined in relation to other indices of threat sensitivity and defensive motivation.

THE ERN AS ENDOPHENOTYPE

We (Olvet and Hajcak, 2008) and others more recently (Manoach and Agam, 2013) have argued that there is considerable evidence that the ERN is a candidate psychiatric endophenotype. An endophenotype must be associated with an illness, heritable, evident in unaffected first-degree family members, and independent of current disease state (Gottesman

and Gould, 2003; Miller and Rockstroh, 2013). Moser et al. dismiss this possibility, citing only one study in which treatment-related reductions in OCD symptoms did not reduce the ERN in a pediatric Obsessive-Compulsive Disorder (OCD) sample (Hajcak et al., 2008). However, there is considerable evidence that the ERN is stable over time and behaves like an endophenotype. For instance, the ERN demonstrates sufficient test-retest reliability over two weeks to more than two years (Olvet and Hajcak, 2009; Weinberg and Hajcak, 2011). Moreover, about 50% of the variation in ERN amplitude appears to be heritable (Anokhin et al., 2008), and variation in the ERN has been linked to a variety of genes (Manoach and Agam, 2013). Two recent studies found an increased ERN in unaffected first-degree relatives of OCD patients (Riesel et al., 2011; Carrasco et al., 2013). These data point toward the ERN as a neural endophenotype.

DISTINGUISHING REACTIVITY TO THREAT FROM SUBSEQUENT COMPENSATORY PROCESSES

A fundamental distinction between our view and the CEMH is that we do not view the relationship between ERN and anxiety as compensatory. We make a strong distinction between temporally earlier defensive motivational responses that vary with threat sensitivity and later compensatory responses that include cognitive processes such as worry (Borkovec et al., 2004; Newman and Llera, 2011; Mennin and Fresco, 2013). We believe that increased threat sensitivity (i.e., behavioral inhibition) precedes the development of compensatory processes such as worry—both phylogenetically and ontogenetically. That is, heightened trait differences in threat sensitivity can lead to various forms of cognitive compensation—including worry. As such, we would argue that worriers actually have two problems: they are more sensitive to uncertain threat, and they have developed maladaptive cognitive coping strategies to deal with their increased threat sensitivity (e.g., worry).

Within this framework, we believe that the ERN relates to trait-like vulnerabilities in threat sensitivity rather than compensatory efforts to modulate increased threat sensitivity such as worry. This distinction is especially relevant in terms of prospective and developmental predictions. For instance, a formal worry process may not be clearly evident in young children (Vasey et al., 1994). However, we found increased ERNs in clinically anxious 6 year-olds, who were mainly phobic (Meyer et al., 2013). This would suggest that increased ERN, reflecting heightened threat sensitivity, develops *before* processes like worry. Our model presumes that an increased ERN would prospectively predict increases in anxiety and worry—and that an increased ERN would be a risk marker for the development and onset of anxiety disorders. Our model would also predict an increased ERN among more anxious non-human animals that are presumably less prone to verbally-mediated compensatory processes such as worry; for instance, the ERN can be measured in non-human primates (Godlove et al., 2011) who show marked differences in behavioral inhibition and anxiety (Fox et al., 2008).

THE ERN IS SENSITIVE TO STATE AFFECT

Many trait-like measures and phenotypes (e.g., anhedonia) can be altered and manipulated in the short-term (e.g., via stressors and mood inductions; also see Coan et al., 2006). Moser et al. argue that changes in state affect do not consistently modulate the ERN. However, it might be important to distinguish between affect that is integrally related to errors and affect that is incidental (see Schmeichel and Inzlicht, 2013). When spider phobics make errors on a flanker task in the presence of a spider, their fear is incidental to error processing (Moser et al., 2005). However, if their fear was related to making an error (e.g., if spider phobics had to view pictures of spiders after making mistakes), then their fear would be integrally related to errors. Emerging data suggests that variation in motivation to make errors does impact the ERN. When integral negative affect is added, such as when errors are punished (Riesel et al., 2012), when performance is evaluated (Hajcak et al., 2005), when errors are more valuable (Hajcak et al., 2005) or personally meaningful (Amodio et al., 2008; Legault and Inzlicht, 2013), the ERN tends to increase; when integral negative affect is subtracted, such as when people are led to misattribute their affect to an external and benign source (Inzlicht and Al-Khindi, 2012) or when they ingest an anxiolytic agent that leads them to care less about their errors (Bartholow et al., 2012), the ERN decreases. In our model, worrying might potentiate the ERN if it were to increase the threat value of errors. It will be important for future studies to determine the extent to which state variability in worry accounts for the relationship between trait anxiety and the ERN.

FUTURE CHALLENGES

Moser et al.'s paper encourage greater phenotypic specificity for understanding the increased ERN in relation to anxiety—and this is a significant contribution (see also Vaidyanathan et al., 2012). Worry is one phenotype that *may* account for the increased ERN in anxiety disorders; however, we would also encourage continued efforts to evaluate the ERN in relation to additional, empirically-derived phenotypes (Watson et al., 2007). Indeed, some extant clinical data already suggests that the relationship between anxiety and the ERN may require examining the *interaction* between key phenotypes. For instance, comorbid major depressive disorder (MDD)—which is also characterized by increased worry—appears to mask the relationship between GAD and an increased ERN; history of MDD, however, does not seem to impact the increased ERN in GAD (Weinberg et al., 2012a). We have suggested that *state*-related characteristics of depression (i.e., anhedonia) may alter the relationship between ERN and *trait* anxiety.

Moser et al. also sound a call for more specific predictions and assertions regarding the relationship between ERN and anxiety. We agree, and our view focuses on possible causes and subsequent development of anxiety disorders (i.e., models of etiopathogenesis). One possibility from the endophenotype perspective is that the same genes that confer risk for the development of anxiety disorders determine variability in the ERN. Another possibility is that environmental (i.e., non-genetic) factors that impact error salience modulate the ERN. In an approach rooted in models of fear conditioning and extinction-based learning, we inflated the threat value of errors by punishing certain mistakes; even

after mistakes were no longer punished, the ERN was potentiated on trials that had formerly been punished (Riesel et al., 2012). Based on these data, we suggested that early learning experiences (e.g., critical parenting) may lead to a larger ERN. Our view is consonant with the possibility that ERN neurodevelopment is impacted by both genetic and environmental factors that shape characteristic defensive motivational responses to errors. There are multiple pathways to increased threat sensitivity.

Our conceptualization gets at a fundamental issue: why are some people more worried to begin with? Our view is that an elevated ERN reflects a broad disposition toward increased sensitivity to uncertain threat, and that some individuals attempt to compensate for this via worry (Mennin and Fresco, 2013). The most significant advantages of the endophenotype approach are the potential for identifying genetic contributions to disorders (e.g., the genetics of the ERN are simpler than the genetics of complex disorder-based phenotypes), for identifying those at risk for disorders, and for bridging human and animal models. Future steps would then include more mechanistic studies to clarify causation and identify novel interventions. Accordingly, we suggest further research to understand the conditions under which variability in the ERN *leads* to pathological outcomes. Could manipulating the ERN causally alter risk for anxiety and compensatory efforts like worry? As a proposed metaphor, we consider the relationship between cholesterol and coronary heart disease (CHD): high levels of low density lipoproteins (LDL) is a partially inherited risk factor for CHD; risk for CHD is lowered by directly manipulating LDL through medication and lifestyle change. LDL levels are trait-like, genetically determined, and yet, are sensitive to state-related (i.e., diet) manipulations; lowering LDL alters subsequent risk for disease. In this way, the ERN itself might be a unique target for intervention and prevention efforts. Our view focuses on leveraging variability in the ERN to understand the development of, and risk for, psychological disorders. This approach requires large and longitudinal studies to delineate trajectories of risk, and to parse the prospective relationship between ERN and increases in anxiety.

CONCLUSION

Although there is much to like about the CEMH, we believe that it does not fully address the critical contribution of emotion to the ERN. Importantly, when examining the influence of anxiety on the ERN, it is vital to account for trait-level differences in emotionality; to distinguish between threat sensitivity and compensatory efforts to deal with threat such as worry, and to differentiate between integral and incidental affect. Emotion is both a core aspect of anxiety and why errors powerfully shape behavior. Emotion is at the heart of the anxiety-ERN relationship.

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The influence of emotions on cognitive control: feelings and beliefs—where do they meet?

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The influence of emotion on higher-order cognitive functions, such as attention allocation, planning, and decision-making, is a growing area of research with important clinical applications. In this review, we provide a computational framework to conceptualize emotional influences on inhibitory control, an important building block of executive functioning. We first summarize current neuro-cognitive models of inhibitory control and show how Bayesian ideal observer models can help reframe inhibitory control as a dynamic decision-making process. Finally, we propose a Bayesian framework to study emotional influences on inhibitory control, providing several hypotheses that may be useful to conceptualize inhibitory control biases in mental illness such as depression and anxiety. To do so, we consider the neurocognitive literature pertaining to how affective states can bias inhibitory control, with particular attention to how valence and arousal may independently impact inhibitory control by biasing probabilistic representations of information (i.e., beliefs) and valuation processes (e.g., speed-error tradeoffs).

Keywords: emotion, inhibitory control, Bayesian modeling, ideal observer model

INTRODUCTION

How do feeling and thinking influence one another? From our subjective experience, and systematic behavioral research, we know that affective states profoundly influence cognitive functions, in both facilitative and antagonistic manners depending on the context. This relationship between affect and behavior is not surprising, given the extensive interactions between the physiological and interoceptive manifestation of emotion (Craig, 2002; Paulus and Stein, 2006) and cognitive control networks (Botvinick et al., 2001; Pessoa, 2009). In particular, impairments in critical executive faculties such as inhibitory control (Miyake et al., 2000) are tightly linked to clinical disorders involving pervasive emotional states and difficulty in regulating emotion. However, little is known about the specific computational and cognitive processes underlying such interactions between emotion and inhibition. Thus, understanding precisely how emotion is integrated into core executive functions, such as inhibitory control, is essential not only for cognitive neuroscience, but also for refining neurocognitive models of psychopathology.

In this review, we propose a computational framework to conceptualize emotional influences on cognition, focusing in particular on inhibitory control. We build upon research suggesting that a wide range of apparently distinct cognitive faculties can be unified under a common "ideal observer" framework of decision-making and dynamic choice. Rational observer models have been applied widely to the study of choice in uncertain environments, and to identify potential neural markers of the iterative processes of belief update underlying such models (Hampton et al., 2006; Behrens et al., 2007). Subsequent modeling work showed that such a framework is readily adapted to various aspects of executive function, including attentional and inhibitory control (Yu and Dayan, 2005; Yu et al., 2009; Shenoy and Yu, 2011; Ide et al., 2013). In particular, this literature suggests that apparently distinct faculties in inhibitory control can be folded into a single framework where subtle differences in task contexts are reflected in their influence on components of the framework, giving rise to the diversity of observed behavior. Building on this research, we argue for an *emotion-aware* rational observer model of inhibitory control, where emotions serve as additional *context* for the computations underlying behavior. Indeed, previous research has explored the idea of emotion providing information about one's internal state to the executive system. Therefore, emotion can be considered part of the information that along with external stimuli is integrated to perform controlled actions (Schwarz and Clore, 1983; Forgas, 2002). Such biases appear to be mediated by mood-congruent effects on memory [i.e., priming access to and retrieval of mood-congruent concepts and outcomes (Bower, 1981)] and interoceptive processes [i.e., conveying information about ones' valuation of / disposition toward choice options (Schwarz and Clore, 1983)]. Therefore, here we propose a wider role for emotional context in cognition, and consider how it may affect beliefs and action valuation in much the same way as other environmental constraints and information do. We consider such interactions within the confines of our decision-making framework for inhibitory control, thereby allowing us to relating emotion directly to other, well-understood computational principles underlying cognition.

In the following sections, we first review Bayesian ideal observer models of inhibitory control using a shared computational framework to guide discussion. The following section is organized into two parts, distinguishing two broad types of computational elements that may be modulated by emotion, namely a) probabilistic computations (i.e., reflecting individuals' beliefs about the frequency of certain events or actions) and b) valuation computations (i.e., reflecting the value or cost associated with potential outcomes and actions). To maximize the theoretical usefulness of our model, we further opt for a dimensional decomposition of emotion rather than considering the impact of multiple separate emotions on inhibitory control. Thus, within this computational framework, we distinguish two empirically validated dimensions of emotion with distinct physiological markers (Lang et al., 1997; Tellegen et al., 1999; Davidson, 2003): valence or motivational tendency (i.e., positive/appetitive vs. negative/aversive tone), and arousal (or emotional salience or intensity). We acknowledge that while valence and motivational tendency are theoretically different constructs and their respective validity still a matter of debate, they have a high degree of overlap in most emotional states. Specifically, most negative emotions are withdrawal based and positive emotions are approach based, with one notable exception being anger (Harmon-Jones and Allen, 1998). Given the limited number of studies specifically attempting to dissociate the effects of these dimensions on inhibitory control, it was not feasible to distinguish between them in the present review. However, we address this distinction in our proposed framework by considering two mediating computational mechanisms through which valence and arousal may infuse the computational underpinnings of inhibitory control, namely outcome vs. action related computational processes. In support of this distinction, separate neural markers have been linked to anticipation of an outcome vs. the appetitive or aversive disposition or *drive* toward a particular outcome [i.e., action tendency; (Breiter et al., 2001; Miller and Tomarken, 2001; Knutson and Peterson, 2005; Boksem et al., 2008)]. Thus, from a computational and neural perspective, these outcome and action tendencies may emerge from very different underlying components. Therefore, we evaluate valence and arousal with respect to their potential impact on (a) action and outcome expectancies (i.e., probabilistic predictions), as well as (b) action and outcome valuation (i.e., relative importance of these events in the decision policy).

We propose several hypotheses linking these affective dimensions (and their attendant behavioral influences) to specific components of the computational framework. Based on the AIM model of affect infusion and extensive literature pointing to a strong interdependence between hedonic valence and the behavioral activation/inhibition system (Niv et al., 2007; Huys et al., 2011; Guitart-Masip et al., 2012), we conjecture that the valence dimension may promote both valence-congruent effects on outcome-related computations and motivational effects on activation and inhibition. In contrast, arousal may primarily modulate action cancellation expectancies and, at higher thresholds, have a more indirect impact on computational processes by redirecting attentional resources and impairing prefrontal cortical function (Arnsten, 2009a). These hypotheses suggest testable, quantitative relationships between emotional state and inhibitory control.

MODELS OF INHIBITORY CONTROL

COGNITIVE MODELS OF INHIBITORY CONTROL

Much of the theoretical literature on inhibitory control focuses on the contrast between action and inhibition and different aspects of inhibition such as attentional and behavioral inhibition. Accordingly, the literature suggests separate functional instantiation of these putative processes, both in abstract cognitive models and in proposals for neural architectures. For instance, several articles propose a *conflict* model of inhibitory control, where certain stimuli may activate multiple action plans, thus generating conflict between competing responses (Botvinick et al., 2001). This notion of conflict has been explored at the neural level using a contrast between trial types in a variety of tasks such as the Stroop task (Barch et al., 2000; Macleod and Macdonald, 2000), the flanker task (Botvinick et al., 1999) the Simon task (Peterson et al., 2002; Kerns, 2006), and the Stop Signal task (Brown and Braver, 2005). As an example, in the Eriksen task, incongruent stimuli are thought to generate conflict between the responses associated with central and flanker stimuli, resulting in behavioral differences and corresponding neural activation. Other work has drawn on the empirical data to suggest architectures for *monitoring and resolution* of conflict (Botvinick et al., 2001; Botvinick, 2007) and error (Brown and Braver, 2005), where specific areas of the brain monitor any resulting conflicts or errors in order to adjust behavior appropriately. Closely related work considers models of the specific *underlying processes* that may give rise to action and inhibition, respectively. For instance, in the stop signal task, the influential *race model* of stopping (Logan and Cowan, 1984) suggests that behavior is an outcome of a race between finishing times of "stop" and "go" processes, corresponding to inhibition and response, respectively. A rich literature has explored potential instantiations of this race model at various levels of neural activity: from neural firing rates (Hanes et al., 1998; Paré and Hanes, 2003; Stuphorn et al., 2010) to population activity in specific brain regions such as the IFC (Aron et al., 2004) to putative "stopping circuitry" involved in inhibition of action (Aron et al., 2007a).

The consensus in much of this work is of a contrast between *inhibition* and *action*, with potentially different mechanisms and neural circuitry involved in these functions. Further, individuals are thought to exercise different kinds of inhibition, depending on the task demands. From this perspective, behavioral and neural measures of performance in inhibitory control tasks measure the *relative efficacy* or dysfunction of these competing systems, and each such measure may reflect the performance of a different subsystem. For instance, (Eagle et al., 2008) compare and contrast the go/nogo and stop signal tasks from behavioral, neural and pharmacological perspectives, suggesting a dissociation between different *kinds* of behavioral inhibition: "restraint" (the go/nogo task) and "cancellation" (the stop signal task). Other work (Nee et al., 2007; Swick et al., 2011) explores, from a neural perspective, the possibility of shared circuitry in various inhibitory control tasks.

In contrast, recent work explores the possibility of studying inhibition using rational observer models, where all behavioral outcomes (various responses, or the absence of a response) are produced by a single, rational (i.e., reward-maximizing) decision-making framework. In the rest of this section, we outline the proposed framework using different inhibitory control tasks as examples. The framework promises to unify the wide variety of behavioral and neural results from studies of different inhibitory control tasks, currently ascribed to different functional systems. In addition, this unifying perspective may suggest how other, apparently distinct, influences such as emotion, may also be integrated into a computational decision-making perspective.

INHIBITORY CONTROL AS RATIONAL DECISION-MAKING

A recent body of work (Yu et al., 2009; Shenoy and Yu, 2011, 2012; Shenoy et al., 2012) recast behavior in a wide variety of inhibitory control tasks as *rational* (i.e., reward-maximizing) tradeoffs between uncertainty and the cost of available actions. This cost-benefit tradeoff is an *ongoing* decision-making process that unfolds over time as noisy sensory inputs are processed, and reconciled with prior expectations about possible outcomes. A general outline of the decision-making framework is shown in **Figure 1**. The figure shows an example where certain events in the real world that are task-relevant (e1, . . . , e3, top panel) are processed gradually over time and represented as *beliefs* or probabilities (middle panel). In the example, e1 and e2 are mutually exclusive events (for instance, a forced-choice stimulus), whereas e3 may or may not occur at some subsequent time. Note that this simple representation captures the general dynamics of most of the discussed inhibitory control tasks. The beliefs (b_t) shown in the figure represent the evolving degree of uncertainty an individual has about the state of the world—e.g., has e3 occurred already? Such beliefs are, naturally, influenced by prior expectations. For example, the initial anticipation that e3 might occur is tempered by the initial lack of sensory evidence, whereas subsequent occurrence of the event is quickly reflected in the belief. Based on the belief state, subjects have to weigh the costs associated with various available actions, and select repeatedly between them. Note that in the model, *inaction* is also an available "action," with an attendant cost determined by the environment, and an advantage of acquiring more information for decision-making. The entire decision-making schematic is depicted in the right panel of **Figure 1**.

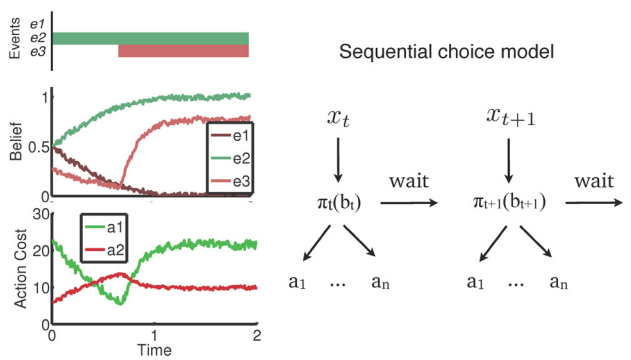

FIGURE 1 | Rational decision-making in inhibitory control. The figure abstracts out ideas common across recent decision-making models for inhibitory control into a single framework. **Left**: an example where task-relevant events e1 and e2 are mutually exclusive (e.g., a forced choice stimulus), and e3 occurs at some later point in time. Sensory evidence from these events are gradually reconciled with prior expectations to form a noisy, evolving belief, or subjective probability, about whether the event occurred. These beliefs form the basis of an ongoing valuation of, and selection between, available actions. **Right**: A representation of this sequential decision-making process. At each time point, noisy sensory inputs (x_i) are incorporated into beliefs (b_i), which are transformed into a choice between actions (a1,. . . an, wait) based on the decision policy ($\prod$).

Below, we illustrate how the framework may be applied to a variety of inhibitory control paradigms. Through this exercise, we aim to demonstrate that (1) different inhibitory control tasks may be understood and interpreted using the same shared framework, and (2) the apparent idiosyncrasies of behavior in the tasks reflect subtle differences in the task contexts, and draw focus on specific components of the proposed model. The first two sections address belief formation and updating, which we show can occur within trial (i.e., based on increased certainty about relevant sensory information) but also on a trial-to-trial basis (i.e., based on cumulative experience with the task). The third section introduces valuation processes as a framework for understanding speed accuracy tradeoffs.

Sensory disambiguation: conflict and resolution

We illustrate the influence of sensory processing models on decision making and inhibitory control using the example of interference paradigms introduced above. These tasks all share a critical similarity in that each one sets up a mismatch between two different features of a perceptual stimulus—i.e., information contained in the features may be *congruent* or *incongruent* with each other. The tasks, however, require a response based only on a single stimulus feature. In each of the tasks, subjects are more error-prone and slower to respond on incongruent trials. This difference has been attributed to various aspects of cognitive processing such as *attentional* or *cognitive* inhibition in terms of suppressing irrelevant information (Stroop & Eriksen tasks), or response conflict (Simon task). Instead, behavior in each of these tasks can be reinterpreted as a process of *within-trial* sensory disambiguation and belief update. In particular, (Yu et al., 2009) proposed that human sensory processing may have a "compatibility bias," where visual features are assumed to vary smoothly over space. This bias could potentially be acquired through experiential or evolutionary means. For instance, in the Eriksen task, this assumption may manifest itself via mixing of sensory evidence between central (C) and flanker (F) stimuli, as illustrated in **Figure 2A** (adapted and simplified from Yu et al., 2009). The figure suggests that, although the relevant sensory evidence (x_t) should only depend on the central stimulus (solid line), perceptual processing is nevertheless affected by flanker stimuli (y_t). As a consequence, decoding the central stimulus identity necessitates also decoding the trial type T (congruent or incongruent). Thus, in the proposed framework, the sensory processing that unfolds over time is tasked with disambiguating

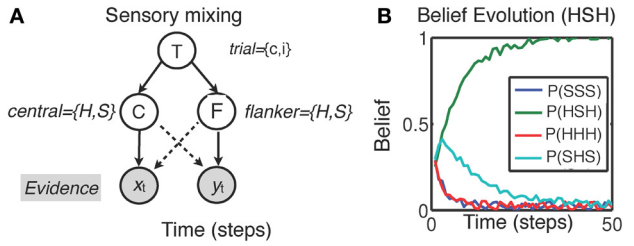

FIGURE 2 | Sensory disambiguation in the Eriksen task (Yu et al., 2009). (A) The model assumes that sensory inputs x_t (central stimulus) y_t (flanker) are mixed. Responding to the central stimulus C necessitates processing all sensory information and simultaneously decoding both the central stimulus and trial type T ($T = c$ on congruent trials; $T = i$ on incongruent trials) which depends on disambiguation of central and flanker (F) stimuli; H,S = stimulus type. **(B)** The corresponding Bayesian inference process (schematic) quickly discovers that the trial has an incongruent stimulus, but decoding the central stimulus identity may take longer due to featural mixing and potentially higher prior expectations of encountering congruent trials (i.e., $\beta > 0.5$).

the trial type and stimulus identity in a *joint* belief state as follows:

$$P\{C, T|X_t, Y_t\} \propto p(x_t|C)p(y_t|C, T)P\{C, T|X_{t-1}, Y_{t-1}\} \quad (1)$$

Here, the central stimulus identity ($C =$ "H" or "S") and the trial type T ($T = c$ for congruent or $T = i$ for incongruent) are both discrete and binary valued. The joint distribution in Equation 1 incorporates all the information gathered from previous observations (x_t, y_t). This iterative process is initialized by a prior distribution representing prior beliefs about the prevalence of congruent trials $[\beta = P(T = c|X_0, Y_0)]$ and the possible central/flankers stimuli configurations (e.g., "SSS" vs. "HHH" for congruent trials, and "SHS" vs. "HSH" for incongruent trials, based on a simplified case of only 2 flankers, see **Figure 2B**). To make a perceptual decision about the central stimulus C, the total (marginal) probability $P(C = H|X_t, Y_t)$ is computed by summing the joint probabilities over the uncertainty about congruency (i.e., $T = c$ and $T = i$):

$$P(C = H|X_t, Y_t) = P(C = H, T = c|X_t, Y_t) + P(C = H, T = i|X_t, Y_t) \quad (2a)$$

Since the stimulus identity only assumes two values ("H" or "S"), the probability of C being S is simply:

$$P(C = S|X_t, Y_t) = 1 - P(C = H|X_t, Y_t) \quad (2b)$$

It can be shown that the *optimal* decision policy compares these two marginal probabilities against a decision threshold q, and decides that the target is H if $P(C = H|X_t, Y_t) > q$, or S if $P(C = S|X_t, Y_t) > q$. If these conditions are not met, the policy continues observing the input data. On congruent trials, the reinforcing effect of the irrelevant flanker features lead to fast, more accurate responses, whereas incongruent trials require much longer to decode due to the corrupting influence of the flankers on stimulus disambiguation. So, for instance, the "compatibility bias" shown by subjects may manifest itself through a skewed *prior belief* in the probability of compatibility (i.e., $\beta > 0.5$; see **Figure 2B**). As outlined in part III, we propose that emotional states may influence sensory processing (hence behavioral performance) via such altered prior probability distributions.

Belief updating: learning to anticipate

In addition to the *within trial* evolution of beliefs observed during sensory disambiguation, recent work (Ide et al., 2013) suggests that prior expectations and belief updating occurring *across trials* also profoundly influence inhibitory control. For example, in a stop signal task, they showed that the immediate experienced history of trial types induced an ever-changing expectation of a stop signal on the upcoming trial, P(stop), and that the prior probability successfully predicted subsequent response times and accuracy on the trials. Formally, if r_k is the stop signal frequency on trial k and s_k is the actual trial type (1 on stop trials and 0 on go trials), P(stop) is the mean of the predictive distribution $p(r_k|S_{k-1})$, which is a mixture of the previous posterior distribution $p(r_{k-1}|S_{k-1})$, and a fixed prior distribution $[p_0(r)]$, with α and $1 - \alpha$ acting as the mixing coefficients, respectively:

$$p(r_k|S_{k-1}) = \alpha p(r_{k-1}|S_{k-1}) + (1 - \alpha)p_0(r_k) \quad (3a)$$

where $S_k = \{s_1, \ldots, s_k\}$
with the posterior distribution being updated according to Bayes' Rule:

$$p(r_k|S_k) \propto P(s_{k-1}|r_k)p(r_k|S_{k-1}) \quad (3b)$$

Note that the probabilities in Equations 3a,b, as those in Equations 1 $[\beta = P(C, T|X_0, Y_0)]$, represent expectancies about the likelihood of encountering various trial types associated with specific action requirements (e.g., frequency of stop trials, congruent trials, etc.), before the onset of each trial. Equations 3a,b show that these expectancies may evolve across trials to form an *iterative prior probability* for the associated action. As we discuss subsequently, while such *action expectancies* are key computational mediators of inhibitory performance, expectations of reward or punishment (i.e., *outcome expectancies*) may be equally relevant to our framework as they tend to co-vary with emotional sates. For instance, the use of inherently rewarding or punishing stimuli as trial type cues (i.e., paired with go or stop action requirement) may provide additional context to bias estimations of trial type probabilities (e.g., which could be modeled by an additional fixed prior that influences stimulus expectation).

Speed-accuracy tradeoffs: go bias and rational impatience

Focusing on inhibition and action valuation, we now introduce a general cost function framework for perceptual decision-making tasks as an example of how action valuation impacts measures of inhibition. Subsequently, we focus on two variants of this perceptual decision-making framework, namely the 2-alternative forced choice (2AFC) task (e.g., flanker) and the go/no-go task. As indicated in **Figure 1**, the moment-by-moment belief state generated through sensory processing results in estimation of inferred costs

of these actions and an appropriate choice. Note that choosing to postpone responding for one more time step is also an available action, and has a specific cost associated with it: the cost of opportunity. An action selection *policy* therefore needs to minimize the overall, or expected, cost of action choice inclusive of decision delay costs. These competing goals are made concrete in the form of a *cost function* that specifies the objective to be minimized through the action selection policy. In perceptual decision-making, as an example, a well-studied cost function minimizes a linear sum of response time and accuracy:

$$Cost = c * RT + c_e * P\,(choice\ error) + P\left(no\ response\right) \quad (4a)$$

The terms in this equation represent the cost of time (parameter c), the cost of choosing the wrong response (c_e), and the cost of exceeding the response deadline (which, for simplicity, is normalized to unit cost). P(choice error) and P(no response) are time varying probabilities of making a choice error (due to stimulus misidentification) and making no response, respectively. This sets up a natural *speed-accuracy tradeoff* where the costs of the two available responses depend on the uncertainty of the stimulus identity, and the cost of waiting one more time step may be offset by the possibility of gaining more information. The parameter c_e includes the intrinsic cost associated with error, but may also include extrinsic reward (e.g., the monetary gain/loss received based on the outcome of each trial). Referring back to **Figure 1**, this cost function forms the basis of estimating action costs based on the current belief state (b_t). More specifically, let τ denote the trial termination time, D the response deadline, and d the true stimulus state (e.g., $d = 0, 1$). Then, an action policy π maps each belief state (b_t) to a choice of actions (i.e., wait, choose A, or choose B), and over the course of repeated action choices within a trial, results in a termination time τ, and an action choice $\delta = 0, 1$. The loss associated with τ and δ is then:

$$l(\tau, \delta; d, D) = c\tau + c_e.1_{\{\tau < D, \delta \neq d\}} + 1_{\{\tau = D\}} \quad (4b)$$

where $1_{\{\cdot\}}$ is the indicator function, evaluating to 1 if the conditions in $\{\cdot\}$ are met and 0 otherwise. Then, on average, the cost incurred by policy π is:

$$L_\pi =< l(\tau, \delta) >= c < \tau > + c_e P(\delta \neq d) + P(\tau = D) \quad (4c)$$

where $P(\delta \neq d)$ is the probability of wrong response, and $P(\tau = D)$ is the probability of not responding before the deadline (omission error). The optimal policy is that policy π which minimizes the average loss, L_π. The modeling work in this domain shows that such an optimal decision policy closely mirrors human and animal behavior in these tasks, in particular, correctly predicting changes in behavior when task constraints are manipulated.

One variant of this forced-choice perceptual decision-making task is the 2-alternative forced choice task (2AFC; e.g., Flanker paradigms), in which two stimuli are associated with distinct "go" responses. Another variant is the go/nogo task, where associating one stimulus with an overt response, and the other stimulus with no response during the response window, fundamentally represents a similar perceptual decision process. While on the surface the go/nogo task is very similar to forced-choice decision-making, behavioral and neural evidence suggests an apparent *bias* toward the go response that manifests as a propensity toward high false alarm rates. Such "impatience" has principally been ascribed to failures of putative inhibitory mechanisms (Aron et al., 2007b; Eagle et al., 2008). In contrast, (Shenoy and Yu, 2012) suggest that this behavior may in fact be a rational adaptation of the speed-accuracy tradeoff for this task. To see why this may be the case, consider the schematic representation of the decision-making process in **Figure 3**. For the 2AFC task, both stimuli eventually lead to a terminating "go" action (one of the two available responses). However, for the go/nogo task, one stimulus leads to a "go" response (and hence termination of the trial), whereas the other stimulus requires waiting until the end of the trial to register a "nogo" response. This asymmetry is reflected in the cost function for the go/nogo task (Shenoy and Yu, 2012):

$$Cost = c * RT + c_e * P\left(false\ alarm\right) + P\,(miss) \quad (5a)$$

where c is the cost of time, c_e is the cost of commission error, P(false alarm) and P(miss) are the probabilities of making commission and miss errors, respectively.

If again τ denotes the trial termination time and D is the trial deadline, $\tau = D$ if no "go" response is made before the deadline, and $\tau < D$ if a response is made. On each trial, the optimum decision policy π has to minimize the following expected loss, L_π:

$$L_\pi = c < \tau > + c_e P(\tau < D | d = 0) P(d = 0) + P(\tau = D | d = 1) P(d = 1) \quad (5b)$$

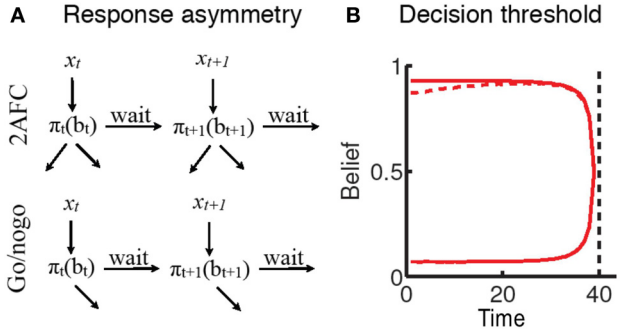

FIGURE 3 | Rational impatience in the go/nogo task (Shenoy and Yu, 2012). (A) The rational decision-making framework suggests that choices unfold over time as sensory uncertainty is resolved. For a forced -choice decision-making task, all stimuli eventually result in responses that terminate the trial. For a go/nogo task, the go stimulus requires a go response that terminates the trial; however, the nogo stimulus requires withholding response until the end of the trial; where (x_i) and (y_i) are the sensory inputs incorporated into beliefs (b_i), and $\prod$ is the decision policy relating specific beliefs to a choice between actions (a1, . . . , an, wait). **(B)** The asymmetry is reflected in the decision thresholds for the two tasks: go-nogo response threshold (dashed red line) is initially lower than forced-choice threshold (solid red line), reflecting the tradeoff between go errors and opportunity cost (see text).

where $P(d = 0) = P(\text{NoGo})$ and $P(d = 1) = P(\text{Go})$ are the probabilities that the current trial is NoGo or Go, respectively, $P(\tau < D|d = 0)$ is the probability that a NoGo trial is terminated by a Go response (false alarm), and $P(\tau = D|d = 1)$ is the probability that no response is emitted before D on a Go trial (miss). Here, $P(\text{Go})$ and $P(\text{NoGo})$ reflect prior beliefs about the current trial type being a Go or a NoGo trial respectively (i.e., action expectancies), whereas $P(\tau < D|d = 0)$ and $P(\tau = D|d = 1)$ are the overall fraction of false alarm or miss error respectively. Note that a correct NoGo response consists of a series of "wait" actions until the response deadline D is reached.

Compare this with the previous cost function (Equations 4a–c), for perceptual decision-making. In both tasks, the decision to "go"/terminate the trial (i.e., $\tau < D$) limits the costs associated with response delay, and the choice to "wait" (i.e., $\tau = D$) decreases error related costs since it results in additional data observation and therefore helps the disambiguation process. Bellman's dynamic programming principle (Bellman, 1952) can be used to determine the optimum decision policy (i.e., smallest expected costs of go vs. wait actions), which is computed iteratively as a function of the belief state b_t, i.e., Q-factors $\text{Qw}(b_t)$ and $\text{Qg}(b_t)$ for wait and go actions, respectively. That is, if $\text{Qw}(b_t) < \text{Qg}(b_t)$, the optimal policy chooses to wait, otherwise it chooses to go (adapted from Shenoy and Yu, 2011, 2012).

In the go/nogo task, however, the cost function directly trades off response times against the go bias, since shorter RT leads to lower overall cost of time, and a lower miss rate, at the cost of an increase in false alarm rate. This is reflected in the *decision boundaries* corresponding to the forced choice and go/nogo tasks (**Figure 3B**). In the forced-choice task, whenever the belief in stimulus identity crosses one of two symmetric thresholds, a response is generated. This threshold decreases as the response deadline approaches, since beliefs are unlikely to change drastically in the remaining time. In contrast, the go/nogo threshold is an initially *increasing* single threshold, capturing the notion that early on in the trial, an erroneous go response may be preferable to the prospect of waiting until the end of the trial.

INHIBITORY CAPACITY, TASK CONTEXT, AND EMOTION

Here, we examined a rational decision-making framework for inhibitory control, where various behavioral effects (and associated measures of inhibitory capacity or failure) were seen as emergent properties of an evolving cost-benefit tradeoff. This view captures behavior in a range of tasks such as the Stroop task, the Eriksen task, the go/nogo task, and the stop signal task, each of which is used to study a putatively different aspect of inhibitory control. Specifically, we described two classes of parameters that capture the dynamic decision-making process supporting inhibitory control, namely those representing (1) individuals' beliefs about task-related events and (2) the relative values associated with these events. In terms of belief estimation, we consider *action expectancies* (e.g., probability of encountering a stop or go trial), as well as *outcome expectancies* (e.g., probability of making an error, of encountering an appetitive stimulus). Similarly, for valuation processes, our model distinguishes action related costs (e.g., time/opportunity or activation costs) and outcome related costs (e.g., cost of error). Summing up the implications of this work, we see that the different behavioral measures of inhibitory capacity are all attributable to one or more specific *constituent parameters* of the decision-making framework which subserves performance in all of these tasks. Thus, seemingly disparate functions such as action, restraint and cancellation, attentional and behavioral inhibition, can be folded into a unifying framework of *information* and *valuation*, where the diversity of behavior principally reflect subtle differences in the task design, and their subsequent influence on components of the model. This perspective guides our view of the potential roles of emotion in inhibitory control: By conceptualizing emotion as *additional context* available to (or imposed upon) the decision-maker, we may then generate constrained hypotheses about how such emotional context may impact behavior within the confines of our proposed decision-making framework. Through this exercise, we aim to relate emotion directly to other, better-understood aspects of cognition such as beliefs, valuation, and choice.

A BAYESIAN FRAMEWORK FOR AFFECT-DRIVEN BIASES IN INHIBITORY CONTROL

We now examine how the computational framework outlined above can be used to understand emotional influences on inhibitory control. In particular, we hypothesize that each of the primary emotional dimensions considered (i.e., valence/motivational tendency and arousal) may be understood in terms of their biasing effects on parameters formalizing: (a) the values and shape of prior probability distributions, and (b) the relative values of various actions/outcomes. The former focuses on the generative models that guide the inference of beliefs from available evidence (i.e., information acquisition and maintenance), while the later refers to cost functions that constrain the action selection policy (i.e., valuation).

In this review, we confine ourselves to computational hypotheses within the decision-making framework—i.e., hypotheses about how emotion may be viewed as additional context informing and constraining existing, ongoing computations. We break down emotional influence into valence/motivational tendency and arousal, two empirically validated dimensions of emotion, and consider their potential impact on both action related computations (**Figure 4** green areas) and outcome related computations (**Figure 4** blue areas). However, we also consider possibilities where emotion processing may act as a separate, *competing process* diverting attentional and executive resources away from task-related computations. As we discuss below, this becomes particularly relevant to the effect of arousal.

PROBABILISTIC COMPUTATION

One way to conceptualize the interaction of emotion and inhibitory control within a Bayesian framework relates to sensory disambiguation and belief formation (e.g., expectations about task relevant stimuli/outcomes). We suggest that the values and shape of the prior probability distributions associated with given events are the computational levels where such affective influences could be implemented. Such probabilistic computations represent an individual's prior knowledge of the environment in which he/she is operating, which is used to make predictions

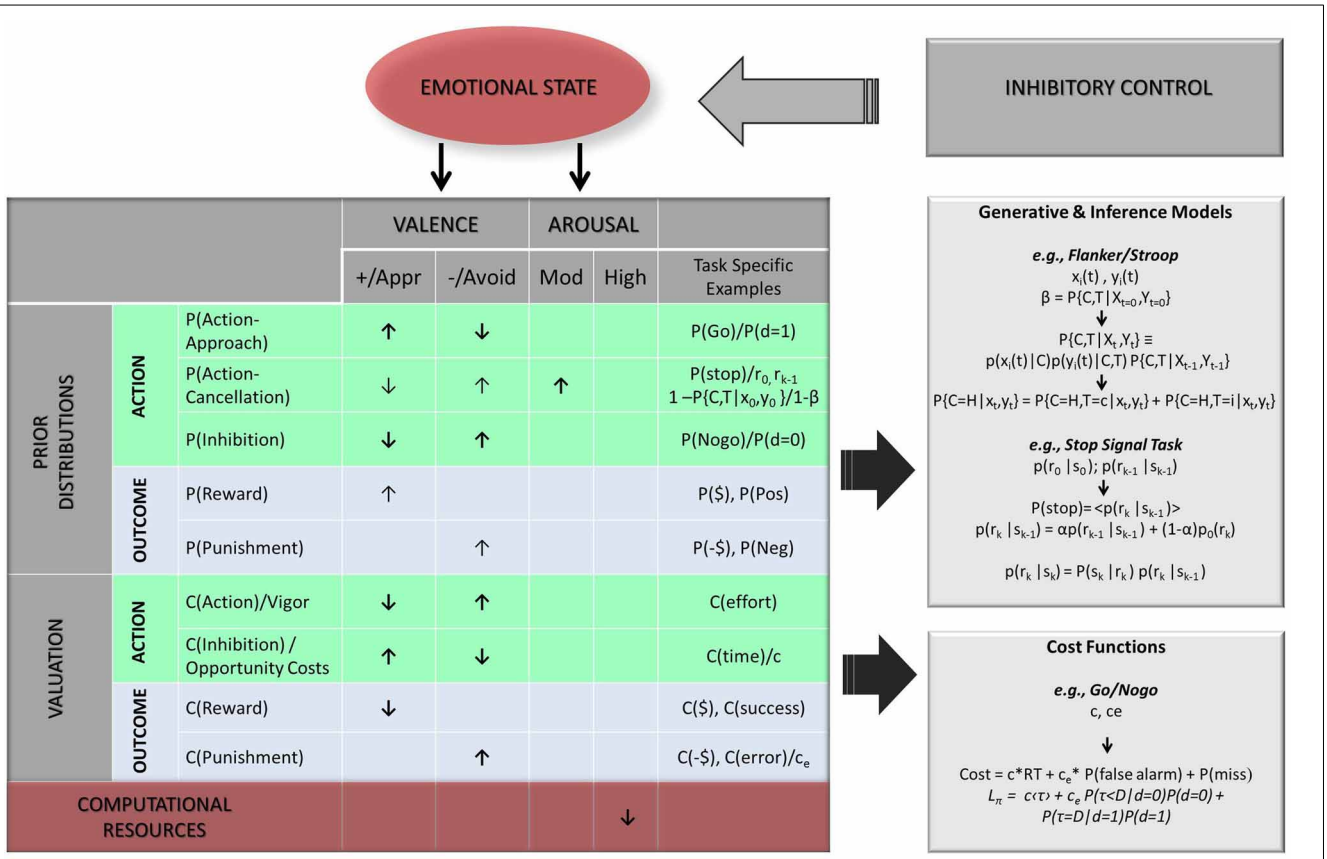

FIGURE 4 | Hypothesized biases of emotional dimensions on Bayesian model parameters. Two categories of parameters are considered: prior probability distributions [means; *P*(); top panel] and relative costs [*C*(); bottom panel], each being further evaluated in terms of primary action related expectancies (green areas) and task contingent outcomes (light blue areas). Legend: arrows indicate hypothesized direction of bias, with bolded arrows indicating stronger or more likely biases (↑, increase/higher value; ↓, decrease/lower value); Valence Dimension: +/Appr, positive/approach; −/Avoid, negative/avoidance; Arousal: Mod., moderate; Pos, positive/rewarding outcome/stimulus; Neg, negative/punishing outcome/stimulus; $, monetary reward; -$, monetary penalty; α, mixing factor; $P(C, T|X_0, Y_0)/\beta$, probability of trial being congruent at trial onset $t = 0$ (e.g., in Stroop or Flanker task); $x(t)$ = sensory input for central stimulus, $y(t)$ = sensory input for flanker stimulus; *P*(pos), probability of positive stimulus/outcome (e.g., happy face), *P*(Neg), probability of negative stimulus/outcome (e.g., angry face, painful stimulus); *P*(go) = $P(d = 1)$ = probability of upcoming trial being Go trial; *P*(NoGo) = $P(d = 0)$ = probability of upcoming trial being Nogo trial, *P*(stop) = probability of upcoming trial (*k*) being Stop trial (r_0 = initialization prior value at first trial; r_{k-1}, initialization prior value from previous trial); α, mixing coefficient; $P(\tau < D|d = 0)$, probability of making "false alarm error" (incorrect go responses), $P(\tau = D|d = 1)$ = probability of making "miss" error (incorrect nogo response); *C*(time) = *c*, cost of time, *C*(effort), cost of effort associated with action; *C*(error) = c_e, cost of error; τ, trial termination time; *D*, trial deadline; d, true stimulus state (e.g., here $d = 0$ for NoGo trials, $d = 1$ for Go trials).

about upcoming events. For instance, a central assumption of the Bayesian ideal observer model is an iterative estimation of the likelihood of certain events as sensory disambiguation proceeds until certain probability thresholds that minimize the cost function are reached (at which point an action is selected). These probability distributions may also be updated over the course of multiple trial/response dyads (generating posterior distributions) based on the history of prior estimates and current trial outcome (Bayes rule; e.g., Equation 3b). Thus, prior distributions are often modeled as the combination of a fixed initial prior (representing pre-task frequency estimates) and the previous posterior distributions capturing the history of multiple trials in the task (Shenoy and Yu, 2011); see Equation 3a). While factors such as previous experience with the inhibitory task are likely to heavily influence these prior values, we propose that emotional attributes could be similarly used as heuristics to gauge how likely an event or upcoming action is, resulting in a general shift in values (i.e., mean change) or changes in the distribution shape (e.g., variance, skew; see **Figure 4** top panel "Prior Distributions"). Supporting the plausibility of this hypothesis, there is robust evidence of similar biases in subjective probability estimation in healthy populations, typically reflecting underestimation of high probabilities and overestimation of low probabilities (Kahneman and Tversky, 1979; Loewenstein and Lerner, 2003).

Based on the reviewed literature and extensive evidence of interdependence between valence laden information and action tendencies (e.g., activation vs. inhibition; see (Huys et al., 2011; Dayan, 2012), we consider two mediating mechanisms by which valence and arousal could bias probabilistic computations, including outcome expectancies (see **Figure 4** top panel, blue

area), and action expectancies (see **Figure 4** top panel, green area). Finally, given evidence of distinct functional and neurochemical systems involved in approach related actions (e.g., "go"), action cancellation (e.g., stopping an initiated action, "stop"), and inhibition (e.g., withholding an action, "no-go" (Frank, 2005; Eagle et al., 2008; Swick et al., 2011), our proposed model distinguishes these three types of action requirements when considering potential emotional influences. We note that approach-based activation in the context of standard inhibitory paradigms is most commonly associated with go actions, which could be in the context of gaining a reward or avoiding "miss" errors. The latter is more akin to a form of *active avoidance* (i.e., performing an action to avoid a negative outcome). In contrast, inhibition or action restraint in the present framework (e.g., "nogo" responses) is related to *passive avoidance* (e.g., not performing an action to avoid "false alarm" errors or other penalties). This is consistent with actor-critic models of reinforcement learning (Maia, 2010; Dayan, 2012) and neural evidence that learning of both approach actions and avoidant actions involve phasic firing of dopamine neurons (predominantly via D1 receptors) in the dorsal striatum (Montague et al., 2004; Samson et al., 2010). In contrast, dips in dopamine (via D2 receptors in the "no-go" indirect pathway) and serotonin may be primarily involved in mediating inhibition or action constraint (Frank et al., 2004; Dayan and Huys, 2008; Kravitz et al., 2012).

Valence/motivational tendency

Action expectancies. The valence of an emotional state provides information about one's disposition toward stimuli or actions in the environment (Schwarz and Clore, 1983), with positive valence promoting approach and negative valence promoting avoidance. Such *motivational* information may in turn be integrated into the interoceptive processes taking place during concurrent inhibitory control behavior. Thus, we suggest that emotion may exert influence on behavior by modulating expectations of encountering specific action requirements (i.e., trial types) relevant to the inhibitory control task. For example, in a go/no-go paradigm, one has to choose between two types of behavioral responses, namely a "go"/approach action or a "no-go"/inhibition response. We hypothesize that positive valence may promote approach actions by increasing expectancies of having to implement an approach action (e.g., expectation to encounter a "go" trial) or decreasing expectancies of implementing action restraint (e.g., "no-go" trial), while negative valence may have the opposite effect. In probabilistic terms, the positive interoceptive information conferred by an emotional state may increase an initial and fixed prior's values (e.g., an overall mean shift of the distribution) for go trials [i.e., $P(d = 1) = P(\text{Go})$], as they involve an approach action, and/or decrease such prior values for no-go inhibitory trials [i.e., $P(d = 0) = P(\text{NoGo}) = 1\text{-}P(\text{Go})$]. Either of these biases would promote faster go decisions (and higher rates of false alarm errors) as shorter go reaction times (τ) would minimize the cost function (see Equation 5b). This is because such higher prior over the frequency of go stimuli would provide a higher starting point for the evidence accumulation process, thus requiring a shorter time for the belief state (b_t) to reach the decision boundary and generate a go response; see (Shenoy and Yu, 2012). Alternatively, a negative emotional state should have the opposite effect in biasing upward no-go prior values (and/or decreasing go prior values), resulting in longer go reaction times (and more miss errors).

An extensive behavioral and neural literature suggests hedonic valence and action tendencies have strong interdependence, supporting our hypotheses. For instance an appetitive state (e.g., conditioned appetitive cue) promotes approach actions and hinders withdrawal and action constraint/no-go responses, while aversive cues have the reverse effect (Huys et al., 2011; Guitart-Masip et al., 2011b). Individuals are also more likely to learn go actions in rewarded conditions and less likely to learn passive avoidance (i.e., no-go choices) in punished conditions (Guitart-Masip et al., 2011b, 2012). Similarly, higher commission rates are observed when appetitive stimuli are paired with a no-go (i.e., action restraint) requirement (Hare et al., 2005; Schulz et al., 2007; Albert et al., 2011). Here, the positive valence/approach motivation may increase expectations of encountering a go trial [i.e., higher $P(\text{Go})$], again promoting earlier responses (i.e., shorter τ; see Equation 5b). Importantly, valence congruent effects are also observed with the valence of an action (i.e., approach vs. withdrawal). For instance, Huys et al. (2011) showed that even after controlling for behavioral activation/inhibition and the valence of contingent rewards/punishments, an active withdrawal response was facilitated by aversive states but inhibited by an appetitive state. Similarly individuals scoring higher on trait measures of reward expectations demonstrate slower SSRTs, while those with higher punishment expectations produce faster SSRTs in stop-signal tasks (Avila and Parcet, 2001). Thus, while appetitive states may increase go trials expectancies, they may *decrease* expectancies of encountering action cancellation trials [i.e., $P(\text{stop}) = < p(r_k|s_{k-1}) >$ in Equation 3a] while the reverse is true for aversive states.

Outcome expectancies. Consistent with connectionist (or neural network) accounts (Mathews and Macleod, 1994), emotional states have been shown to activate mood-congruent information and concepts in memory, which in turn increases the likelihood this information is attended to (Forgas et al., 1984; Eich et al., 1994; Bower et al., 2001). We suggest that these mood-congruent effects, by modulating the "landscape" of information in awareness, produce biased expectations of encountering valence-congruent outcomes. Again, these biases could manifest by increases or decreases in the central tendency and/or shape of the prior probability distributions associated with valence laden events. For instance, negative affect, such as sadness and anxiety, promotes higher expectations of punishment and aversive events (Abramson et al., 1989; Ahrens and Haaga, 1993; Handley et al., 2004), while euphoria is associated with higher expectations or reward and success (Johnson, 2005; Abler et al., 2007). In addition, relative to euthymic controls, sad or depressed individuals are more accurate and faster at recognizing sad affect in human faces (Lennox et al., 2004), while socially anxious individuals are better at identifying angry faces (Joormann and Gotlib, 2006). In contrast, manic individuals are less accurate at identifying sad faces (Lennox et al., 2004). These biases have been linked to different neural patterns in face recognition areas, suggesting a different

prior "expertise," rather than differences in emotional response. In the context of action requirements tied to emotional cues (e.g., in affective go no-go paradigms), such biases would result in a reduced discrepancy between internal predictions of encountering a mood congruent stimulus [e.g., positive or negative facial expression, i.e., P(Pos)/P(Neg) **Figure 4**] and the actual occurrence of this event. This should in turn facilitate (i.e., speed up) the identification of mood-congruent stimuli in emotional relative to euthymic individuals. Consistent with this hypothesis, in affective go no-go paradigms, manic patients respond faster to happy stimuli and slower to negative stimuli on go trials, and depressed patients respond faster to sad stimuli (Murphy et al., 1999; Erickson et al., 2005; Ladouceur et al., 2006). These types of emotional biases could impact inhibitory function more indirectly than those associated with action requirement expectancies, possibly by facilitating or slowing the disambiguation of emotional cues tied to action requirements. This may be particularly relevant for inhibitory control within social interactive contexts.

Arousal

Action expectancies. Increased arousal has been associated with impaired functioning of the prefrontal cortex (PFC), including regions necessary to implement inhibitory control such as the inferior frontal gyrus (Robbins and Arnsten, 2009). In addition, high arousal promotes stronger reliance on habitual/prepotent responses and generally decreases goal-directed responding (Dias-Ferreira et al., 2009; Schwabe and Wolf, 2009). Therefore, we suggest that high arousal is more likely to impair inhibitory control by reducing the attentional and computational resources necessary to disambiguate task relevant information (see **Figure 4**; red area). This is consistent with studies linking arousal prompted by conditioned cues to electric shock to a selective slowing during inhibitory trials in Stroop and Stop-signal tasks (Pallak et al., 1975; Pessoa et al., 2012). Indeed, because incongruent, non-prepotent, responses involve more sensory disambiguation and/or more effort to shift response set, such computational processes may more heavily rely on intact PFC function and executive resources. Therefore, the taxing of PFC function under high arousal would be expected to more selectively impact performance during incongruent trials. Other work, however, points to a more general arousal-driven impairment for both prepotent and inhibitory responses, notably in Stroop (Blair et al., 2007), stop-signal (Verbruggen and De Houwer, 2007), and go/no-go (De Houwer and Tibboel, 2010) paradigms.

In contrast, evidence suggests that *moderate* levels of arousal can facilitate executive and PFC function, consistent with an inverted U shape relationship between arousal and cognitive performance (Easterbrook, 1959; Eysenck, 1982; Arnsten, 1998). Moderate levels of norepinephrine (NE) release strengthen prefrontal cortical functions via actions at post-synaptic α-2A adrenoceptors with high affinity for NE, which has been associated with improved set shifting function and selective attention (Ramos and Arnsten, 2007). Based on this literature, we propose that moderate arousal may facilitate activation, particularly action cancellation (e.g., stop response), by increasing expectancy of encountering stop trials. This is consistent with extensive animal literature highlighting the role of NE as a neural "interrupt" (Sara and Segal, 1991; Dayan and Yu, 2006) and recent studies showing that both NE and dopamine play an important role in regulating impulsivity and speed of behavioral control in ADHD (Arnsten et al., 1984; Frank et al., 2006; Arnsten, 2009b). Consistent with this hypothesis, both human and animal studies point to a selective facilitating effect of norepinephrine in stop-signal paradigms, improving SSRTs while go reaction times are typically unchanged (Overtoom et al., 2003; Chamberlain et al., 2006; Robinson et al., 2007). Moderate arousal induced by *both* positive and aversive images were also found to improve SSRTs in humans (Pessoa et al., 2012). This contrasts with pharmacological studies that suggest no effect of dopamine or serotonin on SSRTs, but rather preferential effects on go/approach actions and action constraint/inhibition respectively (Eagle et al., 2008). Computationally, moderate arousal may increase the mean of the prior distribution associated with the frequency estimate of stop trials $p_0(r_k)$, which in turn would result in a similar upward shift in the predictive probability of stop trials P(stop) [i.e., the mean of the predictive distribution $p(r_k|\boldsymbol{s}_{k-1})$, see Equations 3a and b].

In relation to action cancellation, arousal should similarly bias expectancies related to cancelling automated responses in interference paradigms (e.g., interruption of prepotent responses during incongruent trials in Stroop or Flanker tasks). Specifically, moderate arousal may increase expectations of encountering incongruent events (requiring action cancellation) or decrease expectations of encountering congruent trials, which would result in less impairment in incongruent/inhibitory trials. For instance, in flanker paradigms (and presumably in other interference tasks), modeling the sensory disambiguation process with a joint probability of true stimulus and trial type [i.e., $P(C,\ T|X_t,\ Y_t)$, see Equation 1] produces inferential performance that successfully captures behavioral data. Importantly, increasing its initialization prior to reflect a bias toward compatibility [$P(C,\ T|X_0,\ Y_0)$, $\beta >$ 0.5/chance] produces a shift in inference that would be expected to lead to worse performance on incompatible trials (Yu et al., 2009). This relates to a longer latency for the probability of the trial being incongruent to rise up toward 1 on incongruent trials (as it starts from a lower anchor value). Thus, while such compatibility bias is observed in normative samples (Yu et al., 2009), we hypothesize that moderate arousal could reduce this bias, which would be reflected by a lower value of the β parameter in the model (i.e., closer to 0.5). This is consistent with improved Stroop performance in moderate arousal condition (mild shock expectation; Pallak et al., 1975).

Outcome expectancies. While we are not aware of any studies isolating the effect of arousal from valence on outcome expectations, some work suggests that prolonged physiological arousal in anxiety and trauma conditions may play a role in maintaining expectations of danger (Norton and Asmundson, 2004). It remains difficult, however, to disentangle the role of arousal from valence in these effects, which may be better explained by valence-congruent effects on memory and attention (see above). Thus, we suggest that the arousal dimension is unlikely to impact outcome expectancies (e.g., reward vs. punishment), but rather modulates

action preparedness and expectations of encountering action cancellation trials (via NE release as previously noted). Indeed, based on the affective go/no-go studies, *valence*-congruent response biases in go reaction times were observed in depressed and manic patients (Murphy et al., 1999; Ladouceur et al., 2006) as opposed to a unidirectional effect of emotion (which would be more consistent with an arousal effect). This speaks against a potential role of moderate arousal in biasing probabilistic outcome expectancies. In addition, higher levels of arousal are likely to have a deleterious impact on computational recourses mediated by impaired PFC function (Ramos and Arnsten, 2007).

Neural implementation

Valence-dependent biases on approach activation and inhibition tendencies are likely to preferentially involve the dopamine and serotonin signaling in the dorsal striatum. The approach "go" pathway is facilitated by positive/rewarding states via dopamine (D1 receptors) while serotonin and dopamine (D2 receptors) are preferentially involved in linking negative/aversive valence to the inhibition/"nogo pathway (Frank et al., 2004; Montague et al., 2004; Dayan and Huys, 2008). Active withdrawal and action cancelation may also involve serotonin (Deakin and Graeff, 1991). In addition, norepinephrine and dopamine are likely to play a key role in mediating arousal effects on action cancelation by facilitating fronto-striatal communication (Ramos and Arnsten, 2007; Eagle et al., 2008). In terms of brain regions, probability computation (in contrast to valuation) within an expected utility framework has been associated with activation of the mesial PFC (Knutson and Peterson, 2005), although recent evidence points to subcortical correlates in anterior and lateral foci of the ventral striatum (Yacubian et al., 2007). While this is still an emerging program of research, recent work also suggests that the dorsomedial PFC encodes in a dose-response manner a representation of the history of successive incongruent trials in interference paradigms (Horga et al., 2011). Such neural representations appear critical to maintaining cognitive control in the task, as they influenced the neural and behavioral adaptation to incongruency in this task supported by a network involving the pre supplementary motor areas (SMA) and dorsal anterior cingulate (dACC). Based on this research, computational biases related to the cumulative magnitude of certain event probabilities (e.g., expectancy of action cancellation requirement), including those driven by emotion, may be reflected by differential recruitment of the dorsomedial PFC. In addition, converging evidence suggests that the dACC is involved in tracking conflict (Botvinick et al., 1999, 2001) and more generally expectancy violation (Somerville et al., 2006; Kross et al., 2007; Chang and Sanfey, 2011). In line with a conflict monitoring hypothesis, activation of this region is indeed consistently observed during incongruent/high conflict trials in various inhibitory control tasks (Botvinick et al., 2001) and predicts subsequent prefrontal recruitment and behavioral adjustments (Kerns et al., 2004; Kerns, 2006). Importantly, recent computational work highlights the selective involvement of the dACC in coding the discrepancy between internally computed probabilities of response inhibition and actual outcome, a form of "Bayesian prediction error" (Ide et al., 2013), making this region a plausible candidate for tracking the magnitude of potential emotion-driven biases in Bayesian error prediction.

VALUATION

We now consider emotion-driven biases associated with valuation processes and argue that emotional attributes may increase or decrease the relative costs of task-related actions and outcomes. Based on extensive empirical and computational evidence from the reinforcement learning literature, a representation of the values (or expected reward) associated with possible actions is necessary to support the selection of actions in goal-directed behavior (Montague et al., 2006). Mesolimbic dopamine has been posited to play a crucial role in the "binding" of such hedonic values and reward-related actions or stimuli, providing a motivational weight or "incentive salience" to these actions/stimuli (Berridge and Robinson, 1998; Berridge, 2007). Thus, as with any type of goal-directed behavior, the selection of actions involved in inhibitory control tasks (e.g., go vs. no-go actions) should be modulated by such a valuation system. Consistent with this hypothesis, manipulating the perceived value of response speed vs. accuracy (e.g., with subtle changes in instructions) produces behavioral changes in concert with the expected motivational shifts in stop-signal paradigms (Band et al., 2003; Liddle et al., 2009). Overall this suggests that the relative values associated with task-related actions/events contribute to modulating inhibitory behavior independently of probabilistic computations (e.g., action requirement expectancies). Because emotion again conveys information about one's state and disposition (Schwarz and Clore, 1983), an intuitive prediction is that the *valence* of an emotional state is likely to modulate the incentive salience (i.e., value) of particular task-related actions/outcomes. In Bayesian terms, the relative weight or salience of these actions/events is reflected in the cost function, and most commonly in terms of speed vs. accuracy tradeoffs (see Equations 4a, 5a). As with the probabilistic computation section, we consider valuation biases separately for task-related actions (e.g., go vs. no-go; **Figure 4**, bottom panel, green area) and outcomes (e.g., accuracy; **Figure 4**, bottom panel, blue area). Based on limited evidence for distinct valuation mechanisms for different types of action requirements, and given previous work linking reward with the degree of effort/vigor of a particular action (Niv et al., 2007), we simplify the action category to basic (approach-based) activation and inhibition.

Valence/motivational tendency

Action valuation. Some animal studies suggest that phasic release of dopamine in the NAcc is involved in coding the predictive reward of an action and is directly related to the degree an animal overcomes and maintains effort to obtain this reward (Morris et al., 2006; Phillips et al., 2007; Salamone et al., 2007). This research points to a potential role of NAcc dopamine in representing effort-related costs (i.e., associated with behavioral activation). In a closely related line of work, recent computational accounts suggest that tonic levels of dopamine release encode the average rate of available reward per unit of time, which is inversely proportional to *opportunity costs* associated with slower responses (Niv et al., 2007; Shadmehr, 2010; Guitart-Masip et al., 2011a). In

contrast to those associated with effort (i.e., activation), opportunity costs can be conceptualized as cost of time or "waiting to act" (i.e., inhibition).

Based on this research, we conjecture that the degree to which an emotion is appetitive may modulate the value of engaging in action (e.g., reducing the cost of effort associated with behavioral responses). For instance, in affective go/no-go paradigms, a positive emotional state (or the anticipation of such state) should reduce the cost of effort associated with go actions [or increase opportunity costs associated with inhibition; i.e., $C(\text{time}) = c$ in Equations 4a–c, 5a–b and **Figure 4**]. Computationally, either biases should result in selecting go actions at earlier stages of the sensory disambiguation process (i.e., faster reaction times would minimize cost). Similarly, the aversive tone of an emotional state may have the opposite effect, i.e., increasing activation/effort costs, thus promoting inaction. Consistent with these predictions, appetitive Pavlovian stimuli specifically promote "go" actions and inhibit no-action and withdrawal, while aversive cues promote the opposite pattern (Hare et al., 2005; Huys et al., 2011; Guitart-Masip et al., 2012). Importantly, activations in the striatum (ventral putamen) and ventral tegmental area (VTA) have been found to correlate with the magnitude of go and no-go action values with opposite signs for each respective action (Guitart-Masip et al., 2012).

Outcome valuation. Appetitive vs. aversive emotional states can have valence-congruent modulating effects on hedonic experience. For instance a depressed or sad mood reduces the pleasantness of rewards and amplifies perception of pain, while positive mood lowers pain ratings and increases pain tolerance (Tang et al., 2008; Zhao and Chen, 2009; Berna et al., 2010). This is consistent with extensive evidence that negative mood states are associated with reduced sensitivity to reward (Henriques and Davidson, 2000; Harlé and Sanfey, 2007; Foti and Hajcak, 2010; Disner et al., 2011), as well as increased sensitivity to error (an aversive event) demonstrated by stronger amplitudes of the error related negativity (ERN) (Paulus et al., 2004; Pizzagalli et al., 2005; Olvet and Hajcak, 2008; Wiswede et al., 2009; Weinberg et al., 2010) and more post error slowing (Luu et al., 2000; Boksem et al., 2008; Compton et al., 2008). In contrast, appetitive states have been linked to increased reward sensitivity (Johnson, 2005), increased perception of happiness (Trevisani et al., 2008) and reduced post error slowing in interference tasks, consistent with a reduced monitoring of error (van Steenbergen et al., 2009, 2010).

Accordingly, we suggest that, in addition to modulating action valuation, the valence of an emotional state may bias the relative value/cost of task-related outcomes (e.g., rewards and punishments associated with performance). Specifically, positive emotion should enhance the relative value, i.e., decrease the relative cost of rewarding outcomes [e.g., $C(\$)$ **Figure 4**]. In contrast, negative emotional states would be more likely to prompt an overestimation of the cost of error or other aversive events [i.e., $C(\text{-}\$)$, $C(\text{error})/c_e$, see Equations 4a–c, 5a–b and **Figure 4**)]. For instance, to minimize average costs in a go/no-go task (see Equations 5b), this over-weighing of false alarm costs (i.e., higher value of c_e) would be associated with a lower threshold for the rate of false alarm occurrence across trials [i.e., $P(\text{false alarm}) = P(\tau < D|d = 0)\ P(d = 0) = P(\tau < D|d = 0)\ P$ (NoGo); see Equation 5a,b). This would in turn prompt longer response times needed for sensory disambiguation to unfold and for $P(\text{NoGo})$ to reach a lower threshold. This is because the cost associated with go actions [$\text{Qg}(b_t)$] would be overall higher, requiring more time to drop lower than the cost of waiting [$\text{Qw}(b_t)$]. Although we are not aware of any study specifically testing this relationship, depressed individuals were slower on go trials and made less commission errors in a parametric go no-go paradigm, suggestive of heightened concern for errors (Langenecker et al., 2007). Similarly, in individuals with generalized anxiety disorder, better performance on a classic color-word Stroop has been linked to higher levels of worry and trait anxiety (Price and Mohlman, 2007).

Arousal

Action valuation. The clinical and social psychology literature suggest that physiologically induced arousal can be misattributed in evaluative processes such as interpersonal preferences and risk assessment (Schachter and Singer, 1962; Sinclair et al., 1994). This is reflected by more extreme intensity ratings of either positive or negative stimuli, suggesting a *unidirectional* (i.e., enhancing) role of arousal in modulating hedonic ratings of *concurrent* events. For instance, perceived arousal in the context of positive stimuli leads to higher positive valence ratings, while increased arousal in a negative context leads to higher aversive ratings (Storbeck and Clore, 2008). Thus, rather than arousal independently modulating valuation processes, it is the interaction of arousal and valence which seems to produce valuation biases. This fits with the neural and physiological literature highlighting the role of arousal in modulating *attention* to particular stimuli and action preparedness (Schutter et al., 2008; Gur et al., 2009), hence our proposal it may contribute to probabilistic expectancy biases (see section Probabilistic Computation). Based on this literature, we suggest this generally speaks against an independent effect of arousal on valuation processes.

Outcome valuation. As mentioned above, arousal may play a "magnifying" role in valuation processes by interacting with appetitive or aversive valence. This could argue for arousal promoting unidirectional increase in the relative weights of valence-laden computational elements in the cost function. That is, the value of both positive and negative task-related outcomes, such as performance dependent rewards [i.e., $C(\$)$] and penalties [i.e., $C(\text{-}\$)$ see **Figure 4**] would be increased. Arousal in the context of punishment sensitivity in anxiety may further increase the relative weight of error in the cost function (e.g., c_e in Equations 5a,b), which would in turn lead to slower responses (to minimize overall costs) and possibly decreased error rates. This is consistent with the positive relationship observed between worry/anxious preoccupation and reaction times in anxious individuals (Price and Mohlman, 2007). However, in this study, reaction times were *not* correlated with anxious arousal *per se*, which makes these results more consistent with valence dependent biases (see above). In addition, while higher levels of arousal have been associated with

a general slowing in euthymic individuals independently of positive vs. negative emotional context (Blair et al., 2007; Verbruggen and De Houwer, 2007; Pessoa et al., 2012), this pattern may again be more parsimoniously explained by an impairment of PFC function and related depletion of attentional and executive resources (Arnsten, 2009a).

Neural implementation

At the neural level, the ventral striatum (specifically the nucleus accumbens) has been consistently associated with reward sensitivity and reward based learning; (Knutson et al., 2001; O'Doherty, 2004; Winkielman et al., 2007). An important body of research has shown that phasic release of dopamine in the NAcc is involved in learning the predictive value of conditioned stimuli (Schultz et al., 1997; Flagel et al., 2010), which is thus likely to play a role in the coding of task related outcomes and stimuli (e.g., response cues, error or reward contingent on performance). Other research further suggests that tonic dopamine levels in this region is involved in coding opportunity costs associated with waiting to act (Niv et al., 2007; Shadmehr, 2010), while phasic dopamine release may be involved in the representation of effort associated with goal directed behavior (Phillips et al., 2007; Salamone et al., 2007). This is consistent with findings of caudate activation during inhibition (no-go responses) in positive/appetitive context, which was proportional to commission error rates (Hare et al., 2005). Finally recent computational work has identified areas in the ventral striatum and VTA as specifically encoding instrumentally learnt values of go and no/go actions (Guitart-Masip et al., 2012). These regions are therefore plausible neural markers for tracking action valuation biases. In addition, activation of the anterior insula has been associated with sensitivity to monetary losses (a punishing outcome) and learning from aversive outcomes (Kuhnen and Knutson, 2005; Paulus et al., 2005; Samanez-Larkin et al., 2008) including in the context of a negative mood state (Harlé et al., 2012). Thus, valuation biases related to aversive states and punishment expectancy may involve this region. Finally, given its implication in reward valuation (O'Doherty, 2004; Montague et al., 2006) and in integrating motivational attributes of various stimuli into decision-making [somatic markers; see (Damasio, 1994)], the OFC is likely to be involved in the integration of emotional context in valuation biases.

SUMMARY

We described a simple, unifying framework for inhibitory control that serves as a comprehensive scaffold to integrate emotional influences on cognitive processes. In our view, emotion can be understood as additional context (e.g., interoceptive experience), which constrains and biases the computations in an "ideal observer model" of inhibitory control. That is, the role of affect in inhibitory control can be interpreted in terms of well-understood computational aspects of cognition such as beliefs, action valuation and choice. Thus, emotion may affect inhibitory behavior by biasing (a) prior expectations and associated changes in internal beliefs about various task-relevant events, and (b) action/outcome valuation (see **Figure 4**). Importantly, on the basis of behavioral and neural data, the framework highlights a strong interdependence between the appetitive/aversive nature of emotional states and basic action tendencies that are intrinsic to inhibitory control. Thus, we surmise that the valence dimension may have primary influences on action parameters associated with approach and inhibition (action constraint), and exert valence congruent influences on outcome valuation and expectancies. In contrast, arousal may have a more selective role in biasing expectancies of action cancellation. In addition, we argue that higher levels of arousal may more indirectly modulate the computational processes supporting inhibitory function by redirecting attention away from task-relevant information and generally impairing prefrontal function and related computational mechanisms. Our theoretical framework has some limitations inherent to the challenge of testing these hypotheses. For instance, the separate effect of valence and arousal are difficult to disentangle in both experimental settings and affective disorders. The breadth of individual variability in the experience and regulation of emotion make these potential effects further difficult to pinpoint.

With regard to the potential impact of emotion on sensory disambiguation, we have emphasized the contribution of outcome and action expectancies (i.e., prior distributions associated with valence congruent events and trial type). However, we should note that more downstream effects of emotion have been documented. For instance, valence and arousal have been shown to modulate visual processing style (i.e., global vs. detail) and selective attention (e.g., breadth of attentional focus; (Loftus et al., 1987; Basso et al., 1996; Gasper and Clore, 2002). Although outside the scope of this review, modeling potential biases in sensory input parameters (e.g., sensory input mixing factors) may capture additional aspects of the interaction between emotion and inhibitory control.

Finally, an equally important aspect of such emotion-cognition interactions is the iterative nature of any emotion-cognitions interactions. That is behavioral performance and the dynamic feedback received when engaged in inhibitory control tasks are likely to modulate emotional state. As a consequence, the nature and types of biases impacting inhibitory control are likely to emerge from the dynamic interaction between Bayesian computation of response costs, selection of actions, and reception of outcomes, which subsequently affect the Bayesian updating of beliefs. These dynamic processes might be particularly relevant in psychopathological conditions, which emerge over longer periods of time.

CONCLUDING REMARKS

A Bayesian computational framework provides a fine-grained quantification of emotion and cognitive control interactions by dividing the observed behavior into several contributing neurocognitive subprocesses. This in turn provides a powerful tool to test independent affect infusion hypotheses, which are better able to delineate the complex nature of emotion and psychopathology, and may help refine neurocognitive models of various clinical conditions. For instance, behavioral performance could be used to infer specific quantitative biases in one's cost or reward functions or in one's ability to estimate probability. This approach

could shed light on the heterogeneous nature of conditions such as depression or substance dependence, by mapping different subtype profiles to specific computational processes and associated neural markers (e.g., anhedonia, uncertainty avoidance, impulsiveness). Ultimately, this may help refine our understanding of how specific behavioral and pharmacological treatments might address these various biases and thus refine our tailoring and effectiveness of psychiatric treatment.

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On the relationship between anxiety and error monitoring: a meta-analysis and conceptual framework

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Research involving event-related brain potentials has revealed that anxiety is associated with enhanced error monitoring, as reflected in increased amplitude of the error-related negativity (ERN). The nature of the relationship between anxiety and error monitoring is unclear, however. Through meta-analysis and a critical review of the literature, we argue that anxious apprehension/worry is the dimension of anxiety most closely associated with error monitoring. Although, overall, anxiety demonstrated a robust, "small-to-medium" relationship with enhanced ERN ($r = -0.25$), studies employing measures of anxious apprehension show a threefold greater effect size estimate ($r = -0.35$) than those utilizing other measures of anxiety ($r = -0.09$). Our conceptual framework helps explain this more specific relationship between anxiety and enhanced ERN and delineates the unique roles of worry, conflict processing, and modes of cognitive control. Collectively, our analysis suggests that enhanced ERN in anxiety results from the interplay of a decrease in processes supporting active goal maintenance and a compensatory increase in processes dedicated to transient reactivation of task goals on an as-needed basis when salient events (i.e., errors) occur.

Keywords: anxiety, error monitoring, error-related negativity, conflict monitoring, cognitive control, event-related potential (ERP), meta-analysis, worry

INTRODUCTION

Anxiety is a common human experience characterized by a variety of symptoms, including worrisome thoughts, physiologic arousal, and strategic avoidance behaviors (Barlow, 2002). It generally serves an adaptive response to threat by motivating organisms to increase their vigilance and thus respond more effectively to threats (Marks and Nesse, 1994; Barlow, 2002). Excessive and persistent anxiety, however, represents one of the most prevalent mental health problems in the United States (Kessler et al., 2005, 2012; Kroenke et al., 2007) and elsewhere (e.g., Collins et al., 2011 for a review). Research from diverse literatures indicates that cognitive deficits represent a core aspect of the pathological anxiety that is associated with impairments in personal functioning (American Psychiatric Association, 2000; Eysenck et al., 2007; Beilock, 2008; Sylvester et al., 2012). Better understanding the associations between anxiety and cognitive deficits is therefore of great importance for helping to address problems stemming from pathological anxiety.

One especially active area of neuroscience research aimed at tackling this issue has focused on how anxiety is related to error monitoring. Error monitoring concerns the signaling and detection of errors in order to optimize behavior across a range of tasks and situations, and this monitoring function is therefore a fundamental component of behavioral regulation. A growing body of research indicates that anxiety is associated with enhanced amplitude of the error-related negativity (ERN) of the human event-related brain potential (ERP), suggesting that anxiety is associated with exaggerated error monitoring (Olvet and Hajcak, 2008).

Anxiety is not a monolithic construct, however. Researchers and laypersons alike use the term "anxiety" to refer to many different states and traits such as "stress," "fear," "worry," among others (cf. Barlow, 2002). This confusion contributes to difficulties with describing the *nature* of the relationship anxiety has with error monitoring, and the ERN, more specifically. Nonetheless, many agree that there is a useful distinction between anxious apprehension on the one hand and anxious arousal on the other (Nitschke et al., 2001; Barlow, 2002). Anxious apprehension is defined by worry and verbal rumination elicited by ambiguous future threats whereas anxious arousal is defined by somatic tension and physiological hyperarousal elicited by clear and present threats. We and others have recently suggested that the ERN is more closely associated with anxious apprehension than anxious arousal (Moser et al., 2012; Vaidyanathan et al., 2012; Weinberg et al., 2012b).

The purpose of the current review is to expand on this argument in two important ways: (1) by conducting the first large-scale test of this hypothesis using meta-analysis, and (2) by providing a detailed conceptual framework that can be used to generate mechanistic hypotheses and guide future studies. Regarding the latter, we leverage four key findings about anxiety and cognitive control: (1) anxious apprehension/worry is significantly involved in cognitive abnormalities in anxiety; (2) anxious performance is characterized by processing inefficiency; (3) enhanced ERN in anxiety is observed without corresponding deficits in task performance; and (4) individuals with chronic anxiety exhibit enhanced transient "reactive" control but reduced preparatory "proactive" control. We used these

findings to develop a new *compensatory error monitoring* account of enhanced ERN in anxiety. Specifically, we suggest that the enhanced ERN observed in anxiety results from the interplay of a decrease in processes supporting active goal maintenance, because of the distracting effects of worry, and a compensatory increase in processes dedicated to transient reactivation of task goals on an as-needed basis when salient events (i.e., errors) occur. The overall format of this integrative review follows that of others in the literature by incorporating both empirical and theoretical considerations throughout the narrative (e.g., Holroyd and Coles, 2002; Shackman et al., 2011; Yeung et al., 2004).

THE ERROR-RELATED NEGATIVITY (ERN)

The ERN is an ERP component that reaches maximal amplitude over frontocentral recording sites within 100 ms after response errors in simple reaction time tasks (See **Figure 1**; Falkenstein et al., 1991; Gehring et al., 1993; see Gehring et al., 2012 for a review). Converging evidence suggests the anterior cingulate cortex (ACC) is involved in the generation of the ERN. More specifically, the dorsal portion of the ACC (dACC) or midcingulate cortex (MCC; Shackman et al., 2011) appears particularly important to the generation of the ERN (Gehring et al., 2012). The dACC/MCC has neuronal projections extending to motor cortex, lateral prefrontal cortex, parietal cortex, basal ganglia, and emotional centers such as the amygdala, suggesting that it serves as a "central hub" in which cognitive and emotional information is integrated and utilized to adaptively adjust behavior (Shackman et al., 2011). It is important, however, to distinguish between the ERN and dACC/MCC activity, as the ERN is a scalp-recorded potential that has several possible sources in other regions of cortex, including lateral prefrontal, orbitofrontal, and motor cortices (Gehring et al., 2012).

The confluence of cognitive and emotional processing within the dACC/MCC has contributed to disagreements among researchers regarding the functional significance of the ERN. To date, however, the two dominant models of the function significance of the ERN are the conflict monitoring (Yeung et al., 2004) and reinforcement learning (Holroyd and Coles, 2002) theories. The conflict monitoring theory suggests the ERN reflects detection by dACC/MCC of the co-activation of mutually exclusive response tendencies; the erroneous response and the subsequent error-correcting response activated immediately after error onset (Yeung and Cohen, 2006). The reinforcement learning theory suggests the ERN reflects the impact on dACC/MCC of a phasic dip in midbrain dopamine release whenever outcomes are worse than expected. This mechanism ultimately trains the dACC/MCC to maximize performance on the task at hand (Holroyd and Coles, 2002). These theories have both garnered support in the literature, and more inclusive "second generation" models have been proposed to incorporate both conflict monitoring and reinforcement learning aspects (Alexander and Brown, 2011; Holroyd and Yeung, 2012).

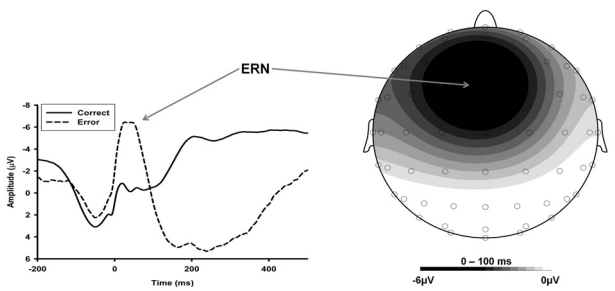

FIGURE 1 | ERN Waveform and Voltage Map. Neural activity recorded in the post-response period during a flanker task. Response-locked waveform is presented on the left. Dashed line: the ERN is shown as the negative deflection peaking at approximately 50 ms; the ERN is followed by a broad, positive deflection—the error-positivity. Solid line: the CRN is the correct-response counterpart to the ERN. It shows a similar time course and scalp distribution. A voltage map depicting the scalp distribution of the ERN is presented on the right. It shows that the ERN is primarily a fronto-centrally maximal negativity.

THE ERN AND ANXIETY

Numerous studies have noted that individual differences in anxiety are associated with increased ERN amplitude (for reviews, see Olvet and Hajcak, 2008; Simons, 2010; Vaidyanathan et al., 2012; Weinberg et al., 2012b). The most robust evidence emerges from research on symptoms and categorical diagnoses of generalized anxiety disorder (GAD; Hajcak et al., 2003; Weinberg et al., 2010, 2012a) and obsessive-compulsive disorder (OCD; see Mathews et al., 2012 for a review)[1]. Because GAD and OCD are largely characterized by worry and verbal rumination (American Psychiatric Association, 2000; Barlow, 2002), we suggested that this work is consistent with our thesis that the ERN is most closely associated with anxious apprehension. Indeed, we directly showed that the ERN was more strongly related to a measure of anxious apprehension than a measure of anxious arousal in a sample of female undergraduates (Moser et al., 2012). Hajcak et al. (2003) demonstrated a similar effect such that the ERN was enhanced in college students high in anxious apprehension but not in students highly phobic of spiders. Other recent descriptive reviews of the literature have come to a similar conclusion that the ERN is aligned most consistently with anxious apprehension (Vaidyanathan et al., 2012; Weinberg et al., 2012b).

AIMS OF THE CURRENT META-ANALYSIS

Despite evidence pointing to a specific association between anxious apprehension and enhanced ERN, very few empirical demonstrations of this specificity have been conducted. We aimed to address this gap by employing meta-analysis to provide a large-scale test of the hypothesis that anxious apprehension is the dimension of anxiety most closely associated with enhanced ERN.

[1]It is important to note that all of these studies examined the relationship between anxiety and the response-locked ERN, as previously defined. The negative going ERP component elicited after negative feedback (i.e., feedback-related negativity or FRN; Miltner et al., 1997) has been less consistently linked to anxiety. In fact, some studies have noted attenuated FRN amplitudes in anxiety (Gu et al., 2010; Aarts and Pourtois, 2012; O'Toole et al., 2012 see Simons, 2010 for a review). Given that the majority of the anxiety research has examined the response-locked ERN, this component will constitute the focus of the present investigation.

Although our main focus for the meta-analysis is on the ERN, we also report findings related to the correct-response negativity (CRN). The CRN is a negative ERP component observed following correct responses that has similar topography, morphology, and perhaps functional significance to the ERN (See **Figure 1**; Vidal et al., 2000, 2003; Bartholow et al., 2005). Some studies have reported that anxiety is associated with enhancement in overall negativity following responses, including both the ERN and CRN, suggesting overactive response monitoring in general (Hajcak and Simons, 2002; Hajcak et al., 2004; Endrass et al., 2008, 2010; Moser et al., 2012). Thus, it is important to investigate how anxiety is related to the CRN. Moreover, to isolate error-specific activity from correct-related activity, we examined the relationship between anxiety and the difference between the ERN and CRN—i.e., the ΔERN (see Weinberg et al., 2010, 2012a).

MATERIALS AND METHODS

STUDY SELECTION

Published studies examining the ERN and anxiety were initially identified using the MEDLINE-PubMed and Google Scholar databases using the terms "anxiety," "OCD," "GAD," "obsessive-compulsive," "generalized anxiety," "worry," "action monitoring," "performance monitoring," "conflict monitoring," "error-related negativity," "Ne," and "ERN." Additional studies were identified from the reference sections of the articles obtained from the online searches and from contacting investigators for additional unpublished datasets. This initial search yielded a total of 75 studies and datasets.

INCLUSION/EXCLUSION CRITERIA

Figure 2 depicts the study selection process used for the meta-analysis. Studies were included in the current meta-analysis if ERN data were reported and they included a measure that specifically identified "anxiety" as the primary construct measured (e.g., the State-Trait Anxiety Inventory—Trait Version; STAI-T) or others tapping closely related constructs such as behavioral inhibition (Behavioral Inhibition System scale; BIS). We did, however, exclude studies in which anxiety was examined as secondary to a different primary psychopathology (e.g., secondary anxiety to a comorbid primary alcohol use disorder; Schellekens et al., 2010). Moreover, we focused on studies of the response-locked ERN elicited in standard conflict tasks, such as the Eriksen flanker task (Eriksen and Eriksen, 1974), the Stroop task (Stroop, 1935), or variants of the Go/No-Go task. Beyond our motivations described above, this decision is further justified by studies showing that enhanced ERN is uniquely associated with OCD diagnosis and symptoms in such response conflict tasks (Nieuwenhuis et al., 2005; Gründler et al., 2009; Mathews et al., 2012). We excluded studies using trial-by-trial motivation manipulations. Studies were also excluded if we were unable to compute a quantitative estimate (i.e., effect size) of the relationship between anxiety and the ERN. One study (Cavanagh et al., 2010) was excluded because it reported a re-analysis of data that were included in the final meta-analysis (Gründler et al., 2009; Study 2 Flankers task). Because Moser et al. (2012) reported on a subset of the full sample reported on in Moran et al. (2012) we only included the Moran et al. (2012) study so as to include the full sample. Moreover, we did not include the anxious arousal data from Moran et al. (2012) in the overall analysis, as the sample is entirely redundant with the anxious apprehension data, but we did include it in moderation analyses described below.

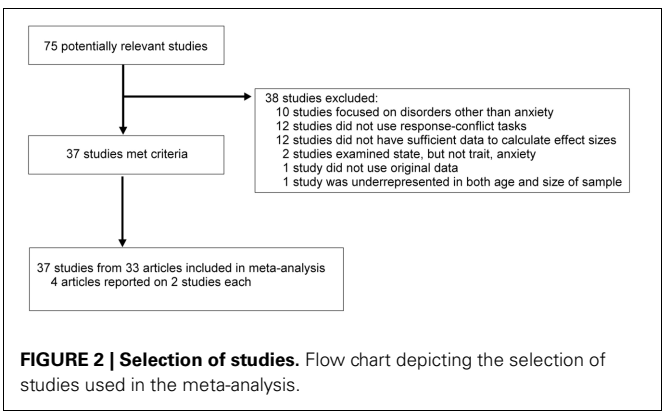

FIGURE 2 | Selection of studies. Flow chart depicting the selection of studies used in the meta-analysis.

Using our inclusion/exclusion criteria, a total of 37 studies were included in the present meta-analysis (see **Table 1**). The selection of studies was nearly equally distributed among healthy adult volunteer samples (19; 51%) and anxiety-disordered samples (16; 43%), with the remaining two studies using samples with healthy children. Of the 37 studies, 27 (73%) used a version of the Eriksen flanker task, 5 (14%) used a Go/NoGo task, 4 (11%) used the Color Stroop task, and 1 (2%) used the Simon task. There were a number of different self-report (and parent-report) measures of anxiety used in the final selection.

OVERVIEW OF ANALYSES

For the present analysis, we used the varying-coefficient model[2] recommended by Bonett (2008, 2009, 2010) and Krizan (2010) because (1) it does not rely on the unrealistic assumptions made by other fixed effects meta-analytic models (e.g., the existence of a single population effect size), (2) Bonett (2008, 2009, 2010) has demonstrated that varying-coefficient models provide more precise confidence intervals than other models, and (3) it performs well in the presence of correlation heterogeneity and non-randomly selected studies (Bonett, 2008; c.f. Brannick et al., 2011). Synthesizer 1.0 (Krizan, 2010) was used for computing point estimates and 95% confidence intervals (95% CIs).

Pearson's *r* was the focal effect size for all studies rather than Cohen's *d* as the former is more consistent with the idea that anxiety is a continuous dimension rather than a distinct category (Watson, 2005; Brown and Barlow, 2009). Cohen (1988) suggested that *r*s ranging between |0.1|and |0.29|represent small effects, *r*s ranging between |0.30|and |0.49|represent medium effects and *r*s exceeding |0.50|are considered large effects. When interpreting the results of the present analyses, it is useful to recall that error-monitoring ERPs are negative deflections—that is, a larger ERN is one that is more negative. Negative correlations therefore indicate that greater anxiety scores are associated with a more negative deflection whereas a positive correlation would

[2]See Appendix for converging findings using a random effects model.

Table 1 | Characteristics of studies included in the meta-analysis.

Study	Population	Task	Anxiety measure	Type
Aarts and Pourtois, 2010[a,b,c]	Volunteers	Go/NoGo	STAI-T	M
Amodio et al., 2008[a]	Volunteers	Go/NoGo	BIS	AA
Beste et al., 2013[a]	Volunteers	Go/NoGo flanker	ASI	M
Boksem et al., 2006[a]	Volunteers	Letter flanker	BIS	AA
Carrasco et al., 2013[a,b,c]	Pediatric OCD	Arrow flanker	K-SADS-PL	AA
Carrasco et al., 2013[a,b,c]	Pediatric OCD	Arrow flanker	K-SADS-PL	AA
Carrasco et al., 2013[a,b,c]	Pediatric anxiety	Arrow flanker	K-SADS-PL	AA
Cavanagh and Allen, 2008[a]	Volunteers	Letter flanker	BIS	AA
Chang et al., 2010[a]	Volunteers	Letter flanker	ASR	M
Gehring et al., 2000[a,c]	OCD	Color stroop	SCID	AA
Gründler et al., 2009[c]	Volunteers	Letter flanker	OCI-R	AA
Hajcak et al., 2008[c]	Pediatric OCD	Simon	Y-BOCS	AA
Hanna et al., 2012[a,b,c]	Pediatric OCD	Arrow flanker	K-SADS-PL	AA
Inzlicht et al., 2009 study 1[a]	Volunteers	Color stroop	BIS	AA
Inzlicht et al., 2009 study 2[a]	Volunteers	Color stroop	BFI-N	M
Johannes et al., 2001[a]	OCD	Go/NoGo	SCID	AA
Kaczkurkin, 2013[a,b,c]	Volunteers	Letter flanker	OCI-R	AA
Ladouceuer et al., 2006[c]	Pediatric anxiety	Arrow flanker	K-SADS-PL	M
Larson and Clayson, 2011[a,b,c]	Volunteers	Arrow flanker	STAI-T	M
Larson et al., 2010[a,b,c]	Volunteers	Color stroop	STAI-T	M
Larson et al., 2011[a,b,c]	Volunteers	Arrow flanker	STAI-T	M
Luu et al., 2000[a,c]	Volunteers	Letter flanker	PANAS	M
Meyer et al., 2012[a,b,c]	Pediatric anxiety	Arrow flanker	Parent-SCARED	M
Moran et al., 2012[a,b,c]	Volunteers	Letter flanker	PSWQ	AA
Moran et al., 2012[a,b,c]	Volunteers	Letter flanker	MASQ-AA	M
Olvet and Hajcak, 2009[a,b,c]	Volunteers	Letter flanker	DASS	M
Olvet and Hajcak, 2012[a,b,c]	Volunteers	Arrow flanker	BFI-N	M
Rabinak et al., 2013[a,b,c]	Veterans	Arrow flanker	SCID	M
Riesel et al., 2011[a,b]	OCD	Arrow flanker	SCID	AA
Ruchsow et al., 2005[c]	OCD	Go/NoGo flanker	SCID	AA
Santesso et al., 2006[a]	Pediatric OC	Letter flanker	CBCL-OC	AA
Stern et al., 2010[a,b,c]	OCD	Letter flanker	SCID	AA
Tops and Boksem, 2011[a,b,c]	Volunteers	Letter flanker	BIS	AA
Weinberg et al., 2010[a,b,c]	GAD	Arrow flanker	SCID	AA
Weinberg et al., 2012a[a,b,c]	GAD	Arrow flanker	SCID	AA
Xiao et al., 2011[a,b,c]	GAD	Letter flanker	Chinese MINI	AA
Xiao et al., 2011[a,b,c]	OCD	Letter flanker	Chinese MINI	AA

[a] *ERN data available.*

[b] *CRN data available.*

[c] *ΔERN data available.*

Population Acronyms: GAD, Generalized Anxiety Disorder Patients; OCD, Obsessive-Compulsive Disordered Patients; OC, Obsessive-Compulsive.

Anxiety Measure Acronyms: ASI, Anxiety Sensitivity Index; ASR, Achenbach Self-Report; BFI-N, Big Five Inventory -Neuroticism; BIS, Behavioral Inhibition System Scale; CBCL, Child Behavior Checklist (OC, Obsessive-Compulsive Scale); DASS, Depression Anxiety Stress Scale; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; MASQ-AA, Mood and Anxiety Symptom Questionnaire: Anxious Arousal Subscale; MINI, Mini-International Neuropsychiatric Interview; OCI-R, Obsessive-Compulsive Inventory-Revised; PANAS, Positive and Negative Affect Schedule; PSWQ, Penn State Worry Questionnaire; SCARED, Screen for Child Anxiety Related Disorders; SCID, Structured Clinical Interview for DSM Disorders; STAI-T, State and Trait Anxiety Inventory-Trait Version; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

Type refers to Anxiety Type; AA, Anxious Apprehension (worry); M, Mixed anxiety.

Nine (24%) of the studies included in the current meta-analysis were also reported on in the Mathews et al. (2012) meta-analysis.

indicate that anxiety is associated with a less negative deflection (i.e., a smaller ERN).

We attempted to obtain data for all measures from all published studies and known unpublished datasets, but complete coverage was not possible in all cases. Thus, many of the following analyses were conducted with subsets of the total number of datasets.

The first set of analyses aimed to quantify the overall relationships between anxiety—broadly defined—and ERN, CRN, and ΔERN. Effect sizes were computed across studies using the reported associations between anxiety measures or groups and the ERN. Most studies reported on a single anxiety-related measure or group. In some other cases, investigators included more than one anxiety-related measure. In these cases, we chose the anxiety-related measure that was most consistently used across studies so as to maximize the potential for comparability across studies.

The focal analyses tested the hypothesis that anxious apprehension is the dimension of anxiety most closely associated with the ERN (as well as the CRN and ΔERN). To do this, we created two groups of studies based on their measures of anxiety. The first group was called the "anxious apprehension" group, which included studies of GAD and OCD diagnoses and symptoms as well as studies of the BIS. Our decision to include the BIS in the anxious apprehension group was based on four considerations: (1) three of the seven items (42%) making up the BIS measure used in ERN research include the word "worry" (Carver and White, 1994); (2) a recent large-scale study demonstrated that anxious apprehension (as measured by the Penn State Worry Questionnaire; PSWQ) was nearly twice as highly correlated with an avoidance motivation factor, including a measure of BIS, than anxious arousal (as measured by the Mood and Anxiety Symptom Questionnaire—Anxious Arousal subscale; MASQ-AA; Spielberg et al., 2011); (3) data from our own research team indicates that anxious apprehension correlates three times as highly with BIS, itself, than anxious arousal [3] and (4) existing theory that links BIS to anxious apprehension and conflict between competing responses (Gray and McNaughton, 2000; Barlow, 2002; Amodio et al., 2008). The second group of studies was called the "mixed" group, which included all other studies. Our reasoning for grouping all other studies together was that they involved non-specific measures of anxiety-related constructs that often mix anxious apprehension with anxious arousal (e.g., the Anxiety Sensitivity Index; ASI) or combine anxiety with depression-related symptoms (e.g., STAI-T). To formally test our differential specificity hypothesis, we compared the magnitude of the aggregated correlation coefficients between the anxious apprehension and mixed studies using Synthesizer software (Krizan, 2010).

RESULTS AND INTERIM DISCUSSION

See **Table 2** for details of the results. Overall, we found that anxiety—broadly defined—demonstrated a small to medium association with the ERN and ΔERN. The CRN, however, was not reliably associated with anxiety symptoms. Critical to our focal hypothesis, we confirmed that anxious apprehension was more strongly related to enhanced ERN than non-specific, "mixed," forms of anxiety-related symptoms (see **Table 2**). The relationships between anxious apprehension and the ERN and

[3] In a sample of over 500 undergraduates, PSWQ was more than three times as highly correlated with BIS ($r = 0.65$, $p < 0.001$, $n = 531$) than was MASQ-AA with BIS ($r = 0.21$, $p < 0.001$, $n = 526$).

Table 2 | Results from the meta analysis.

Sample	*r*	*n*	*k*	95% CIs	r_{diff}	95% CIs_{-diff}
ERN						
Overall†	**−0.253**	1757	32	**−0.302**; **−0.203**	**0.253**	**0.153**; **0.370**
Apprehension	**−0.345**	1077	20	**−0.403**; **−0.285**	–	–
Mixed	**−0.093**	826	13	**−0.175**; **−0.009**	–	–
CRN[a]						
Overall	−0.063	1264	20	−0.129; 0.004	0.041	−0.086; 0.168
ΔERN						
Overall	**−0.207**	1437	26	**−0.264**; **−0.148**	**0.247**	**0.132**; **0.375**
Apprehension	**−0.305**	889	16	**−0.374**; **−0.233**	–	–
Mixed	−0.058	694	11	−0.150; 0.035	–	–

[a] *Only one effect is presented for the CRN as no moderation was found (see **Table 2**).*

Key:

r: aggregate effect size of association with anxiety.

n: is the total number of participants across all studies.

k: number of studies/samples.

95% CIs: 95% confidence intervals for the aggregate correlation (bold type indicates that the confidence interval does not include 0).

r_{diff}*: difference between the aggregate effect sizes between anxious apprehension and mixed anxiety. 95%* CIs_{-diff}*: 95% confidence intervals for the difference (bold type indicates that the confidence interval does not include 0). Adjusting for three comparisons, these moderator analyses remain significant.*

†*In the initial analysis, we did not include the anxious arousal data from Moran et al. (2012) as the sample is entirely redundant with the anxious apprehension data. When the anxious arousal data from are included, the ERN ($r = -0.25$, $k = 33$, $n = 1903$, 95% CIs: −0.30; −0.20) and ΔERN ($r = -0.21$, $k = 27$, $n = 1583$, 95% CIs: 0.26; −0.15) continued to show significant associations with anxiety.*

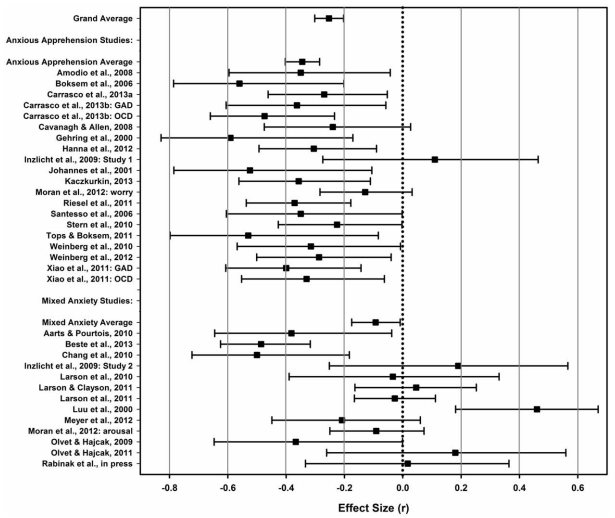

FIGURE 3 | ERN forest. A forest plot depicting effect sizes (*r*) between the ERN and measures of anxiety for the meta-analytic average (top), the anxious apprehension and mixed anxiety averages, and individual studies. Error bars depict the 95% confidence interval for the effect size. The dotted line indicates an effect size of 0.

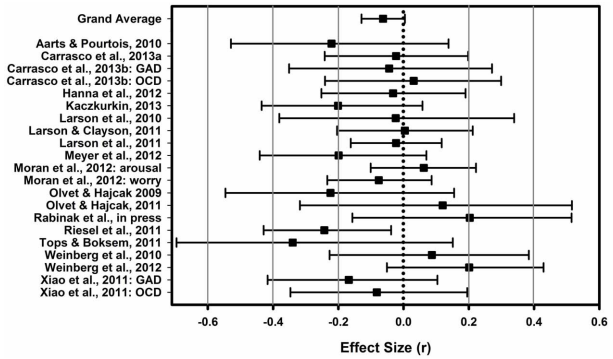

FIGURE 4 | CRN forest. A forest plot depicting effect sizes (*r*) between the CRN and measures of anxiety for the meta-analytic average (top) and individual studies. Error bars depict the 95% confidence interval for the effect size. The dotted line indicates an effect size of 0.

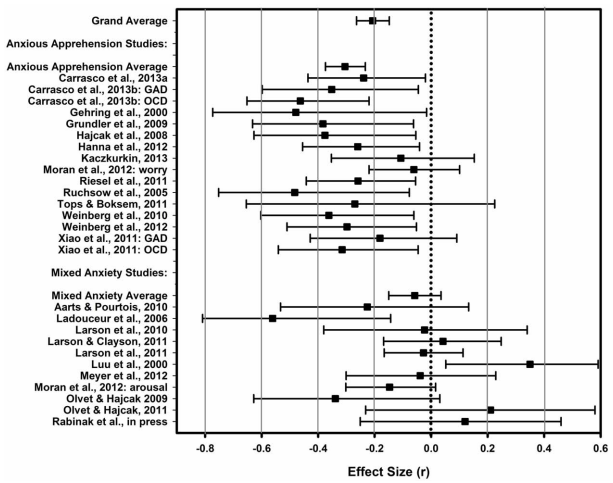

FIGURE 5 | ΔERN forest. A forest plot depicting effect sizes (*r*) between the ΔERN and measures of anxiety for the meta-analytic average (top), the anxious apprehension and mixed anxiety averages, and individual studies. Error bars depict the 95% confidence interval for the effect size. The dotted line indicates an effect size of 0.

ΔERN were medium in size whereas the relationships between mixed anxiety and the ERN and ΔERN were quite small (*r*s < 0.10). Results from individual studies for the ERN, CRN, and ΔERN can be found in **Figures 3–5**, respectively. As can be gleaned from the figures, the mixed anxiety studies were much more variable in their effect sizes, with many studies showing very large confidence intervals as well. Estimates of the CRN effect sizes were likewise quite variable and, in all but one study, demonstrated non-significant results. Together, these results support the notion that the association between error-related brain activity and anxious apprehension is robust whereas the association with less specific forms of anxiety is significantly weaker. Moreover, given the non-specific nature of the measures employed in the "mixed" studies, it is also possible that any associations we detected may, in fact, be driven by the anxious apprehension-related items.

One concern is that nearly all studies conducted with patient samples were included in the anxious apprehension group thus potentially conflating the dimension of anxiety under study with patient status[4]. To address this issue, we tested moderation for the ERN using non-patient studies; the mixed anxiety group contained only a single patient study thus precluding our ability to test moderation for the patient studies. After removing patient studies, anxious apprehension studies ($r = -0.301$, $k = 8$; $n = 410$; 95% CIs: -0.400; -0.195) continued to show greater effect sizes than mixed anxiety studies ($r = -0.101$, $k = 12$, $n = 794$; 95% CIs: -0.186; -0.016; $r_{diff} = 0.199$; 95% CIs for the difference: 0.064; 0.349). Therefore, the difference in effect sizes between the anxious apprehension vs. mixed anxiety studies cannot be accounted for by patient studies alone.

All told, the results of the current meta-analysis indicate that anxiety, broadly defined, demonstrates a small to medium association with ERP indices of error monitoring. Most importantly, the findings are consistent with the hypothesis that an enhanced ERN is more strongly associated with the anxious apprehension dimension of anxiety as opposed to other anxiety-related constructs. Specifically, associations between anxious apprehension and ERN and ΔERN were more than three times as large as those with other forms of anxiety[5]. In contrast, anxiety showed no reliable association with the CRN, irrespective of the way in

[4]We thank Editor Alex Shackman for pointing out this potential confound.

[5]With respect to the ΔERN, it is important to note that it includes variance accounted for by the ERN and it is therefore difficult to discern whether its association with anxiety is driven by variance attributable to the ERN itself. Multivariate analyses are necessary to address this issue in future studies.

which anxiety was operationalized. This finding provides critical information for developing mechanistic models of the links between anxiety and error monitoring. Before detailing a conceptual framework to understand these findings, however, it is useful to point out caveats regarding the current meta-analysis and present a few practical considerations for future research.

First, the current meta-analysis included a relatively small number of studies. However, this is the first meta-analysis of its kind and the total number of studies ($N = 37$) is in line with previous meta-analyses of associations between psychopathology and ERPs (e.g., Polich et al., 1994; Bramon et al., 2004; Mathews et al., 2012). Second, the precision of effect size estimates will also be improved if researchers collect larger samples than have typically been used in this literature to date (sample sizes in the current analysis were as low as $n = 18$; Median $= 40$, $SD = 40.49$), especially because most effect sizes in the social sciences are relatively small (Cohen, 1988; Richard et al., 2003).

Third and most importantly, the task of pin-pointing the association between type of anxiety and error monitoring has received limited attention in the literature. Most studies have taken a more global approach by focusing on individuals with symptoms of GAD or OCD, or by considering associations between relatively generic anxiety symptoms and error monitoring ERPs. We are aware of only two studies that have attempted to empirically isolate specific relationships between facets of anxiety and error monitoring: our recent study (Moser et al., 2012) showing that anxious apprehension was more related to enhanced ERN than anxious arousal and Hajcak and colleagues' (2003) study showing that high anxious apprehensive students showed enhanced ERN compared to spider phobic students. With the current meta-analysis we aimed to significantly extend this line of research. However, because so little data exist that parse dimensions of anxiety in relation to the ERN, we had to create groups of studies, many of which included overall measures that tap a variety of anxiety-related constructs.

We acknowledge that we took a conservative approach to classifying the content of specific measures and compared studies that used fairly clear measures of anxious apprehension—GAD and OCD-related measures—to all others. It is evident from the effect size estimates and figures that there is much more consistency of positive findings in the studies using more precise measures of anxious apprehension. Ideally, there would be more studies directly comparing ERN magnitudes across groups of participants created using targeted instruments of different anxiety constructs—e.g., anxious apprehension vs. anxious arousal. This is a challenge we hope future research will undertake, as it is not only important to the current topic but also to building a more biologically informed rubric for mental disorder classification (cf. Cuthbert and Insel, 2010; Sanislow et al., 2010). In this way, our current analyses build on seminal work by Heller and colleagues that has differentiated anxious apprehension from anxious arousal across psychometric and physiologic studies (Heller et al., 1997; Nitschke et al., 1999, 2001; Engels et al., 2007; Silton et al., 2011; Spielberg et al., 2011).

In the next section, we use the results of this meta-analysis as a starting point for building a conceptual framework to explain why anxious apprehension/worry is the dimension of anxiety most closely associated with enhanced ERN. In short, we propose a *compensatory error-monitoring hypothesis* to explain the association between anxiety and enhanced ERN. Our core claim is that enhanced ERN in anxiety results from the interplay of a decrease in processes supporting active goal maintenance, because of the distracting effects of worry, and a compensatory increase in processes (e.g., effort) dedicated to transient reactivation of task goals on an as-needed basis when errors occur.

DISCUSSION

THE COMPENSATORY ERROR MONITORING HYPOTHESIS

Our conceptual framework is an extension of existing affective-motivational models of the association between anxiety-related constructs and enhanced ERN (Luu and Tucker, 2004; Pailing and Segalowitz, 2004; Weinberg et al., 2012a,b). The foundation of our account rests on four key findings about anxiety and cognitive function: (1) that anxious apprehension/worry is significantly involved in cognitive abnormalities in anxiety, (2) that anxious performance is characterized by processing inefficiency, (3) that enhanced ERN in anxiety is observed without corresponding deficits in task performance, and (4) that individuals with anxiety exhibit enhanced transient "reactive" control but reduced preparatory "proactive" control. We further incorporate the conflict monitoring theory of the ERN (Yeung et al., 2004) in order to cast the anxiety-ERN relationship in more mechanistic terms.

The role of anxious apprehension/worry

The present proposal builds on our earlier explanation for why anxious apprehension shows a particularly strong association with enhanced ERN (Moran et al., 2012; Moser et al., 2012), which in turn drew heavily on Eysenck and colleagues' (2007) Attentional Control Theory (ACT). ACT is a recent extension of Eysenck and Calvo's (1992) original Processing Efficiency Theory (PET), which itself drew on Sarason's (1988) earlier Cognitive Interference Theory. What all of these theories have in common is their emphasis on the deleterious effects of anxious apprehension on cognition. That is, all posit that distracting worries interfere with the ability of anxious individuals to stay focused on affectively neutral cognitive tasks. These early theories were supported by several studies showing the specific effects of worry on cognitive performance (e.g., Morris et al., 1981).

ACT increased specificity of the earlier work by proposing that anxiety is associated with a deficit in attentional control that results from an imbalance in activity between the frontal goal-directed attention system—concerned with goals and plans—and the parietal stimulus-driven attention system—concerned with salience and threat. Specifically, the ACT suggests that anxious individuals are characterized by enhanced activity of the stimulus-driven attention system and decreased functionality of the goal-driven system. Anxious individuals are therefore tuned to prioritize salient internal (e.g., worry) and external (e.g., angry face) sources of potential threat at the expense of affectively-neutral task-relevant stimuli. When no source of external threat or distraction is present (e.g., during performance of a standard conflict task) worry is distracting and likely to deplete goal-driven resources. Our initial formulation of the anxiety-ERN relationship (Moran et al., 2012; Moser et al., 2012) applied this common

assertion that the worry component of anxiety is responsible for cognitive processing abnormalities in affectively-neutral tasks, using this idea to explain that this anxiety dimension, in particular, is most closely related to the ERN.

The notion that anxiety's influence on cognitive performance is primarily the result of the distracting effects of worry also appears as the cornerstone of work by Beilock and colleagues (Beilock and Carr, 2005; Beilock, 2008) who study relationships between anxiety and academic performance. Beilock (2008, 2010) suggests that worry co-opts available working memory resources that would otherwise be allocated to the task at hand. Their work has demonstrated that a variety of types of academic anxiety—from math anxiety to spatial anxiety (Ramirez et al., 2012)—impair performance because of worry's drain on resources. Thus, there is significant precedent from a variety of researchers for focusing on the unique effects of worry on cognition in anxiety.

Anxiety is associated with processing inefficiency

As initially noted by Eysenck and Calvo (1992) in their seminal review paper on Processing Efficiency Theory, anxious individuals often perform just as well as their non-anxious counterparts. The reason performance is spared, they suggested, is that anxious individuals employ compensatory effort because, although worries are distracting, they also motivate anxious individuals to overcome the negative effects of their anxiety on performance. This dual-pathway compensatory effort idea helped to reconcile inconsistencies in the literature regarding the effects of anxiety on performance.

How did they come to hypothesize the role of compensatory effort? First, Eysenck and colleagues showed that anxiety is often related to longer reaction times, but intact accuracy, across a range of reasoning, reading, attention, and working memory tasks (as reviewed by Eysenck and Calvo, 1992 and later again by Eysenck et al., 2007). Thus, to achieve the same level of performance accuracy seems to require anxious individuals to deploy enhanced effort and processing resources that take longer to implement. Second, their reviews showed that anxious individuals also self-report using more effort on tasks in which they perform at the same level as non-anxious individuals. PET and ACT therefore suggest that anxiety is associated with *processing inefficiency*—more effort or resources allocated to achieve comparable level of accuracy—but not necessarily ineffectiveness (i.e., low accuracy).

More recently, neuroimaging studies have provided additional support for the claim that enhanced processing resources (compensatory effort) help anxious individuals maintain typical levels of performance (for a review see Berggren and Derakshan, 2013). For example, enhanced dorsolateral prefrontal cortex activity was reported on incongruent relative to congruent Stroop trials in a sample of anxious college students (Basten et al., 2011). Similarly, enhanced NoGo N2 was reported in anxious students despite comparable performance to non-anxious students (Righi et al., 2009). Berggren and Derakshan (2013) summarized a number of additional consonant effects—i.e., greater processing resources and compensatory effort revealed in anxious individuals despite comparable behavioral performance –across a range of attention and memory paradigms.

In addition, a recent neuroimaging study showed that anxiety's deleterious effect on math performance was curtailed to the extent that high math anxious participants recruited frontal control brain regions (Lyons and Beilock, 2011). Thus, the impact of anxiety on academic performance was mitigated by compensatory cognitive control—precisely as PET/ACT would predict. There is therefore strong support for the notion that anxious individuals can perform as well as non-anxious individuals; however, they draw on more processing resources and effort to do so.

Directly related to the ERN, processing inefficiency provides an explanation for a curious finding from Endrass et al. (2010) who showed that although non-anxious control participants demonstrated an enhanced ERN during a punishment condition, OCD patients did not. Specifically, ACT (Eysenck et al., 2007) predicts that motivational manipulations should have minimal impact on anxious individuals because compensatory effort is already being employed during baseline performance whereas such manipulations should cause increases in performance in non-anxious individuals because they allocate more effort to achieve the incentive. Indeed, Eysenck and colleagues demonstrated this effect in early behavioral work (as reviewed in Eysenck et al., 2007). In this light, Endrass and colleagues' (2010) results suggest that enhanced ERN in non-anxious individuals during punishment reflected increased compensatory error monitoring that was already at ceiling in the OCD group during the standard condition.

Enhanced ERN in anxiety is observed in the absence of compromised performance

Consistent with PET/ACT and the above-reviewed studies, anxious individuals seem to demonstrate typical levels of performance in the standard conflict tasks used in ERN studies. Yet, they consistently show enhanced ERN. Indeed, only three individual studies of the 37 included in the present meta-analysis of the ERN reported a significant relationship between anxiety and error rate. A binomial test suggests that this is consistent with a 5% false positive rate ($z = 1.02$, $p = 0.16$). Moreover, no individual study reported a significant relationship between anxiety and reaction time.

To further evaluate this issue, we conducted an additional meta-analysis on error rate and reaction time for those studies reported on in our meta-analysis of the ERN. As we did with the ERN, we first conducted the meta-analysis across all studies for which we could calculate effect sizes. Then, we conducted moderation analysis by anxiety type. This analysis yielded no significant relationship between anxiety (across all studies) and error rate ($k = 29$; $N = 1668$; $r = -0.02$, 95% CIs: -0.08; 0.03). There was, however, significant moderation by anxiety type such that anxious apprehension was associated with lower error rate ($r = -0.08$; 95% CIs: -0.15; -0.004) and mixed anxiety was associated with non-significantly higher error rate ($r = 0.08$; 95% CIs: -0.02; 0.18; $r_{diff} = 0.16$, 95% CIs for the difference: 0.04; 0.28). Both of these effects are notably small in magnitude. With regard to overall reaction time, there was no significant effect of anxiety ($k = 26$; $N = 1480$; r = -0.06, 95% CIs: -0.12; 0.002), nor was there any significant evidence of moderation ($r_{diff} = 0.09$; 95% CIs: -0.05; 0.23). Together, these findings suggest the small-to-medium association between anxiety (across all studies) and

the ERN is observed in the absence of altered behavioral performance. Importantly, the associations between error rate and anxious apprehension and mixed anxiety unlikely contribute to ERN effects, as they emerge as small effects and in opposing directions for the two anxiety types.

Thus, in line with the notion that anxiety is characterized by processing inefficiency, we suggest that enhanced ERN in anxiety may index a compensatory effort signal aimed at maintaining a standard level of performance (Moran et al., 2012; Moser et al., 2012). That is, enhanced ERN related to anxiety reflects *inefficient error monitoring*, in that anxious individuals may rely on greater error monitoring resources to achieve the same level of performance as non-anxious individuals. Together, then, we suggest that the specific distracting effects of worry during affectively-neutral conflict tasks requires anxious individuals to engage in compensatory effort to perform up to par, with enhanced ERN being one index of this compensatory effort/greater utilization of processing resources.

Anxiety is associated with enhanced reactive control, but reduced proactive control

Braver (2012) and colleagues' (Braver et al., 2007) dual mechanisms of control (DMC) model provides another compatible context in which to understand the role of enhanced ERN as a compensatory effort signal in anxiety. The DMC model suggests that cognitive control is achieved through two distinct modes: proactive and reactive. Proactive control—the more cognitively taxing of the two modes—involves active maintenance of rules and goals within lateral areas of prefrontal cortex in a *preemptive* fashion to facilitate future performance. In contrast, reactive control—the less effortful mode—involves allocating attention to rules and goals on an *as-needed* basis, once a problem (such as the occurrence of conflict or an error) has arisen. Furthermore, Braver (2012) refers to reactive control as a "'late correction' mechanism" (p. 106) and links it to activity of the ACC, such that ACC-mediated conflict monitoring may help individuals reactivate task goals in a transient, as-needed fashion. The DMC model is therefore immediately relevant to the current discussion because it directly parallels the focus of ACT on the interaction between goal-driven (or proactive control) and stimulus-driven (or reactive control) attention systems (Eysenck et al., 2007).

According to Braver (2012), non-anxious individuals are able to alternate flexibly between reactive and proactive control modes in accordance with changing task demands. In contrast, Braver (2012) suggests that anxious individuals are distracted by worries that deplete resources needed for active goal maintenance, thereby interfering with proactive control and throwing chronically anxious individuals into a reactive control mode. That is, anxious individuals rely more heavily on reactive control. Increasing evidence supports this propensity for anxious individuals to preferentially engage in reactive control (Gray et al., 2005; Fales et al., 2008; Krug and Carter, 2010, 2012). For example, Fales et al. (2008) showed that anxious individuals demonstrated decreased sustained, but increased transient, activity in working memory regions consistent with the notion of decreased proactive and increased reactive control.

A recent study by Nash et al. (2012) showing that increased behavioral activation system (BAS) activity, as indexed by left-sided prefrontal EEG asymmetry, was associated with a reduced ERN provides additional support for our proposed differential effects of proactive and reactive control on ERN. Indeed, BAS has been associated with proactive control and reduced dACC/MCC activity (see Braver et al., 2007 for a review). Thus, while anxiety/BIS is associated with reactive control and therefore an enhanced ERN—as demonstrated in our meta-analysis—BAS is associated with proactive control and therefore a reduced ERN.

Formalizing the model using the conflict monitoring theory of the ERN

We adopt the conflict monitoring theory of the ERN and its recent extensions (Yeung and Cohen, 2006; Steinhauser and Yeung, 2010; Hughes and Yeung, 2011; Yeung and Summerfield, 2012) so as to leverage a well-articulated computational model of the ERN to help explain the relationship between anxiety and enhanced ERN. According to the conflict monitoring theory, the ERN reflects conflict that is detected when continued target processing after an error leads to activation of the correct response, resulting in conflict with the error just produced. This notion is rooted in the classic finding that individuals tend to automatically correct their mistakes as a result of continued stimulus processing (Rabbitt, 1966; Rabbitt and Vyas, 1981). Thus, the ERN indexes processes involved in the rapid correction of errors that reflects the current level of cognitive demand or effort—i.e., the level of response conflict (see also Hughes and Yeung, 2011; Yeung and Summerfield, 2012). In the context of broader theories of the ACC—the neural source of the ERN—the ERN provides information about current conflicts in order to optimize action selection and behavior (Botvinick et al., 2001; Botvinick, 2007). The conflict monitoring theory of the ERN nicely dovetails with the DMC in that both suggest the ACC is involved in reactive control, insofar as the ERN reflects ACC-mediated conflict monitoring arising from activation of the error-correcting response (Yeung and Summerfield, 2012)—i.e., a late correction mechanism.

Thus, our *compensatory error-monitoring hypothesis* of enhanced ERN in anxiety first draws on the above reviewed theory and evidence in assuming that anxiety increases sustained attention to internal sources of threat (i.e., worry) thereby reducing available resources dedicated to active maintenance of task rules and goals. As a result, the anxious individual is forced to rely on reactive control as a compensatory strategy. *Critically, when errors occur, reactive control causes an increase in stimulus processing around and after the time of the incorrect response, leading to enhanced conflict between the just-produced error and the correct (target) response that gives rise to an enhanced ERN (Yeung et al., 2004). Detection of this conflict could then help to reactivate task goals in the moment and normalize performance in anxious individuals (Braver, 2012).* At least with respect to conflict tasks, this dynamic seems to provide a mechanistic account of an enhanced ERN in the presence of comparable performance among anxious individuals, because the interactive effects of reduced proactive control and increased reactive control would cancel each other out at the behavioral level. Having detailed our compensatory error-monitoring hypothesis, we now turn to

new sources of evidence that provide additional support for our claims.

New sources of support for the compensatory error-monitoring hypothesis

Our compensatory error-monitoring hypothesis largely hinges on two ideas: (1) that the cognitive load of worry begins a cascade of processes that lead to enhanced ERN in anxious individuals, and (2) enhanced ERN in anxiety reflects a compensatory attention/effort response. In this section, we present data from our own lab that provides more direct support for these underlying assertions of our model.

If enhanced ERN in anxiety results from the cognitive load of worries on processing resources, it follows that experimentally induced cognitive load should also lead to enhanced ERN. Recent experimental data from our lab supports this notion that cognitive load—an affectively-neutral analog to distracting worries—enhances the ERN. In a study by Schroder et al. (2012), we showed that the ERN is enhanced when stimulus-response rules are switched, resulting in the need for individuals to simultaneously inhibit old rules and maintain current rules. We suggested that as a result of this need to juggle old and current rules, a cognitive load was placed on subjects during trials in which stimulus-response rules were switched. When errors occurred, then, compensatory attentional effort was employed as a reactive control strategy resulting in enhanced ERN.

More directly, we conducted an experiment examining the effect of verbal working memory load (WML) on the ERN (Moran and Moser, 2012), the details of which we present here. Twenty-nine undergraduates (21 Female, *M* age = 19.52 years, *SD* = 2.72) completed a flanker task interleaved with a successor-naming task (for a similar method, see (Lavie and Defockert, 2005): Experiment 2). Prior to each flanker stimulus, participants saw a string of five numbers to remember. Each five-number string was either in numerical order (low WML) or in a random order (high WML). Participants were instructed to memorize these digits. Following each flanker stimulus, a memory probe, which consisted of a randomly-selected number from the five-number memory set, was presented and participants were instructed to input the digit that followed the memory probe digit in the memory set for that trial. The experimental session consisted of 480 trials grouped into six blocks. Load was randomly varied by block such that a given block contained only one type of WML. There were an equal number of high- and low-WML blocks. The ERN (and CRN) elicited by flanker errors was calculated as the average activity in the 0–100 ms post-response time window relative to a −200 to 0 ms pre-response baseline at FCz. ERN/CRNs were then submitted to a 2 (Accuracy: Error vs. Correct) × 2 (WML: High vs. Low) repeated-measures analysis of variance (ANOVA).

Of key interest was the prediction that ERN amplitude should be increased in conditions of increased WM load. The main effect of accuracy [$F_{(1,\ 28)} = 39.54$, $p < 0.01$, $\eta_p^2 = 0.59$] confirmed the presence of a clear ERN in this paradigm. Crucially, and consistent with our hypothesis, the WML × accuracy interaction was significant [$F_{(1,\ 28)} = 9.69$, $p < 0.01$, $\eta_p^2 = 0.28$; See **Figure 6** top right panel]. The ERN was enhanced on high load trials [$t_{(28)} = 3.50$, $p < 0.01$] whereas the CRN was unaffected by the WML manipulation ($t < 1$). Moreover, the ERN-CRN difference wave was greater on high WML trials than low WML trials [$t_{(28)} = 3.11$, $p < 0.01$].

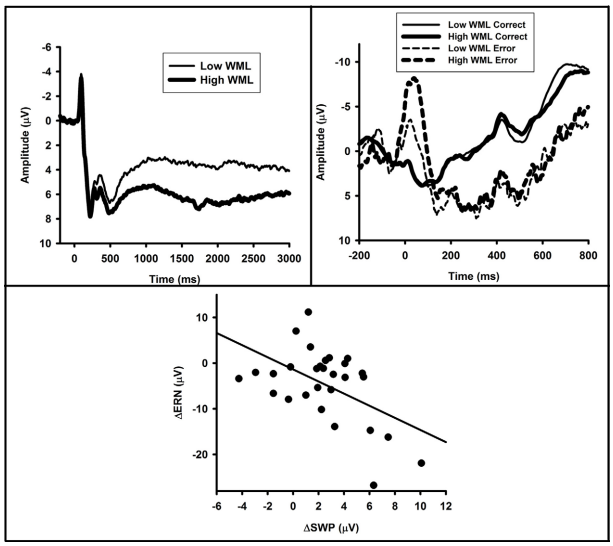

FIGURE 6 | Working memory load enhances ERN. (Top Left) SWPs elicited during the memory retention interval. **(Top Right)** Response-locked ERPs as a function of accuracy and WML. **(Bottom)** A scatterplot depicting the association between WM-related changes in SWPs and ERNs.

To test the prediction that individual differences in sensitivity to load should correlate with changes in ERN amplitude, we also correlated the ERN with a well-validated ERP index of WM-retention. In particular, we measured the left-anterior positive slow-wave potential (SWP) that shows greater magnitude on high- vs. low-WML trials (Ruchkin et al., 1997; Berti et al., 2000; Kusak et al., 2000). By examining the relationship between the SWP (WM-retention) and the ERN, we intended to provide evidence that occupying WM functions under load, like worry, directly leads to increased ERN. The SWP was computed across the 500–3000 ms post-stimulus window with respect to a baseline consisting of the average activity in the 200 ms window immediately prior to the presentation of the memory set. The SWP was quantified as the average activity recorded at F3. SWPs were submitted to a single-factor (WML: High vs. Low) repeated-measures ANOVA.

Consistent with previous work, high WML memory sets elicited greater left-anterior positivity than low WML memory sets during the rehearsal period [$F_{(1,\ 28)} = 18.21$, $p < 0.01$, $\eta_p^2 = 0.39$; see **Figure 6** top left panel]. To directly link WM operations with the ERN, we first computed WM-related changes for each of our measures: ΔERN was computed as the ERN-CRN difference on high WML trials minus the ERN-CRN difference on low WML trials—that is, the extent to which error-related brain activity was modulated by the WML manipulation; ΔSWP was computed as the difference in activity between high and low WML trials during memory-set presentation. We focused on the ERN-CRN difference due to the significant Accuracy × WML

interaction. However, if we compute ΔERN as the ERN on high-WML trials minus the ERN on low-WML trials the interpretation of the results does not change. Critically, findings revealed that ΔERN was strongly related to ΔSWP ($r = -0.51, p < 0.01$) indicating that enhanced ERN under high WML can be attributed to increased WM operations during rehearsal (**Figure 6** bottom panel). Such data provide particularly strong causal evidence that current cognitive load leads to enhanced ERN. Together, they provide a proof-of-concept for the notion that the enhanced ERN that characterizes anxiety may result from WML imposed by worry.

Regarding our assertion that enhanced ERN in anxiety reflects a compensatory attention/effort response, we present results from a novel analysis examining associations between anxious apprehension, ERN, and academic performance—as measured by grade-point average (GPA)—on a subsample of data from a larger dataset (Moran et al., 2012). Past work has shown that larger ERN amplitudes correlate with higher GPA, suggesting that enhanced cognitive control is associated with higher academic achievement (Fisher et al., 2009; Hirsh and Inzlicht, 2010). However, no studies have examined whether anxiety moderates this relationship. We predicted that if enhanced ERN in anxious apprehension reflects a reactive compensatory control signal, a larger ERN in worriers should be associated with higher GPA. Following this logic, a low ERN in worriers would be associated with poorer academic performance. If, on the other hand, the ERN is not related to compensatory control in anxiety, the ERN-GPA relationship should not differ as a function of anxiety.

We tested these predictions in 59 undergraduates (24 female, M age = 20 years, $SD = 3.20$) who had useable cumulative GPA data collected from the University's Office of the Registrar. EEG recording procedures and task descriptions have been described elsewhere (Moran et al., 2012); participants engaged in a letter flanker task and then completed the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990). The ERN was calculated as the average activity in the 0–100 ms post-response time window relative to a −200 to 0 ms pre-response baseline correction at FCz (where it was maximal) on error trials.

Consistent with previous work (Hirsh and Inzlicht, 2010), larger ERN amplitude was significantly correlated with higher GPA across the whole sample ($r = -0.30$, $p < 0.05$). However, the relationship was small and non-significant among individuals below the median on PSWQ scores (Low Worriers, $n = 31$; $r = -0.17$, $p = 0.37$) but was significant and more than double the size among those above the median on the PSWQ (High Worriers, $n = 28$; $r = -0.44$, $p < 0.05$, see **Figure 7**). To explore further the relationships between worry, ERN amplitude, and GPA, the median scores on the PSWQ (Median = 51.00) and ERN (Median = −4.42 μV) were used to categorize participants into one of four groups: Low Worry—Low ERN ($n = 13$), High Worry—Low ERN ($n = 16$), Low Worry-High ERN ($n = 18$), and High Worry—High ERN ($n = 12$). A one-way analysis of variance (ANOVA) with Worry-ERN Group as the between-subjects factor and cumulative GPA as the dependent variable revealed a significant effect of Group [$F_{(3, 58)} = 3.17$, $p = 0.03$]. This effect is depicted in **Figure 7**. Fisher's least significant difference procedure indicated that participants in the High Worry-High ERN group had a significantly higher GPA ($M = 3.32$, $SD = 0.53$) than the High Worry-Low ERN group ($M = 2.83$, $SD = 0.51$; $p < 0.05$) and that the Low Worry-High ERN group ($M = 3.31$, $SD = 0.61$) also had a significantly higher GPA than the High Worry-Low ERN group ($p < 0.01$). The difference between the Low Worry-Low ERN group ($M = 3.15$, $SD = 0.50$) and High Worry-Low ERN group was marginal ($p = 0.10$). Critically, the High Worry-High ERN and Low Worry-High ERN groups did not differ on GPA ($p > 0.90$).

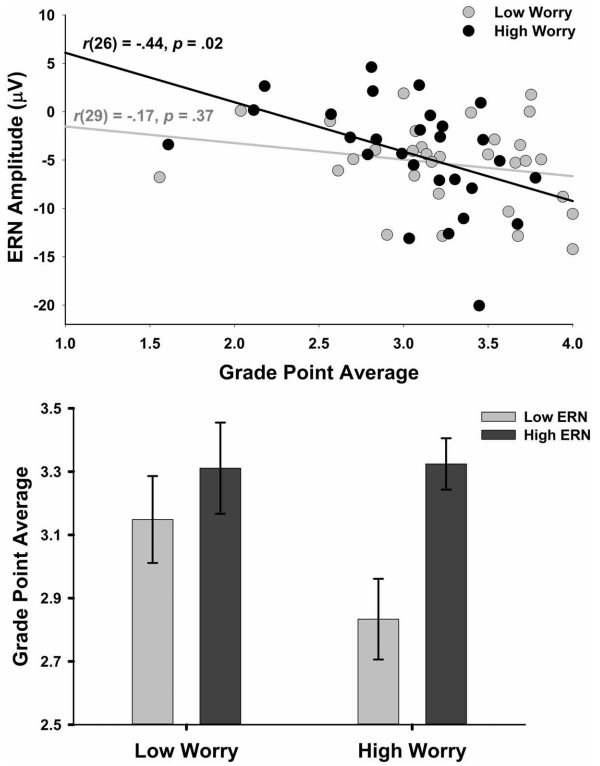

FIGURE 7 | Relationship between ERN and GPA is moderated by worry. **(Top)** Scatterplot showing the relationship between ERN and GPA in the top 50% of the PSWQ distribution (black) and the bottom 50% (gray). **(Bottom)** Bar graph depicting GPA as a function of ERN and Worry groups which were created by median splits and described in the text. Error bars represent standard error of the mean.

Together, these exploratory analyses provide further evidence that enhanced ERN among worriers functions as a compensatory control signal insomuch as worriers with a large ERN achieved the same GPA as non-worriers. In contrast, individuals with high worry and a low ERN, suggesting a lack of effortful compensatory control, tended to have significantly poorer academic achievement. Although preliminary, these findings are consistent with the Lyons and Beilock (2011) study showing that anxiety's deleterious effect on math performance was curtailed to the extent that high math anxious participants recruited frontal control brain regions.

PREDICTIONS AND DIRECTIONS FOR FUTURE RESEARCH

To this point, we have provided theoretical rationale and empirical evidence for our *compensatory error-monitoring hypothesis*

of the association between anxious apprehension and enhanced ERN. In this next section, we develop a set of additional predictions and key avenues for future research to pursue.

The first, and perhaps most obvious, prediction for future research to test is that inducing worry should lead to an enhancement of the ERN. Borkovec and Inz (1990) have developed and implemented a standard worry induction procedure for decades that could be easily utilized in the context of an ERN study. Previous anxiety inductions have demonstrated negative results with regard to their effects on the amplitude of the ERN. For instance, Moser et al. (2005) induced fear in spider phobic undergraduates and showed no effect on ERN magnitude. Similarly, Larson et al. (2013) failed to show an effect of an anxiety induction on ERN magnitude. Our prediction is that enhanced ERN will only be elicited to the extent that anxious apprehension—worry—is induced. The failure of existing studies to find effects of anxiety induction on ERN may therefore be the result of their use of anxious arousal inductions instead of worry inductions.

Similarly, we predict that worries captured at ERN testing should relate to enhanced ERN and may mediate the association between trait worry and enhanced ERN. Specifically, on- and/or off-task worries could be measured following flanker performance and related to the ERN. If worries during task performance are responsible for co-opting goal-driven resources and causing compensatory deployment of reactive control resources, then such measures of worry should relate to enhanced ERN. The Cognitive Interference Questionnaire (CIQ; Sarason and Stoops, 1978; Sarason et al., 1986) would be one measure of this construct worth exploring in this regard. Self report and thought sampling methods for measuring mind wandering and task-unrelated thoughts (Matthews et al., 1999; Schooler et al., 2011; Mrazek et al., 2011, 2013) would also be important for future tests of our hypotheses.

Following from our formulations and the preliminary findings of Endrass et al. (2010), we would also predict that incentive and motivation manipulations should have less effect on ERN amplitude in anxious than non-anxious populations. There are numerous ways to manipulate incentive and motivation and thus this effect could be tested in a variety of contexts. Previously, Hajcak et al. (2005) showed that the amplitude of the ERN was enhanced on trials that were worth more points toward a monetary incentive as well as under a condition of performance evaluation. We predict that such manipulations would not lead to enhanced ERN in anxious individuals because they already employ compensatory effort during baseline conditions.

Treatment studies not only offer the chance to help improve anxious peoples' functioning but also to test theory-derived hypotheses. With respect to our view that the anxiety-ERN relationship reflects reductions in proactive control and compensatory increases in reactive control, one treatment possibility is to train anxious individuals to adopt more of a proactive control strategy. Proactive control training has been successfully implemented in individuals with schizophrenia, resulting in decreased symptoms and more proactive brain activity (Edwards et al., 2010), as well as in older adults who tend to engage in reactive control strategies before, but not after, training (Braver et al., 2009; Czernochowski et al., 2010; Jimura and Braver, 2010). We predict that proactive control training in worriers would result in reductions in ERN magnitude that might also mediate the effectiveness of the intervention in terms of symptom reduction. Similarly, another possibility for testing our hypothesis comes from Ramirez and Beilock's (2011) recent demonstration that emotional expressive writing improves test performance in high test anxious individuals via its effects on reducing worries and freeing up proactive resources for active goal maintenance. We expect that expressive writing about worries would likewise result in reduced ERN magnitude in highly apprehensive individuals.

A particularly exciting feature of this last set of predictions concerning treatment effects on the ERN in anxious individuals is that it provides a context in which to interpret broader effects of anxiety treatment on the ERN. To date, one study in pediatric OCD patients showed that the ERN did not change with successful cognitive-behavioral treatment (CBT) of OCD (Hajcak et al., 2008). This study has been cited as evidence for a "trait" biomarker or "endophenotype" interpretation of enhanced ERN in anxiety (e.g., Olvet and Hajcak, 2008). However, there seem to be three problems with this conclusion: (1) despite symptom reduction in the OCD patients, post-treatment scores still placed them around the clinical cutoff for an OCD diagnosis, (2) CBT is an intervention designed to reduce anxiety symptoms, not alter underlying neural mechanism involved in cognitive control (i.e., ERN), and (3) the study was conducted in children and adolescents for whom the anxiety-ERN relationship may be different than in adults (Meyer et al., 2012). In this way, even though patients showed reduced OCD symptoms after treatment, they still demonstrated anxiety-related compensatory effort, as reflected in enhanced ERN. The focus of our predictions is not on reducing anxiety symptoms *per se*, but rather to change the functional relationship between worry and cognitive functioning (cf. Ramirez and Beilock, 2011). For instance, the purpose of the expressive writing intervention is to target the *mechanism* involved in anxiety's effects on cognition. This approach will not only help test our predictions set forth here but it may also inform treatments of anxiety and their impact on performance.

The current framework provides an important link between anxiety research and computational models of cognition. Thus, we suggest that future research in this area (and in other allied areas as well) apply computational modeling to test predictions about the associations between anxiety and error-monitoring ERPs and related performance measures. Yeung and Cohen (2006), for instance, demonstrated the power of applying computational modeling to understand ACC-mediated monitoring deficits in lesion patients. Interestingly, they showed that reduced ERN in patients with ACC lesions could be modeled as resulting from impaired attention control rather than specific impairments in conflict-monitoring *per se*. Applying this modeling technique to the anxiety-ERN relationship, in particular by implementing distinct proactive and reactive control modes in a single model (e.g., De Pisapia and Braver, 2006), represents an exciting direction for future research. This approach might help illuminate whether anxiety affects ACC-mediated monitoring functions directly, as envisioned in current theories that emphasize tight linkages between control and affective functions in ACC (e.g.,

Shackman et al., 2011; Hajcak, 2012), or rather has an indirect impact through its effects on cognitive control modes (e.g., Braver, 2012), as suggested by our analysis.

This framework also provides the foundation for incorporating other conflict- and error-monitoring ERPs that have failed to be adequately addressed by researchers primarily interested in the anxiety-ERN relationship. Regarding the CRN, for example, the results of the current meta-analysis suggest that it is not reliably associated with anxiety, thus failing to support the notion of general overactive action monitoring in anxiety (e.g., Hajcak et al., 2003; Endrass et al., 2008). The error positivity (Pe)—a centro-parietally maximal ERP that follows the ERN (See **Figure 1**; Falkenstein et al., 2000)—is another error-monitoring ERP that has received limited attention in the anxiety literature. The Pe appears to index explicit error-related processing, including the detection and signaling of errors (Yeung and Summerfield, 2012). To date, research is equivocal, with some studies showing reduced Pe (Moser et al., 2012), some showing enhanced Pe (Weinberg et al., 2010) and still others showing no association (Weinberg et al., 2012a) in anxiety. Again, such inconsistent findings argue against a general impairment in error/action monitoring.

The N2, a fronto-central negativity observed around 250–350 ms in the stimulus-locked ERP on correct trials, is a relevant action-monitoring ERP that is purported to reflect pre-response conflict elicited by the co-activation of correct and incorrect responses when stimuli are associated with both (e.g., incongruent flanker stimuli; Yeung et al., 2004). Unfortunately, the N2 is even more ignored than the Pe in anxiety research. Two studies, not included in the current analysis because they did not report ERN data, however, suggest enhanced N2 in trait anxious college students (Righi et al., 2009; Sehlmeyer et al., 2010). If enhanced N2 were to emerge as a reliable marker of anxiety in future studies, it would suggest a more general effect of anxiety on conflict monitoring (Yeung et al., 2004).

RELATED ACCOUNTS OF ENHANCED ERN IN ANXIETY

The major advance of our proposal is that it attempts to directly account for the relationship between anxiety and the ERN. Although there exist emotional-motivational accounts of the ERN and its within- and between-subjects variation (Pailing and Segalowitz, 2004; Weinberg et al., 2012b), none make specific predictions about the relationship between anxiety and the ERN. Rather, existing accounts are much broader in their assertions regarding the functional significance of the ERN and its variation across individuals. Nonetheless, to the extent that existing emotional-motivational accounts can be applied to the anxiety-ERN relationship, we next address how they fare with regard to their ability to explain existing data.

Researchers have suggested that the ERN is an affective or emotional response to errors (Luu and Tucker, 2004; Pailing and Segalowitz, 2004), in large part because of associations noted between the ERN and individual differences in emotional traits like anxiety. According to this view, then, an enhanced ERN in anxious individuals reflects their heightened negative emotional response to or concerns over mistakes (Bush et al., 2000; Gehring and Willoughby, 2002; Hajcak et al., 2005). Many earlier studies pointed to both heightened ERN amplitude and overactive error-related ACC activity in anxiety as evidence of a dysfunctional affective response to errors, particularly in individuals with OCD (Gehring et al., 2000; Johannes et al., 2001). Functional imaging evidence showing *rostral* ACC enhancement in response to errors in OCD patients (Fitzgerald et al., 2005) was considered strong support for this claim, as the rostral subdivision is often considered the "affective/emotional" portion of ACC, as opposed to the "cognitive" subdivision that lies dorsally (Bush et al., 2000).

A related conceptualization suggests that variation in the magnitude of the ERN reflects individual differences in defensive reactivity (Hajcak and Foti, 2008; Hajcak, 2012; Weinberg et al., 2012a). That is, the ERN carries information aimed at mobilizing resources to protect the organism against subsequent negative events, with this response being sensitive to individual differences in aversiveness of errors. These authors situate the ERN in a broader network of defensive motivational systems involved in executing a cascade of physiological, cognitive, and behavioral responses when potential threats are detected (Lang et al., 1997; Bradley et al., 2001; Bradley, 2008). In this view, the ERN is a neural marker of a broader neurobehavioral trait—that is, a stable individual difference with identifiable referents in neurobiology and behavior (Patrick and Bernat, 2010; Patrick et al., 2012)—of defensive reactivity. Anxiety is included in this model as reflecting individual differences in defensive reactivity thereby supporting the theory's primary contention.

Although the affective response and defensive reactivity models provide plausible accounts of heightened ERN amplitude in anxiety, they only loosely address the fact that some forms of anxiety are more closely tied to enhanced ERN than others. Our conceptual framework, on the other hand, uses this distinction as foundational for specifying the relationship between anxiety and the ERN. There are also contradictory findings in the literature that point to additional weaknesses in current approaches to conceptualizing the connection between anxiety and the ERN.

With regard to the affective response interpretation, the cognitive vs. affective subdivision model of the ACC is not supported by extant research (Shackman et al., 2011). Thus, it is unclear whether enhanced rostral ACC activation following errors in anxious individuals is indicative of an affective response *per se* (cf. Poldrack, 2011 for problems with reverse inference in general). Rather, as Shackman et al. suggest, such ACC activation in anxious individuals may reflect a more domain general "adaptive control" response. Moreover, modulations of ACC activity should not be conflated with those of the ERN given the potential for multiple sources to contribute to the generation of the ERN (Gehring et al., 2012). Evidence from our own work further demonstrates this point. Specifically, although ACC activity is enhanced during symptom provocation in simple phobics (e.g., spider phobics; Rauch et al., 1995), we showed that the ERN is not (Moser et al., 2005).

Regarding the defensive reactivity interpretation, evidence speaking directly to the assertion that "…anxious individuals who are characterized by increased ERNs may exhibit a greater defensive response to errors compared with non-anxious individuals" (Hajcak and Foti, 2008, p. 106) is lacking. In fact, Endrass and colleagues' (2010) failure to show modulation of the ERN by punishment in an OCD sample is inconsistent with a

defensive reactivity account. If enhanced ERN in anxiety reflects the aversiveness of errors, it stands to reason that the ERN should have been enhanced during the punishment condition in the OCD sample. That this result was not observed suggests the aversiveness of the error did not significantly contribute to enhanced ERN in the OCD sample in either the baseline or punishment condition. Riesel et al. (2012), on the other hand, did find that punishment enhanced the ERN in high trait anxious individuals but not low trait anxious individuals. However, the authors utilized the STAI-T, which we have shown here is not reliably associated with enhanced ERN. Indeed, high STAI-T individuals in the Riesel et al. study did not show enhanced ERN in the control condition, only a larger enhancement of the ERN from the control to punishment condition. Taken together, extant data are equivocal as to the ability of the defensive reactivity account to explain enhanced ERN in anxiety.

CONCLUDING REMARKS

Our overarching goal in this paper has been to provide a foundation for future research addressing the relationship between anxiety and error processing, both quantitatively and conceptually. In particular, we provide estimates of the effect sizes concerning associations between dimensions of anxiety and error-monitoring ERPs elicited in standard conflict tasks. This meta-analytic result provides a more exact understanding of the previous literature and can serve to help researchers design better studies for the future with an eye toward statistical power and precision. We have also articulated a framework that focuses on what enhanced ERN reflects about cognitive dysfunction in anxiety. Our view is that enhanced ERN in anxiety indexes the impact of anxious apprehension—i.e., worry—on post-decisional response conflict by way of its negative influence on active goal maintenance mechanisms and a resulting compensatory increase in "as-needed" reactive control. Such a dynamic reflects what Berggren and Derakshan (2013) call the "hidden cost" of anxiety. As has been suggested, under simple task conditions, this compensatory effort allows anxious individuals to perform as well as non-anxious individuals. Unfortunately, compensatory effects can break down when tasks become more difficult. That is, enhanced ERN provides an index of how hard a worried mind has to work to complete even simple tasks. It can serve as a harbinger of struggle and potential failure on more complex tasks and presumably real-world adaptation. Indeed, the constant distraction and compensatory re-focus is illustrative of how anxiety, and worry, in particular, can drain resources and lead to functional disability.

In sum, we hope this model and our initial ideas for future research represents just the beginning of a deeper understanding of what error- and conflict-related ERPs can tell us about the impact of anxiety on cognition. The promise of more formalized models of cognitive dysfunction in anxiety will be realized to the extent that they offer new insights into how better to identify and treat the world's most ubiquitous mental health problem.

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APPENDIX

Given that the varying-coefficient model—the basis for the analysis presented in the main text—has rarely been applied in the published literature, we also present results computed from a more common meta-analytic framework. As these studies were rather heterogeneous in their reported effect sizes, our second analysis was conducted within the context of a random effects model (Cumming, 2012). Point estimates, 95% CIs and heterogeneity statistics were computed using Comprehensive Meta-Analysis software (v.2; Borenstein et al., 2005).

The results of this analysis are presented in **Table A1**. Overall, these results closely mirror the findings from the main analysis. As in the main analysis, both the ERN and ΔERN showed significant associations with measures of anxiety. Importantly, analyses of the heterogeneity between data sets revealed that effect sizes were significantly larger in studies examining anxious apprehension compared to mixed anxiety for the both the ERN and ΔERN. The results of this analysis diverge from those presented in the text in two, relatively minor, ways: first, mixed anxiety no longer shows a significant association with either the ERN or ΔERN. Second, the CRN now shows a small, but significant, association with anxiety. As before, the CRN does not show moderation by anxiety dimension group.

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Table A1 | Results from the Meta-Analysis using the random effects model.

Sample	*r*	Lower limit	Upper limit	*Q*	*p*
ERN					
Overall†	**−0.254**	**−0.331**	**−0.173**	8.95	0.003
Apprehension	**−0.329**	**−0.411**	**−0.241**	–	–
Mixed	−0.110	−0.224	0.007	–	–
CRN					
Overall	**−0.059**	**−0.115**	**−0.002**	0.88	0.358
ΔERN					
Overall	**−0.195**	**−0.273**	**−0.115**	13.05	< 0.001
Apprehension	**−0.275**	**−0.350**	**−0.197**	–	–
Mixed	−0.043	−0.142	0.056	–	–

Key:

r: aggregate effect size of association with anxiety.

Lower Limit/Upper Limit: The bounds for the 95% confidence intervals for the aggregate correlation (bold type indicates that the confidence interval does not include 0).

Q: The heterogeneity statistic used to test for moderation between Anxious Apprehension and Mixed anxiety.

p: Significance for the Q statistic. Both the ERN and ΔERN continue to show significant moderation after adjusting for three comparisons.

†As before, we first conducted this analysis without the anxious arousal data from Moran et al. (2012). When these data an included, both the ERN (r = −0.247; 95% CIs: −0.321; −0.169) and ΔERN (r = −0.191; 95% CIs: −0.264; −0.116) continued to show significant associations with anxiety. The CRN, however, did not (r = −0.046; 95% CIs: −0.099; 0.008).

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Evidence from neuroimaging for the role of the menstrual cycle in the interplay of emotion and cognition

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Women show increased predisposition for certain psychiatric disorders, such as depression, that are associated with disturbances in the integration of emotion and cognition. While this suggests that sex hormones need to be considered as modulating factors in the regulation of emotion, we still lack a sound understanding of how the menstrual cycle impacts emotional states and cognitive function. Though signals for the influence of the menstrual cycle on the integration of emotion and cognition have appeared as secondary findings in numerous behavioral and neuroimaging studies, this has only very rarely been the primary research goal. This review summarizes evidence: (1) that the menstrual cycle modulates the integration of emotional and cognitive processing on a behavioral level, and (2) that this change in behavior can be associated with functional, molecular and structural changes in the brain during a specific menstrual cycle phase. The growing evidence for menstrual cycle-specific differences suggests a modulating role for sex hormones on the neural networks supporting the integration of emotional and cognitive information. It will further be discussed what methodological aspects need to be considered to capture the role of the menstrual cycle in the emotion-cognition interplay more systematically.

Keywords: menstrual cycle, neuroimaging (anatomic and functional), emotion-cognition interaction, mood, emotion regulation, sex hormones, reward

INTRODUCTION

Sex hormones have been shown to influence emotional states and cognition (Schmidt et al., 1998; Bloch et al., 2000). This is supported by a wide body of animal data and reflected in diverging prevalence rates for men and women for many psychiatric diseases that are associated with cognitive biases to emotional information, such as depression and anxiety (Soares and Zitek, 2008). While hormonal transitions across the lifespan represent periods of heightened vulnerability for development of mood disorders for women, the prevalence rates for depression between the sexes are most prominent during the reproductive years. The most extreme changes in gonadal hormones, such as the postpartum period, have consistently been reported as a time of increased risk for depression (O'Hara, 2009). The menstrual cycle offers a unique opportunity to study whether subtle fluctuations of sex hormones can influence neuronal circuits implicated in the cognitive regulation of emotional processing.

The menstrual cycle can be divided in a follicular and a luteal phase (Terner and De Wit, 2006): the follicular phase is used generally to refer to the period after completion of menses until ovulation. During menses and early in the follicular phase, levels of both progesterone and estrogen are very low, while toward the middle and later portions of the follicular phase estrogen levels begin to rise (Griffin and Ojeda, 2004). During the luteal phase, the period between ovulation and menses-onset, estrogen levels decrease to a moderate level until they fall sharply just before the onset of menstruation. Progesterone levels rise after ovulation, peak at the mid-luteal phase, and fall rapidly just before menstruation (Griffin and Ojeda, 2004; Terner and De Wit, 2006). Most studies addressing menstrual cycle dependent changes compare an assessment during the late follicular phase (when estrogen levels are high and progesterone levels low) and during the late luteal phase (when estrogen levels are low and progesterone levels high).

It has been established that sex hormones act on the central nervous system and influence the organization of neural circuits during the prenatal period (Collaer and Hines, 1995). Sex hormones are known to directly influence the hypothalamus and the hippocampus: areas that are implicated in emotional processing, perception and memory, as well as in the interpretation of sensory information (Fanselow and Dong, 2010; Hines, 2010). As it becomes clearer that hormonal transition periods across the life span also affect brain organization, some neuroimaging studies have started addressing the relevance of subtle hormonal fluctuations across the menstrual cycle on brain architecture and connectivity. However, in most cases, the menstrual cycle is entered to statistical analyses as a nuisance regressor (Lonsdorf et al., 2011), or controlled for by only testing male samples (Karama et al., 2011).

In the few instances that the menstrual cycle phase was the primary research aim, typically the research focused on cognitive domains, using mental rotation or language tasks (Masters and

Sanders, 1993; Fernandez et al., 2003; Schoning et al., 2007; Pletzer et al., 2011). Few studies investigated the impact of the menstrual cycle on the interplay of emotion and cognition. This lack of knowledge is striking, considering the many interwoven aspects of emotion and cognition. The findings summarized hereafter (for a detailed overview see **Table 1**) show that menstrual cycle phase affects the reaction to emotional stimuli and reward, as evidenced by behavioral biases in reaction time and neural activation. In line with this evidence, the menstrual cycle also appears to impact a neural network implicated in cognitive control of emotion. This evidence suggests that the menstrual cycle should be considered as a modulating factor when examining the behavioral and neural response to emotional information. The unique combination of sex hormones in different phases of the menstrual cycle may assist in furthering our understanding of inter- and intra-individual differences in emotional reactions.

NEUROPLASTIC CHANGES IN THE HUMAN BRAIN ACROSS THE MENSTRUAL CYCLE

As evidence for short-term modification of brain plasticity is growing, we continue to adapt our understanding of how brain structure is organized throughout the lifespan. With proliferating documentation supporting a substantially less rigid architecture of the brain than previously hypothesized, identifying the mechanisms that drive neuroplastic modification has become a major focus of interest. Among those factors that are discussed to induce such neuroplastic changes are deliberate training (Draganski et al., 2004), exercise (Taubert et al., 2011), stress (Liston et al., 2009), as well as hormones (Baroncini et al., 2010).

MENSTRUAL CYCLE DEPENDENT CHANGES IN STRUCTURAL AND FUNCTIONAL CONNECTIVITY: IMPACT ON EMOTION AND COGNITION INTERACTION

The subtle hormonal fluctuations induced by the menstrual cycle have been explored as potential neuroplastic factors in a few neuroimaging studies at rest. A voxel based morphometry (VBM) study comparing women suffering from cyclic menstrual pain with peri-ovulatory cycle-matched healthy women found substantial brain morphological changes in brain regions implicated in pain transmission but also in affect regulation and top-down modulation of negative affect including the medial prefrontal cortex (mPFC), the anterior/dorsal posterior cingulate cortex (ACC/dPCC), hippocampus, hypothalamus and insula (Tu et al., 2010). A pilot within-subject positron emission tomography (PET) study reported significantly higher glucose metabolism for the mid-follicular menstrual cycle phase in thalamic, prefrontal, temporo-parietal and inferior temporal regions whereas during the mid-luteal menstrual cycle phase increased glucose metabolism in superior temporal, anterior temporal, occipital, cerebellar, cingulate and anterior insular regions was found (Reiman et al., 1996). In a second preliminary VBM study, a change in overall brain size according to menstrual cycle phase, more specifically an increase in gray matter and loss of cerebral spinal fluid (CSF) during the time of ovulation, was found (Hagemann et al., 2011). This brain volume change could be associated with progesterone levels and also correlated, after excluding one outlier, with the estradiol rise prior to ovulation.

A volumetric MRI study including twenty-one women in an intra-individual design reported an increase in the right anterior hippocampus in the late follicular versus the late luteal menstrual phase (Protopopescu et al., 2008a). The hippocampus has been implicated in self-referencing during recall and prospection (Muscatell et al., 2010), the formation of emotional memories (Eisenberger et al., 2007) and the processing of facial expressions (Critchley et al., 2000; Fusar-Poli et al., 2009). Traditionally often referred to as the "memory-region," the hippocampus has recently been discussed as a crucial integrator of emotion and cognition (Small et al., 2011). Particularly the caudal/ventral hippocampal region (corresponding to anterior in primates) has been linked to controlling the hormonal stress response via the hypothalamic-pituitary-adrenal axis. In addition, smaller hippocampal size and deficient function were related to psychopathologies characterized by maladaptive emotional behavior, such as depression, post-traumatic stress disorder and bipolar disorder, whose drug treatment impact hippocampal structure and function (Fanselow and Dong, 2010).

Proptopopescu and colleagues (Protopopescu et al., 2008a) further reported a volumetric decrease in the dorsal basal ganglia during the late follicular menstrual phase. A trend for a neurochemical change in the basal ganglia was observed to fluctuate with the menstrual cycle as a secondary finding in a PET-study exploring sex- and age-differences in dopamine receptors: lower D2 binding in the late follicular menstrual cycle phase was detected but did not meet the threshold for statistical significance (Wong et al., 1988). While the authors acknowledged the preliminary character of their dataset comprised of six healthy women, they made the interesting point that the signal observed was present in each of the six subjects.

CHANGES IN THE REWARD-RELATED NEURAL SYSTEM ACROSS THE MENSTRUAL CYCLE

Dopamine represents a key regulator in the integration of cognitive and emotional information processing in the basal ganglia and has been implicated in synaptic plasticity. If these preliminary findings can be replicated in a larger sample, this would argue for the menstrual cycle to impact a major neurochemical axis relevant to numerous neuropsychiatric diseases that display sex-disparity, such as attention deficit disorder, schizophrenia, addiction, and Parkinson's. Recent fMRI results corroborate the link between dopamine and the menstrual cycle: performance in a working memory task increased with dopaminergic transmission rate (indicated by catechol-O-methyltransferase, COMT, enzyme activity) in the late follicular phase but decreased with dopaminergic transmission rate in the early follicular phase and could be predicted by activation of PFC in both conditions (Jacobs and D'Esposito, 2011). These findings suggest that the hormonal fluctuations caused by the menstrual cycle set the stage for a dynamic modulation of cognition and emotion by dopaminergic transmission.

In addition to the above-mentioned roles in cognitive and emotional processes, dopamine is involved in mediating reward. To directly examine the notion that the reward system is influenced by menstrual cycle phase, a study exploring monetary reward in a counter-balanced intra-individual design collected

Table 1 | Summary of imaging studies exploring the impact of the menstrual cycle on neuroplastic changes of relevance to the interplay of emotion and cognition.

Study	Number of subjects	Design	Time of menstrual cycle assessed	Imaging modality	Main findings
Protopopescu et al., 2008a,b	21	Within-subject, two time-points per subject	Late follicular phase Late luteal phase	VBM-MRI	Right anterior hippocampus (GM-increase) Right dorsal basal ganglia (GM-decrease)
Tu et al., 2010	32 vs. 32	Healthy control group vs. PDM subjects	Peri-ovulatory phase	VBM-MRI	Medial prefrontal cortex (mPFC), insula (GM-decrease). Anterior/dorsal posterior cingulate cortex (ACC/dPCC), hippocampus, hypothalamus, (GM-increase)
Hagemann et al., 2011	8 Note: association with estradiol found in 7 women	Within-subject, two time-points per subject	Early follicular Mid-luteal phase	VBM-MRI	Global GM-volume increase, volume loss in CSF during ovulation
Dreher et al., 2007	13 healthy regularly cycling women	Within-subject, two time-points per subject	Mid-follicular Mid-luteal	fMRI during a monetary reward task	Enhanced activation in the amygdala and the OFC during mid-follicular; Enhanced activation in the DLPFC and the dACC during mid-luteal
Protopopescu et al., 2008a,b	8 PMDD; 12 asymptomatic women	Within-subject, two time-points per subject	Late-follicular Late-luteal	fMRI during a Go/No-go task	Late luteal vs. late follicular: PMDD women showed reduced activation in medial OFC and ventral striatum, and enhanced activation in the amygdala and the lateral OFC, compared to healthy controls
Jacobs and D'Esposito, 2011	24 healthy regularly cycling women	Within-subject, two time-points per subject	Early follicular Late-follicular	Behavioral and fMRI	COMT activity has been shown to drive the direction of the effect estrogen had on working memory
Ossewaarde et al., 2011	28 healthy regularly cycling women	Within-subject, two time-points per subject	Late-follicular Late-luteal	fMRI during a delayed incentive monetary reward task	Enhanced ventral striatal activation in the late luteal compared to the late follicular phase
Mareckova et al., 2012	10 healthy regularly cycling women	Within-subject, two time-points per subject	Early follicular (perimenstrual) Late-follicular	fMRI during passive viewing of faces (angry vs. moving circles; ambiguous faces vs. moving circles)	Stronger BOLD response to angry faces in the right FFA, left IFG, left temporal gyrus; and to ambiguous faces in the right STS, bilateral IFG, right lingual gyrus, in late follicular compared to early follicular (perimenstrual) phase

(Continued)

Table 1 | Continued

Study	Number of subjects	Design	Time of menstrual cycle assessed	Imaging modality	Main findings
Reiman et al., 1996	10	Within-subject, two time-points per subject	Mid-follicular phase	FDG-PET	Higher glucose metabolism in thalamus, prefrontal, temporo-parietal, inferior temporal cortex
			Mid-luteal phase		Higher glucose metabolism in superior temporal, anterior temporal, occipital cortex, cerebellum, cingulate, anterior insula

Note: CSF, cerebral spinal fluid; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FDG, [^{18}F]-fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; GM, gray matter; OFC, orbitofrontal cortex; FFA, fusiform face area; IFG, inferior frontal gyrus; STS, superior temporal sulcus; PDM, primary dysmenorrheal; PET, positron emission tomography; PMDD, pre-menstrual depressive disorder; VBM, voxel based morphometry.

fMRI data in thirteen healthy women (Dreher et al., 2007): The authors found greater blood-oxygen-level-dependent (BOLD) response in the amygdala, the orbitofrontal cortex (OFC), midbrain and the striatum during the mid-follicular phase, brain areas that are highly inter-connected both anatomically and functionally and that are key for autonomic control, emotional processing and reward. A possible interpretation of these findings may be a more responsive reward system shortly before ovulation. Complementary neuroimaging work on the dopaminergic system in 28 healthy women also revealed differences in mesolimbic incentive processing at distinct times of the menstrual cycle (Ossewaarde et al., 2011). Applying a monetary reward incentive delay task, the authors could show an enhanced ventral striatal response in the late luteal versus the late follicular phase and suggest that changes in functioning of mesolimbic incentive processing circuits may underlie premenstrual increases in normal and abnormal motivated behaviors such as food and drug cravings (Ossewaarde et al., 2011).

CYCLE-DEPENDENT BIASES IN EMOTIONAL CONTROL

As noted, Dreher et al. (2007) found altered functional activity in the DLPFC and dACC during the mid-luteal phase. These brain regions have important roles in the control of emotional interference to cognitive performance. Recent findings (Mareckova et al., 2012) report stronger BOLD fMRI responses during passive viewing of ambiguous and angry faces (compared to control stimuli) in neural regions related to emotion processing and control, when comparing the mid-cycle and the menstrual phases in freely-cycling women. These regions included the right superior temporal sulcus, bilateral inferior frontal gyrus (IFG), and the right lingual gyrus for ambiguous faces, and the right fusiform face area (FFA), the left IFG, and the left middle temporal sulcus for angry faces. Stronger activation in the right FFA was also found when comparing women taking oral contraceptives compared to controls, and were further replicated in a group of 110 adolescent girls. In line with these findings, several studies showed an impact of the menstrual cycle on the ability to control emotional behavior. Specifically, it was suggested that biased processing of information during the late luteal phase facilitates symptoms of premenstrual depressive disorder (PMDD) (Cunningham et al., 2009). PMDD patients have been shown to demonstrate a luteal phase–dependent negative bias in facial emotion discrimination (Rubinow et al., 2007). This processing bias is in line with higher negative affect and impaired cognitive performance, particularly in memory tasks, in PMDD women during the late luteal phase (Reed et al., 2008). Protopopescu et al. (2008b) used an emotional modification of a Go/No-go inhibitory task in an fMRI experiment: women with PMDD showed enhanced processing of negative information, decreased processing of positive information, and diminished inhibitory control, especially in the context of negative information. Furthermore, these findings were accompanied by reduced activation in medial orbitofrontal cortex (mOFC) and ventral striatum, and enhanced activation in the amygdala and the lateral orbitofrontal cortex, in PMDD subjects versus controls, when comparing the late follicular and the late luteal cycle phases. These findings suggest reduced top-down inhibition of negative information in the late luteal phase in PMDD.

CHALLENGES AND QUESTIONS

Exacerbation of psychiatric illness has been associated with phases of steep sex hormonal fluctuations (Soares and Zitek, 2008). Several studies demonstrate the impact of such substantial hormonal change on several cognitive and affective domains (Greendale et al., 2010; Ladouceur, 2012; Workman et al., 2012). For the interaction between more subtle sex hormone fluctuations, such as the menstrual cycle, and mood-regulation, reports have been more controversial (Romans et al., 2012). However, one cannot draw the conclusion that the menstrual cycle has no role in the interplay of emotion and cognition from the observation that many studies in this emerging field have been underpowered or methodologically inconsistent. With regards to such methodological inconsistencies, it would be helpful to introduce to the field some sort of standardization to confirm regular menstrual cycles and ovulation of participants. Urine ovulation kits or blood

samples demonstrating the pre-ovulatory LH/FSH surge could provide this information in order to ensure that subjects indeed go through the hormonal fluctuation characteristic of a regular menstrual cycle.

A major challenge reviewing the neuroimaging evidence for the impact of the menstrual cycle on brain regions is the lack of consistency in timing of assessment. With a few exceptions, most of the work reviewed did follow an intra-individual design comparing two or more menstrual cycle phases. Most studies included a comparison between follicular and luteal cycle phase, however both of these phases are approximately 12–14 days in length. As reviewed here, the choice to look at an early follicular time (when both estrogen and progesterone levels are low) or at a late follicular time (when progesterone levels are still minimal but estrogen levels are highest) is likely going to impact the results and can make it hard to evaluate data collected at different times.

One approach that has been taken by many in the endeavor to study the impact of sex hormones on the interplay of emotion and cognition is analyzing the correlations between hormone level and a neuroimaging parameter, such as changes in BOLD signal in emotional processing circuits. However, these reports tend to be difficult to interpret since a specific sex hormone can impact neurotransmitter-signaling differently in different states of hormonal environment. For example, data in rodents, primates, and humans have demonstrated that estrogen modulates behavioral sensitization to cocaine differently in the presence of progesterone than in the absence of progesterone (Evans and Foltin, 2010). The menstrual cycle thus provides a unique natural set-up to study the interactions of sex hormones in synergy and move beyond looking at simple correlations.

CONCLUSION AND PERSPECTIVES

To summarize, studies have provided preliminary evidence for neuroplastic changes across the menstrual cycle, including the striatum, thalamus, hippocampus, insula, hypothalamus, amygdala, ACC, frontal cortex (OFC, DLPFC) and parietal areas. Most of these regions have substantial roles in the perception, processing or regulation of responses to emotional information. Menstrual cycle-dependent changes have also been demonstrated in reward-related behavior and to interact with dopaminergic transmission. Different patterns of neural activation have been found in women with clinical premenstrual mood change, also pointing to an influence of sex hormones on the neural activation related to cognition-emotion interaction. While the data are still sparse and substantial methodological differences have to be accounted for, it is likely that the subtle hormonal fluctuations that characterize the menstrual cycle modulate emotional behavior in women during their reproductive years.

The neural networks mediating cognition-emotion interactions are a topic of a long and on-going debate. Based on advanced analysis of neuroimaging data, Pessoa (2012) emphasized the interactions between evaluative and control sites as mediators of the impact of cognition on emotional perception. In line with this network view, effects of cognitive load on emotional processing were shown in fronto-parietal attention regions (Culham et al., 2001; Schwartz et al., 2005; Bishop, 2008; Tomasi et al., 2011) as well as limbic (Van Dillen et al., 2009) and sensory regions (Muggleton et al., 2008). Sex hormones are known to influence a number of neurotransmitters implicated in the regulation of cognition and affect, including acetylcholine, serotonin, dopamine, and norepinephrine (Genazzani et al., 1997; Mitsushima, 2010). Functional consequences of genetic polymorphisms in those neurotransmitter-systems need to be considered for the interaction between neurochemical environment and hormonal states in the brain. Genetic vulnerabilities for anxiety and depression in the serotonergic system (Lesch et al., 1996) may relate to the differential response across women to antidepressant treatment targeting the serotonin transporter. The enzyme metabolizing dopamine, catechol-O-methyltransferase (COMT), accounts for the majority of dopaminergic turnover in the PFC (Mannisto and Kaakkola, 1999). For COMT, carriers of the variant met/met (opposed to the met/val allele variant) showed better performance in an executive task and displayed enhanced PFC activation (Egan et al., 2001). Furthermore, COMT activity has been shown to drive the direction of the effect estrogen had on working memory (Jacobs and D'Esposito, 2011). The integration of epigenetic information to neuroimaging data across the menstrual cycle will be important in characterizing the functional consequences of genetic polymorphisms that are implicated in these neurochemical underpinnings of emotion and cognition.

Studies in healthy women during their reproductive years are no substitute for directly studying mood disorders associated with the menstrual cycle, such as PMDD. They do, however, provide an important framework to build upon as confounding factors like comorbidities can be excluded. For intervention studies it will be necessary to include clinical populations. The exploration of neural patterns in the emotional circuits that can be associated with techniques such as cognitive behavioral therapy (CBT) (Goldapple et al., 2004) and mindfulness stress reduction (Schwartz et al., 1996) in order to provide helpful alternatives or add-ons to psychopharmacological interventions in PMDD are promising new research directions. However, research on the menstrual cycle and the interplay of emotion and cognition has a broader scope than menstrual-cycle related disorders. An interaction of reproductive hormones and neuroplasticity has been reported for diseases that can generate abnormalities in emotional processing and social cognition, like multiple sclerosis (Tomassini et al., 2005) Alzheimer's (Pike et al., 2009) and migrane (Gupta et al., 2011). Furthermore, we know that treatment responses can differ immensely between the sexes, and within different hormonal states (Lukas et al., 1996; Justice and De Wit, 1999; Evans and Foltin, 2010).

In conclusion, the emerging research field of neuroimaging the menstrual cycle has already contributed many clinically relevant insights into powerful interactions between sex hormones and neural processes in emotion and cognition. While the majority of endocrinological neuroimaging research has focused on the role of estrogen on traditional aspects of cognition, more studies start to address the interwoven processing of emotion and cognition. The menstrual cycle provides a natural set-up to do so and it will be critical for the interpretation of studies across imaging centers to confirm the endocrine status on each test day of women undergoing a scanning protocol during their reproductive years.

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Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity

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Stressful experiences modulate neuro-circuitry function, and the temporal trajectory of these alterations, elapsing from early disturbances to late recovery, heavily influences resilience and vulnerability to stress. Such effects of stress may depend on processes that are engaged during resting-state, through active recollection of past experiences and anticipation of future events, all known to involve the default mode network (DMN). By inducing social stress and acquiring resting-state functional magnetic resonance imaging (fMRI) before stress, immediately following it, and 2 h later, we expanded the time-window for examining the trajectory of the stress response. Throughout the study repeated cortisol samplings and self-reports of stress levels were obtained from 51 healthy young males. Post-stress alterations were investigated by whole brain resting-state functional connectivity (rsFC) of two central hubs of the DMN: the posterior cingulate cortex (PCC) and hippocampus. Results indicate a 'recovery' pattern of DMN connectivity, in which all alterations, ascribed to the intervening stress, returned to pre-stress levels. The only exception to this pattern was a stress-induced rise in amygdala-hippocampal connectivity, which was sustained for as long as 2 h following stress induction. Furthermore, this sustained enhancement of limbic connectivity was inversely correlated to individual stress-induced cortisol responsiveness (AUCi) and characterized only the group lacking such increased cortisol (i.e., *non-responders*). Our observations provide evidence of a prolonged post-stress response profile, characterized by both the comprehensive balance of most DMN functional connections and the distinct time and cortisol dependent ascent of intra-limbic connectivity. These novel insights into neuro-endocrine relations are another milestone in the ongoing search for individual markers in stress-related psychopathologies.

Keywords: fMRI, resting-state functional connectivity, default-mode network, recovery, limbic connectivity

INTRODUCTION

Psychological stress is prevalent and strongly related to mental illnesses. The brain mediates stress responses and thus influences the individual's capacity to cope with them. Such coping depends on functions manifesting during several stages of the stress response, evolving gradually from early disturbances to later recovery and homeostasis restitution; processes that ultimately support the link between stress and psychopathology (McEwen, 2004; Yehuda and LeDoux, 2007). These processes may involve various internally-driven mental processes, such as drawing on past experiences and envisioning future events, known to increase during resting-state (Gruberger et al., 2011) and are therefore expected to be mediated by the default mode network (DMN) (Greicius et al., 2003; Buckner and Carroll, 2007). The DMN, defined as a cluster of regions deactivated during task performance and activated at rest, includes mainly the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), inferior parietal lobule (IPL) and the hippocampal formation (Buckner et al., 2008). The relevance of integrated DMN activation during rest to stress-related psychopathology has been demonstrated by abnormal DMN connectivity in post-traumatic stress disorder (Bluhm et al., 2009; Rabinak et al., 2011) and depression (Greicius

et al., 2007). Monitoring changes in resting-state functional connectivity (rsFC) was established as a tool for the identification of whole brain spontaneous co-activation clustering in functional magnetic resonance imaging (fMRI) (Fox and Raichle, 2007). Previous research highlights the importance of rest to mental homeostasis by demonstrating that cognitive and affective tasks have prolonged affects on neural activity at rest (Waites et al., 2005; Pyka et al., 2009; Eryilmaz et al., 2011). Therefore, it is reasonable to expect that stress will also show similar traces. Indeed, recent studies demonstrated modified amygdala rsFC, up to 1 h following stress (Van Marle et al., 2010; Veer et al., 2011). Despite preliminary evidence for the effect of stress on rsFC, the chronometry of such effects remains relatively limited and poorly specified.

The present study examined the chronometry of stress-rsFC relationships using three "rest" conditions: before stress induction, immediately after, and following a 90 min recess outside the scanner. Stress elicitation was achieved using a documented procedure for the induction of social stress via arithmetic calculations, monitored on-line (Wang et al., 2005, 2007; Gray et al., 2007). We selected two core DMN hubs as seeds for rsFC analyses; the PCC and hippocampus (Greicius et al., 2004; Buckner et al., 2008). The PCC has been documented as a pivotal node of the DMN that directly interacts with all other network nodes (Fransson and Marrelec, 2008; De Pasquale et al., 2012). Furthermore, both the hippocampus and PCC have been previously shown to be involved in stress responsiveness (Pruessner et al., 2008). Finally, we repeatedly measured subjective stress intensity, heart rate (HR), and cortisol levels.

We anticipated a decline in the stress response by the third rest condition, 2 h post stressor-task, generating rsFC patterns similar to those observed at baseline. We further hypothesized that recovery dynamics for rsFC with the hippocampus, an area supporting affective memory of the stressful experiences, would differ from the dynamics in other regions, and be individually determined by stress indices (e.g., cortisol response, stress rating).

MATERIALS AND METHODS

PARTICIPANTS

The study was conducted on 61 healthy males (age 19–22). Participants consisted of mandatory military soldiers who volunteered to participate in our study. All participants were positioned in the same service unit, amidst the same military course, and before operational employment. Of the 61 individuals 4 were excluded from cortisol analysis due to an insufficient saliva samples and 10 were excluded from the fMRI data analysis due to signal artifacts. Participants had no reported history of psychiatric or neurological disorders, no current use of psychoactive drugs, no family history of major psychiatric disorders, and no previous exposure to abuse during childhood and/or potentially traumatic events before entering the study. In addition, all participants had normal or corrected-to-normal vision and provided written informed consent approved by Tel Aviv Sourasky Medical Center Ethics Committee and conformed to the Code of Ethics of the World Medical Association (Helsinki Declaration).

EXPERIMENTAL PROCEDURE

The experiment was performed at the Wohl Institute for Advanced Imaging in Tel Aviv. To minimize unwanted effects on cortisol levels, participants were awake for at least 3 h before arriving at the institute, and were instructed to eat breakfast and avoid further food intake, nicotine, caffeine, and exercise for at least 2 h before arrival. The study consisted of four phases: acclimation (15 min), 1st session in the MRI scanner (65 min), intermission (90 min), and a 2nd session in the MRI scanner (30 min). In the acclimation phase, participants were given a 15-min resting period, signed the informed consent forms and were introduced to the experimental procedure. In the 1st session in the MRI scanner participants underwent the acute stress task. Three "rest" conditions were integrated into the study design: before the tasks ("rest 1"), immediately afterwards ("rest 2"), and at the beginning of the 2nd scanning session, following a 90 min recess outside the scanner ("rest 3"). During the intermission phase outside the scanner participants completed questionnaires and were given a light meal. In "rest" conditions (5 min each) participants were instructed to stare at a fixation point in the center of a screen.

STRESS ELICITATION TASK

Acute stress was induced via a serial subtraction arithmetic task (Wang et al., 2005), a component of the Trier Social Stress Test (Kirschbaum et al., 1993) incorporated into the scanner. Participants were instructed to continuously subtract 13 from 1022 for a period of 6 min, and respond verbally, while the experimenters monitored and communicated with each subject on-line, constantly demanding faster and more accurate performance. A timer appeared at the top left corner of the screen to indicate to the participant how much time had elapsed. The stress task was preceded by a non-stressful condition-backward counting from 1000 for a period of 6 min, without external monitoring (**Figure 1**).

PHYSIOLOGICAL AND BEHAVIORAL DATA COLLECTION

Psychological and physiological effects of stress were evaluated at 4 time points (**Figure 1**) through repeated self reports of stress levels (on a 9 point Likert scale, marked as R) and salivary cortisol sampling (marked as S), collected with a cotton swab, placed in the participants mouth for 3 min (Sarstedt, Numbrecht, Germany). Samples were stored at −20°C immediately after collection until further analyzed. Salivary concentrations of cortisol rose to peak levels 15–30 min after stress (De Kloet et al., 2005). Due to delayed peripheral response, final cortisol samples were obtained 20 min post-stress. Following peak measurements, cortisol levels gradually decline to pre-stress levels 60–90 min later (De Kloet et al., 2005). To avoid leakage of the effect, participants did not perform any additional tasks during this time interval.

ENDOCRINE DATA ANALYSIS

Salivary cortisol levels were assayed using Coat-A-Count radioimmunoassay (Siemens, Los Angeles, CA), inter- and intra-assay coefficient of variation (CV) 14.4%, 8.9%, respectively. Inter-assay % CVs of less than 15 and intra-assay % CVs of less

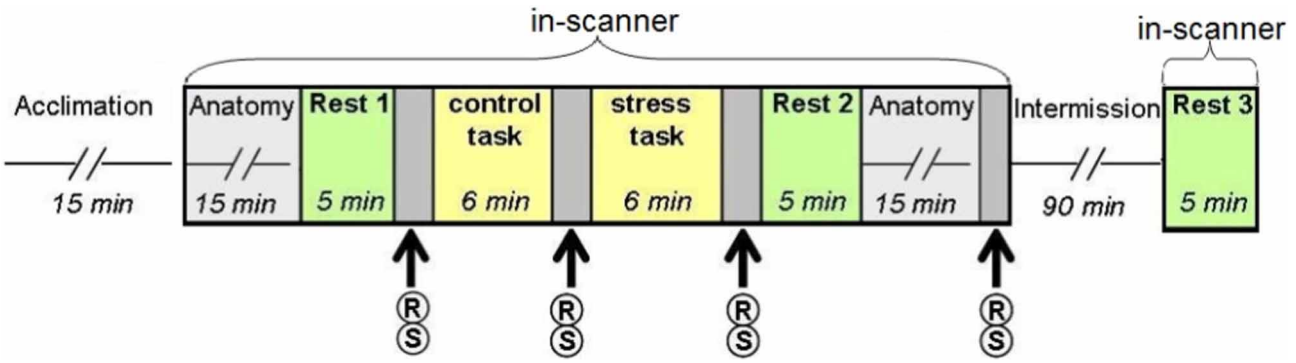

FIGURE 1 | Study design. Following the acclimation phase, participants underwent two scanning sessions: the first included two "rest" conditions interspersed with the control (backward counting) and stress (serial subtraction) tasks; the second session, following a 90 min intermission outside the scanner, included a third "rest" scan. R, report of stress level; S, salivary cortisol sampling.

than 10 are considered to indicate assays with good and reliable performance. In order to obtain a reliable measure of the individual's cortisol reactivity, in accordance to the expected gradual ascent, we calculated the area under the curve increase (AUCi) using the equation from Pruessner et al. (2003), with trapezoidal integration.

ELECTROPHYSIOLOGICAL DATA COLLECTION AND ANALYSIS

Electrocardiography (ECG) was recorded continuously during scanning via a BrainAmp ExG MRI-compatible system (BrainProducts, Munich, Germany). The sampling rate was 5000 Hz. For each participant, bipolar Ag/AgCl electrodes were attached to the right and left side of the chest. Preprocessing of the ECG signal and RR interval analysis was performed similarly to Raz et al. (2012). Briefly, gradient artifacts were removed using FASTR algorithm (Niazy et al., 2005), implemented in FMRIB plug-in for EEGLAB (Delorme and Makeig, 2004). R peaks of ECG were detected using the FMRIB toolbox, and corrected for mis-detection (maximum correction rate over participants was 5.95%) and presence of ectopic beats. Finally, RR intervals were used to derive a beats-per minute HR index. Due to motion artifacts, 44 participants were included in the final HR analysis, for which a reliable R peak signal could be detected for all conditions.

fMRI DATA ACQUISITION AND ANALYSIS

Brain scanning was performed on a 3T (GE, HDXt) MRI scanner with an 8-channel head coil. Functional imaging was acquired with gradient echo-planar imaging (EPI) sequence of T2*-weighted images (TR/TE/flip angle: 3000/35/90; FOV: 20 × 20 cm; matrix size: 96 × 96) in 39 axial slices (thickness: 3 mm; gap: 0 mm) covering the whole cerebrum. fMRI data analysis was performed with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing of the fMRI data included correction for head movements (subjects with movement above 2 mm were discarded) via realignment of all images to the mean image of the scan using rigid body transformation with six degrees of freedom, normalization of the images to Montreal Neurological Institute (MNI) space by co-registration to the EPI MNI template via affine transformation, and spatial smoothing of the data with a 6 mm FWHM. Finally, the first 6 images of each functional resting scan were rejected to allow for T2* equilibration effects. Seed regions of interest (ROIs); the bilateral PCC and bilateral hippocampus, were defined anatomically and additionally masked to include gray matter only using the WFU Pick Atlas Tool (Maldjian et al., 2003, see also Stamatakis et al., 2010). To examine rsFC between seed ROIs and the whole brain, BOLD signal was filtered to low frequency fluctuations (0.01–0.08 Hz) using DPARSF toolbox (Chao-Gan and Yu-Feng, 2010). A mean time series across voxels in the seed ROIs was calculated for each participant using the MarsBaR software package (http://marsbar.sourceforge.net). GLM analyses were then performed between the ROI time series and the time series for each brain voxel. To reduce the effect of the physiological artifacts and nuisance variables, the whole-brain mean signal, six motion parameters, cerebrospinal fluid, and white matter signals were introduced as covariates in the design matrix (Chao-Gan and Yu-Feng, 2010).

First, random effect group analysis (RFX) was used to identify regions that altered connectivity to the seed ROIs when comparing rest conditions before and immediately after the stressful manipulation. In this RFX analysis a one sample *t*-test was applied to the images of contrast between the two rest sessions of all subjects (i.e., random subject effects with fixed condition effects). Next, these connectivity alterations were further explored in the third rest condition. Statistical maps for the PCC seed were corrected for multiple comparisons (FDR < 0.05) and the Statistical maps for the hippocampus seed were set at a threshold of $p < 0.001$, small volume corrected (with a cluster size of at least 20 voxels). The resulting brain areas were anatomically validated with the WFU Pick Atlas Tool. Beta weights were extracted and averaged across all voxels within each functional area that altered connectivity to the seed ROIs.

PSYCHOLOGICAL ASSESSMENT

Participants were asked to complete a self-report questionnaire to assess trait anxiety the State Trait Anxiety Inventory-Trait Version (STAI-T) (Spielberger, 1983).

STATISTICAL ANALYSES

Neural, behavioral, and physiological measures were statistically analyzed using repeated-measures ANOVA (STATISTICA 7) to assess the effect of the experimental condition. The correlations between brain measures and individual cortisol response (AUCi) were assessed using Pearson's regression analysis followed by a hierarchical multiple regression (STATISTICA 7).

RESULTS

BEHAVIORAL AND PHYSIOLOGICAL MEASURES OF STRESS INDUCTION

All measures of stress induction revealed a general effect of stress-elicitation at the group level. Specifically, a main effect of time was found for subjective ratings of stress [$F_{(3,\ 180)} = 17.562$, $p < 0.001$]; Fisher's least significant difference (LSD) *post-hoc* analyses revealed an increase in ratings in response to stress (R3) as compared to the two previous measures (R1 and R2, both p's < 0.001), and a decline to baseline following the second rest period (R4, $p < 0.001$, **Figure 2A**). The means and standard deviation (in parenthesis) of R1, R2, R3, and R4 were 3.69 (1.82), 4.21 (1.96), 5.34 (1.9), and 4.08 (2.39), respectively. Notably, the four measures of subjective stress were within the normality range (values of Skewness and Kurtosis were within the range of ±2 standard errors). For salivary cortisol a marginally significant main effect of time was found [$F_{(3,\ 171)} = 2.4579$, $p = 0.064$; 4 participants were excluded from cortisol analysis due to insufficient saliva samples], according to *post-hoc* analysis, we found a marginally significant peak in cortisol level in the final sample (S4) as compared to post "rest 1" sample (S1, $p = 0.057$). In accordance with stress literature, two distinct cortisol groups emerged in response to stress: *responders*, who were defined by an increase of at least 1.5 nmol/L and a 15% rise from pre-stress levels (suggested earlier by Fehm-Wolfsdorf et al., 1993; Lupien et al., 1997; Schwabe et al., 2008) (38% of participants, $n = 22$); and *non-responders*, who showed no change or diminished cortisol level (62% of participants, $n = 36$). The analysis of cortisol levels at the 4 time periods by cortisol response groups revealed a main effect of group [$F_{(1,\ 56)} = 9.64$, $p < 0.001$], an effect of time of measurement [$F_{(3,\ 168)} = 9.14$, $p < 0.001$] and a significant interaction [$F_{(3,\ 168)} = 34.81$, $p < 0.001$]. For the *responders* group, Fisher's LSD *post-hoc* comparison revealed a significant increase in cortisol level 20 min following stress-induction (S4) relative to all previous levels (p's < 0.001), and an increase post stress (S3) relatively to control (S2, $p < 0.01$). Whereas, a significant decrease in cortisol was found for *non-responders* at the two post stress measurements (S3, S4) relatively to post "rest 1" (S1) (both p's < 0.005, **Figure 2B**, red and blue, respectively). A significant difference between groups was found for post stress sample (S3, $p < 0.05$) and final sample (S4, $p < 0.001$). The means and standard deviation (in parenthesis) of S1, S2, S3, and S4 for cortisol *responders* (in nmol\lL) were 7.35 (2.13), 6.93 (2.42), 8.69 (4.10), and 10.81 (4.65), respectively. Means and standard deviation for cortisol *non-responders* were 6.46 (4.39), 5.83 (4.01), 5.08 (3.50), and 4.88 (3.02), respectively.

Finally, HR (beats per minute) analysis also revealed a main effect of time [$F_{(3,\ 129)} = 38.88$, $p < 0.001$; 44 participants with a reliable R peak signal were included in this analysis]; Fisher's LSD *post-hoc* analyses revealed an increase in HR in response to stress, as compared to pre-stress conditions ($p < 0.001$), and a decrease to initial levels during the second rest period ($p < 0.001$, **Figure 2C**). The means and standard deviation (in parenthesis) of the 4 HR measures (in bpm) were 57.97 (9.36), 65.25 (10.44), 69.39 (9.60), 58.99 (9.82), respectively. One of the 44 subjects included in HR analysis had no sufficient cortisol

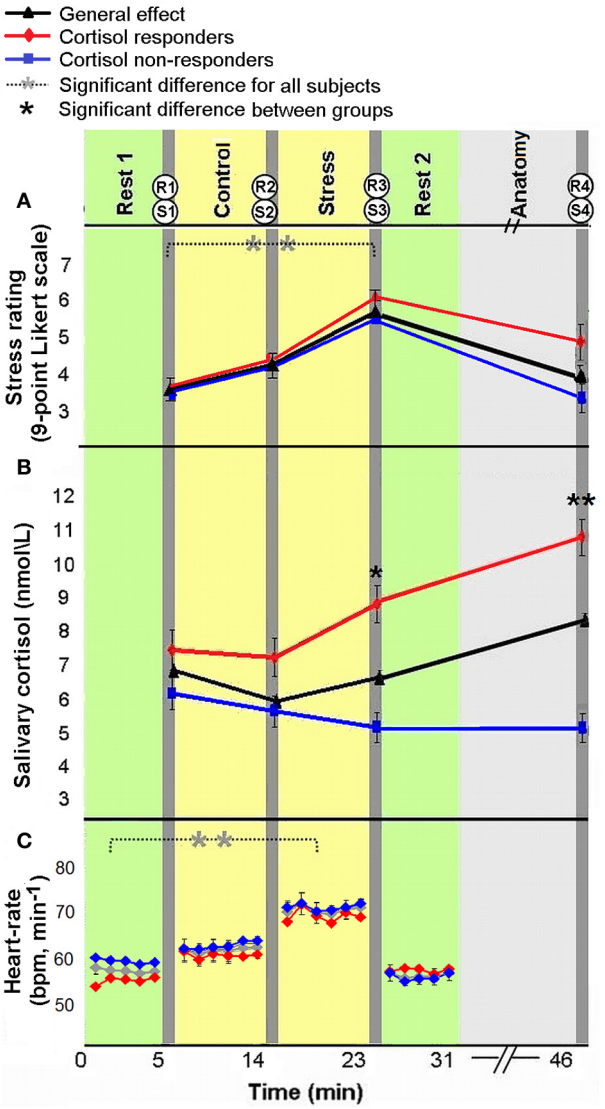

FIGURE 2 | Physiological and psychological response to stress. Subjective ratings of stress **(A)**, average salivary-cortisol level **(B)**, and heart rate (HR, bpm) **(C)** presented in reference to the time course of the experiment. Time 0 indicates the start of experiment. The yellow columns represent control and stress tasks (6 min each), green columns represent "rest" conditions (fixation, open eyes, 5 min) and light gray column represents an anatomical scan (15 min). Between scans (dark gray columns), behavioral rating of stress [R(1–4)] and salivary-cortisol samples [S(1–4)] were taken. HR was continuously recorded. The error bars indicate standard error. *$p < 0.05$, **$p < 0.001$.

samples. Notably, as in the whole group (the 58 subjects for which we obtained reliable endocrine data), 17 of the 43 participants included in HR and cortisol analyses (39.53%) were cortisol *responders*. Importantly, in the repeated measures ANOVA analyses for HR and subjective stress measures, no significant interaction was found between group and time [$F_{(3,\ 123)} = 1.09$, $p = 0.36$; $F_{(3,\ 168)} = 2.36$, $p = 0.074$, respectively]. Additionally, *responders* and *non-responders* did not differ in measure of trait anxiety [$F_{(1,\ 56)} = 0.158$, $p = 0.69$].

EARLY-STAGE RESTING STATE MANIFESTATIONS OF STRESS

We first compared rsFC patterns with the bilateral PCC and hippocampus seed ROIs between "rest 1" and "rest 2" conditions (interspersed with the stressful arithmetic task), localizing immediate post-stress rsFC alterations. Peak voxels and corresponding *T*-values for all locations of the significant clusters are presented in **Table 1**. We next probed late-stage rsFC alterations, comparing "rest 2" (immediately following the stressor) and "rest 3" (2 h following the stressful task).

Figures 3, **4A** demonstrate rsFC to the seed ROIs in the three rest conditions, in reference to the timeline of the experiment. Results from the first comparison indicate six brain areas that alter time course coupling to the PCC between "rest 1" and "rest 2" (**Table 1A**; **Figures 3A–F**, right hand side). The mPFC, thalamus, caudate nucleus and IPL increased their connectivity with the PCC following stress, whereas the posterior insula and lingual gyrus decreased their connectivity with the PCC; all regions showed bilateral effects. Two areas altered their rsFC with the hippocampus seed between "rest 1" and "rest 2," the left amygdala and right middle temporal gyrus (MTG), both of which increased their connectivity with the hippocampus following stress (**Table 1B**; **Figure 4A**).

Table 1 | (A) Peak voxels and corresponding *T*-values for regions that show altered rsFC with the PCC seed in the following contrasts; **(B)** Peak voxels and corresponding *T*-values for regions that show rsFC with the bilateral hippocampus in the following contrasts.

	Hem	MNI coordinates			*t*-value
		x	*y*	*Z*	
(A) "REST 2" > "REST 1" CONTRAST					
Inferior parietal lobule	R	54	−63	39	3.89**
	L	−45	−69	42	4.03**
Thalamus	R	15	−12	18	5.09**
	L	−3	−12	12	4.58**
Caudate nucleus	R	9	0	15	5.08**
	L	−12	0	12	5.15**
Medial PFC	R	3	54	6	4.59**
"REST 1" > "REST 2" CONTRAST					
Posterior insula	R	36	−24	15	4.93**
	L	−42	−30	18	3.86**
Lingual gyrus	R	15	−51	−9	4.7**
	L	−15	−57	−9	4.58**
(B) "REST 2" > "REST 1" CONTRAST					
Amygdala	L	−21	−3	−21	4.85*
Middle temporal gyrus	R	42	−63	18	3.65*
"REST 1" > "REST 2" CONTRAST					
	None				

*$p < 0.001$, small volume corrected, with a cluster size of at least 20 voxels; **$p < 0.05$ (FDR corrected).

CORRELATING SUBJECTIVE STRESS SENSATION TO BRAIN MEASURES

An investigation of the relation between the psychological and neural measures of stress revealed that early-stage rsFC alterations in amygdala-hippocampal connectivity (contrasting "rest 2" and "rest 1") is significantly correlated to changes in subjective stress (last sample, R4, vs. first sample, R1; $r = 0.34$, $p = 0.025$, **Figure 4B**). Notably, no significant correlations were obtained between the change in subjective stress and the difference in connectivity found between "rest 1" and "rest 2" over the MTG, mPFC, posterior insula, IPL, thalamus, lingual, and caudate (*p*-values = 0.19, 0.24, 0.09, 0.13, 0.25, 0.88, 0.22, respectively).

Considering the correlation between amygdala-hippocampal connectivity and the subjective stress report, we also investigated the relation between task performance (measured as number of mistakes) and this change in connectivity. We found no correlation between performance and limbic connectivity ($r = -0.35$, $p = 0.120$).

PROLONG ALTERATIONS IN rsFC TO THE SEED ROIs

A repeated-measures ANOVA followed by Fisher's LSD *post-hoc* comparisons were used to detect differences between the third rest condition and the two previous ones. Regarding the PCC, when comparing "rest 3" to "rest 2," all regions presented an opposing pattern of correlation compared to the pattern found between "rest 1" and "rest 2" conditions. When comparing "rest 3" to "rest 1," no significant differences were found for PCC connectivity with all areas. Regarding the hippocampus seed, the right MTG presented the same opposing connectivity pattern when comparing "rest 3" to "rest 2." Furthermore, MTG-hippocampal connectivity in "rest 3" decreased to initial "rest 1" levels. Nonetheless, as opposed to all other functionally connected areas presented in this study, only the amygdala-hippocampal connectivity showed a clear difference between "rest 3" and "rest 1" conditions, demonstrating a sustained increase (**Table 2**).

AMYGDALA-HIPPOCAMPAL SUSTAINED rsFC CHANGE AND CORTISOL RESPONSIVENESS

The anomalous lingering rise in limbic rsFC led to the conjecture that the interactions of both the hippocampus and the amygdala with the hypothalamic-pituitary-adrenal (HPA) axis may contribute to this effect. This was explored by correlating the individual cortisol AUCi values with the degree of sustained change in amygdala-hippocampal connectivity in "rest 3" vs. "rest 1." Three participants were excluded from this analysis as outliers due to beta values exceeding ±2.5 Std from group average. Taken together, the final analyses regarding the relation between limbic connectivity and cortisol included 45 subjects. The analysis

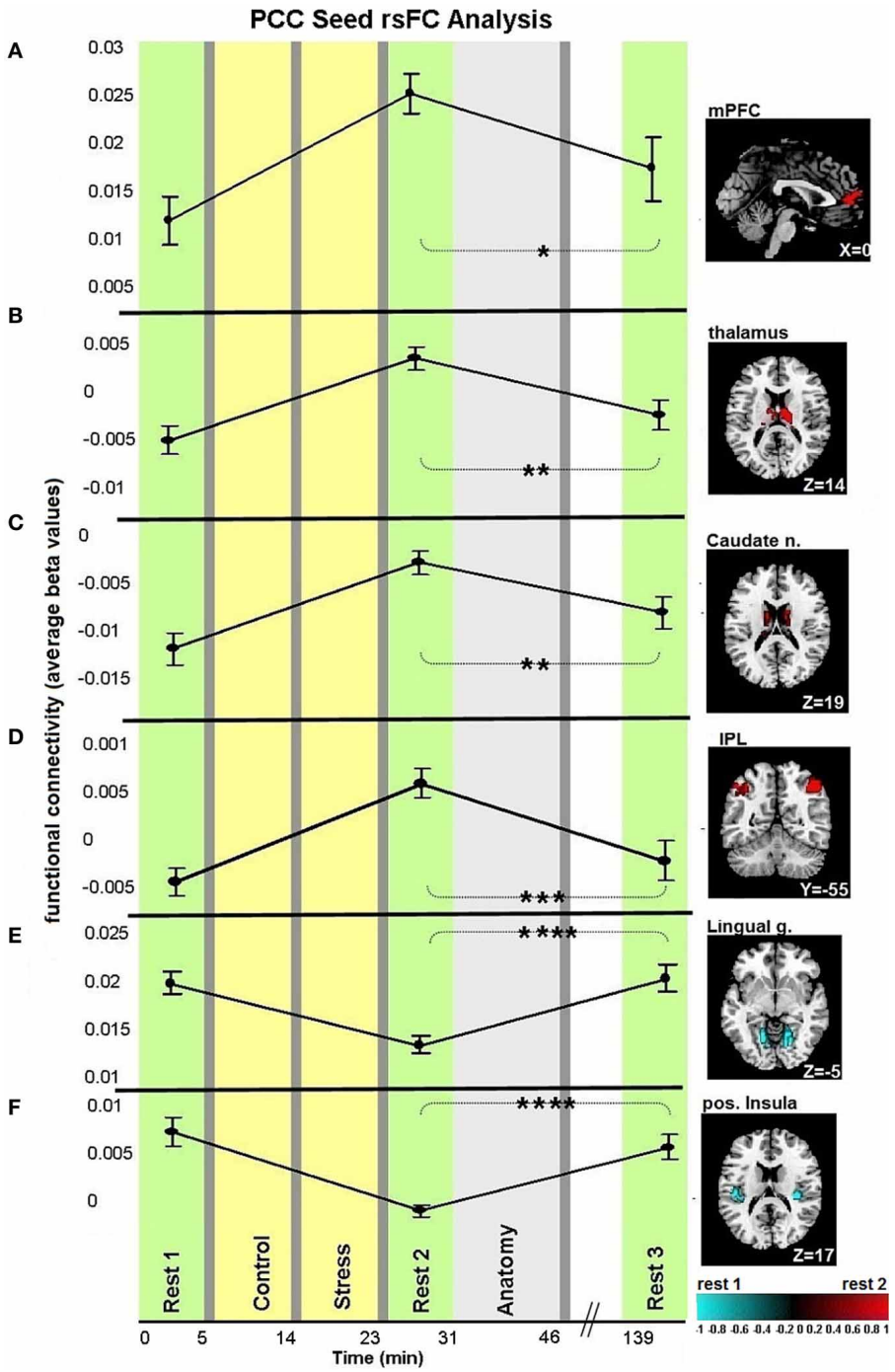

FIGURE 3 | Dynamics in rsFC to the PCC seed ROI in the three "rest" conditions. Localized areas that changed connectivity to the PCC seed **(A–F)** when contrasting "rest 1" and "rest 2" are presented on the right hand side. rsFC at "rest 1," "rest 2," and "rest 3" are presented in reference to the timeline of the experiment. Statistic maps were corrected for multiple comparisons (FDR < 0.05) *T*-score scale is shown at the bottom. Error bars indicate standard error. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. See **Table 2** for specific *p*-values.

revealed a significant negative correlation to cortisol responsiveness ($r = -0.42$, $p = 0.0049$, **Figure 5A**), suggesting that more cortisol secretion was associated with less limbic connectivity enhancement. No significant correlations were obtained between AUCi and the difference in connectivity between rest 1 and 3 over all other functional connections mentioned. We further investigated whether our behavioral measures of stress may have played a role in the sustained increase in limbic connectivity.

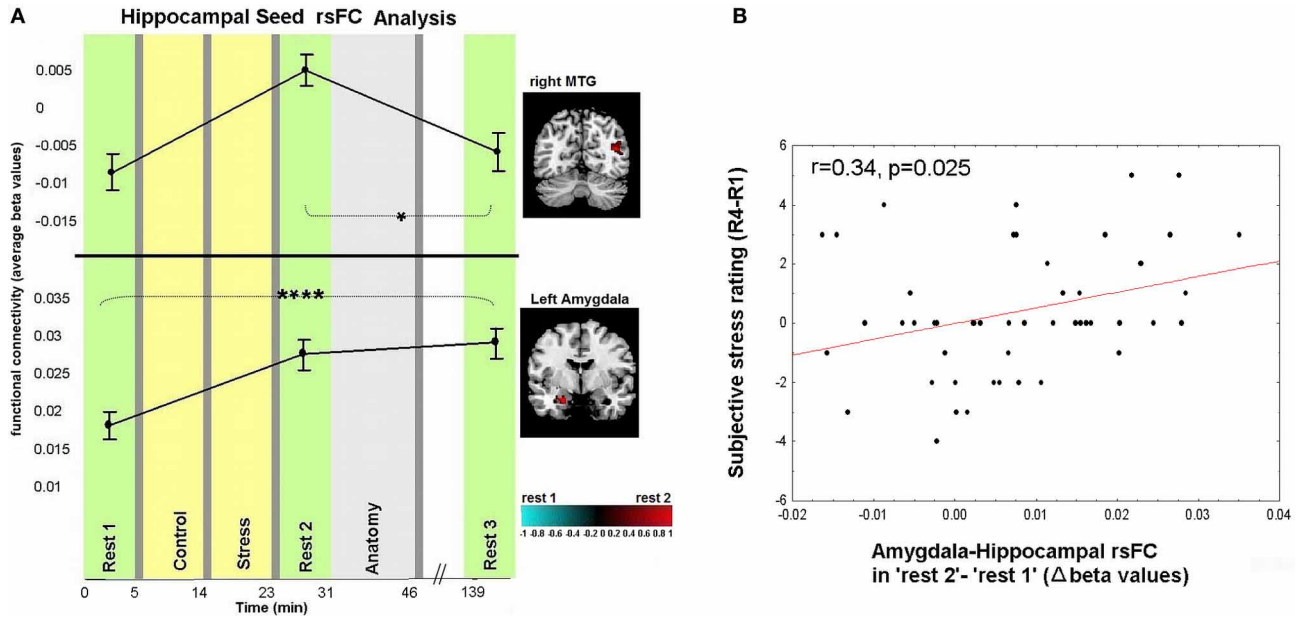

FIGURE 4 | Dynamics in rsFC to the hippocampus seed ROI and association between subjective stress and early-stage limbic connectivity. (A) Localized areas that changed connectivity to the hippocampus seed when contrasting "rest 1" and "rest 2" are presented on the right hand side. rsFC at "rest 1," "rest 2," and "rest 3" are presented in reference to the timeline of the experiment. Statistic maps for the hippocampus seed were set at a threshold of $p < 0.001$, small volume corrected (with at least 20 voxels). *T*-score scale is shown at the bottom. Error bars indicate standard error. $^{*}p < 0.05$, $^{****}p < 0.0001$. See **Table 2** for specific *p*-values. **(B)** Pearson correlation between subjective stress sensation (measured 20 min post-stress subtracting the initial rating post-"rest 1," R4-R1), and early stress-induced change in amygdala-hippocampal rsFC as measured during "rest 2" relative to "rest 1."

Table 2 | (A) Fisher's LSD *post-hoc* comparisons between rsFC with the PCC seed ROI in different rest conditions; **(B)** Fisher's LSD *post-hoc* comparisons between rsFC with the hippocampus seed in different rest conditions.

Conditions compared	"rest 3" to "rest 2" *p*-value	"rest 3" to "rest 1" *p*-value
(A)		
Bilateral inferior parietal lobule	0.0002***	0.359
Bilateral thalamus	0.0019**	0.220
Bilateral caudate nucleus	0.0077**	0.122
medial PFC	0.036*	0.106
Bilateral posterior insula	0.27×10^{-4} ****	0.385
Bilateral lingual gyrus	0.35×10^{-4} ****	0.914
(B)		
Right middle temporal gyrus	0.032*	0.187
Left amygdala	0.61	2.71×10^{-4} ****

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

A hierarchical regression was performed for predicting the change in limbic connectivity between "rest 1" and "rest 3." The regression was computed in order to assess the added value of behavioral indices to the endocrine measure (AUCi). We tested the subjective stress rating (4 rating values) and trait anxiety (STAI-T score). To note, No correlation was found between predictors (all *p*'s > 0.23). At the first step AUCi was introduced, at the second step the group was introduced, at the third step the 4 rating values, STAI-T scores and at the fifth step the interaction between group and ratings (as 4 variables composed by the product between group and each of the 4 ratings). The effect of AUCi was significant when entered alone [in the first step, $F_{(1, 41)} = 8.21$, $p = 0.007$, *R* square $= 0.167$], however, when additional variables were added (since the second step) it's unique value in the explanation of the change in limbic connectivity in "rest 3" relative to "rest 1" was no longer significant.

To further specify the early and late-stage relations of amygdala-hippocampal rsFC and the cortisol response, connectivity was investigated separately for the two groups (i.e., cortisol *responders* and *non-responders*, **Figure 5B**). Results indicated a significant interaction between the strength of the amygdala-hippocampal rsFC in the different cortisol response groups and the timing of the rest condition [$F_{(2, 86)} = 4.29$, $p = 0.016$]. Fisher's LSD *post-hoc* analysis revealed that among *responders* limbic connectivity in "rest 3" decreased to "rest 1" levels, whereas among *non-responders* a sustained rise in amygdala-hippocampal connectivity was exhibited ($p < 0.001$). Additionally, *responders* had a significantly higher amygdala-hippocampal rsFC in "rest 1" compared to *non-responders* ($p = 0.036$). In "rest 3," on the other hand there was no group difference in limbic connectivity.

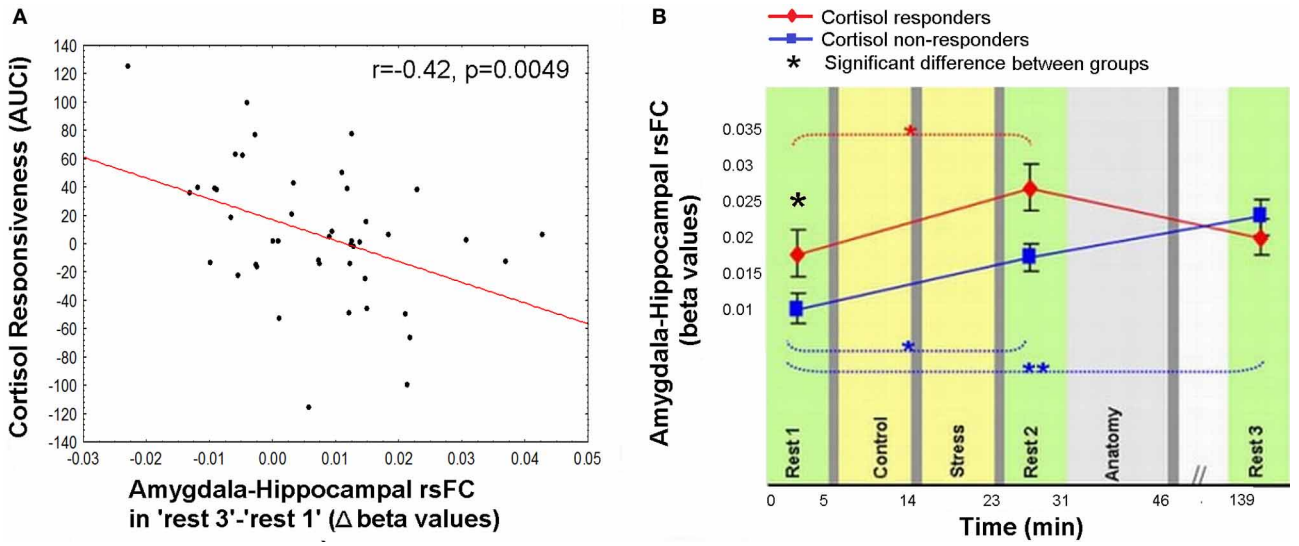

FIGURE 5 | Relation between cortisol response and prolong changes in amygdala-hippocampal rsFC. (A) Negative correlation between individual cortisol response (AUCi value) and the sustained increase in amygdala-hippocampal connectivity as measured during "rest 3" relative to "rest 1"; **(B)** amygdala-hippocampal rsFC in the three rest conditions, calculated separately for cortisol *responders* (red) and *non-responders* (blue), and presented in reference to the timeline of the experiment. Between-groups differences were found in "rest 1" and "rest 2," and within the *non-responders* group between "rest 1" and "rest 3." The error bars indicate standard error. $*p < 0.05$, $**p < 0.001$.

DISCUSSION

EARLY-STAGE ALTERATIONS OF rsFC FOLLOWING A STRESSFUL EXPERIENCE

We studied the trajectory of acute stress responsiveness in a group of 51 healthy males. As expected, our task induced stress, reflected in subjective reports and HR (**Figure 2**). Consistent with our hypothesis, both a network with a node in the PCC and a network with a node in the hippocampus showed immediate post-stress rsFC modulations (i.e., the difference between rsFC in "rest 2" vs. "rest 1"), though with different clusters of regions and dynamics. For the PCC seed, our results regarding early stage alterations indicate increased coupling with other major DMN nodes, including the mPFC and bilateral IPL, as well as with other areas (**Figure 3**). This generally extends prior work (Fransson, 2005; Jiao et al., 2011) and is consistent with suggestions of the importance of the PCC as a DMN node that directly interacts with all other network nodes (Fransson and Marrelec, 2008). Increased DMN connectivity in successive rest following a cognitive task is supported by previous studies (Waites et al., 2005; Pyka et al., 2009). Here we show the enhancement of DMN connectivity in the immediate aftermath of a socially stressful experience. Increased PCC coupling with other DMN nodes may reflect engagement of neural processes supporting self-referential mental processes and immediate reflections on the preceding stressful experience, possibly with regards to previous experiences (Fransson, 2005). Notably, modifications of coupling with the PCC occurred also in areas not included in the DMN, such as the caudate nucleus and posterior insula. These brain areas have been previously shown to have a strong presence in a PCC related network (Greicius et al., 2007; Uddin et al., 2009; Grigg and Grady, 2010). Specifically, diminished connectivity of the PCC with the posterior insula in the early aftermath of stress might reflect on the relocation of brain processing resources due to the enhanced cognitive and emotional demands related to task performance under a stressful and socially critical atmosphere.

Additionally we found increased early-stage rsFC of the hippocampus with the right MTG and left amygdala (**Figure 4A**). The hippocampal contribution to DMN has been attributed to its involvement in episodic memory (Greicius et al., 2004). The MTG has also been linked to the core DMN (Buckner et al., 2008) and thus its connectivity modification with the hippocampus might relate to the same mental reflection processes described above. The amygdala, on the other hand, is less commonly regarded as part of the DMN. In fact, amygdala-hippocampal pairing is considered a major limbic pathway for generation and regulation of emotional reaction in response to stressful stimuli (LeDoux, 2000). Support of this is shown by the correlation found between the reported subjective stress and early-stage rise in limbic connectivity (**Figure 4B**). Furthermore, enhancement in amygdala-hippocampal connectivity was suggested to be required for both emotional memory encoding and consolidation (Richter-Levin and Akirav, 2000; Roozendaal et al., 2003; Dolcos et al., 2004; Phelps, 2004; Smith et al., 2006). Taken together, we believe that the demonstrated early increase in intra-limbic connectivity may be related to the major role these two regions play in the memory processes of stressful events, encouraging future studies to address this issue.

LATE-STAGE ALTERATIONS OF rsFC FOLLOWING A STRESSFUL EXPERIENCE

Our study design enabled the identification of recovery patterns of rsFC with the PCC and hippocampus, as measured 2 h

following the period of induced stress, considered here to be late stage modulation. To our knowledge, this time window of rsFC recovery following stress has not been previously examined in humans. Notably, both increased and decreased connections to the PCC in the early aftermath of stress returned to their initial levels once the last sampling point was reached (**Figure 3**). The post-task recovery nature of the DMN has been recently demonstrated by Barnes and colleagues, who also found that a more demanding task was followed by a slower recovery pattern, as compared to an easier task (Barnes et al., 2009). This recovery occurred on a scale of minutes, yet stress was shown to induce alterations in rsFC even an hour following task performance (Veer et al., 2011). Uniquely, we demonstrate the late comprehensive recovery nature of rsFC following a documented stressful arousing experience. Our observation emphasizes the notion that the brain has the capacity to recover and restore homoeostasis over time. However, contrary to our expectations, the revealed dynamics of recovery, related to co-activation with the PCC, was neither related to subjective stress report nor to cortisol response.

On the other hand, the increase in the rsFC between the amygdala and hippocampus was sustained even 2 h after stress induction. Moreover, the lingering increase in connectivity between these two major limbic nodes was inversely related to the level of secreted cortisol in response to the stressful challenge (AUCi, **Figure 5A**). The hierarchical regression we performed pointed to the individual AUCi value as the only contributing factor to the sustained limbic connectivity. This result is in line with the attenuated positive connectivity previously found between the amygdala and the hippocampus following hydrocortisone intake (Henckens et al., 2012). In accordance with the notion that people may be grouped as cortisol *responders* and *non-responders* to induced stress, we unraveled that only the *responders* exhibited a recovery pattern of amygdala-hippocampal connectivity 2 h post-stress (**Figure 5B**). In other words, the persistently elevated limbic rsFC seemed to be selective to the group who did not exhibit increased cortisol secretion in response to acute stress. Since no difference was found between groups in repeated measure analysis of subjective stress rating and HR, we can assert, in accordance with previous studies that the cortisol effect is separate from autonomic and behavioral measures of arousal (Schwabe et al., 2008).

What might such interpersonal variability in cortisol response represent? Reciprocal interactions exist between both the amygdala and the hippocampus and the HPA-axis, which stimulates these elements and is regulated by them (Tsigos and Chrousos, 2002). The limbic network, high in glucocorticoid receptors, influences the activation of the HPA-axis, and these afferent pathways are exposed to the concentrations of the axis end-effector; cortisol (De Kloet et al., 2005). Therefore, causal factors contributing to our results may derive from both the variations in limbic connectivity and the degree of negative feedback exerted by cortisol secretion. The significantly higher limbic connectivity in the *responders* group found before the actual stress induction (in "rest 1," **Figure 5B**), might have a pivotal contribution to the tendency to increase cortisol secretion. From a reciprocal perspective, we also presume that cortisol may have played an essential role in the regulation and balance of limbic interregional connectivity in the *responders* group when the stressor has gone. Whereas the lack of increase in cortisol among the *non-responders*, may have led to the demonstrated delayed rise in limbic rsFC and possibly to slower neural recovery.

The correlation found between early-stage post-stress limbic connectivity and the subjective report of stress sensation (**Figure 4B**) led us to presume that a reduction in prolonged limbic rsFC may be an indication of a reduced sensation of stress. This assumption is in line with the study of Het and colleagues, which presented an association between cortisol and attenuated negative affect (measured by Positive and Negative Affect Schedule) in response to acute stress [TSST; (Het et al., 2012)]. However, subjective stress was not rated following "rest 3." Thus, future studies may test our proposal on the dependence between cortisol stress-induced secretion and the dynamics of neural recovery from stress, with regard to long-term psychological outcomes following stressful encounters.

Studies have shown that cortisol secretion following an arousing stimuli increases consolidation and attenuates long-term recall of emotional context, as reviewed by (Wolf, 2009); in addition, this effect is presumed to depend on the interaction between the amygdala and hippocampus (Roozendaal et al., 2003). Clinical trials suggest that post-exposure treatment with mild doses of cortisol might be beneficial in patients suffering from psychiatric conditions in which aversive memories are at the core of the problem [e.g., social phobia (Soravia et al., 2006) or PTSD (Aerni et al., 2004)]. Our results of inverse relations between post-stress sustained limbic connectivity and the cortisol response to stress might therefore add a new vantage point for future studies of the effects of stress on memory.

To note, our study was conducted on military soldiers in training, prior to operational employment. At the time of the experiment subjects were positioned in the same unit, thereby presenting a high homogeneity of life events over the months preceding our study. Nonetheless, we encourage future validation of our results on civilian populations as well. Additionally, an intriguing issue for further exploration is the responsiveness of our subjects, as well as their inter-individual differences following operational employment; a period that tends to include numerous life-threatening and stressful events.

In summary, our multiple time-point study demonstrates both early and late effects of a stressful challenging task on interregional rsFC. Our observations have important implications for the broader understanding of the impact of acute stress, and thus may be of substantial value in the search for a neuroendocrine individual profile of stress responsiveness and related psychopathologies.

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Individual differences in emotion-cognition interactions: emotional valence interacts with serotonin transporter genotype to influence brain systems involved in emotional reactivity and cognitive control

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The serotonin transporter gene (5-HTTLPR) influences emotional reactivity and attentional bias toward or away from emotional stimuli, and has been implicated in psychopathological states, such as depression and anxiety disorder. The short allele is associated with increased reactivity and attention toward *negatively-valenced* emotional information, whereas the long allele is associated with increased reactivity and attention toward *positively-valenced* emotional information. The neural basis for individual differences in the ability to exert cognitive control over these bottom-up biases in emotional reactivity and attention is unknown, an issue investigated in the present study. Healthy adult participants were divided into two groups, either homozygous carriers of the 5-HTTLPR long allele or homozygous carriers of the short allele, and underwent functional magnetic resonance imaging (fMRI) while completing an Emotional Stroop-like task that varied in the congruency of task-relevant and task-irrelevant information and the emotional valence of the task-irrelevant information. Behaviorally, participants demonstrated the classic "Stroop effect" (responses were slower for incongruent than congruent trials), which did not differ by 5-HTTLPR genotype. However, fMRI results revealed that genotype influenced the degree to which neural systems were engaged depending on the valence of the conflicting task-irrelevant information. While the "Long" group recruited prefrontal control regions and superior temporal sulcus during conflict when the task-irrelevant information was positively-valenced, the "Short" group recruited these regions during conflict when the task-irrelevant information was negatively-valenced. Thus, participants successfully engaged cognitive control to overcome conflict in an emotional context using similar neural circuitry, but the engagement of this circuitry depended on emotional valence and 5-HTTLPR status. These results suggest that the interplay between emotion and cognition is modulated, in part, by a genetic polymorphism that influences serotonin neurotransmission.

Keywords: 5-HTTLPR, Stroop, fMRI, prefrontal cortex (PFC), eye-gaze, anxiety, positive affect

INTRODUCTION

How does emotion influence cognition? Here we examine the degree to which cognitive control, the ability to engage in goal-directed behavior, is influenced by salient but task-irrelevant information that is emotional in nature. Currently, the evidence is divided, with some studies suggesting that emotional information can facilitate, impede, or have no effect on cognitive control (Cohen and Henik, 2012). Research has identified factors that can influence or mediate these effects, including the valence of the emotional material (i.e., positive vs. negative e.g., Kahan and Hely, 2008), individual differences in negative affect such as anxiety (Cisler and Wolitzky-Taylor, 2011), and genetic polymorphisms that may contribute to these individual differences, such as the serotonin transporter gene (Beevers and Wells, 2009). The present study aims to investigate the interaction of these factors in healthy individuals and in doing so, shed light on the underlying neurobiology of emotion-cognition interactions.

One of the most replicated findings regarding genetic polymorphisms is that the 5-HTTLPR genotype influences emotional reactivity to negative information (Pergamin-Hight et al., 2012) and sensitivity to stressors (Karg et al., 2011). A polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) results in short (S) and long (L) variants. The S allele is linked to lower expression of serotonin transporter mRNA. Further, the L allele contains an A to G single

nucleotide polymorphism (SNP rs25531) that influences transcriptional efficiency, rendering the L_G allele functionally similar to the S allele (Hu et al., 2006). A variety of evidence drawn from studies comparing S carriers (SS alone or with SL_G) with homozygous L carriers (e.g., LL or L_AL_A) suggests that the S allele is associated with higher negative affect. First, genetic association studies suggest that the S allele contributes to risk for affective psychiatric disorders as it is overtransmitted in those patients (Caspi et al., 2003; Karg et al., 2011; but see Munafò et al., 2009). Second, healthy carriers of the S allele score higher on measures of depressive and anxiety-related behaviors (Lesch et al., 1996; Gonda et al., 2009; Lonsdorf et al., 2009). Third, they tend to show a stronger bias toward negative content (e.g., angry faces) in an emotional dot-probe task (Beevers and Wells, 2009; Pérez-Edgar et al., 2010) and show increased interference from negative stimuli (e.g., threat words or angry faces) in Stroop-like tasks (Koizumi et al., 2010). Fourth, numerous functional neuroimaging studies demonstrate that the amygdala, a critical brain region underlying emotional behavior, is more responsive to negative stimuli in healthy S carriers [see meta-analyses (Munafò et al., 2008; Murphy et al., 2013)]. Recent studies suggest that the Long allele may be associated with a bias away from negative stimuli and/or increased sensitivity to *positive* emotional stimuli. For example, L carriers show a bias away from negative stimuli (Kwang and Wells, 2010) and toward happy faces (Pérez-Edgar et al., 2010) in a behavioral dot-probe paradigm. Together, these findings indicate that S (and L_G) carriers differ in emotional reactivity from L carriers (and L_A alone), with S carriers showing a "negativity bias" and L carriers potentially showing a "positivity bias."

What is not clear is how such individual differences in emotional biases may interact with or influence the ability to exert cognitive control, a question we address here. However, there is good reason to believe that emotional biases are likely to influence the degree to which cognitive control can be exerted and the activation of neural systems supporting such control. For example, in non-clinical samples of individuals who do not reach criteria for a psychiatric disorder, a higher tendency toward anhedonic depression is associated with decreased activity in posterior regions of the dorsolateral prefrontal cortex during performance of a color-word Stroop task (Herrington et al., 2010). As the color-word Stroop task does not involve emotional information, but cognitive conflict, this finding suggests that individual differences in emotional biases may influence the activity of brain regions involved in cognitive control. Additional evidence suggests that engagement of cognitive control regions may be influenced not only by such trait individual differences, but also by the nature of task-irrelevant emotional information. For example, individuals high in anxious apprehension (i.e., worry) show greater activity in left lateral prefrontal regions in the face of emotionally negative as compared to neutral task-irrelevant words in an emotion-word Stroop task (Engels et al., 2007). As these two examples illustrate, both the emotional make-up of an individual as well as the emotional valence of task-irrelevant information may serve to influence neural systems that exert cognitive control.

In consideration of these prior findings, we investigated the effect of certain variants of the 5-HTTLPR genotype on neural systems underlying cognitive control. In prior studies of cognitive control examining individual differences in trait emotional biases, there have been two types of task-irrelevant information. In some cases, the task-irrelevant information has been emotional in nature (e.g., a task-irrelevant emotion word when the task goal is to identify the word's ink color). In these paradigms, cognitive control must be exerted in the face of such emotional information because it is likely to capture attention (Ishai et al., 2004). In other cases, cognitive control must be exerted because the non-emotional task-irrelevant information (e.g., a color word) conflicts, semantically and/or with regards to response-mappings, with the task-relevant information (e.g., the word's ink color, as in the case of the word "red" printed in blue ink) (see Banich et al., 2009 for a longer discussion).

In the present investigation, we utilize a task that allowed us to integrate these two types of task-irrelevant information to determine how genotype affects cognitive control. In our task (similar to that of Barnes et al., 2007), individuals were asked to press a button corresponding to a word (left, right) placed on the forehead of a face. On incongruent trials, the position of the person's pupils was opposite that of the word on the forehead (e.g., pupils on the left when the word says "right) and required more cognitive control than on congruent trials, in which the position of the person's pupils corresponds to the word on the forehead (e.g., pupils on the left when the word says "left"). Here cognitive control is required both because of the spatial incompatibility between the word and eye gaze, and also because eye gaze is a salient emotional feature of the face that will capture attention (Barnes et al., 2007; Schwartz et al., 2010; Vaidya et al., 2011).

In addition, we varied the emotional expression of the face to be negative, neutral or positive. Like the word in the standard emotion-word Stroop task, the facial expression in this task is unrelated to the task goals (which in the current task is to determine the spatial meaning of a word). Yet we can explore whether such information influences the ability to exert cognitive control. The emotional expression is likely to be a potent distractor as it, like eye gaze, is an integral part of the facial expression, which will attract attention.

We predicted that across all participants, the task should engage regions previously identified as underlying cognitive control and interference resolution, such as the dorsolateral prefrontal cortex (PFC), anterior cingulate cortex, and inferior frontal regions. In addition, it should also engage regions involved in face processing, most likely including the portions of the fusiform gyrus (Kanwisher and Yovel, 2006) and the superior temporal sulcus (STS), which has been found to be sensitive to aspects of facial expression that can change over time and have social significance, including eye gaze (Nummenmaa et al., 2010).

Our key prediction was that because of increased sensitivity to negative affective stimuli in S (and L_G) carriers, carriers of the 5-HTTLPR S or L_G alleles (SS, SL_G, L_GL_G; "Short") would show differential activation of cognitive control systems during conflict when the emotional context was negative in nature. This prediction was based on the idea that the task-irrelevant negative information contained in the facial expression is likely to

capture attention in these individuals, and make the implementation of cognitive control more demanding. We also predicted that this pattern should be absent or perhaps even reversed in the homozygous carriers of the L_A allele (L_AL_A; "Long"), who are likely to ignore negative information and/or be more sensitive to positive information. Our study did not include S/L_A heterozygotes because unlike the short and long carriers, it is not clear what bias they would show toward affective stimuli.

In conjunction, we also examined whether the two groups would differ in regards to the engagement of cognitive control regions in response to conflict that is not highly emotional in nature. There is at least some evidence that cognitive control mechanisms may differ between the groups (Fallgatter et al., 2004; Althaus et al., 2009; Holmes et al., 2010). To address this issue, we examined activation of these cognitive control and face-processing regions in a neutral emotion condition.

METHODS

PARTICIPANTS

fMRI participants were drawn from a pool of 221 University of Colorado Boulder undergraduate students (105 male; 47.5%) of primarily European descent (93%) without history of psychiatric diagnosis or medication, who were right-handed and were native English speakers or fluent by age 10, who participated in the initial screen for course-credit or payment. Consent was acquired according to Institutional Review Board guidelines. Potential participants provided a saliva sample that was analyzed for 5-HTTLPR and the rs25531 SNP in the serotonin transporter gene (SLC6A4). Genotype frequencies were in Hardy-Weinberg equilibrium ($X^2 = 1.310$, $df = 2$, $p > 0.1$). In light of evidence indicating functional similarity between the low-expressing S and L_G alleles (Hu et al., 2006), we included L_G carriers in the S group as done in past work (Armbruster et al., 2009). Carriers who had two copies of either the high-expressing (L_A) or low-expressing (S or L_G) alleles were invited to participate in the fMRI study. SL_A and L_AL_G heterozygotes, that is, carriers of both high and low expressing alleles, were excluded in order to maximize observed allelic differences (Roiser et al., 2009).

Our final fMRI study sample included two groups, L_AL_A (high-expressing "Long" genotype) and $SS/SL_G/L_GL_G$ (low-expressing "Short" genotypes). The Long group ($N = 21$; 52% Male; Age: $M = 20.8$, $SD = 8.6$) did not differ from the Short group ($N = 21$; 48% Male; Age: $M = 19.6$, $SD = 1.7$) in age ($p > 0.5$), gender ($p > 0.7$) or ethnicity ($p > 0.2$). The Short group comprised low-expressing alleles were composed of individuals with the SS ($n = 16$), SL_G ($n = 3$), and L_GL_G ($n = 2$) phenotypes.

STIMULUS MATERIALS

Stimuli consisted of faces selected from the NimStim stimuli (Tottenham et al., 2009) with a target direction ("LEFT" or "RIGHT") printed just above the naison of face. The eye gaze, which was manipulated using Photoshop (Adobe, version CS2 software), could either be to the left or right (**Figure 1**). In addition, the emotional expression of the face was happy, angry, or neutral. Hence, the three key stimulus features were (1) target direction (task-relevant), (2) eye gaze (task-irrelevant) and (3) emotional expression (task-irrelevant). For congruent trials, target direction matched eye gaze (*LEFT-left* or *RIGHT-right*). For incongruent trials, target direction conflicted with eye gaze (*LEFT-right* or *RIGHT-left*). For conflict-neutral trials, eye gaze was straight ahead, and therefore neither conflicted nor matched the target direction word (*LEFT-straight ahead* or *RIGHT-straight ahead*). Thus, trials varied by target-gaze congruency (congruent, incongruent, conflict-neutral) and valence of emotional expression (Negative, Positive, Neutral), creating nine conditions: Negative Congruent, Negative Incongruent, Negative Conflict-Neutral, Positive Congruent, Positive Incongruent, Positive Conflict-Neutral, Neutral Congruent, Neutral Incongruent, and Neutral Conflict-Neutral (**Figure 1**). Conditions were equated for gender and other irrelevant stimulus features (e.g., hair color), as each condition contained the same 12 exemplar faces (6 male, 6 female).

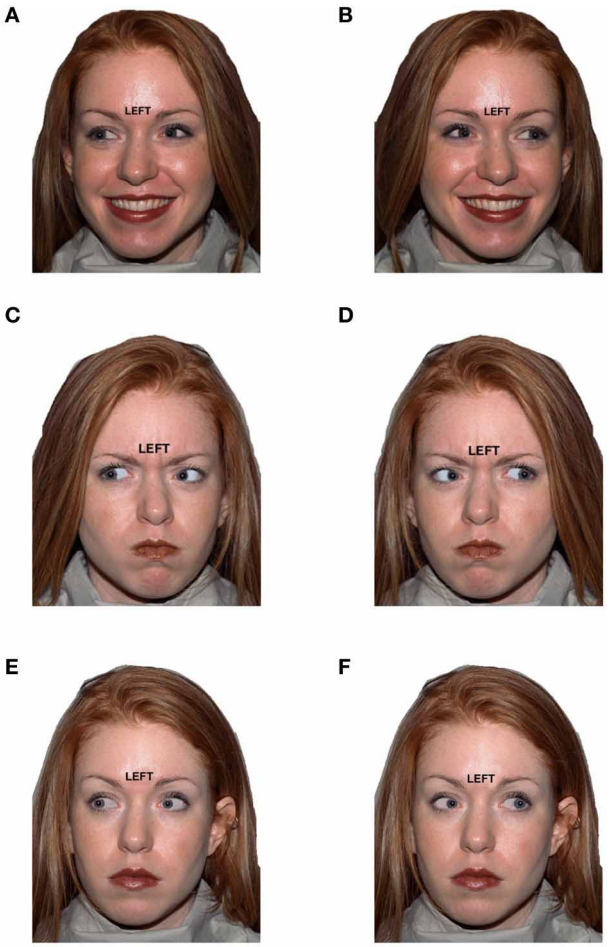

FIGURE 1 | Example stimuli for six conditions that varied by target direction to eye gaze (distractor) congruency and by emotional expression valence: (A) Happy/Congruent, (B) Happy/Incongruent, (C) Angry/Congruent, (D) Angry/Incongruent, (E) Neutral/Congruent, (F) Neutral/Incongruent.

PROCEDURE

All potential MRI participants were recruited between 2 and 8 months prior to scanning (Mean = 3.7 months, $SD = 1.9$), which did not differ across genotypes ($p > 0.2$). During an initial visit to the laboratory, all 221 participants completed the Neuroticism Extraversion Openness Five-Factor Inventory [(NEO-FFI Costa and McCrae, 1992)], and two computerized tasks designed to measure cognitive control, an N-back task (Stollstorff et al., 2010) and a Stop Signal Reaction Time Task (Logan et al., 1984), and provided a saliva sample for subsequent genotyping.

A subset of participants were invited to return for fMRI scanning based on their 5-HTTLPR homozygosity. On the day of scanning, they first received verbal instructions for the task outside the magnet, followed by an anatomical scan and the experimental task while undergoing fMRI scanning; they then completed the state anxiety questionnaire from the State-Trait Anxiety Inventory [STAI; (Spielberger and Vagg, 1984)] outside the magnet.

TASKS AND QUESTIONNAIRES PERFORMED OUTSIDE THE MAGNET

Trait negative and positive affect questionnaires

To obtain measures of negative and positive trait affect, which are suggested to be associated with the short and long 5-HTTLPR genotypes, respectively, we administered two questionnaires. The STAI is a self-report measure of state and trait anxiety that includes 20 statements, rated on a scale of 1 (not at all) to 4 (very much so), about the participant's immediate state of anxiety, and 20 statements, on a scale of 1 (almost never) to 4 (almost always), about trait anxiety. We used the overall percentile score derived from the STAI-State subscale (taken at the time of scanning) as a proxy for a trait tendency toward negative affect. The NEO is a questionnaire designed to measure a number of basic personality measures. We used the positive affect and negative affect subscales of the extraversion and neuroticism measures derived from the NEO as a proxy for a trait tendency toward positive and negative affect, respectively. The NEO-FFI was administered 2 and 8 months prior to scanning during the participants' initial visit to the laboratory; test-retest reliability for the NEO-FFI is quite high; 0.83 at 6 months (Murray et al., 2003).

Cognitive control tasks

To determine whether the two genotype groups varied in terms of basic cognitive control ability, we administered a variety of behavioral tasks designed to measure different aspects of cognitive control.

N-back working memory. This task was designed to measure aspects of cognitive control related to the ability to filter and update information in working memory. Participants completed a verbal *N*-back task, consisting of 6 alternating 1.2-min blocks of 1-, 2- and 3-back conditions ("low," "medium," and "high" working memory load, respectively). Each block comprised 24 trials preceded by an instruction screen stating the type of trial in the block ("1-back," "2-back," or "3-back"). For all conditions, one letter was presented on the screen at a time (for 0.5 s followed by a 2.5 s inter-trial interval) and the participant was instructed to press a button with their right index finger on the keyboard when the letter on the screen was the same as the one presented *n* trials previously. In the 1-back condition, participants were instructed to press the button if the letter was the same as the letter before it (e.g., "T" then "T"). In the 2-back condition, participants were instructed to press the button if the letter was the same as 2 before it (e.g., "R" then "L" then "R"); in the 3-back condition, participants were instructed to press the button if the letter was the same as 3 before it (e.g., "M" then "K" then "P" then "M"). The number of target responses was identical across trial conditions. Stimuli comprised consonants only; vowels were omitted to prevent encoding series of letters as pronounceable strings.

SSRT (stop signal reaction time) task. This task was administered to assess the ability to exert cognitive control to interrupt prepotent responses. Participants were instructed to press a button in response to a cue (an arrow pointing Left or Right) unless they saw a stop signal (a white square) presented immediately after the cue, in which case they were to withhold a button press on that trial. Each trial began with a visual masking stimulus presented for 200 ms, followed by a fixation ring. The fixation ring persisted for 200 ms, and was then followed by a left- or right-pointing arrow subtending approximately 2° of visual angle. Subjects were required to press the "z" key to left-pointing arrows, and the "m" key to right-pointing arrows as quickly and accurately as possible. On 25% of trials, these arrow stimuli were replaced by a white square after a variable "signal delay," and subjects were required to inhibit their response to these stop signals. The signal delay was initially set to 250 ms and thereafter adjusted using an adaptive algorithm, such that the ISI was increased by 50ms following unsuccessful stop trials and decreased by 50ms following successful stop trials. SSRT was then calculated using the integration method, and was therefore equal to the nth percentile of Go signal RT minus the average SSD, where n corresponds to the proportion of successfully inhibited trials.

GENOTYPING

Participants delivered 2 mL of saliva into a sterile 15 mL tube, after which the experimenter placed a cotton-tipped swab containing a lysis buffer consisting of 1% sodium dodecyl sulfate, TRIS buffer, and proteinase K. Tubes were delivered to the laboratory where the DNA was isolated using standard procedures, which were subsequently analyzed for 5-HTTLPR using a two-step process. First, the long (L) and short (S) variants were determined. The repeat polymorphism in the promoter region of the 5-HTT gene was genotyped by PCR as previously described (Lesch et al., 1996) using the following primers at concentrations of 10 μM; Forward: 5′- GGCGTTGCCGCTCTGAATGC -3′ Reverse: 5′-GAGGGACTGAGCTG-GACAACCAC-3′. PCR was performed using the AccuPrime™ GC-Rich DNA polymerase system (Invitrogen) with the following PCR program: 95°C for 10 min, followed by 35 cycles of 95°C for 30 s, 65°C for 30 s, and 72°C for 1 min. A final extension time of 72°C for 10 min was performed after the 35 cycles were complete. The PCR products were then run out on a 2% agarose gel stained with ethidium bromide. The amplification yielded distinct bands at 484 bp (S allele = 14 copies of repeat) and 528 bp (L allele = 16 copies of repeat), which

were distinguished by a 100 bp DNA ladder run on the same gel. Second, the L_A and L_G variants were determined for the rs25531 single nucleotide polymorphism (SNP), present only on the long allele. Genotyping for rs25531 was performed by digesting the PCR products generated from the 5-HTTLPR PCR reactions with the restriction enzyme MspI (New England BioLabs). Specifically, 10 μL restriction digestion reactions were performed by combining 8 μL of the 5-HTTLPR PCR product, 1 μL of 10X NEBuffer 4, and 1 μL of MspI (concentration = 100,000 U/mL) and incubating the reactions for 2 h at 37°C followed by heat inactivation of the enzyme at 80°C for 20 min. The substitution of the G for A in the SNP produces an additional MspI recognition site (CCGG) on the long allele of the 5-HTTLPR PCR product. Genotypes were determined by running the digested PCR products out on a 2% agarose gel stained with ethidium bromide. Samples with two copies of the A allele for rs25531 showed a band at 340 bp (as well as bands at 127 and 62 bp due to multiple MspI recognition sites on the 5-HTTLPR PCR product), while samples with two copies of the G allele for rs25531 had additional digestion of the 340 bp product, yielding bands at 166 and 174 bp (as well as bands at 127 and 62 bp). Samples that were heterozygous for rs25531 showed a combination of these two band patterns.

IMAGING PROCEDURE

Imaging data were acquired using a 3T Siemens magnet (Siemens Magnetom Trio, Erlangen, Germany). Head movement was minimized by foam padding that held the subject's head in the coil firmly and comfortably. Prior to functional imaging, a high resolution sagittal T_1-weighted structural scan was acquired using a 3D MPRAGE sequence with the following parameters: TR = 2530 ms, TI = 1200 ms, 256 × 256 mm FOV, 192-mm slab with 1-mm-thick slices, 256 × 256 × 192 matrix (effective resolution of 1.0 mm^3), and a 7° flip angle.

Participants viewed the stimuli via a mirror mounted on the coil that reflected the images that were projected onto a screen (209 × 279 cm) at the back of the bore of the magnet approximately 950 mm from the mirror. Stimuli were generated in E-prime (Version 2.0, Psychology Software Tools Inc., 2010) and viewed via a magnet-compatible projector. Fifty axial slices (3.4 × 3.4 × 4.0 mm) were positioned to be parallel to the base of orbitofrontal cortex and covering the whole brain (TR = 2500 ms, TE = 29 ms, 220 × 220 mm FOV, 75° flip angle). A total of 404 volume images were acquired over a single run (16:55 min) using a T2*-sensitive gradient EPI sequence.

Alternating task and fixation blocks were presented in counterbalanced order (same for each participant). Each task block comprised three out of nine experimental conditions; each block consisted of 10 trials. Each 2.5 s trial began with a face stimulus, which remained on the screen for 1 s. The face cleared and a fixation-cross appeared for 1.5 s. Participants could respond at any point during the trial to indicate the direction of the word on the forehead by pressing one of two buttons on a button box (with the right hand); the left button with Index finger for "LEFT" and the right button with middle finger for "RIGHT." No feedback was provided. Fixation blocks consisted of five trials of a blank white screen (1 s) followed by a fixation cross (1.5 s), to which participants were instructed not to respond.

fMRI PROCESSING AND DATA ANALYSIS

Images were analyzed in SPM5 (www.fil.ion.ucl.ac.uk/spm). The first 4 volumes were discarded to allow for T1 equilibration effects, leaving 400 volumes. Images were corrected for slice acquisition timing and were then corrected for translational and rotational motion by realigning to the first image of the run. All subjects demonstrated less than 2 mm of absolute translational motion in any one direction and less than 2° of rotation around any one axis in each run. Images were coregistered with the high-resolution structural images of the participant. The structural images were segmented into separate gray and white matter images, and the gray matter image was normalized into standard MNI space by comparison with a template gray matter image. The normalization parameters used were then applied to the functional images to bring them into MNI space. All images were smoothed using a Gaussian kernel with full-width at half-maximum (FWHM) of 8 mm.

fMRI responses were modeled by a canonical hemodynamic response function. At the individual subject level, activation maps were generated using linear contrasts identifying regions that were more active during incongruent relative to congruent blocks ("interference/conflict contrast"), separately for each emotional valence condition.

Five second-level analyses were performed: (1) To identify clusters engaged by the Stroop-like task in general, a one-sample t-test on the conflict contrast was performed (all subjects and all valences). (2) To test whether emotionally neutral cognitive control activation did not differ between genotype groups, a 2-sample t-test was performed on the conflict contrast in the neutral-valence condition only. (3) To test our hypothesis of a 5-HTTLPR × Valence interaction, our key analysis of interest, a 2 × 2 mixed analysis of variance (ANOVA) with 5-HTTLPR (Long, Short) as a between-subject factor and Valence (Happy, Angry) as a within-subject factor was performed. For each analysis, maps were thresholded at $p < 0.005$, $k = 150$ which is an overall significance level of $p < 0.05$ corrected for multiple comparisons based on Monte Carlo simulation of random noise distribution [using 3dClustSim module of AFNI (Forman et al., 1995)]. To further examine the ANOVA, contrast estimates were extracted from activated clusters using MARSBAR (Brett et al., 2002) and analyzed for genotype and valence differences with t-tests. (4) To test which regions correlate with trait negative affect while viewing angry faces, for each genotype group separately, we ran a covariate analysis on the Incongruency Contrast (incongruent—congruent) for the negative valence (angry faces) condition only using the covariate of STAI state anxiety. (5) To test which regions correlate with trait positive affect while viewing happy faces, for each genotype group separately, we ran a covariate analysis on the Incongruency Contrast for the positive valence (happy faces) condition only using the covariate of scores on Positive Affect subscale of the NEO-FFI.

RESULTS

NEGATIVE AND POSITIVE AFFECT

Self-report measures

A between-subjects ANOVA of subscales from the NEO-FFI revealed that mean Extraversion-Positive Affect scores were

higher in Long ($M = 16.48$, $SD = 2.01$) than Short ($M = 14.33$, $SD = 2.65$) participants [$F_{(1, 41)} = 8.69$, $p = 0.005$, $\eta^2 = 0.82$] and that Neuroticism-Negative Affect scores were marginally higher in Short ($M = 14.67$, $SD = 2.09$) than Long ($M = 12.95$, $SD = 3.21$) participants [$F_{(1, 41)} = 3.29$, $p = 0.077$, $\eta^2 = 0.42$]. No other scales or subscales from the NEO-FFI were significant (ps > 0.1; **Table 1** reports Extraversion and Neuroticism scales and subscales). A between-subjects ANOVA showed that mean percentile State anxiety scores from the STAI were higher in Short ($M = 46.65$, $SD = 19.68$) than Long ($M = 33.95$, $SD = 20.04$) participants [$F_{(1, 40)} = 4.19$, $p = 0.048$, $\eta^2 = 0.51$]. Thus, the Short group scored higher on measures of Negative Affect as would be expected. In addition, the Long group scored higher on a measure of Positive Affect (see **Table 1**).

COGNITIVE CONTROL MEASURES

To test whether groups were equivalent in cognitive control ability, we used two tasks that tap aspects of cognitive control: (1) the N-back task, designed to measure the ability to update and remove information from working memory; and (2) the Stop-Signal Reaction Time (SSRT) task, designed to measure inhibitory control over motoric responding.

N-back working memory

Groups did not differ in performance at any working memory load for accuracy (ps > 0.3) or reaction time (ps > 0.4), indicating that short and long genotype groups had similar working memory ability (**Table 1**).

SSRT

Groups did not differ in stop signal reaction time ($p > 0.9$), indicating that short and long genotype groups had similar inhibitory control ability (**Table 1**).

BEHAVIORAL RESULTS

A response was scored as "correct" if the participant pressed the button (left or right) in accordance with the target direction, and "incorrect" if the opposite button was pressed or if there was no response within 1.5 s ("timed-out"; $M = 0.002\%$ of trials, which did not differ by genotype, $p > 0.3$). For each participant, mean accuracy (% correct) and mean reaction time (ms) for correct responses was computed for congruent and incongruent trials for each emotional valence (**Table 1**) and this was subsequently entered into 2 mixed $2 \times 2 \times 3$ ANOVAs (for accuracy and reaction time, separately), with genotype (Short,

Table 1 | Demographics, cognitive control, and trait affect measures for short and long 5-HTTLPR genotype groups; mean (SD).

		Short ($SS/SL_G/L_GL_G$)	Long (L_AL_A)	*p*-value
DEMOGRAPHICS				
N (sample size)		21	21	1.0
Age in years		19.6 (1.7)	20.8 (8.6)	0.57
Gender		F: 11	F: 10	0.76
		M: 10	M: 11	
Ethnicity (No. of Caucasian)		18	21	0.18
COGNITIVE CONTROL TASKS				
***N*-back working memory**				
Accuracy	1-back:	95.9% (9)	96% (15)	0.98
	2-back:	95.5% (11)	92.3% (10)	0.34
	3-back:	81.6% (19)	84.8% (18)	0.61
Reaction Time	1-back:	597 ms (159)	556 ms (167)	0.45
	2-back:	674 ms (164)	678 ms (186)	0.95
	3-back:	747 ms (228)	723 ms (311)	0.79
Stop signal reaction time (SSRT)				
		220 ms (29)	222 ms (49)	0.90
TRAIT AFFECT SELF-REPORT MEASURES				
STAI state anxiety		46.6 (19)	33.9 (20)	0.048*
Percentile score				
NEO-FFI				
Neuroticism		30.05 (7)	27.74 (6)	0.19
Negative affect		14.67 (3)	12.95 (3)	0.07
Self-reproach		15.38 (5)	14.29 (5)	0.46
Extraversion		42.52 (5)	45.48 (8)	0.17
Positive affect		14.33 (3)	16.48 (2)	0.005*
Sociability		13.86 (2)	14.33 (4)	0.60
Activity		14.05 (3)	14.76 (3)	0.43

**Significant group difference.*

Long) as a between-subjects factor and congruency (congruent, incongruent) and valence (happy, angry, neutral) as within-subject factors.

Accuracy

A main effect of congruency [$F_{(1, 40)} = 15.66$, $p < 0.001$, $\eta^2 = 0.28$] indicated that participants were more accurate for congruent ($M = 98.5\%$, $SD = 2.3$) than incongruent ($M = 96.6\%$, $SD = 4.8$) trials. Thus, participants' accuracy exhibited an interference, or "Stroop" effect. No other main effects or interactions reached significance ($ps > 0.1$, see **Table 2**).

Reaction time

A main effect of congruency [$F_{(1, 40)} = 11.70$, $p < 0.001$, $\eta^2 = 0.23$] indicated that participants were faster to respond to congruent ($M = 561$ ms, $SD = 56$) than incongruent ($M = 574$ ms, $SD = 52$) trials. Thus, participants' response latencies exhibited an interference, or "Stroop" effect. There was a main effect of valence [$F_{(2, 80)} = 8.43$, $p < 0.001$, $\eta^2 = 0.17$]; pairwise comparisons revealed that reaction time was significantly faster for the neutral emotion condition ($M = 558$ ms, $SD = 59$) than positive ($p = 0.002$; $M = 571$ ms, $SD = 53$) and negative ($p = 0.001$; $M = 574$ ms, $SD = 50$) emotional conditions, which did not differ from each other ($p = 0.43$). Furthermore, there was a congruency × valence interaction [$F_{(2, 80)} = 11.47$, $p < 0.001$, $\eta^2 = 0.22$]; paired t-tests revealed that the interference effect (congruent faster than incongruent) was significant for neutral [$t_{(41)} = 2.50$, $p = 0.016$] and positive [$t_{(41)} = 7.05$, $p < 0.001$] valence conditions, but not for the negative valence condition [$t_{(41)} = 0.80$, $p = 0.428$]. Importantly, there was no main effect of genotype or interaction with genotype ($ps > 0.3$), indicating that the effect of congruency and valence did on reaction time did not differ by genotype (see **Table 2**).

Table 2 | Mean accuracy (SD in parenthesis) and reaction time (in ms; SD in parentheses) for congruent and incongruent trials by emotional valence condition in short and long genotype carriers.

			Short $N = 21$	Long $N = 21$
Accuracy	Angry	*Congruent*	98.4% (2.5)	98.8% (1.9)
		Incongruent	96.4% (5.0)	94.8% (4.9)
	Happy	*Congruent*	99.0% (1.8)	98.2% (2.1)
		Incongruent	97.0% (4.6)	98.0% (3.1)
	Neutral	*Congruent*	98.2% (2.5)	98.4% (3.1)
		Incongruent	97.2% (4.4)	96.4% (6.6)
Reaction Time	Angry	*Congruent*	569 (51)	585 (51)
		Incongruent	572 (51)	572 (48)
	Happy	*Congruent*	549 (56)	565 (61)
		Incongruent	576 (46)	595 (52)
	Neutral	*Congruent*	545 (55)	557 (66)
		Incongruent	562 (64)	568 (53)

NEUROIMAGING RESULTS

Cognitive control activation—main effect of congruency

To ensure that our task engaged neural systems involved in cognitive control, we performed a one-sample t-test on the conflict contrast (incongruent > congruent) across all valences (i.e., all emotional expressions) for all participants. This analysis revealed activation in a wide-spread range of regions, most all of which are seen in tasks involving cognitive control (**Table 3**): right inferior and middle frontal gyri, right medial superior frontal gyrus, bilateral superior parietal gyrus/precuneus, right posterior superior temporal gyrus, right fusiform gyrus (fusiform face area; FFA) and left cerebellum.

Effects of valence

To determine whether the faces were engaging emotional processing as we had hypothesized, we ran a number of contrasts. First, we examined the contrast of Faces with Negative Emotion vs. Fixation as well as the contrast of Faces with Positive Emotion vs. Fixation. These two contrasts revealed similar patterns, with extensive activation in the ventral visual processing stream, ventral striatum, and amygdala bilaterally (see **Table 3**, top). These latter findings indicate that our face stimuli did indeed engage regions involved in emotional processing. In addition, we compared activation for stimuli in which the face had a negative emotion compared to a positive one, which yielded great activation in visual cortex and portions of the superior temporal sulcus for negative compared to positive emotional expressions (see **Table 3**, bottom).

Group comparison of cognitive control activation—neutral emotion

Next we examined whether there were any differences in activation of cognitive control regions for the two genotype groups when there was no salient emotional expression of the face (i.e., the neutral facial expression). A 2-sample t-test (for the interference contrast, incongruent > congruent) for the neutral valenced (non-emotional) condition revealed that the Short group had more activation of left middle frontal gyrus and left posterior middle temporal gyrus relative to the Long group. The reverse comparison (Long > Short) revealed no significant group differences in activation (**Table 3**). This finding suggests that the short group may engage cognitive control regions more than the long group, but to a somewhat limited degree.

5-HTTLPR × valence interaction

To address the main question of interest, that is, whether genotype influences the degree to which neural systems involved in cognitive control are differentially engaged depending on the emotional nature of distracting stimuli, we performed a analysis to determine those brain regions that would exhibit a genotype × valence interaction for the interference contrast (incongruent > congruent trials). A significant effect was observed in four regions: bilateral middle prefrontal cortex, left medial superior PFC, and left posterior superior temporal gyrus (**Table 3**, **Figure 2**). Comparison of contrast estimates from each region revealed a similar pattern; that is, activation was higher in Short carriers relative to Long carriers for negatively-valenced faces, and higher in

Table 3 | Regions involved in negatively and positively valenced face processing (task minus fixation baseline contrast, $p = 0.05$ corrected).

	BA	Voxels	Voxel coordinates			*Z*-Score
			x	*y*	*z*	
MAIN EFFECT OF NEGATIVE EMOTION (ANGRY FACES > FIXATION)						
Bilateral ventral visual stream		12220				
Right occipital (cuneus)	17/18		28	−94	6	24.18
Left occipital (cuneus)	17/18		−18	−102	4	23.50
Right fusiform face area (FFA)	37		40	−44	−20	18.50
Left fusiform face area (FFA)	37		−38	−48	−21	15.92
Right amygdala	n/a	364	20	−6	−16	6.19
Right putamen/ventral striatum			22	6	8	6.71
Left amygdala	n/a	1097	−16	−10	−12	6.83
Left putamen/ventral striatum			−22	2	8	6.85
Medial frontal gyrus/anterior cingulate	6	533	−6	8	52	10.94
Left middle frontal gyrus/premotor cortex	6	1430	−28	−2	48	6.88
Left superior parietal gyrus	7	908	−32	−60	50	6.45
MAIN EFFECT OF POSITIVE EMOTION (HAPPY FACES > FIXATION)						
Bilateral Ventral Visual Stream		11459				
Right occipital (cuneus)	17/18		26	−96	6	26.26
Left occipital (cuneus)	17/18		−20	−100	2	24.26
Right fusiform face area (FFA)	37		38	−48	−20	17.67
Left fusiform face area (FFA)	37		−40	−46	−20	14.68
Right amygdala	n/a	729	22	4	10	7.18
Right putamen/ventral striatum			28	6	−6	6.89
Left amygdala	n/a	925	−16	−8	−14	6.03
Left putamen/ventral striatum			−26	2	−8	8.15
Medial frontal gyrus/antierior cingulate	6	594	−6	6	54	10.93
Left middle frontal gyrus/premotor cortex	6	1068	−44	0	30	6.88
Right middle frontal gyrus/premotor cortex	6	576	44	6	54	5.96
Right middle frontal gyrus	46		46	30	38	5.62
Left superior parietal gyrus	7	1019	−28	−56	48	8.02
Right superior parietal gyrus	7	616	34	−56	48	6.56
MAIN EFFECT OF VALENCE						
Negative > positive						
Right fusiform face area (FFA)	37	271	42	−40	−18	3.83
Right posterior middle temporal gyrus	39		−50	−72	8	4.22
Left middle temporal gyrus	37/39	175	−54	−66	10	3.61
Right occipital	17/18	539	4	−86	−2	4.21
Left occipital			−12	−84	−6	3.54
Positive > negative						
Left posterior superior temporal sulcus (STS)	41	154	−40	−36	16	3.35

Long relative to Short carriers for positively-valenced faces (see **Figure 2**).

Individual differences analysis—fMRI

A covariate analysis using the interference contrast (incongruent minus congruent) was run for the negative valence condition (negative faces) using STAI state anxiety as the covariate in order to determine regions that are sensitive to cognitive conflict in a negative emotional context that vary by anxiety self-report in each group. This analysis in the Short group revealed that increased activation of the ventromedial prefrontal cortex and the frontal pole was associated with greater anxiety. The Long group did not show this pattern (**Table 4**, **Figure 3**). A similar covariate analysis using the interference contrast was run using the Negative Affect subscale from the NEO-Neuroticism questionnaire (assessed during initial visit 2–8 months prior to scanning). This analysis in the Short group while viewing angry faces revealed ventromedial prefrontal cortex, frontal pole, left middle frontal gyrus and left posterior middle temporal gyrus. The Long group did not show any significant activation (**Table 4**). A second complementary covariate analysis on the interference contrast was run for the positive valence condition (happy faces) using NEO-Positive Affect as the covariate in order to determine regions that are sensitive to cognitive conflict in a positive emotional context. In the

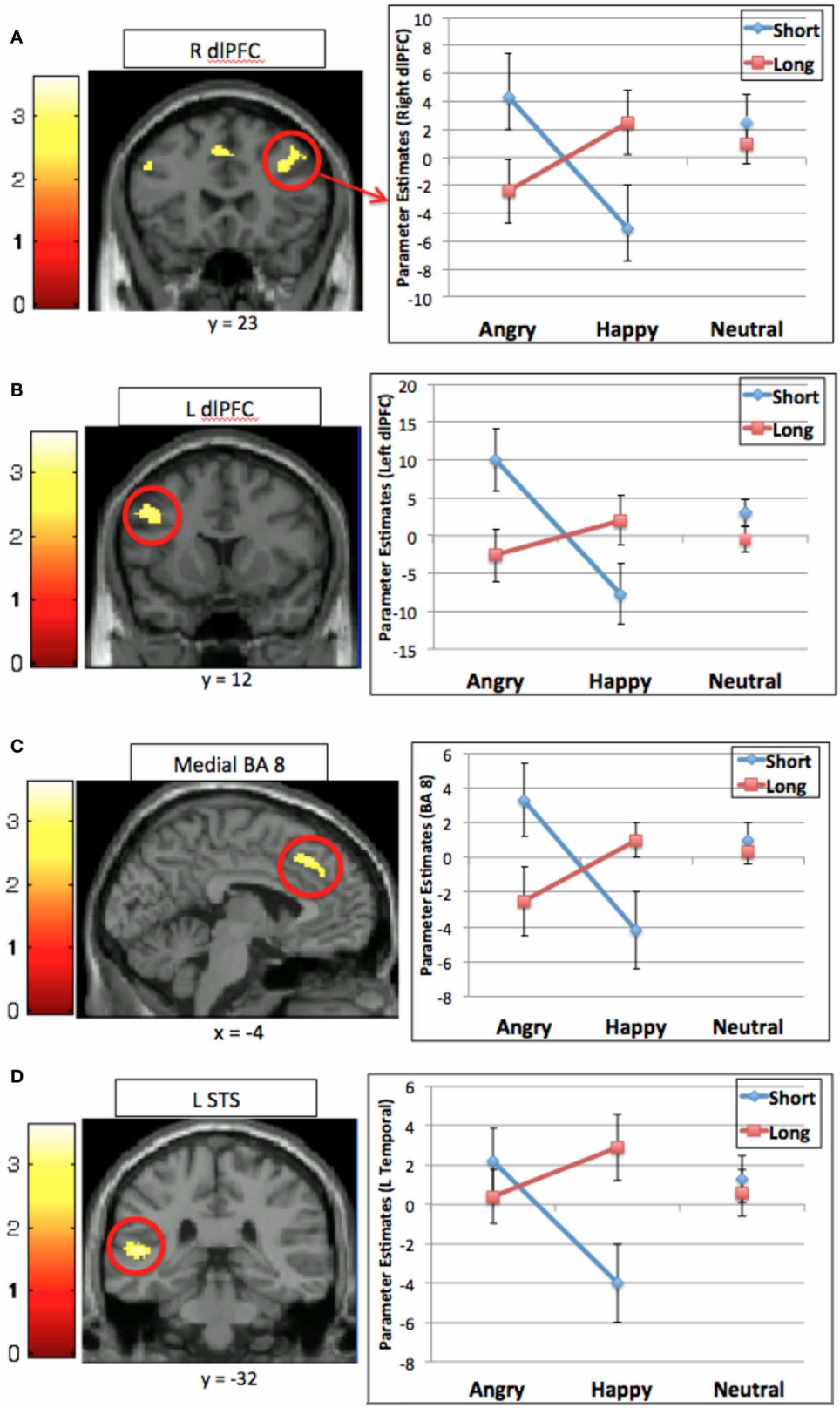

FIGURE 2 | Interaction between emotional valence and 5-HTTLPR for the interference contrast (incongruent > congruent) in four regions: (A) right dorsal lateral prefrontal cortex (R dlPFC); (B) left dorsal lateral prefrontal cortex (L dlPFC); (C) medial superior prefrontal cortex (BA 8); (D) left superior temporal sulcus (L STS). Graphs show mean contrast estimates (± standard error) in the activated cluster by genotype and emotional valence.

Table 4 | Regions involved in cognitive control under various emotional conditions in individual carriers of the short and long 5-HTTLPR genotype ($p = 0.05$ corrected).

	BA	Voxels	Voxel coordinates			*Z*-Score
			x	*y*	*z*	
MAIN EFFECT OF CONGRUENCY (INCONGRUENT > CONGRUENT)						
Right inferior prefrontal gyrus	45	186	52	22	−4	3.09
Right middle frontal gyrus	6/8/9	367	46	8	52	3.84
Right superior medial prefrontal gyrus	6/8	290	0	12	56	3.68
Right posterior superior temporal gyrus	21/22	626	62	−44	12	3.44
Right fusiform gyrus (FFA)	n/a	558	38	−50	−16	4.21
Right intraparietal sulcus/precuneus	7/40	964	30	−46	44	3.62
Left intraparietal sulcus/precuneus	7/40	241	−26	−52	44	3.20
Left cerebellum	n/a	233	−40	−70	−26	3.85
	n/a	706	−8	−76	−24	3.61
NON−EMOTIONAL CONGRUENCY EFFECT (NEUTRAL FACES)						
Short > Long						
Left middle frontal gyrus	6	184	−38	−4	40	3.52
Left posterior middle temporal gyrus	36	317	−54	−54	4	3.39
Long > Short	No significant clusters					
GENOTYPE × VALENCE INTERACTION (2 × 2 ANOVA)						
Right middle prefrontal gyrus	9/46	201	48	34	26	3.07
Left middle/inferior prefrontal gyrus	9	408	−42	6	34	3.48
Medial superior prefrontal gyrus	8	218	−6	28	42	3.06
Left posterior superior/middle temporal gyrus	21/22	211	−50	−34	8	3.31
TRAIT AFFECT COVARIATE ANALYSIS						
Short group, angry faces, anxiety						
Frontal pole	10	166	14	62	6	3.75
Ventromedial prefrontal cortex	10/47		12	54	−6	3.20
Long group, happy faces, positive affect						
Left ventral striatum	n/a	1072	22	10	−14	3.74
Right ventral striatum	n/a		−20	8	−12	3.60
Short group, angry faces, negative affect						
Right frontal pole	10	107	12	54	20	3.39
Left frontal pole	10	73	−18	58	16	3.10
Ventromedial prefrontal cortex	11/47	78	−4	42	−14	3.14
Left middle frontal gyrus	9	212	−32	14	34	3.22
Left posterior middle temporal gyrus	21	152	−60	−52	−4	3.47

Long group, greater activation in ventral striatum was associated with greater positive affect. The Short group did not show a similar pattern (**Table 4**, **Figure 3**).

DISCUSSION

The present study clearly demonstrates an interaction between neural systems involved in cognitive control and those involved in emotional processing that varies with genotype. Our results demonstrate that the distracting effect of valenced emotional information, which engages the need for cognitive control, differs depending on an individual's alleles for the serotonin transporter genotype (5-HTTLPR). Specifically, when the distracting information was negatively-valenced, individuals carrying the Short genotype recruited prefrontal cognitive control regions to a greater extent than individuals with the Long genotype. In contrast, when the distracting emotional information was positively-valenced, individuals with the Long genotype recruited these regions to a greater extent than those with the Short genotype. Of note, these data do not simply show that one genotype has more activity in one region or one condition. Rather, this double-dissociation highlights the opposing effects depending on emotional valence and 5-HTTLPR genotype.

We interpret this finding as indicating that regions involved in cognitive control become engaged when emotional information is distracting in nature. What is distracting, however, depends, in part, on genotype. Supporting the idea that the valence of emotional information has differential affects depending on genotype was the pattern of activation in regions processing the emotional expression of the face, including the superior temporal sulcus. The Short genotype group exhibited greater activation for the negatively-valenced (i.e., angry) faces than the Long genotype

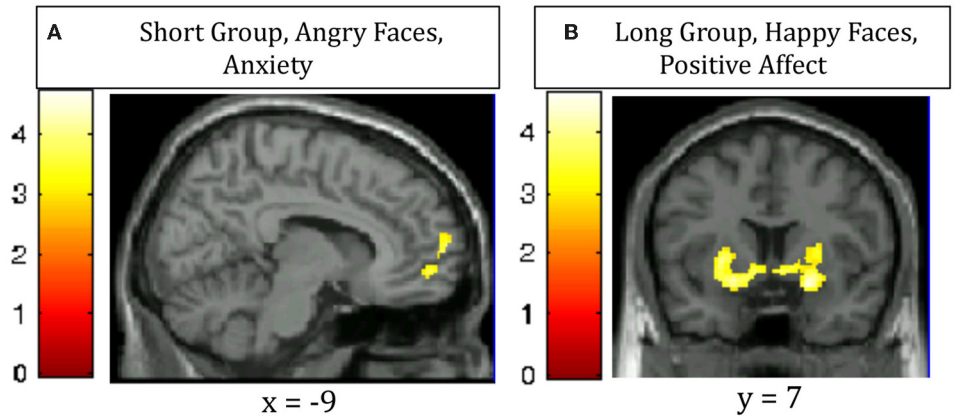

FIGURE 3 | Regions in which increased activation for the contrast of incongruent—congruent trials correlates with (A) increased anxiety in Short 5-HTTLPR individuals viewing Angry faces (ventromedial prefrontal cortex and frontal pole); (B) increased trait positive affect in Long 5-HTTLPR individuals viewing Happy faces (bilateral ventral striatum).

group and the Long genotype group exhibited greater activation for the positively-valenced happy faces than the Short genotype group.

Two findings regarding our groups and their phenotypes are important. First, our behavioral data (in addition to the pattern of activation in regions processing facial expression discussed above), suggest differential processing of emotional information. The sample of individuals selected as homozygous for the short serotonin-transporter (5-HTTLPR) genotype had higher self-reported negative affect, while the long serotonin-transporter genotype had higher self-reported positive affect. Of note, these results suggest, moreover, that our sample is relatively representative, as this pattern is consistent with previous findings.

Second, in contrast to the clear group differences in the processing of emotional information, we found little evidence for group differences in their ability to exert cognitive control generally. We included assessment of cognitive control ability on two standard behavioral measures, the N-back task and the Stop-Signal Reaction Time Task, which tap different aspects of executive function. The former assesses the ability to manipulate the contents of working memory while the latter assessed the ability to override a pre-potent response. The groups performed equivalently. Obviously, one cannot draw strong conclusions from a null result as it may reflect a Type 1 error. However, the pattern of differences in emotional self-report combined with no differences on tasks of cognitive control, supports the possibility that genotype is mainly influencing the processing of emotional information.

Also supporting this speculation are the neuroimaging results for faces with a neutral emotional expression. This analysis revealed only minor group differences in activation, which were observed in the left posterior middle temporal gyrus and the middle frontal gyrus with increased activation for the Short group. This finding is consistent with the idea that there are not large differences between the groups in the basic ability to engage neural mechanisms involved in cognitive control. Rather, such a pattern suggests that any differences in activation of cognitive control regions are more influenced by bottom-up effects, with increased sensitivity to the neutral facial expression in the short than long group (as evidenced by the activity in the left posterior middle temporal gyrus), which then, in turn, engages cognitive control. We speculate that for the short group, a neutral facial expression may not really be perceived as neutral, but potentially somewhat negatively valenced (Bistricky et al., 2011). Although other studies have found reductions in activation in prefrontal regions involved in cognitive control in individuals with depressive tendencies (Herrington et al., 2010) individuals in those studies have more severe trait negative affect. Our short carriers, however, did not have such high levels of negative affect, probably accounting for the relative lack of group differences in activation of prefrontal regions involved in cognitive control.

Rather than group differences in activation of cognitive control regions in general, the engagement of cognitive control regions in our task appears to be driven by the interaction of genotype and emotional valence. Aside from regions of the posterior superior temporal gyrus, which likely reflect group differences in processing of facial expression, all remaining regions showing a significant interaction of genotype and valence are involved in cognitive control. More specifically, the genotype by valence interaction was observed for activations in regions of the middle prefrontal cortex bilaterally, extending from the inferior frontal junction toward anterior portions of BA 9 and medial BA 8 in the cingulate gyrus extending upwards into pre-SMA. These are regions implicated across a large number of studies as playing an important role in cognitive control.

We postulate that the prefrontal regions (bilateral IFJ and medial pre-SMA), which are consistently active in paradigms requiring cognitive control such as the Stroop task (Nee et al., 2007), are engaged differentially by emotional valence due to differing cognitive control demands experienced by each group

based on 5-HTTLPR status. These bottom-up differences in sensitivity to affective information, despite the fact such information is peripheral to the task and therefore task-irrelevant, nonetheless place additional demands on cognitive control, as such affective information is likely to capture attention. Cognitive control of Short genotype carriers is heightened when there is distracting emotional information of a negative nature, while that of Long carriers is heightened when there is distracting emotional information of a positive nature. We propose that this affective attentional bias feeds forward to trigger cognitive control to suppress task-irrelevant information (eye-gaze for emotional facial expressions) and increase attention toward task-relevant information. This attentional interference then gives rise to differential engagement of prefrontal regions. Moreover, we speculate that such top-down control is sufficient to control bottom-up affective biases so as to not influence behavior, as we found no significant differences in performance as a function of genotype, measured either by accuracy or reaction time. Of course, we cannot preclude the possibility that the lack of differences in behavioral performance reflect other mechanisms besides compensatory activation of brain regions involved in top-down control.

Our research expands upon existing findings in a number of ways. While prior neuroimaging studies have demonstrated differential neural responses in attentional biases to emotional information based on the serotonin transporter genotype (Pérez-Edgar et al., 2010) and behavioral studies have shown that groups differ in cognitive control ability depending on emotional valence (Koizumi et al., 2010), our study is the first to show differential engagement of neural systems for cognitive control over such emotional biases based on serotonin transporter genotype. We also show that these attentional biases influence engagement of cognitive control not only for the 5-HTTLPR Short carriers, but also for the 5-HTTLPR Long carriers. Typically, the negative consequences of the 5-HTTLPR genotype is associated with the short allele (e.g., increase risk of affective disorder and negative personality traits). However, in our paradigm we show that a bias toward processing task-irrelevant positive information (in the Long group) can engage the need for activation of regions involved in cognitive control just as much as a bias toward processing task-irrelevant negative information (in the Short group). This highlights the extra cognitive burden for Long carriers in positive contexts, a potential downside to this allele typically associated with "positive" outcomes (see discussion by Homberg and Lesch, 2011).

Our correlational analyses revealed individual variation within each group as well. While viewing angry faces, Short carriers who had higher anxiety tended to have higher activation of the ventromedial prefrontal cortex (vmPFC) and frontal polar regions, known to be involved in affective modulation and reappraisal (Diekhof et al., 2011). In a similar analysis, Short carriers who reported higher negative affect in their initial visit 2–8 months prior to scanning also tended to have higher activation of these regions (vmPFC and frontal pole) while viewing angry faces. While viewing happy faces, Long carriers who had higher positive affect tended to have more activation of the ventral striatum, known to be involved in reward processing (Haber and Knutson, 2010). These correlations were not present in control analyses (e.g., in Short carriers, positive affect did not correlate with any brain region). Thus, Short carriers who seem to have more extreme negative bias recruit regions that could suppress the negative affect, while Long carriers who seem to have high positive affect engage the reward system when "in their element" (i.e., happy faces promoting a positive context).

Although the present results are intriguing, a limitation of the present study is its small sample size ($N = 42$). Thus, replication would be advisable. However, an advantage of the current study, relative to most other fMRI studies of this kind, is that we included only homozygotes. Most fMRI studies of 5-HTTLPR differences include heterozygous carriers of both the Short and Long alleles (S/La) into one or the other group (S/S or La/La), thereby diminishing possible group differences and possibly clouding analyses. Future studies will need to explore the phenotype, both behaviorally and with regards to neural activation, displayed by heterozygotes. In addition, our results do not clearly isolate the process that is affected by cognitive control, whether it be a reduction in bias toward certain types of emotional information, an increased ability to deal with conflict, either at the perceptual or response level, or some other process.

In sum, our results further our understanding of the neural mechanisms underlying the inherent emotional biases of homozygous 5-HTTLPR Short carriers as compared to the inherent emotional biases of homozygous 5-HTTLPR Long carriers. Both groups show heightened engagement of face processing regions, but do so differentially depending on the valence of the face. For the Short Group, greater activity is observed in these regions when the task-irrelevant facial expression is negative in valence. In contrast, for the Long group, greater activity is observed when the task-irrelevant facial expression is positive in valence. Increased activation, and likely attention, to such task-irrelevant information appears to engage cognitive control for both groups, but differentially depending on valence. Our work suggests that when assessing the interplay between emotion and cognition, consideration of genotype, in this case related to 5-HTTLPR status, may play an important role.

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Neurophysiological processing of emotion and parenting interact to predict inhibited behavior: an affective-motivational framework

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Although inhibited behavior problems are prevalent in childhood, relatively little is known about the intrinsic and extrinsic factors that predict a child's ability to regulate inhibited behavior during fear- and anxiety-provoking tasks. Inhibited behavior may be linked to both disruptions in avoidance-related processing of aversive stimuli and in approach-related processing of appetitive stimuli, but previous findings are contradictory and rarely integrate consideration of the socialization context. The current exploratory study used a novel combination of neurophysiological and observation-based methods to examine whether a neurophysiological measure sensitive to approach- and avoidance-oriented emotional processing, the late positive potential (LPP), interacted with observed approach- (promotion) and avoidance- (prevention) oriented parenting practices to predict children's observed inhibited behavior. Participants were 5- to 7-year-old ($N = 32$) typically-developing children ($M = 75.72$ months, $SD = 6.01$). Electroencephalography was continuously recorded while children viewed aversive, appetitive, or neutral images, and the LPP was generated to each picture type separately. Promotion and prevention parenting were observed during an emotional challenge with the child. Child inhibited behavior was observed during a fear and a social evaluation task. As predicted, larger LPPs to aversive images predicted more inhibited behavior during both tasks, but only when parents demonstrated *low* promotion. In contrast, larger LPPs to appetitive images predicted less inhibited behavior during the social evaluative task, but only when parents demonstrated *high* promotion; children of high promotion parents showing smaller LPPs to appetitive images showed the greatest inhibition. Parent-child goodness-of-fit and the LPP as a neural biomarker for emotional processes related to inhibited behavior are discussed.

Keywords: inhibited behavior, emotional processing, parenting, late positive potential, children

Social reticence and heightened fearful reactivity to novelty and threat are relatively stable aspects of behavior that emerge early in life (Kagan et al., 1988; Kagan and Snidman, 1991; Hane et al., 2008) and represent specific risk factors for a range of problems related to inhibited behavior and anxiety (Biederman et al., 2001; Pérez-Edgar and Fox, 2005; Kagan, 2008; Degnan et al., 2010). However, precious little is known about the intrinsic and extrinsic factors that predict a child's ability to regulate behavior during fear- and anxiety-provoking tasks. This question is particularly challenging given that signs of inhibited behavior show immense heterogeneity and are stable across development in only 10–15% of children (Kagan, 1994; Fox et al., 2001). Recent models highlight the interactive roles of child emotional processing sensitivities and the caregiving environment in predicting inhibited and anxious behavior in children (Fox et al., 2007; Murray et al., 2009; Schmidt and Miskovic, 2013), but empirical evidence remains scarce.

The goal of the current study was to use an affective-motivational framework to identify measures of emotional processing and parenting that may interact to influence a child's ability to regulate behavior during fear- and anxiety-provoking tasks. We target core motivational dimensions of approach and avoidance because they represent separable but interacting systems that are thought to organize patterns of biobehavioral self-regulation in children and adults (e.g., Fowles, 1994; Derryberry and Rothbart, 1997; Panksepp, 1998; Carver et al., 2000; Davidson, 2000; Gray and McNaughton, 2000) Approach reflects sensitivity to rewards, emotionally positive anticipation for pleasurable activities, and behavioral approach to novelty and challenge; in contrast, avoidance reflects sensitivity to potential threats, fear and shyness, and behavioral withdrawal and inhibition in response to novelty and challenge (Derryberry and Rothbart, 1997; Panksepp, 1998; Kagan, 1999; Carver, 2004). In a typically-developing group of children, we

explored whether a neurophysiological measure of emotional processing, the late positive potential (LPP), in response to avoidance-oriented (aversive) and approach-oriented (appetitive) images interacts with avoidance- or approach-oriented parenting practices to predict the degree to which children show inhibited behavior. This exploratory research has the potential to identify a target biomarker and a target measure of caregiving relevant to individual differences in inhibited behavior, thus laying the groundwork for future, large-scale studies examining intrinsic and extrinsic mechanisms in the emergence of problems with behavioral inhibition and anxiety.

EMOTIONAL PROCESSING AND ANXIETY-RELATED INHIBITED BEHAVIOR

Across numerous studies, vigilance to and enhanced processing of aversive, fear-, and threat-relevant stimuli have been associated with anxiety (MacLeod et al., 1986; Vasey et al., 1996; Theall-Honey and Schmidt, 2006; Bar-Haim et al., 2007; Roy et al., 2008; Telzer et al., 2008; Waters et al., 2010) and have been used to explain which children at temperamental risk for anxiety go on to develop anxiety disorders (Pérez-Edgar et al., 2010, 2011). For example, Perez-Edgar and colleagues (2010) found that temperamental behavioral inhibition predicted social anxiety in adolescents, but primarily among those who evidenced biased attention to threat.

However, other studies suggest that anxious individuals show *reduced* processing of aversive or threat-relevant stimuli, suggesting attentional avoidance (Weierich et al., 2008; Bar-Haim et al., 2010). For example, in a recent large-scale community-based study, among children diagnosed with distress-related disorders (e.g., generalized anxiety disorder), high levels of internalizing symptoms predicted vigilance to angry faces, whereas among children diagnosed with social anxiety disorder, internalizing symptoms predicted avoidance of angry faces (Salum et al., 2013). These findings are consistent with models proposing that anxious individuals may show both vigilance and avoidance of threatening and aversive stimuli (Mogg et al., 2004; Weierich et al., 2008).

Compounding the complexity of this research, additional studies suggest that inhibited and anxious individuals show greater sensitivity not only to these avoidance-related aversive cues, but also to approach-related appetitive cues (Hardin et al., 2006; Bar-Haim et al., 2009; Helfinstein et al., 2011). For example, in one study, adolescents with a childhood history of inhibition, in comparison to those with no such history, showed greater striatal activation in anticipation of both monetary gain and loss (Guyer et al., 2006). Moreover, a childhood history of inhibition has also been associated with the presence of an anxiety disorder for adolescents demonstrating greater reactivity to high-incentive rewards (Pérez-Edgar et al., 2013). One interpretation of these results is that in anxiety-provoking tasks, strong approach motives may exacerbate approach-avoidance conflicts, leading to intensified fear and inhibition at the expense of approach inclinations (Asendorpf, 1990; Schmidt and Fox, 1994; McNaughton and Corr, 2004). Thus, increased processing of approach-related appetitive stimuli may indicate a specific affective sensitivity promoting inhibited behavior during fear- and anxiety-eliciting tasks (Helfinstein et al., 2012).

To examine whether processing of both aversive and appetitive stimuli is related to individual differences in inhibited behavior, the current study explored, in typically-developing children, whether a neurophysiological measures of emotional processing, the LPP, was systematically related to inhibited behavior in tasks designed to elicit fear and social-evaluative anxiety. This question represents a crucial first step in identifying whether the LPP is a viable candidate biomarker for affective vulnerability factors related to inhibition.

NEUROPHYSIOLOGICAL MEASURES OF EMOTIONAL PROCESSING: THE LATE POSITIVE POTENTIAL

Disruptions in emotional processing are often covert and rapid, and thus might not be readily apparent in observable behavior (MacLeod et al., 1986; Bar-Haim et al., 2007). Moreover, high temporal sensitivity may be necessary for measuring both facilitation and avoidance of emotional processing, which may emerge at distinct time point along the emotional processing continuum (Amir et al., 1998; Mogg et al., 2004). Scalp-recorded event-related potentials (ERPs) derived from electroencephalography (EEG) are particularly well suited for this goal given their highly sensitive temporal specificity on the order of milliseconds. Moreover, stimulus-locked ERPs are relatively independent from behavioral response requirements, and are highly feasible for measuring brain processes across a range of age and clinical groups (Fox et al., 2005; Banaschewski and Brandeis, 2007).

Research using very early-emerging ERPs suggests that anxiety-related traits and disorders are associated with both facilitation and avoidance of aversive stimuli. For example, Mueller and colleagues (2009), using a dot probe task, found that individuals with social phobia evinced greater P1 amplitudes in response to angry compared to happy faces, indicative of early facilitation of attention, but reduced P1 amplitudes once the angry faces were replaced by probe stimuli, suggesting later avoidance. On the other hand, Jetha and colleagues (2012) showed that shy adults evidence *reduced* P1 amplitudes to fearful faces, whereas Kolassa and Miltner (2006) failed to find any association between social phobia and P1 amplitudes but did find increased face-specific N170 amplitudes in response to angry faces. Although these findings suggest that anxiety-related traits are linked to both enhanced emotional processing and avoidance very early in the processing stream, results are contradictory and cannot address the full time course of emotional processing.

The LPP, is a promising candidate ERP component for measuring individual differences in approach- and avoidance-related emotional processing. The LPP reflects facilitated attention to motivationally salient emotional vs. neutral stimuli in both children and adults (Keil et al., 2002; Schupp et al., 2004; Foti and Hajcak, 2008; Hajcak and Dennis, 2009; Kujawa et al., 2012; Solomon et al., 2012). Specifically, the amplitudes of the LPP are larger for emotional vs. neutral stimuli beginning around 250 or 300 ms after a stimulus is presented and extending throughout the course of picture processing as well as after picture offset (Hajcak and Olvet, 2008). The LPP combines very rapid temporal resolution on the order of milliseconds with the ability to measure sustained emotional processing of aversive and appetitive images over seconds. In terms of its scalp distribution, the

LPP is topographically dynamic, tending to shift over time from posterior to relatively anterior regions (Solomon et al., 2012). Moreover, the LPP shows good to excellent reliability across trials (Moran et al., 2013). Despite subtle developmental differences in the LPP's latency and topography (Hajcak and Dennis, 2009; Kujawa et al., 2012; Solomon et al., 2012) that may result from brain maturation in regions involved in emotion regulation and cognitive control (Casey et al., 2000), preliminary evidence suggests that the LPP is also relatively stable over time (Kujawa et al., under review). Thus, the LPP is able to capture an extended time course of emotional processing (Moser et al., 2008; MacNamara and Hajcak, 2009, 2010; MacNamara et al., 2011) that may reflect stable individual differences in emotional processing. Moreover, previous research has shown that greater LPP amplitudes in response to aversive stimuli are associated with greater state anxiety in adults (Moser et al., 2008; MacNamara and Hajcak, 2009, 2010) and with greater trait anxiety in children (Decicco et al., 2012). No studies to date have examined whether individual differences in the LPP are related to observed inhibited behavior in children.

In the current study, our primary hypothesis was that enhanced processing of aversive stimuli measured via the LPP will predict greater inhibited behavior during fear- and social evaluative tasks. In addition, drawing on the anxiety literature documenting enhanced sensitivity to appetitive and reward-related cues (e.g., Pérez-Edgar et al., 2013), we tested the exploratory hypothesis that enhanced processing of appetitive stimuli would also be associated with greater inhibition. As discussed below, however, these associations should be moderated by caregiving context.

THE ROLE OF CAREGIVING CONTEXT

Given that individual differences in emotional processing may contribute to the ability to regulate behavior during fear- and anxiety-provoking situations, it is critical to examine extrinsic social factors, such as parenting, that shape patterns of emotional responding (Fox et al., 2007; Hane et al., 2008; Penela et al., 2012). Indeed, children showing temperamental negative affectivity may be more susceptible to the influence of parenting (Belsky and Pluess, 2009), in particular those aspects of parenting that serves to highlight approach or avoidance motives (Howes and Phillipsen, 1998; Hay et al., 2004; Dennis, 2006; Fox et al., 2007). Despite strong theoretical support for the idea that neurobiological factors influence developmental pathways to inhibition and anxiety *in conjunction* with social context, few studies have brought together these areas of research.

Mounting evidence suggests that specific patterns of parenting influence the expression of inhibited behavior, in particular via parenting's impact on emotional processing tendencies (Fox et al., 2005, 2007). Fox and colleagues (2007), in their Plasticity for Affective Neurocircuitry model, provide a framework for examining the role of environmental factors, such as parenting, in the developmental trajectory toward anxiety. They propose that the interplay between early caregiving environment and emotional processing of threat-relevant stimuli influence the link between temperament and later problems with anxiety and behavioral inhibition. In particular, this model posits that caregiving environments that highlight threat or fail to remediate a threat focus, such as low caregiver sensitivity or high caregiver intrusiveness (Ghera et al., 2006; Hane and Fox, 2006), exacerbate disrupted processing of threat-relevant stimuli and thus alter affective neurocircuitry in such a way that promotes and maintains anxiety-related behaviors in children.

This model focuses on caregiver sensitivity and intrusiveness, but does not articulate the possibility that parenting strategies that *directly* promote avoidance-related threat sensitivity or approach-related appetitive sensitivities may play a crucial role in the link between emotional processing tendencies and inhibited behaviors in anxiety-provoking circumstances. Based on motivational models of self-regulation (Higgins, 1997; Higgins and Silberman, 1998; Keller, 2008), our lab has developed an observation-based measure of parenting that reflects the degree to which parenting is characterized by behaviors that increase approach sensitivity (promotion parenting) by emphasizing accomplishment and the possibility of positive or desired outcomes, or by behaviors that increase avoidance and threat sensitivity (prevention parenting) by emphasizing safety, rules, and the need to avoid negative outcomes. For example, in one study (Dennis, 2006) levels of observed promotion parenting influenced whether child temperamental approach was associated with frustration and persistence during an emotional challenge.

Children showing greater emotional processing of aversive images in particular may benefit from high levels of promotion parenting because it fosters greater approach sensitivity by explicitly encouraging accomplishment, exploration and social participation (Higgins and Silberman, 1998). This "antidote" to enhanced avoidance-related emotional processing may ameliorate tendencies toward inhibited behavior, or even promote adaptive behavior when approach and avoidance motivations are in conflict (Asendorpf, 1990; Derryberry and Tucker, 2006; Hardin et al., 2006; Helfinstein et al., 2012; Schmidt and Miskovic, 2013). In contrast, prevention parenting, which highlights potential danger and threat, may exacerbate threat and avoidance-related emotional processing tendencies (Fox et al., 2007).

The notion that the effects of caregiving depend upon the transactions between child and parent characteristic, or goodness-of-fit, is a crucial concept here. In the current study, we examined goodness-of-fit in terms of whether the motivational fit between child emotional processing of aversive and appetitive stimuli (measured via the LPP) and promotion and prevention parenting predicts child inhibited behavior. We predicted that among children showing enhanced processing of aversive images, low levels of promotion and/or high levels of prevention would predict more inhibited behavior during fear- and anxiety-provoking tasks. Predictions concerning enhanced processing of appetitive stimuli are more difficult to generate given the lack of previous research on this topic. However, if high approach sensitivity exacerbates approach-avoidance conflicts during anxiety-provoking tasks (Asendorpf, 1990), leading to intensified inhibition, then one possibility is that if children showing enhanced processing of appetitive images experience *low* levels of promotion parenting, this reflects poor goodness-of-fit

and engenders more approach-avoidance conflict and inhibited behavior.

THE CURRENT STUDY

The study included typically-developing, early school-aged children (5- to 7-year-olds). The goal of the current study was to examine whether, in this normative group, enhanced processing of aversive and appetitive stimuli interacts with parenting that promotes approach or avoidance motivational tendencies to predict the regulation of behavior during fear- and anxiety-provoking tasks—specifically the degree to which children showed inhibition in response to these challenges. This study is novel in that it is among the first to use the LPP as a biomarker for biased emotional processing in relation to inhibited behavior, and the first to use an affective-motivational framework to conceptualize the interplay, or goodness-of-fit, between a neurophysiological measure of emotional processing and parenting that may be relevant to the emergence of problems with inhibited behavior and anxiety.

We tested the following two hypotheses: (1) Children showing larger LPP amplitudes to aversive vs. neutral images will show more inhibited behavior, but mainly when mothers show high prevention or low promotion; and (2) Children showing larger LPP amplitudes to appetitive vs. neutral images will show more inhibited behavior, but mainly when mothers show low promotion.

METHOD

PARTICIPANTS

Participants were 32 (19 males) typically developing school-aged children between the ages of five and seven ($M = 75.72$ months, $SD = 6.01$) and their caregivers. Parent-child dyads were recruited from in and around New York City. Our sample comprised of 10 Caucasian children, 13 African American children, two Asian American children, five Hispanic children and two children were reported as multiracial by their caregivers. Each child and caregiver spent ∼3 h in the laboratory as part of a larger study on emotional development and was compensated $100 for their time. Additionally, children were given certificates of completion and astronaut ice cream at the end of their visits.

This study was derived from a larger study that yielded a previous publication examining the LPP in school-aged children (Solomon et al., 2012). This goal of this study was to test the neurodevelopmental question of whether, like adults, children at this age evidence larger LPP amplitudes to emotional vs. neutral images; this study did not examine the LPP in relation to parenting to predict inhibited behavior, the goal of the current study. Eighty-two percent of ($n = 39$) participants from the previous study were included in the current analyses. The selection criterion was the presence of observed parenting data, which was missing for seven children due to task refusal (three) and data loss due to poor or lost video recording (four).

PROCEDURES AND MATERIALS

Upon arrival to the laboratory, an experimenter played a game with the children, while another experimenter obtained informed consent from the parents. Immediately following, verbal assent was obtained from the child. Children were subsequently escorted by an experimenter to another room to begin the EEG portion of the visit. While EEG was recorded from children, parents completed various questionnaires pertaining to their child's temperament and behavior. After the EEG recording was completed and children took a short break, children proceeded to complete the behavioral portion of the visit with their parents, including the black box, storytelling and wait task in addition to several behavioral tasks not included in the current study.

PASSIVE VIEWING PROCEDURE AND STIMULI

Once EEG setup was complete, children were moved to a dimly lit experiment booth equipped with a video camera and were instructed not to move or talk while passively viewing 90 images from the IAPS. Children were seated 65 cm from a 17″ computer monitor as images were presented in full screen and color using Presentation software (Version 2, Neurobehavioral Systems, Inc.; Albany, CA) on an IBM computer. The images were presented in a randomized order, and each stimulus was presented for 2000 ms with an inter-stimulus interval of 500 ms.

Images were 30 unpleasant [1], 30 pleasant [2], and 30 neutral [3] pictures selected from the International Affective Picture System (IAPS; Lang et al., 2005). Unpleasant images are characterized by the IAPS developers as aversive: meaning to elicit affect related to defensive motivation, such as fear and disgust. In contrast, pleasant images are characterized as appetitive, in that they elicit affect related to approach motivation, such as joy, excitement, desire, or affiliation. The specific aversive images in the current study were chosen to reflect threat or potential threat (e.g., wreckage and war images) in a developmentally appropriate way. Aversive images had a mean valence of 3.32 ($SD = 1.74$) and a mean arousal of 5.79 ($SD = 2.10$). Appetitive images (e.g., food, babies, cuddly animals) had a mean valence of 7.45 ($SD = 1.50$) and a mean arousal of 4.76 ($SD = 2.30$). Neutral images (e.g., household and nature images) had a mean valence of 5.29 ($SD = 0.74$) and a mean arousal of 2.81 ($SD = 0.65$)[4]. Valence and arousal ratings are on a 9-point scale, with lower ratings for valence and arousal corresponding to more aversive and less arousing, respectively.

[1]The IAPS numbers for aversive images were 1050, 1120, 1201, 1300, 1321, 1930, 2120, 2130, 2688, 2780, 2810, 2900, 3022, 3230, 3280, 5970, 6190, 6300, 6370, 7380, 9050, 9250, 9421, 9470, 9480, 9490, 9582, 9594, 9600, 9611.

[2]The IAPS numbers for appetitive images were 1460, 1463, 1601, 1610, 1710, 1750, 1811, 1920, 1999, 2070, 2091, 2165, 2224, 2311, 2340, 2345, 2791, 4603, 5831, 7325, 7330, 7400, 7502, 8031, 8330, 8380, 8461, 8490, 8496, 8620.

[3]The IAPS numbers for neutral images were 5220, 5711, 5740, 5750, 5800, 5820, 7000, 7002, 7004, 7006, 7009, 7010, 7025, 7031, 7035, 7041, 7050, 7080, 7090, 7100, 7140, 7150, 7175, 7190, 7224, 7233, 7235, 7236, 7595, 7950.

[4]Of the stimuli included in this study, 15 unpleasant, 8 pleasant, and 6 neutral images have normative ratings obtained by the IAPS developers from children aged seven to nine using the same rating system as adults and are as follows for valence and arousal respectively: Unpleasant ($M = 3.74$, $SD = 1.22$; $M = 6.04$, $SD = 1.05$), Pleasant ($M = 8.27$, $SD = 0.84$; $M = 6.04$, $SD = 0.69$), and Neutral ($M = 5.90$, $SD = 0.18$; $M = 2.91$, $SD = 0.13$). We did not select all child-normed stimuli because the current study was part of a larger study initiated when children were aged 5–6 (outside the norm age group) and stimuli were selected for age- and task-appropriateness rather than norms.

OBSERVED INHIBITED BEHAVIOR

After EEG was recorded, inhibited behavior was measured during the black box and storytelling tasks, both adapted from the Laboratory Temperament Assessment Battery (LabTAB; Goldsmith et al., 1995).

The 2-min black box task was designed to elicit inhibited behavior to a novel and fear-inducing stimulus while in the presence of an adult. After an opaque black box with a covered opening on its side was placed on the center of the table, the experimenter neutrally told the child, "This is my special black box. There is something kind of scary inside. Would you like to put your hand in this hole to feel what is inside?" The task ended when the child reached his or her hand into the opaque box and removed the brightly colored soft squeezable ball covered in tentacles or after 2 min had passed. Inhibited behavior was measured as the latency (in seconds) before children placed their hand in the black box, with higher scores indicating greater inhibition.

The 7-min storytelling task was designed to elicit inhibited behavior related to social anxiety in response to the threat of criticism. Children were given a picture book and told that an assistant who was an expert on telling stories would listen to them tell a story and assign them a grade. After the child was finished telling his story, the experimenter praised him and gave him an "A+." Inhibited behavior was quantified as the amount of time the child waited (latency score) before beginning storytelling, with higher scores indicating greater inhibition. Coders were trained to record latency using practice videotapes until reaching 80% agreement.

OBSERVED PARENTING AND BEHAVIORAL CODING

Parenting was observed during a waiting task (WT; Carmichael-Olson et al., 1985). The WT is a parent-child task designed to both elicit child frustration as well as enable observation of parenting behaviors in response to child frustration. Parent-child dyads were alone in a room for 10 min after the experimenter handed the parent a clipboard of several papers to complete, gave the child a boring plastic toy and placed an attractively wrapped surprise on the table. The parent was previously instructed as soon as the experimenter left the room to tell the child, "This is a surprise for you, but you must wait until I finish my work to open it" (Cole et al., 2003). The parent was given no further instructions on how to interact with his or her child through the duration of the task. After the wait task was complete, the child was permitted to open and play with the wrapped yo-yo.

Parenting behavior focusing on reward or threat was coded using the Promotion/Prevention Parenting Coding System (Dennis and Cole, 2001; Dennis, 2006). Parenting behaviors and verbalizations were coded within 10-s epochs during the waiting task and were summed to create a total score. Parental behaviors that fit neither category were labeled non-codable (50.01% were coded as non-codable).

Promotion parenting focuses on the promotion of positive child behavior and orienting children toward potential reward. Examples include eliciting competent action ("Do you know what that is?"), encouraging compliance for a positive reason ("If you wait, you can open the present."), guiding ("They're going to bring your snack in just a minute."), commenting on the positive ("This won't take long."), giving encouragement through affection and appreciation ("Great job.") and maternal withdrawal of maternal positive reinforcement (I'm sad that you're not listening to me.").

Prevention parenting focuses on child safety, the prevention of negative outcomes, and orienting children toward potential threat. Examples include eliciting appropriate behaviors and safety ("They asked you to wait."), rewarding conformity with rules ("Thank you for not opening the present."), prohibiting and intervening ("Listen I don't want you to…"), encouraging compliance for a negative reason or rule (" Because I said so."), commenting on the negative ("Uh oh."), and criticizing ("You're being bad."). Two coders were trained to code promotion/prevention parenting by using practice videotapes until they reached 80% agreement. Then, inter-rater reliability using Cohen's Kappa was conducted to determine consistency among raters on the basis of 20% of the videos (7 videos), randomly chosen. The Kappa coefficient was 0.73, ($p < 0.001$), reflecting substantial agreement (Landis and Koch, 1977).

EEG RECORDING AND DATA REDUCTION

Using the Biosemi system (BioSemi; Amsterdam, NL), EEG activity was recorded continuously via 64 Ag/AgCl scalp electrodes embedded in an elasticized nylon cap based on the international 10/20 system. Eye movements were monitored by electrooculogram (EOG) signals from electrodes placed 1 cm above and below the left eye (to measure vertical eye movements) and one cm on the outer edge of each eye (to measure horizontal eye movements). The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio. EEG was recorded at a sampling rate of 512 Hz and amplified with a band pass of 0.16–100 Hz. The voltage from each active electrode was referenced online with respect to a common mode sense active electrode producing a monopolar (non-differential) channel. All data preparation after recording was conducted using Brain Vision Analyzer (Version 2.2, GmbH; Munich, DE). Data were re-referenced offline to an average mastoid reference and filtered with a high pass frequency of 0.1 Hz and a low pass frequency of 30 Hz. The EEG was segmented for each trial beginning 400 ms prior to picture onset and continuing for 2000 ms. Baseline correction was performed for each trial, using the 400 ms prior to picture onset.

EEG was corrected for blinks using independent components analysis. Artifacts were identified using the following criteria: any data with voltage steps exceeding 75 μV, changes within a segment that were greater than 200 μV, amplitude differences greater than ±120 μV within a segment, and activity lower than 0.2 μV per 100 ms were considered artifacts and excluded from analyses. Trials were also visually inspected for remaining artifacts. Data from individual channels containing artifacts were rejected on a trial-by-trial basis.

The LPP was measured as mean amplitudes for each picture type separately, in three time windows based on visual inspection of the data: early (300–700 ms), middle (700–1200 ms) and late (1200–2000 ms). Examining multiple time windows is particularly important because vigilance-avoidance patterns of processing aversive stimuli have been shown to vary over time (Holmes et al., 2008; Mueller et al., 2009), including studies of the LPP showing reduced LPPs to aversive stimuli among

anxious individuals in *later* time windows (Weinberg and Hajcak, 2011). The LPP was calculated as the mean amplitude separately for each window in three broad regions. Regions were chosen based on visual inspection of the topographical distribution of the LPP (see **Figure 2**) and were consistent with previous findings regarding the diffuse scalp distribution of the LPP in children (Dennis and Hajcak, 2009). Regions were: posterior (PO4, PO8, O2, Oz, POz, PO3, PO7, and O1), central (C4, C6, CP6, Cz, CPz, C3, C5, and CP5), and anterior (FC4, F4, F6, Fpz, AFz, FC3, F3, and F5). Difference scores were generated for each four window/region combinations in which LPP amplitudes were maximal (e.g., posterior/early, central/middle, central/late, and anterior/late) to quantify the degree to which aversive or appetitive vs. neutral images generated larger LPPs (e.g., LPPs aversive—LPP neutral images). These difference scores were used as an index of the degree of emotional processing of aversive and appetitive images.

ANALYTIC PLAN

Interactions between parenting behavior (promotion or prevention) and each of the four LPP aversive –neutral difference and four LPP appetitive-neutral difference scores (e.g., early/posterior) predicting inhibitory behavior (Black Box and Storytelling tasks) were tested using Ordinary Least Squares multiple-regression interactions. For both dependent variables, two predictors (e.g., promotion parenting and LPP aversive-neutral difference scores) were entered in step one, and their interaction term in step two. Simple models were used to maximize power and ensure that sample size was over 30 and more than 10 cases per predictor were in each model[5]. A total of 16 regression models were estimated.

All variables in these analyses were screened first for univariate normality. Our storytelling latency variable was positively skewed (2.08) because of a few very inhibited children who delayed storytelling to the maximum time limit of 300 s. Kurtosis was also high (3.81) so violations of normality led us to do a square-root transformation (square root is taken of each score) which brought it within normal parameters (skew = 1.25, kurtosis = 0.79). This transformation was chosen because the data had no negative values or scores between 0 and 1. Also it produced a normal distribution without completely removing the inherent skew in the data which reflects variation in the inhibitory behavior that is of interest (Osborne, 2002). All other study variables were relatively normal with skewness and kurtosis indices less than ±2. The Mahalanobis Distance statistic was used to test multivariate normality and potential undue influence of outliers–cases with an unusual combination of scores on two or more variables. No cases were found to be significant multivariate outliers (with four predictors the critical value for the Mahal distance = 18.467), so follow-up analyses were not run. Predictor variables were centered (deviated from their mean) to reduce potential multicollinearity between interaction terms and their constituent variables. Significant interactions were probed following procedures described by Jaccard et al. (1990) and figures were created using high/low values one standard deviation above/below the mean.

[5]Most experts recommend a minimum sample size at least 30, and at least 8 cases per predictor in multiple regression. We did meet these minimum standards with a sample size of 32 and no more than 3 terms in each equation. Although a larger sample size would be preferred for testing interactions. The most obvious limitation created by a small sample size is the lack of power to find hypothesized effects and an inflated type II error rate. Thus, the ability to find moderator effects is attenuated. These theoretically-driven predictions are testing joint effects of context and psychophysiology not previously tested. We believe this is currently the largest data set available to test moderating effects of temperament, parenting and LLP, and that regression analyses provide the best test of the predicted linear interactions between continuous predictors.

RESULTS

DESCRIPTIVE STATISTICS AND CORRELATIONS AMONG STUDY VARIABLES

Table 1 presents descriptive statistics for observed maternal promotion and prevention during the waiting task, and observed child inhibited behavior during the black box and storytelling tasks. Child gender and ethnicity were not significantly associated with any study variables and are thus not included in analyses below. As can be seen in **Figures 1**, **2**, which shows the scalp distribution of the LPP aversive—neutral and appetitive—neutral difference scores during each time window, the scalp topography of the LPP shifts from posterior to relatively anterior (central-frontal) regions over the duration of the LPP (300–2000 ms). **Figure 3** shows the waveform for the LPP to aversive, appetitive, and neutral images. Bivariate correlations were conducted among observed maternal promotion and prevention during the waiting task, observed child inhibited behavior during the black box and storytelling tasks, and the LPP aversive-neutral and appetitive-neutral difference score at the early/posterior, middle/central, late/central, and late/anterior time-window/region.

Parenting and child inhibited behavior variables were not significantly intercorrelated, although inhibited behavior during each task was marginally positively correlated ($p = 0.07$). In contrast, LPPs were significantly positively intercorrelated. The multiple time-window/regions of the LPP aversive-neutral difference scores correlated with one another (significant *rs* ranged from 0.47 to 0.64). The same was true of the LPP appetitive-neutral difference scores (significant *rs* ranged from 0.37 to 0.89). Additionally, there were positive associations between LPP aversive-neutral and appetitive-neutral difference scores (significant *rs* ranged from 0.37 to 0.54). Given that inhibited behavior during each task was only marginally positively correlated and we believe that these two tasks tap into different dimensions of inhibited behavior, with the black box task eliciting fear and the storytelling task eliciting social anxiety, we examined each separately in analyses below.

Table 1 | Descriptive statistics.

Variable	Mean	*SD*	Range
Promotion parenting	6.00	4.16	0.00–13.00
Prevention parenting	12.28	8.67	0.00–30.00
Inhibited behavior black box task	37.44	38.53	4.00–120.00
Inhibited behavior social storytelling task	56.13	80.61	1.00–300.00

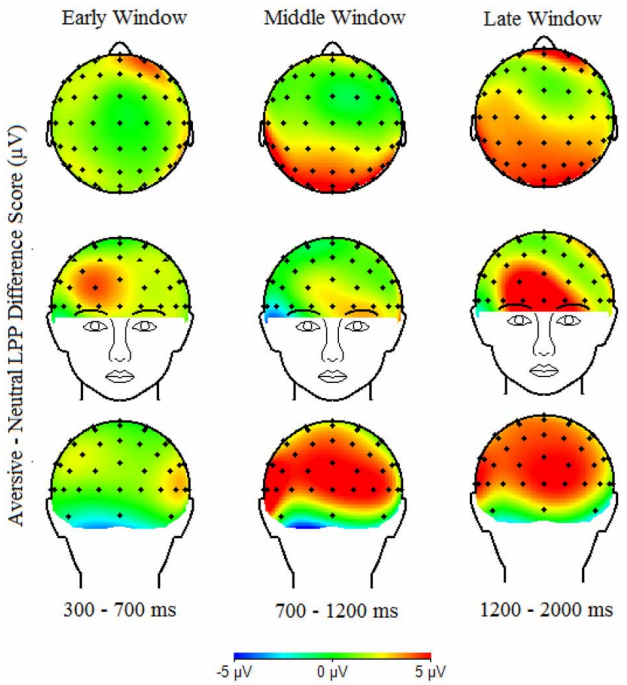

FIGURE 1 | Scalp topography of the LPP Aversive—Neutral difference score in the early (300–700 ms), middle (700–1200 ms) and late (1200–2000 ms) time windows.

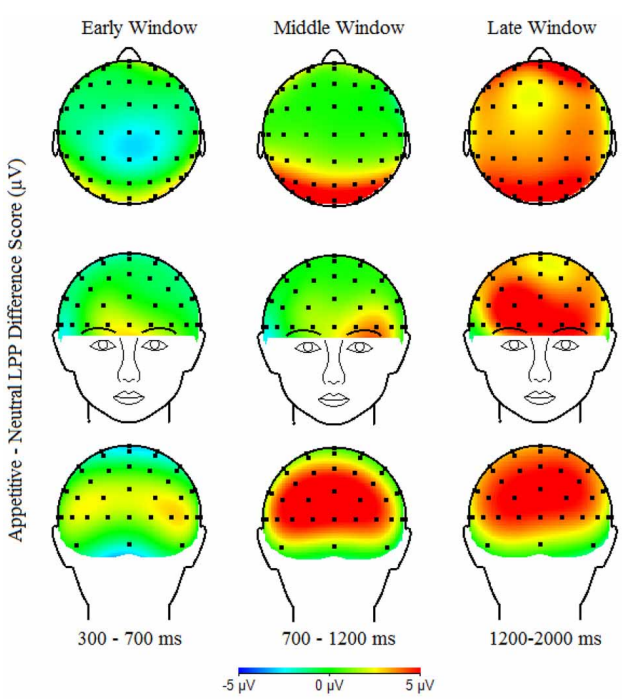

FIGURE 2 | Scalp topography of the LPP Appetitive—Neutral difference score in the early (300—700 ms), middle (700–1200 ms) and late (1200–2000 ms) time windows.

EMOTION PROCESSING × PARENTING PREDICTING INHIBITED BEHAVIOR

We tested the specific hypothesis that children showing greater emotional processing of aversive stimuli (greater LPPs to aversive vs. neutral images) will show more inhibited behavior, but mainly when mothers show high prevention or low promotion parenting. We also tested the exploratory hypothesis that children showing greater emotional processing of appetitive stimuli who also have mothers showing low promotion will also show more inhibited behavior. Dependent variables were observed inhibited behavior during black box task and storytelling tasks. **Figures 4**, **5** show the significant interactions between LPPs (anterior/late and central/middle windows) to aversive stimuli and maternal promotion parenting on inhibited behavior during the black box task and the storytelling task, respectively ($t = -2.67$, $p < 0.05$, $\Delta R^2 = 0.186$ and $t = -2.37$, $p < 0.05$, $\Delta R^2 = 0.155$). **Figure 6** shows the marginally significant interaction between the LPP (central/late window) to appetitive stimuli and maternal promotion parenting on inhibited behavior during the storytelling task, $t = -1.86$, $p = 0.07$, $\Delta R^2 = 0.108$ (see **Table 2**).

As predicted, as preferential processing of aversive stimuli (larger LPPs) increased, observed behavior during the black box ($b = 4.44$) and storytelling tasks ($b = 0.67$) also becomes more inhibited, but only for children with relatively low promotion (approach-focused) parenting (see **Figures 4**, **5**, respectively). For children with high promotion parenting, larger LPPs to aversive vs. neutral stimuli did not predict inhibited behavior during the black box task ($b = 0.03$) nor during the storytelling task ($b = -0.07$). Interestingly, it was the children with smaller LPPs to aversive stimuli and low promotion parenting that show the *least* inhibited behavior. Prevention parenting did not significantly interact with LPP measures of aversive image processing to predict inhibited behavior.

In contrast to our predictions, as preferential processing of appetitive vs. neutral stimuli (smaller LPPs) *decreased*, inhibition during the storytelling task increased ($b = -0.37$), but only for children with relatively high promotion (approach-focused) parents (see **Figure 6**). For children of parents showing low promotion, individual differences in LPPs to appetitive vs. neutral stimuli did not predict inhibited behavior during the storytelling task ($b = 0.23$). Moreover, as seen in **Figure 6**, it is the children with larger LPPs to appetitive stimuli with parents showing high promotion that show the *least* inhibited behavior.

DISCUSSION

The goal of the current study was to use an affective-motivational framework to identify measures of emotional processing and parenting that interact to influence a child's ability to regulate inhibited behavior during fear- and anxiety-provoking tasks. We explored whether the LPP, as a highly sensitive measure of emotional processing, could capture individual differences in the processing of approach-related (appetitive) and avoidance-related (aversive) stimuli that predicted the degree of inhibited behavior during fear and anxiety-related emotional challenges *in interaction* with avoidance- or approach-oriented parenting practices. Consistent with hypotheses, we found that children showing larger LPPs to aversive images also showed more inhibited

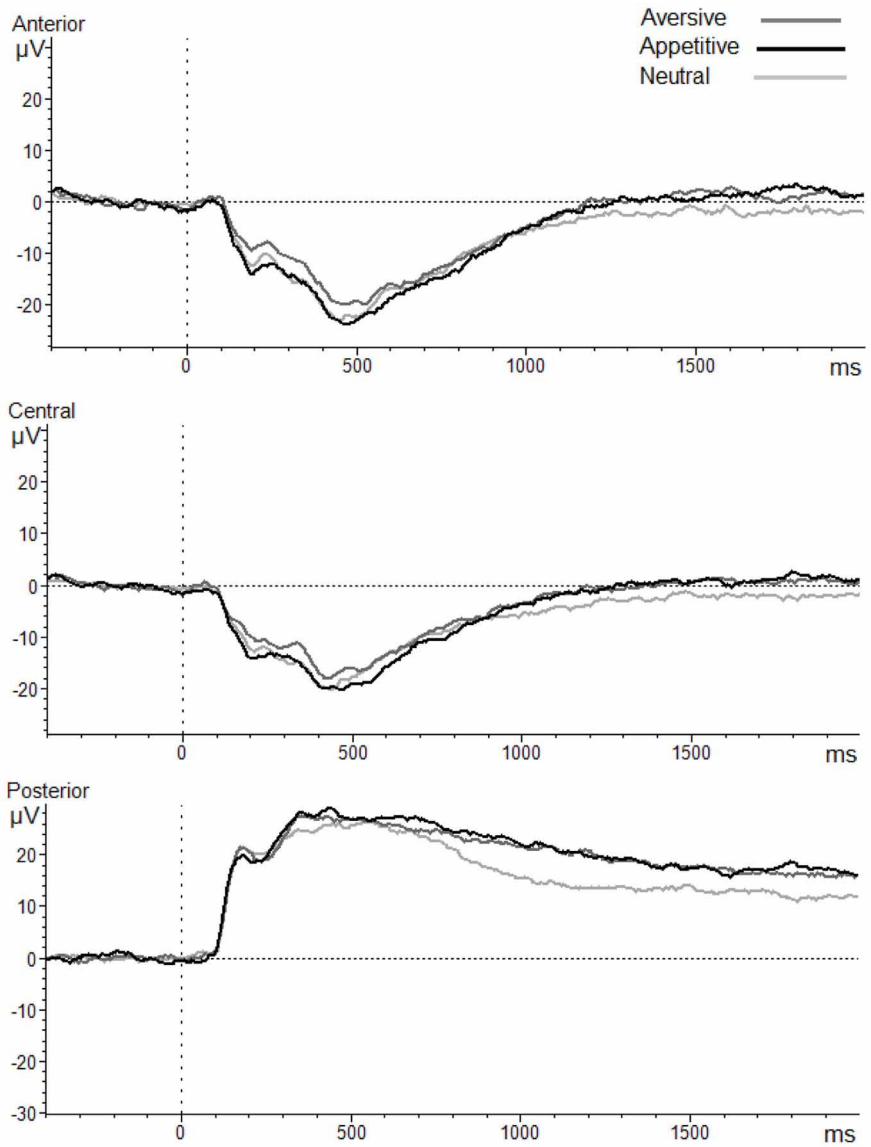

FIGURE 3 | LPP amplitudes in posterior, central and anterior regions during passively viewing aversive, appetitive, and neutral IAPS images.

behavior during both tasks, but only when parents demonstrated *low* promotion. In contrast, larger LPPs to appetitive images predicted less inhibited behavior during the social evaluative task, but only when parents demonstrated *high* promotion. Interestingly, those children of high promotion parents who also evidenced smaller LPPs to appetitive images showed the greatest inhibition. Results suggest that emotional processing of both appetitive and aversive stimuli should be considered when examining inhibited behavior. Results also suggest that it is crucial to further investigate how parenting that highlights approach and avoidance may be important social contexts in which to examine a child's emotional processing sensitivities, and their role in risk and resilience.

Findings of the current study capitalize on the use of both neurophysiological and observation-based measures to examine the interplay among intrinsic and extrinsic processes that predict the expression of inhibited behavior during emotional challenges that trigger fear and anxiety associated with social evaluation. To our knowledge, this was the first study to provide evidence to suggest that the LPP, when examined within the social context of parenting, may be a useful measure of emotion processing sensitivities in future studies examining the developmental trajectory of inhibited behavior and risk for anxious pathology.

As predicted, children showing enhanced processing of aversive stimuli also showed more inhibited behavior during both tasks, but only for children whose mothers demonstrated low levels of approach-focused promotion parenting. Interestingly, for children of mothers with high levels of promotion parenting, increasing LPP amplitudes to aversive images did not predict change in inhibited behavior. These findings highlight that high

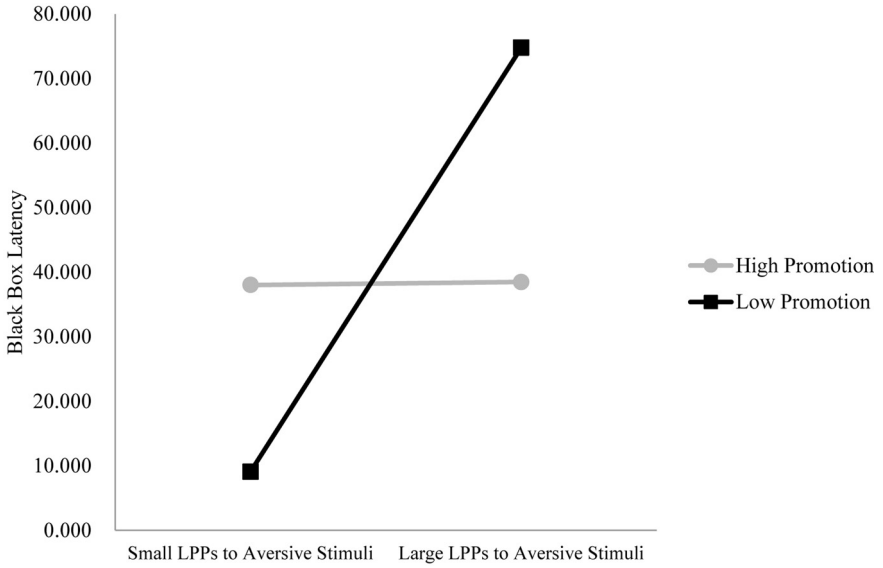

FIGURE 4 | LPPs to aversive stimuli interact with promotion parenting to predict inhibited behavior during the black box task. *Note*: Longer latencies indicate more inhibited behavior. LPPs are quantified as the difference between LPP amplitudes to aversive minus LPPs to neutral images in the anterior region/late window. Model with LPP (anterior/late), Promotion Parenting, LPP × Promotion: $\Delta R^2 = 0.186$; unstandardized regression coefficients: High Promotion group $b = 0.03$, $t_{(28)} = 0.02$, $p > 0.05$; Low Promotion group $b = 4.44$, $t_{(28)} = 2.63$, $p < 0.01$.

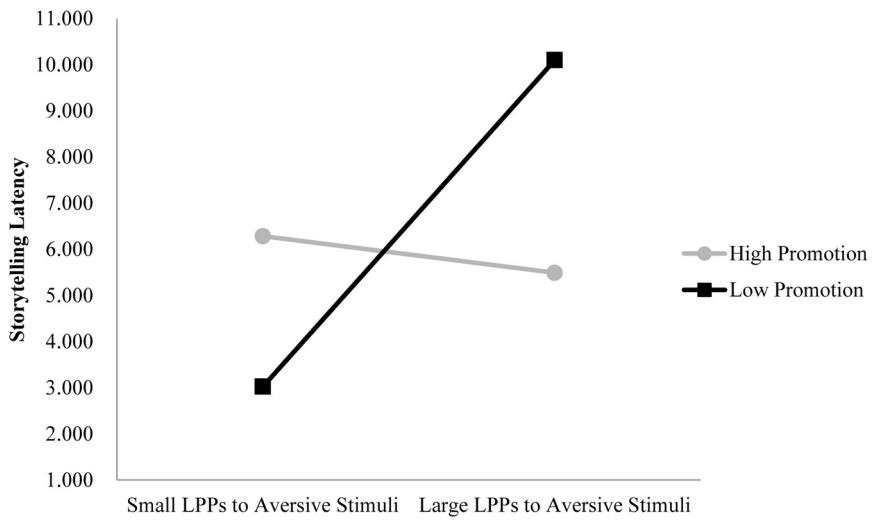

FIGURE 5 | LPPs to aversive stimuli interact with promotion parenting to predict inhibited behavior during the storytelling task. *Note*: Longer latencies indicate more inhibited behavior. LPPs are quantified as the difference between LPP amplitudes to aversive minus LPPs to neutral images in the central/middle window. Model with LPP (central/middle), Promotion Parenting, LPP × Promotion: $\Delta R^2 = 0.155$; unstandardized regression coefficients: High Promotion group $b = -0.07$, $t_{(28)} = -0.40$, $p > 0.05$; Low Promotion group $b = 0.67$, $t_{(28)} = 3.47$. $p < 0.01$.

promotion parenting may serve a protective role for children who show enhanced avoidance-related processing of aversive stimuli – these children's behaviors are indistinguishable from children showing less emotional processing of aversive stimuli. Moreover, findings suggest that *reduced* opportunities to interact with caregivers in ways that could counteract avoidance-motivated affect—rather than increased opportunities to interact in ways that promote avoidance sensitivity (prevention parenting)—influenced children's abilities to regulate behavior in anxiety-related contexts. If children who show greater neurocognitive sensitivity to aversive stimuli have parents who do *not* highlight approach-related goals, this could exacerbate processing of aversive and threat-related stimuli, reduce ability to detect appetitive cues or cues for safety, and alter affective neurocircuitry accordingly to promote or maintain inhibition in children (Fox et al., 2007; Schmidt and Miskovic,

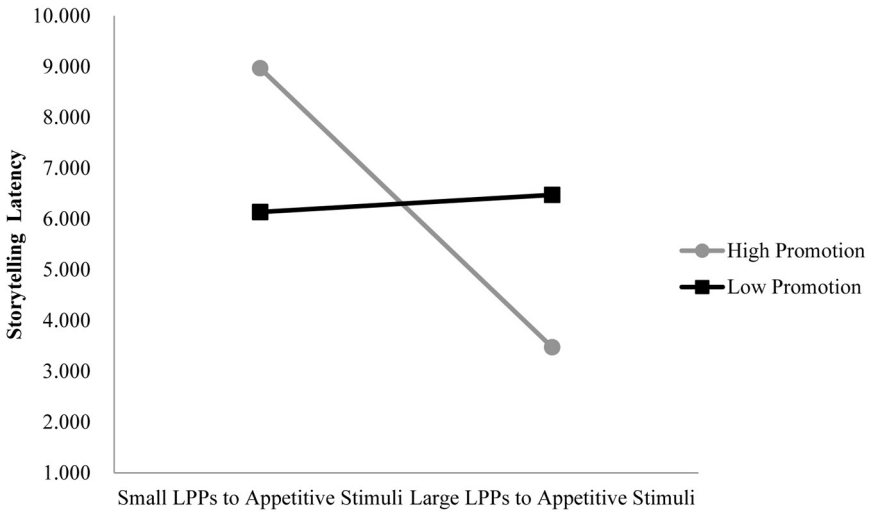

FIGURE 6 | LPPs to appetitive stimuli interact with promotion parenting to predict inhibited behavior during the storytelling task. *Note*: Longer latencies indicate more inhibited behavior. LPPs are quantified as the difference between LPP amplitudes to appetitive minus LPPs to neutral images in the central/late window. Model with LPP (central/late), Promotion Parenting, LPP × Promotion: $\Delta R^2 = 0.108$; unstandardized regression coefficients: High Promotion group $b = -0.37$, $t_{(28)} = -1.91$, $p < 0.05$, one tailed; Low Promotion group $b = 0.02$, $t_{(28)} = 0.12$, $p > 0.05$.

Table 2 | Standardized regression coefficients for interaction terms.

	Beta	*t*	*p*-value
DEPENDENT VARIABLE—BLACK BOX LATENCY		$F_{(3, 28)} = 3.14^{*}\ \Delta R^2 = 0.186^{**}$	
Step 2			
Promotion parenting	0.048	−0.29	0.78
Lpps to aversive stimuli (anterior/late)	0.429	2.4	0.02*
Promotion parenting × lpps to aversive stimuli (anterior/late)	−0.474	−2.64	0.01**
DEPENDENT VARIABLE—STORYTELLING LATENCY		$F_{(3, 28)} = 2.71^{\dagger}\ \Delta R^2 = 0.155^{*}$	
Step 2			
Promotion parenting	−0.08	−0.45	0.66
Lpps to aversive stimuli (central/middle)	0.34	2.02	0.05*
Promotion parenting × lpps to aversive stimuli (central/middle)	−0.4	−2.37	0.03*
DEPENDENT VARIABLE—STORYTELLING LATENCY		$F_{(3, 28)} = 1.36\ \Delta R^2 = 0.108^{\dagger}$	
Step 2			
Promotion parenting	−0.01	−0.05	0.96
Lpps to appetitive stimuli (central/late)	−0.3	−1.47	0.15
Promotion parenting × lpps to appetitive stimuli (central/late)	−0.36	−1.86	0.07†

$^{\dagger}p < 0.10$, $^{*}p \leq 0.05$, $^{**}p \leq 0.01$.

2013). Taken together, these results suggest that parents who show relatively low levels of promotion with children who show greater emotional processing of aversive stimuli may miss opportunities to bolster children's abilities to effectively regulate behavior when confronted with fear- and anxiety-related challenges.

Exploratory analyses also revealed that children showing enhanced processing of appetitive stimuli also showed *less* inhibited behavior during the storytelling task, but only for children whose mothers demonstrated high levels of promotion. For children of mothers with low levels of promotion, increasing LPP amplitudes to appetitive images did not predict change in inhibited behavior (the inverse was true for findings with aversive image processing reported above). Moreover, we found, counter to prediction, that children of high promotion parents who showed *less* processing of appetitive images showed the most inhibited behavior. This effect is puzzling, but one possibility is that the poor fit between a child showing low approach-related emotional processing and a parent showing high approach-related promotion parenting leads to less effective regulation during emotional challenges. Mirroring these results, Dennis (2006) found that the degree to which there was poor goodness-of-fit between high parental promotion and low child temperamental approach reactivity predicted whether a child evidenced both increased frustration and decreased persistence during lab-based tasks.

In the current study, the fact that appetitive picture processing effects only emerged in the social-evaluative storytelling task may relate to a conflict between task demands and motivational drive. That is, the motive to obtain positive social feedback is a strong approach-related motive, which could be in conflict with blunted appetitive emotional processing tendencies indicated by reduced LPPs to appetitive images. High levels of promotion parenting attempting to motivate a child's behavior with approach cues to which a child may be relatively insensitive may fail to appropriately scaffold a child's self-regulatory abilities. In contrast, for children who evidenced enhanced appetitive image processing, high promotion parenting may be an advantageous parenting practice to socialize children to effectively tackle achievement-oriented task demands when confronted with social-evaluative threat.

Taken together, findings underscore the possibility that promotion parenting is a social context that influences links between child emotional processing and inhibited behavior in typically-developing children. These results could thus set the stage for future research on the impact of motivationally-distinct patterns of parenting on positive outcomes in children at risk for problems with behavioral inhibition and anxiety (Belsky and Pluess, 2009). Of note, while promotion parenting interacted in distinct ways with LPP measures of aversive and appetitive picture processing, it did so at later stages of processing (the middle and late windows). This hints at the possibility that later-emerging and perhaps more effortful attentional processes are more sensitive to both costs and benefits of the socialization context (Dennis, 2006).

In addition, we found that promotion, but not prevention parenting, influenced whether emotional processing sensitivities influenced children's behavior during both the fear task (black box) and the social evaluative task (storytelling task). It may be that in this typically-developing group of children, the beneficial presence of approach-focused promotion parenting may be particularly important for predicting the expression of inhibition in response to fear and anxiety (Shechner et al., 2011). Future studies should measure sensitivities to both aversive and appetitive stimuli in the context of parenting when examining predictors of inhibited behavior during fear- and anxiety-inducing tasks. It is important to note that, given the greater frequency of observed prevention parenting, it is possible that some elements of the waiting task, such as concerns of compliance in a lab setting, were more likely to elicit prevention-focused parenting (although promotion parenting is also used to promote compliance; Higgins and Silberman, 1998). This is consistent with a previous study documenting greater frequency of prevention vs. promotion parenting in the waiting task (Dennis, 2006). If prevention parenting was preferentially elicited, this might have reduced our ability to detect subtle individual differences in this aspect of parenting, thus reducing predictive power.

In interpreting findings, we must consider that the current study differed from others in several important ways. First, an important methodological difference is that previous studies examining emotional processing or attention to emotion, particularly to threat, typically generate scores based on reaction times on a task involving attentional competition between threat and neutral stimuli, such as the dot probe or emotional Stroop (Bar-Haim et al., 2007). In contrast, in the current study, the LPP was generated in response to passive viewing of individual images with no task demands, and thus reflect performance-independent aspects of emotional processing. Indeed, in one study using an emotional interruption task in children age 8–13, the LPP was not consistently associated with behavioral responses (Kujawa et al., 2012).

Another important methodological difference was that the previous studies use a range of stimuli to measure emotional processing tendencies, most notably human faces, threat-relevant words, and, in the case of appetitive processing, rewards. In the current study, stimuli were taken from the IAPS, which reflect general aversive and appetitive affective dimensions, rather than being specific to reward or threat (although a large percentage of the IAPS selected in this study (87%) were specifically threat-related, such as images of threatening animals, angry human faces, guns pointed in the direction of the viewer). Moreover, some appetitive images in the present study (e.g., cute, furry animals and babies) were relatively low salience and arousal compared to studies using reward, erotica, or other such stimuli, many of which are not developmentally appropriate. Overall, however, IAPS may be more evocative and have more robust effects on both behavior and electrocortical activity compared to face (Kujawa et al., 2012) or word stimuli typically used to measure biased attention. Thus, the relatively high salience of the IAPS images used in the current study may have strengthened measurement of individual differences in emotional processing.

Limitations of this current research study include a relatively small sample size, which restrict the statistical power of our analysis, although we did meet sample size requirements to test for interactions. Additionally, we did not include any self-report data on the children's subjective ratings of both the valence and the arousal level of the IAPS images, given that in previous studies in our lab, children were unable to reliably rate the images (Derryberry and Rothbart, 1997). Thus, we are unable to determine the degree to which the children found the aversive images to be threatening, although previous research using these images shows that like adults, children perceive these images as aversive and arousing (Sharp et al., 2006). Since this is a normative group of children, results are inconclusive in terms of the utility of the LPP for measuring emotional processing sensitivities in clinically anxious and inhibited children. This is a crucial direction for future research, but the current study is an important first step in pursuit of this goal.

The current study is the first study how the LPP as a measure of attention to aversive and appetitive stimuli interacts with the socialization context to predict inhibited behavior. This question is particularly important for the target age group, school-aged children, which is a developmental period during which behavioral inhibition may trigger a cascade of biopsychosocial processes that

create risk for later anxious psychopathology (Fox et al., 2005). Taken together, results suggest that the LPP holds promise as a biomarker for biased emotional processing of aversive and appetitive stimuli which may shape the developmental trajectory of inhibition, and that parenting that is motivationally-relevant is an important social context in which to examine this development. Future research should test this model in the context of pediatric anxiety, tracking whether individual differences in the LPP in response to aversive and appetitive stimuli and parental focus on approach and avoidance predict change and continuity in anxiety symptoms and atypical behavioral inhibition over time.

AUTHOR NOTE

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Cortical organization of inhibition-related functions and modulation by psychopathology

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Individual differences in inhibition-related functions have been implicated as risk factors for a broad range of psychopathology, including anxiety and depression. Delineating neural mechanisms of distinct inhibition-related functions may clarify their role in the development and maintenance of psychopathology. The present study tested the hypothesis that activity in common and distinct brain regions would be associated with an ecologically sensitive, self-report measure of inhibition and a laboratory performance measure of prepotent response inhibition. Results indicated that sub-regions of DLPFC distinguished measures of inhibition, whereas left inferior frontal gyrus and bilateral inferior parietal cortex were associated with both types of inhibition. Additionally, co-occurring anxiety and depression modulated neural activity in select brain regions associated with response inhibition. Results imply that specific combinations of anxiety and depression dimensions are associated with failure to implement top-down attentional control as reflected in inefficient recruitment of posterior DLPFC and increased activation in regions associated with threat (MTG) and worry (BA10). Present findings elucidate possible neural mechanisms of interference that could help explain executive control deficits in psychopathology.

Keywords: inhibition, anxiety, depression, DLPFC, attentional control

INTRODUCTION

Despite a lack of consensus on how best to define executive function (EF), neuropsychological and neuroimaging (Collette et al., 2005) research indicates that EF may be usefully characterized as a collection of correlated yet dissociable processes: inhibition, set shifting, and working memory updating (e.g., Miyake et al., 2000). Inhibition-related processes in particular are considered to be critical for top-down cognitive control and its translation to real-word, everyday behavior, including self-regulation and emotion regulation (Zelazo and Cunningham, 2007). Further, inhibition-related functions are essential for efficient working memory function, limiting access to and removing information that is no longer necessary (Friedman and Miyake, 2004). Cognitive disruptions in these processes are a prominent source of distress and impairment and have been implicated in anxiety and depression (Eysenck et al., 2007; Levin et al., 2007; Joormann and Gotlib, 2010; Snyder, 2013; Warren et al., under review). To the degree that the experience of negative mood states and negative life events activates mood-congruent representations in working memory (Siemer, 2005), identifying specific inhibition-related dysfunctions associated with anxiety and depression could lead to relatively specific targets for intervention.

Not only do inhibition-related processes contribute to aspects of daily life, they play a critical role in psychopathology, as deficits in these processes have been implicated in the affective and cognitive symptoms of anxiety and depression. In particular, intrusive thoughts such as worry and rumination are hallmark characteristics of anxiety and depression, respectively, and several researchers have suggested that these symptoms are a result of impaired inhibition (Hertel, 1997; Eysenck et al., 2007; Joormann, 2010; see Anticevic et al., 2012, and Fox et al., 2012, for potential contributions of neural networks to psychopathology symptoms). Anxiety has been associated with broad impairments in attentional control, including increased distractibility and impaired processing efficiency (e.g., resource utilization) as opposed to performance effectiveness (e.g., percentage of correct responses; Eysenck et al., 2007; Eysenck and Derakshan, 2011). Research in depression has repeatedly demonstrated problems with attention, memory, and problem-solving abilities (Yee and Miller, 1994; Weiland-Fiedler et al., 2004; Levin et al., 2007; Warren et al., 2008), and impaired inhibition is hypothesized to facilitate these cognitive disruptions via effects on working memory (e.g., Joormann and Gotlib, 2010). Thus, making an explicit link among individual differences in specific inhibition-related functions and dimensions

of anxiety and depression is important for understanding the intricate relationship between affective experiences and cognitive control.

Colloquially, the term inhibition is used with respect to control of behaviors in everyday life (e.g., distraction, impulsivity), although the contribution of specific inhibition-related functions is not well understood. Notably, most formal tests of EF were developed and administered in understandably artificial environments (e.g., laboratory or controlled testing environment). Although research is advancing in determining the cognitive processes that these formal tests of EF actually measure (e.g., Miyake et al., 2000), the degree to which activities of daily life require these same processes is unclear (Burgess et al., 2009). The present study sought to identify empirically specific neural mechanisms implementing the type of inhibition that has been demonstrated clearly in a laboratory setting, (e.g., prepotent response inhibition) as well as behavioral inhibition measured in everyday life. Given that impaired inhibition-related functions have been implicated as risk factors for a broad range of psychopathology, it is important that the nature of inhibition-related processes be specified.

Individual differences in specific inhibition-related functions at the level of neural mechanisms might be more strongly tied to the development and maintenance of psychopathology than the broader construct of inhibition as a whole. Neuroimaging studies exploring inhibition have demonstrated the involvement of various regions, including dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (IFG), and anterior cingulate cortex (ACC), although lesion studies implicate right IFG in particular (see Aron et al., 2004, for a review). DLPFC, ACC, and IFG appear to facilitate task performance in inhibition paradigms. However, it is likely that inhibition co-exists with other cognitive functions required by these tasks (e.g., updating, shifting), making it difficult to determine which brain regions are involved in the implementation of specific inhibition processes. DLFPC is associated with top-down attentional control (e.g., Dosenbach et al., 2008), maintaining goals, and updating information (e.g., Wager and Smith, 2003), whereas ACC is involved in detecting response conflict and monitoring performance (Nelson et al., 2003; Banich et al., 2009). IFG is activated when an individual needs to resolve interference among potentially conflicting attributes of stimuli (Nelson et al., 2003; for review of left IFG, see Jonides and Nee, 2006) and may function to inhibit incorrect responses (Aron et al., 2004). Further, IFG appears to play a more general role in responding to salient, task-related cues as part of an EF network (Hampshire et al., 2010).

Although there is some support for inhibitory dysfunction in both anxiety and depression, the literature to date is mixed (Derakshan and Eysenck, 2009; Snyder, 2013; Snyder et al., under review). Several methodological and conceptual issues could account for discrepant results. Cognitive tasks that are commonly employed often each rely on multiple aspects of EF that might be impaired in psychopathology, making it difficult to draw firm conclusions about the presence of inhibition-related deficits specifically (Henry and Crawford, 2005). In addition, the concept of "inhibition" is broad, and tasks that are assumed to measure inhibition vary in their definition and implementation, making it difficult to ascertain the nature of the function measured. Finally, evidence suggests that co-occurring disorders may have both additive and interactive effects on brain activity and EF (Keller et al., 2000; Moritz et al., 2001; Basso et al., 2007; Engels et al., 2010; Herrington et al., 2010) as well as on clinical outcomes (e.g., Emmanuel et al., 1998). Yet many studies fail to assess or control comorbidity, making it difficult to parse the effects of specific dimensions of anxiety and depression on inhibition impairments and related brain activity.

Depression is distinguishable from two types of anxiety, anxious apprehension and anxious arousal (Heller et al., 1997; Nitschke et al., 1999, 2001). Anxious apprehension is characterized by worry and verbal rumination (Andrews and Borkovec, 1988; Barlow, 1991, 2002), whereas anxious arousal is characterized by somatic tension and sympathetic hyperarousal (Watson et al., 1995a,b). In contrast, depression is characterized by decreased responsivity to pleasurable stimuli (i.e., anhedonia; APA, 2000) and low positive affect (Watson et al., 1995a).

Hemodynamic neuroimaging studies of anxiety and depression have identified abnormal function in regions associated with inhibition-related processes, including prefrontal cortex (particularly DLPFC and IFG), ACC, and areas within parietal cortex (Mayberg, 1997; Mayberg et al., 1999; Rogers et al., 2004; Pizzagalli et al., 2006; Engels et al., 2007, 2010; Herrington et al., 2010). Further, when distinctions between depression and types of anxiety are taken into account, distinct patterns of neural activity emerge. For example, Engels et al. (2007, 2010) demonstrated that anxious apprehension is associated with increased left IFG (Broca's area) activity, whereas anxious arousal is associated with increased right inferior temporal gyrus (ITG) activity. Herrington et al. (2010; see also Miller et al., 2013) demonstrated that depression is associated with rightward lateralization of DLPFC activity. Given that individual differences in inhibition-related functions have been implicated as risk factors for anxiety and depression, a second goal of the present study is to examine how these dimensions of psychopathology (anxious apprehension, anxious arousal, and anhedonic depression) modulate neural mechanisms supporting specific inhibition-related functions. Understanding these relationships could contribute to an account of psychological or neural mechanisms involved in the development and maintenance of symptoms of psychopathology, as well as inform current and potential methods of treatment targeting the cognitive biases and impairments associated with anxiety and depression.

Based on the review above, it was hypothesized that regions involved in a frontal-parietal network supporting inhibition-related processes will be associated with both self-reported behavioral inhibition in everyday life and prepotent response inhibition. In addition, it was anticipated that distinct neural mechanisms would be associated with the two aspects of inhibition under investigation. It was hypothesized that Stroop reaction time (RT) interference, a measure of prepotent response inhibition that likely reflects greater active suppression than self-reported inhibition in everyday life, would be associated with DLPFC, ACC, and IFG activity. These regions have been implicated in implementing cognitive control, as well as response inhibition (Banich et al., 2000; Milham and Banich, 2005; Banich,

2009). In particular, it was anticipated that RT interference would be associated with posterior DLPFC activity, as this region is considered to be critically involved in performance on the Stroop task, in part by biasing other brain regions toward processing task-relevant information (e.g., color of the ink) and away from task-irrelevant information (e.g., reading the color word). Thus, posterior DLPFC is thought to be particularly involved in implementing resistance to a dominant response. In contrast, it was hypothesized that self-reported behavioral inhibition would be associated with mid-DLPFC activity, as this region is implicated in multitasking functions and responding to context (Crocker et al., 2012), as well as maintaining task-relevant information (Kane and Engle, 2002; Banich, 2009). Thus, mid-DLPFC is associated with resisting distraction. Further, given mid-DLPFC's role in maintaining task-relevant information and resisting distraction, it was anticipated that worse self-reported inhibition (e.g., impulsivity, distractibility) would be associated with increased activity in this area. Given that response-inhibition paradigms have dominated much of the inhibition neuroimaging literature, it is unknown whether self-reported inhibition as measured in everyday life will elicit IFG and ACC activity. To the degree that self-reported inhibition relies on stopping behavioral responses, it is likely to be associated with IFG activation. A correlation with ACC may be less likely, as this region is recruited during tasks that generate conflicting, response-related representations, such as the incongruent condition of a Stroop task ("RED" printed in blue ink; Banich, 2009).

Further, given empirical support from hemodynamic neuroimaging studies that have properly accounted for comorbidity between depression and anxiety or comorbidity among anxiety types (Engels et al., 2007, 2010; Herrington et al., 2010), it was hypothesized that depression and anxiety would be associated with opposing effects on inhibition-related brain activity. For both prepotent response inhibition and self-reported inhibition in everyday life, it was anticipated that depression would be associated with decreased left DLPFC and ACC activity. It was also hypothesized that depression would be associated with decreased posterior DLPFC response inhibition activity, as previous work has shown hypoactivation in this area (e.g., Herrington et al., 2010). In contrast, anxiety should be accompanied by greater activation in brain areas associated with attentional control in distracting conditions (see Eysenck and Derakshan, 2011, for review). It was expected that anxiety of either type (anxious apprehension and anxious arousal) would increase activity in mid-DLPFC associated with self-reported inhibition, activity in posterior DLPFC associated with response inhibition, and ACC activity associated with both measures of inhibition, as these regions have been shown to play prominent roles in attentional control (e.g., Engels et al., 2007, 2010; Banich, 2009). It was also anticipated that anxious apprehension would increase left IFG activity associated with response inhibition, as previous work has shown hyperactivation in this area (Engels et al., 2007).

MATERIALS AND METHODS

PARTICIPANTS

Eighty-five paid undergraduate participants (52 females, age $M = 19.08$, $SD = 1.04$) with varying levels of anxiety and depression were recruited from a larger study examining personality, affective, and cognitive risk factors for psychopathology ($N = 1123$; Warren et al., under review; analyses reported here are novel and are orthogonal to Warren et al., under review). From this larger study, participants were selected to be at risk for psychopathology according to their scores on dimensional measures of anxiety and depression (see Psychopathology questionnaires section under Measures). Specifically, participants were selected if they (1) scored at or above the 80th percentile on one of the three psychopathology dimensions and at or below the 50th percentile on the other two dimensions, (2) or if they scored at or above the 80th percentile on all three psychopathology dimensions, or (3) if they scored at or below the 50th percentile on all three psychopathology dimensions. All participants were right-handed, native speakers of English with self-reported normal color vision and hearing, with no neurological disorders or impairments. The Structured Clinical Interview for Axis I Disorders, Non-Patient Edition (First et al., 1997) was administered to all participants. Although participants were not specifically selected based on DSM-IV-TR anxiety or mood disorder diagnosis, approximately 22% met criteria for anxiety disorder only (Anxiety NOS, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Post Traumatic Stress Disorder, Social Phobia), 9% met criteria for mood disorder only (Major Depressive Disorder or Dysthymia), and 18% met criteria for an anxiety and mood disorder. Participants were given a laboratory tour, informed of the procedures of the study, and screened for claustrophobia and other contraindications for MRI participation. The study was approved by the University of Illinois at Urbana-Champaign Institutional Review Board. Participants were excluded if they had ever experienced loss of consciousness $\geq$10 min or exhibited current substance abuse or dependence, mania, or psychosis. Additional exclusion criteria included excessive motion or scanner artifact ($n = 8$), signal loss due to substantial uncorrected magnetic susceptibility in areas of interest ($n = 1$), or Stroop reaction time errors greater than 3 standard deviations from the sample mean ($n = 1$).

MEASURES

Inhibition in everyday life

The Behavior Rating Inventory of Executive Function (BRIEF; self-report version; Guy et al., 2004) is an ecologically sensitive, self-report questionnaire that measures several aspects of EF in an individual's everyday life, including inhibition. Through a series of item-level factor analyses using the BRIEF Warren et al. (under review), identified inhibition, shifting, and updating latent factors consistent with Miyake et al.'s (2000) EF framework. For the present study, the inhibition-item weights (λs; $N = 1123$) identified in Warren et al. (under review) were used to compute participants' behavioral inhibition in everyday life scores. The BRIEF inhibition factor score indexes an individual's ability to resist impulsive responses by pre-empting or stopping one's behavior at the appropriate time and the tendency to act prematurely without foresight in social contexts (Guy et al., 2004). Elevated scores represent impaired cognitive control, manifesting behaviorally as disinhibition and impulsivity.

Inhibition in the laboratory

The color-word Stroop task was used as a measure of prepotent response inhibition. Participants completed the color-word Stroop task (Stroop, 1935) during fMRI data acquisition (see below) in which they were asked to press a button indicating the color of the ink in which color words and neutral words were printed, ignoring the dominant tendency to read the words. During the incongruent condition of the Stroop task, cognitive interference is created by the actual meaning of the presented word relative to the ink color in which it is presented (e.g., "RED" in blue ink).

Average RT for correct-response trials was computed for incongruent (e.g., "RED" in blue ink) and neutral trials (e.g., "LOT" in red ink). RT interference scores were computed by subtracting each participant's average neutral RT from their average incongruent RT, divided by their sum ([incongruent RT minus neutral RT]/[incongruent RT plus neutral RT]), and converted to *z* scores across all subjects. Higher interference scores indicated that participants took longer to respond to the ink color of incongruent than of neutral words. No-response trials were excluded from behavioral analyses.

Psychopathology questionnaires

Dimensional measures of anxiety and depression, the Penn State Worry Questionnaire (PSWQ; Molina and Borkovec, 1994) and the Anxious Arousal and Anhedonic Depression scales of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995b), were administered during the participant's first visit to the laboratory (see **Table 1**). Anxious apprehension was measured using the 16-item PSWQ (e.g., "My worries overwhelm me"). Anxious arousal was measured using the relevant 17-item subscale of the MASQ (MASQAA; e.g., "startled easily"). Anhedonic depression was measured using an 8-item subscale from the MASQ (MASQAD8; e.g., "Felt like nothing was very enjoyable"), as it has been shown to predict current and lifetime depressive disorders (Bredemeier et al., 2010). Past research has shown that these measures have good test-retest reliability and good convergent and discriminant validity in undergraduate and clinical samples (Watson et al., 1995a,b; Nitschke et al., 2001).

Table 1 | Descriptive statistics.

	M	*SD*	Min	Max
QUESTIONNAIRE				
1. PSWQ (Anxious apprehension)	49.08	18.03	17	80
2. MASQAA (Anxious arousal)	27.56	7.58	17	48
3. MASQAD8 (Anhedonic depression)	16.89	5.77	8	33
INHIBITION MEASURE				
1. BRIEF factor score	9.18	2.09	6.32	15.82
2. RT interference	0.11	0.60	−0.30	0.23

N = 85. PSWQ, Penn State Worry Questionnaire. MASQAA, Mood and Anxiety Symptom Questionnaire Anxious Arousal scale. MASQAD8, Mood and Anxiety Symptom Questionnaire Anhedonic Depression 8-item subscale. RT Interference computed by ([incongruent RT minus neutral RT]/[incongruent RT plus neutral RT]).

EXPERIMENTAL TASK AND STIMULI

Color-word Stroop task

Participants completed color-word and emotion-word Stroop tasks during an fMRI session, and also completed an EEG procedure and a diagnostic interview in other sessions. Only findings from the color-word Stroop task during fMRI are presented here. Hemodynamic data from this same task for an overlapping set of participants was used in a separate study addressing an entirely different research question (Spielberg et al., 2011). The order of presentation of the two tasks within the fMRI session was counterbalanced. The color-word Stroop task consisted of blocks of color-congruent or color-incongruent words alternating with blocks of neutral words. Half of the trials in the congruent and incongruent blocks were neutral to prevent the development of word-reading strategies. This type of blocked-design color-word Stroop task has been shown to effectively elicit Stroop interference (Banich et al., 2000; Milham and Banich, 2005). There were eight orders of stimulus presentation blocks that were counterbalanced across subjects (each participant received one out of eight possible orders). In addition to the word blocks, there were four fixation blocks (one at the beginning, one at the end, and two in the middle of the session) and five rest blocks (one at the beginning, one at the end, and one between each word block). In the fixation condition, a fixation cross intensified in place of word presentation, and in the rest condition the subject was instructed to rest and keep their eyes open while the screen was blank.

Each trial consisted of one word presented in one of four ink colors (red, yellow, green, blue) on a black background, with each color occurring equally often with each word type. The task consisted of congruent trials in which the word named the ink color in which it was printed (e.g., the word "RED" printed in red ink), incongruent trials in which the word named a color incongruent with the ink color in which it was printed (e.g., "GREEN" printed in red ink), and neutral trials in which the word was unrelated to color (e.g., "LOT" in red ink). Neutral words were matched with color words on word frequency and length. Participants responded to the color of the ink with their middle and index fingers using left- and right-hand response boxes.

Participants received 256 trials presented in 16 blocks (four congruent, four incongruent, and eight neutral) of 16 trials each, with a variable ITI (±225 ms) averaging 2000 ms between trial onsets. A trial began with the presentation of a word for 1500 ms, followed by a fixation cross for an average of 500 ms. There was a brief rest period after every fourth block. Additionally, there were four fixation blocks (one at the beginning, one at the end, and two in the middle) in which a brighter fixation cross was presented for 1500 ms. Participants completed 32 practice trials during a low-resolution anatomical scan. No participants failed to understand the task instructions or the mapping between colors and buttons after completing practice trials. Stimuli, word presentation, and reaction-time measurement were controlled by STIM software (James Long Company, Caroga Lake, NY).

Image acquisition

A series of 370 fMRI images (16 images per block of 16 stimuli plus rest and fixation periods) were acquired using a gradient-echo echo-planar pulse sequence (TR 2000 ms, TE 25 ms, flip

angle 80°, FOV = 22 cm) on a 3T Siemens Allegra head-only scanner. Thirty-eight contiguous oblique axial slices (slice thickness 3 mm, in-plane resolution $3.4375 \times 3.4375\,mm^2$, 0.3 mm gap between slices) were acquired parallel to the anterior and posterior commissures. After the EPI sequence, a 160-slice MPRAGE structural sequence was acquired (slice thickness 1 mm, in-plane resolution 1×1 mm) for registering each participant's functional data to standard space. Prior to the EPI sequence, standard Siemens magnetic field maps were collected with the same slice prescription as the functional scans using a multi-echo gradient echo acquisition (TE's of 10 and 12.46 ms). This field map was used for correction of geometric distortions in the EPI data caused by magnetic field inhomogeneity.

fMRI data reduction and analysis

Functional image processing and analysis relied on tools from the FSL analysis package (e.g., MCFLIRT, PRELUDE, FILM, FUGUE, FEAT, FLAME; http://www.fmrib.ox.ac.uk/fsl) and AFNI (http://afni.nimh.nih.gov/afni/). Additional region-of-interest (ROI) analyses were carried out using locally written Matlab programs (e.g., Herrington et al., 2005) and IBM SPSS Statistics version 19.0.

Functional data for each participant were motion-corrected using rigid-body registration, implemented in FSL's linear registration tool, MCFLIRT (Jenkinson et al., 2002). Temporal low-pass filtering was carried out using AFNI's 3dDespike tool (http://afni.nimh.nih.gov/) to remove intensity spikes. The ends of two participants' time series were truncated due to excessive motion. All other participants demonstrated less than 3.3 mm absolute motion or 2 mm relative motion. After motion correction and temporal low-pass filtering, each time series was corrected for geometric distortions caused by magnetic field inhomogeneity (Jezzard and Balaban, 1995; Jenkinson, 2004). Remaining preprocessing steps, single-subject statistics, and group statistics were completed with FEAT. The first three volumes of each participant's functional data were discarded to allow the MR signal to reach a steady state. Each time series was temporally filtered with a nonlinear high-pass filter to attenuate frequencies below 1/212 Hz (to remove drift in signal intensity), mean-based intensity-normalized by the same single scaling factor, and spatially smoothed using a 3D Gaussian kernel (FWHM 5 mm) prior to analysis.

Blood-oxygen-level-dependent (BOLD) activity during the color-word Stroop task was assessed using FILM (FMRIB's Improved Linear Model). Statistical maps were generated via multiple regression on each intracerebral voxel (Woolrich et al., 2001). An explanatory variable (EV) was created for each trial type (congruent, neutral, incongruent, and rest; fixation condition left unmodeled) and convolved with a gamma function to better approximate the temporal course of the BOLD hemodynamic response function (e.g., Aguirre et al., 1998). The contrast of particular interest for this study is the incongruent versus neutral contrast, because incongruent trial performance requires executive function to exert top-down control and resolve conflict. Each EV (i.e., regressor) yielded a per-voxel effect-size parameter estimate (ß) map representing the magnitude of activity associated with that EV for a given participant. Functional activation maps for each contrast were transformed into MNI stereotactic space (ICBM152 2009a Nonlinear Symmetric, $1 \times 1 \times 1$ mm T1 Atlas; Fonov et al., 2009) using FMRIB's Non-Linear Image Registration Tool, FNIRT (Andersson et al., 2007).

Group inferential statistical analyses were carried out using FLAME and SPSS. To identify ROIs for subsequent analysis, activated voxels were identified for the incongruent vs. neutral contrast via two-tailed, per-voxel *t*-tests on contrast β maps converted to z-scores. Monte Carlo simulations via AFNI's AlphaSim program estimated the overall significance level (probability of a false detection) for thresholding these 3D functional z-map images (Ward, 2000). These simulations used a gray-matter mask to limit the number of voxels under consideration ($2340\,mm^3$) and provided a cluster size (390) and z-value ($z = 2.97$; corresponding p-value = 0.003) combination to use for thresholding, resulting in an overall family-wise error rate of 0.05. In order to explore brain regions uniquely associated with inhibition-related constructs, BRIEF inhibition factor score and RT interference (each converted to *z* scores) for each participant were entered as predictors in whole-brain, per voxel, cross-subject regression analyses in FSL. Updating and shifting factor scores (Warren et al., under review) were entered as covariates in order to isolate the specific effects of inhibition. Although there is empirical support for moderate correlations and some overlap among some aspects of EF (Warren et al., under review), inhibition, updating, and shifting components are also behaviorally, genetically, and neurally dissociable (e.g., Miyake et al., 2000; Collette et al., 2005; Friedman et al., 2008; Warren et al., under review). Thus, in order to isolate the specific effects of inhibition in everyday life and the type of inhibition typically observed in the laboratory, brain activity showing distinct relationships with BRIEF inhibition and RT interference was examined by including all EF measures (BRIEF inhibition factor score, RT interference, updating and shifting factor scores) simultaneously in one regression model. This regression analysis produced a β map corresponding to the unique variance associated with each inhibition construct.

Clusters associated with inhibition in everyday life and RT interference that surpassed statistical thresholding were identified as ROIs. To assess the potential effect of psychopathology on neural activity related to these specific inhibition processes, a score for each ROI identified in which BRIEF inhibition factor score and RT interference predicted fMRI was created by averaging β values across voxels in each ROI, for each participant. ROI scores were then entered as the dependent variable in three separate hierarchical linear regressions: (1) PSWQ, MASQAA, and MASQAD8 were entered together as independent variables, (2) their two-way interactions were added together, and (3) their three-way interaction was added. In order to illustrate the resulting moderating effects of psychopathology on ROIs, interactions were plotted and simple slopes tested whether the relationship between brain activity and psychopathology was significantly different from zero at different combinations of high and low levels of anxiety types (see Engels et al., 2010, for details of a similar approach). In **Figures 2–4**, the relationship between brain activity and anxious apprehension was plotted at high and low levels of anxious arousal. In **Figure 5**, the relationship between brain activity and depression was plotted at high and low levels of anxious

apprehension. For all figures that plot interactions, "high" and "low" refer to ±1 *SD*.

RESULTS

BEHAVIORAL DATA

All participants demonstrated color-choice accuracy of at least 85%. As a manipulation check, we examined RT interference for color-word trials. As expected, participants demonstrated more RT interference for incongruent-word trials ($M = 814$ ms, $SD = 160$ ms) than for congruent-word trials ($M = 633$ ms, $SD = 103$ ms), $t_{(84)} = 15.3$, $p < 0.001$, and neutral-word trials ($M = 652$ ms, $SD = 103$ ms), $t_{(84)} = 15.2$, $p < 0.001$.

Descriptive statistics for all of the measures are presented in **Table 1**, and zero-order correlations among psychopathology and inhibition measures are presented in **Table 2**[1].

fMRI DATA

Brain regions uniquely associated with BRIEF inhibition

Table 3 lists seven regions that were positively correlated with the BRIEF inhibition factor score. In line with hypotheses, higher BRIEF inhibition factor scores were associated with more activation in left mid-DLPFC (middle frontal gyrus; see **Figure 1**) and left IFG, regions that are generally associated with implementing inhibition-related processes. Additional clusters emerged in frontal pole, OFC, and supramarginal and angular gyrus regions. There were no significant clusters negatively correlated with BRIEF inhibition factor scores.

Moderation of brain activity by psychopathology associated with BRIEF inhibition factor score

No significant moderation by anxiety, depression, or their interactions emerged with any of the self-reported inhibition ROIs.

Brain regions uniquely associated with RT interference

Table 4 lists a network of regions that were negatively correlated with RT interference. In line with hypotheses, higher RT interference was associated with less activation in left posterior DLPFC (middle frontal gyrus), bilateral IFG, and ACC (rostral, dorsal, and anterior mid-cingulate), as well as regions that are generally associated with attentional control and motor response coordination (e.g., premotor cortex, frontal eye fields, posterior parietal cortex, precuneus; see **Figure 1**). Additional clusters emerged in occipital cortex, thalamus and caudate, parahippocampal gyrus, frontal pole, OFC, and supramarginal and angular gyrus regions (see **Figure 1**). There were no significant clusters positively correlated with RT interference.

Moderation of brain activity by psychopathology associated with RT interference

No significant main effect of anxiety type, depression, or their three-way interaction emerged. **Table 5** lists regions with two-way interactive effects for anxiety and depression for response-inhibition-related brain activity. Three regions were moderated by four, two-way interactions. A PSWQ × MASQAA interaction emerged for left posterior DLPFC (**Figure 2**). As illustrated in **Figure 2**, increased anxious apprehension was associated with increased left posterior DLPFC activation, but only when anxious arousal was low. Tests of simple slopes showed that this was the only significant slope [$t_{(78)} = 2.84$, $p < 0.01$]. A PSWQ × MASQAA interaction was found for right middle temporal gyrus (MTG; **Figure 3**). Tests of simple slopes showed that increased anxious apprehension was associated with decreased right MTG activation at high levels of anxious arousal [$t_{(78)} = -2.86$, $p < 0.01$] but with increased activation at low levels of anxious arousal [$t_{(78)} = 2.02$, $p = 0.05$]. Finally, two interactions emerged for right frontal pole (**Figures 4** and **5**). Similar to right MTG, increased anxious apprehension was associated with decreased right frontal pole activation at high levels of anxious arousal [$t_{(78)} = -3.47$, $p < 0.001$] but with increased activation at low levels of anxious arousal [$t_{(78)} = 2.91$, $p < 0.01$; **Figure 4**]. Additionally, a PSWQ × MASQAD8 interaction emerged in which high levels of anhedonic depression were associated with decreased right frontal pole activity at low levels of anxious apprehension. Tests of simple slopes showed that this was the only significant slope [$t_{(78)} = -3.55$, $p < 0.001$; **Figure 5**].

Table 2 | Zero-order correlations among psychopathology and inhibition-related measures.

Measure	1	2	3	4
1. PSWQ (Anxious apprehension)	–			
2. MASQAA (Anxious arousal)	0.48**	–		
3. MASQAD8 (Anhedonic depression)	0.49**	0.51**	–	
4. BRIEF inhibition factor score	0.10	0.35**	0.29**	–
5. RT interference	0.12	0.13	0.11	0.13

$^{**}p \leq 0.01$ (two-tailed).

[1]Given the significant zero-order correlations among the BRIEF Inhibition Factor Score and psychopathology questionnaires, there is a potential for selection bias with respect to brain activity in regions of interest. However, given that the psychopathology measures did not significantly moderate the relationship between brain activity and BRIEF Factor Score, the potential for non-independence is not an issue.

DISCUSSION

The present study examined neural mechanisms supporting ecologically sensitive versus laboratory-based measures of inhibitory function in order to clarify the broader construct of inhibition as well as their role in psychopathology. Brain-activation results were consistent with regions of interest predicted to be associated with inhibition-related processes. In general, worse self-reported inhibition in everyday life (elevated BRIEF factor score) was associated with increased activity in brain regions typically associated with inhibitory function (left DLPFC, left IFG, bilateral inferior parietal cortex; **Figure 1**). In contrast, worse performance on the laboratory task (increased RT interference) was associated with decreased brain activity in these regions as well as ACC (see **Figure 1**). Importantly, although DLPFC activity was associated with both measures of inhibitory functions, each measure exhibited unique relationships with DLPFC. As predicted, worse self-reported inhibition was associated with increased activity in mid-DLPFC, and greater RT interference was associated with less activity in posterior DLPFC. These differential patterns

Table 3 | Distinct effects of brief inhibition factor score.

Region	Cluster size	Mean Z	COM Location			Max Z Location		
			x	*y*	*z*	*x*	*y*	*z*
INCONGRUENT VERSUS NEUTRAL WORDS[a]								
L frontal pole, OFC	397	3.30	−46	39	−16	−48	40	−17
L inferior frontal gyrus (IFG), anterior insula	1346	3.25	−46	16	0	−51	17	−2
L frontal pole, IFG-pars triangularis	423	3.35	−47	39	6	−46	40	6
R lateral occipital cortex, angular gyrus, TPJ	498	3.18	53	−59	21	53	−60	20
L middle frontal gyrus (mid-DLPFC)	402	3.19	−40	26	28	−43	25	27
L supramarginal gyrus	4851	3.26	−54	−53	41	−54	−44	52
R angular gyrus, lateral occipital cortex	558	3.31	48	−55	54	50	−56	54

N = 85. COM, center of mass; R, right; L, left; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; TPJ, temporoparietal junction.

[a] z-scores > 2.9677, cluster-size ≥ 390 (corrected p < 0.05).

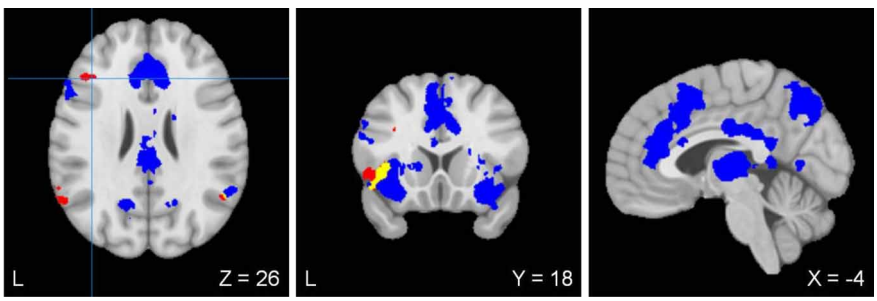

FIGURE 1 | Areas of activation uniquely associated with either self-reported inhibition in everyday life or prepotent response inhibition. Red, increased brain activation associated with behavioral inhibition as measured by BRIEF inhibition factor score. Blue, decreased brain activation associated with prepotent response inhibition as measured by RT interference. Yellow, brain activation overlap between BRIEF inhibition factor score and RT interference. L, Left. Location of crosshairs emphasizes a differentiation of mid-DLPFC (red) and posterior DLPFC (blue) regions.

of inhibition-related processes suggest a distinct role for each DLPFC area.

The cascade of control model (Banich et al., 2000, 2009; Milham and Banich, 2005; Banich, 2009) identifies aspects of EF that are critical for inhibiting responses, including biasing responses toward task-relevant processes, biasing attention toward task-relevant representations, response selection, and response evaluation. This model proposes that distinct areas of DLPFC implement these functions, which are necessary for cognitive control. Posterior DLPFC imposes a top-down attentional set toward task-relevant processes, maintains the overall task goals, and subsequently biases other brain regions (e.g., mid-DLPFC, dorsal ACC, parietal cortex) toward processing task-relevant information. In contrast, mid-DLPFC is involved in selecting and maintaining the most relevant aspects of task stimuli (Banich, 2009) and has been suggested to play an important role in stimulus-driven attentional control (Crocker et al., 2012). Mid-DLPFC is thought to be involved in interrupting top-down processing to reorient attention to stimuli that have been identified as relevant (Corbetta et al., 2008; Crocker et al., 2012) and therefore could be said to be critically involved in tracking and multitasking functions. In the context of present findings, a behavioral manifestation of a high BRIEF inhibition factor score is impulsivity. Thus, mid-DLPFC hyperactivity associated with increased BRIEF inhibition factor score could reflect paying attention to too many task representations and/or hyper-focusing on stimulus properties, which could disrupt relevant task goal maintenance. In line with this interpretation, hyperactivity in mid-DLPFC has been linked to over-engagement with irrelevant features of stimuli (the meaning of threat-related words in an emotion-word Stroop task), interfering with processing task-relevant features (word color; Engels et al., 2010).

In contrast, a negative correlation between RT interference and posterior DLPFC was observed, such that the greater the RT interference, the less the brain activity. Given DLPFC's prominent role in top-down attentional control (Milham et al., 2003), if posterior DLPFC fails to impose a top-down attentional set toward task-relevant processes (inferred by decreased activity), one would anticipate greater RT interference. Present results are consistent with other findings (Banich et al., 2000; Milham et al., 2003; Milham and Banich, 2005).

In line with the cascade-of-control model, RT interference was also associated with areas of ACC that are involved in response selection and response evaluation. Specifically, the model asserts that there is a temporal cascade of cognitive operations, such that, following DLPFC activation, dorsal ACC selects the appropriate response among available response options. When incorrect responses are made during a task, more anterior regions of ACC

Table 4 | Distinct effects of RT interference.

Region	Cluster size	Mean Z	COM location			Max Z location		
			x	*y*	*z*	*x*	*y*	*z*
Incongruent vs. neutral words[a]								
Bilateral thalmaus, caudate; LH OFC, insula, IFG	30997	−3.67	−12	−5	5	−6	−21	11
R OFC, insula, IFG	7029	−3.45	36	17	−11	28	17	−16
R temporal occipital fusiform cortex	442	−3.23	37	−47	−21	36	−42	−21
R lingual gyrus	566	−3.31	5	−81	−15	4	−80	−12
L lateral occipital cortex, posterior ITG	4764	−3.32	−38	−77	−11	−46	−62	−8
R temporal occipital fusiform cortex, ITG	1119	−3.25	45	−61	−16	46	−56	−18
L lateral occipital cortex, occipital pole	581	−3.20	33	−89	−10	35	−86	−9
R middle temporal gyrus	1316	−3.44	54	−30	−7	54	−31	−7
R parahippocampal gyrus	549	−3.42	20	−30	−9	22	−28	−8
rACC, dACC, aMCC	19171	−3.49	0	25	32	10	25	24
Bilateral precuneous cortex	14804	−3.54	−7	−67	39	−7	−66	45
R frontal pole	942	−3.40	26	54	13	28	55	9
L middle frontal gyrus (posterior DLPFC)	1980	−3.49	−54	15	32	−53	13	41
R angular gyrus	399	−3.28	58	−52	24	58	−51	23
L supramarginal gyrus	462	−3.16	−52	−41	38	−50	−37	43
L supramarginal gyrus, angular gyrus	491	−3.17	−33	−46	38	−31	−44	36
L middle frontal gyrus (DLPFC), premotor cortex, FEF	1981	−3.40	−26	−2	53	−32	−3	54

N = 85. COM, center of mass; R, right; L, left; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex; aMCC, anterior mid-cingulate cortex; FEF, frontal eye field.

[a] z-scores > 2.9677, cluster-size ≥ 390 (corrected $p < 0.05$).

Table 5 | Regression analyses for two-way interactive effects of anxiety and depression on RT interference ROIs.

Region		R^2	ΔR^2	Test	*p*
L middle frontal gyrus (posterior DLPFC)	PSWQ × MASQAA		0.08	$t_{(78)} = -2.65$	0.01
	Full model	0.156		$F_{(6, 78)} = 2.40$	0.04
R middle temporal gyrus	PSWQ × MASQAA		0.07	$t_{(78)} = -2.57$	0.01
	Full model	0.164		$F_{(6, 78)} = 2.55$	0.03
R frontal pole	PSWQ × MASQAA		0.13	$t_{(78)} = -3.48$	<0.01
	Full model	0.185		$F_{(6, 78)} = 3.00$	0.01
R frontal pole	PSWQ × MASQAD8		0.04	$t_{(78)} = -2.96$	0.05
	Full Model	0.185		$F_{(6, 78)} = 3.00$	0.01

N, 85. PSWQ, Penn State Worry Questionnaire; MASQAA, Mood and Anxiety Symptom Questionnaire Anxious Arousal scale; MASQAD8, Mood and Anxiety Symptom Questionnaire Anhedonic Depression 8-item subscale; R, right; L, left; DLPFC, dorsolateral prefrontal cortex. ΔR^2 is the incremental variance associated with the interaction term, with its individual constituents already in the model.

signal posterior DLPFC to assert greater top-down control for task performance, requiring re-initiation of certain steps in the temporal cascade of events. In addition to posterior DLPFC and ACC, present findings for regions of activation for RT interference were consistent with those implicated in a distributed network associated with response inhibition, including bilateral IFG, as well as regions that are generally associated with attentional control and coordinating motor responses (e.g., premotor cortex, frontal eye fields, posterior parietal cortex, precuneus; Corbetta et al., 2008; Banich, 2009).

Contributing to understanding EF deficits in psychopathology, select patterns of brain activation for response inhibition (RT interference) were modulated by anxiety and depression. A two-way interaction emerged for left posterior DLPFC in which greater activity was associated with high anxious apprehension, but only when anxious arousal was low. Anxious apprehension typically involves elaborated verbal processing and worry. Given that posterior DLPFC is involved in imposing top-down attentional control and maintaining task set, greater activity in this area may reflect an attempt to compensate for anxious apprehension (which can be inferred to impair the efficiency of this inhibition-related function). Considerable evidence suggests that anxiety is often associated with increased susceptibility to distraction (see Derakshan and Eysenck, 2009, for review), hypothesized to reflect impaired inhibition (e.g., Eysenck and Derakshan, 2011). According to attentional control theory, anxiety impairs

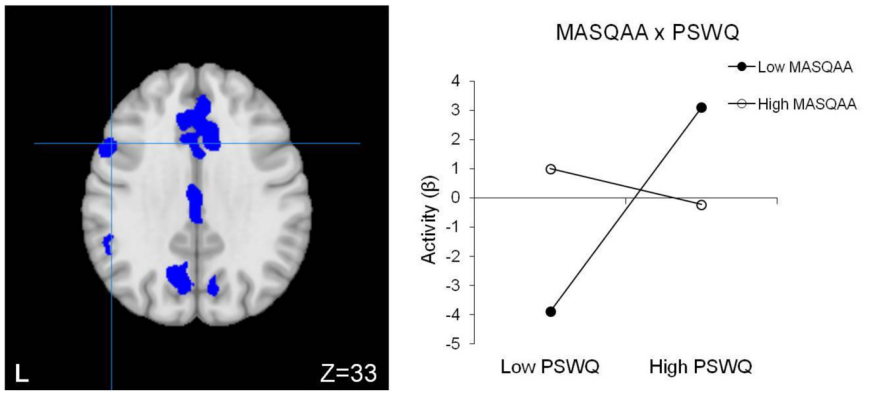

FIGURE 2 | Posterior DLPFC activation for RT interference. Blue, decreased brain activation associated with RT interference. L, left. Graphing the MASQAA × PSWQ interaction illustrates that anxious apprehension's relationship with left posterior DLPFC depends on the level of co-occurring anxious arousal.

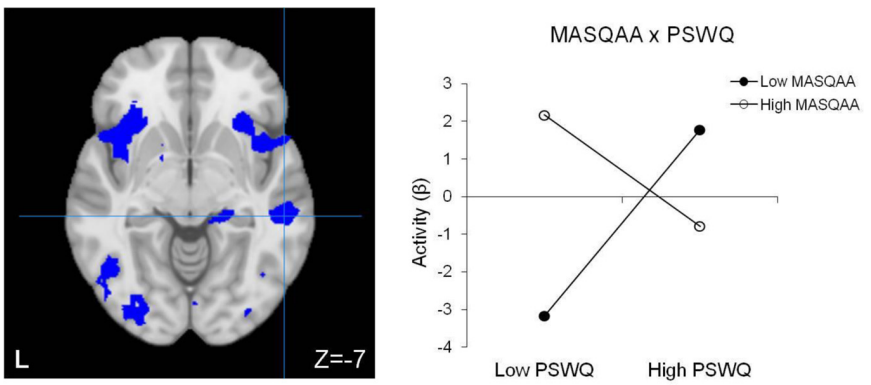

FIGURE 3 | Right MTG activation for RT interference. Blue, decreased brain activation associated with RT interference. L, left. Graphing the MASQAA × PSWQ interaction illustrates that anxious apprehension's relationship with right MTG depends on the level of co-occurring anxious arousal.

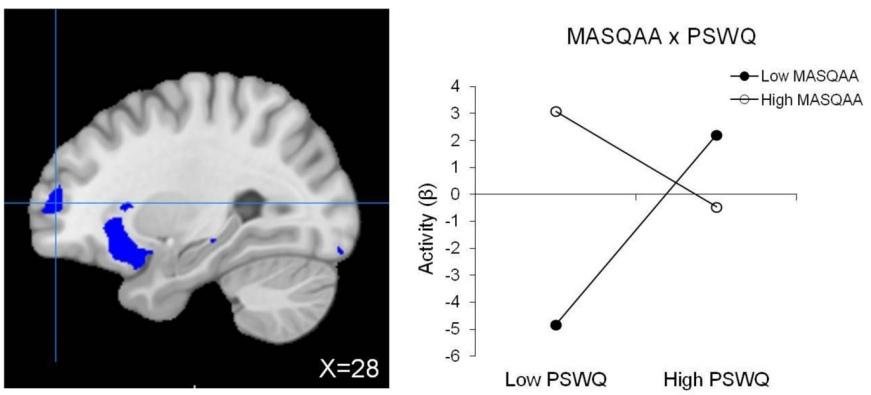

FIGURE 4 | Right frontal pole activation for RT interference. Blue, decreased brain activation associated with RT interference. Graphing the MASQAA × PSWQ interaction illustrates that anxious apprehension's relationship with right frontal pole depends on the level of co-occurring anxious arousal.

processing *efficiency* to a greater extent than it impairs performance *effectiveness* (i.e., quality of performance; Eysenck et al., 2007) and manifests in greater activation in brain regions associated with attentional control. Present findings suggest that individuals high in anxious apprehension (worry), a specific dimension of anxiety, especially when anxious arousal is low, are more susceptible to distraction and thus to impaired efficiency of inhibition during cognitively demanding tasks (i.e., inhibiting the

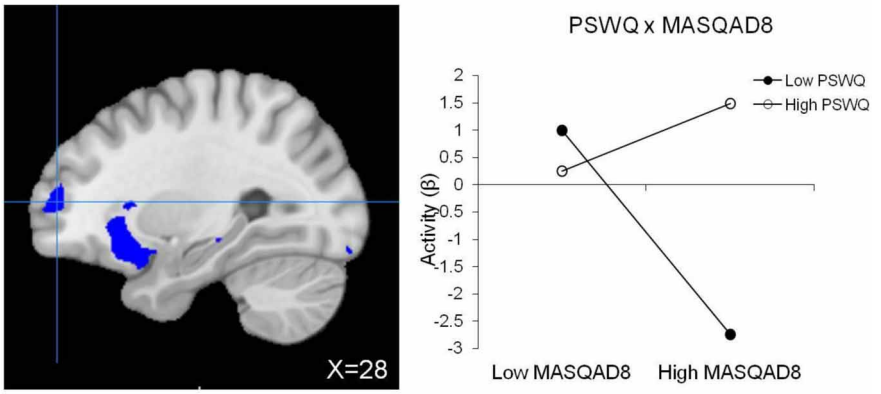

FIGURE 5 | Right frontal pole activation for RT interference (same region pictured in Figure 4). Blue, decreased brain activation associated with RT interference. Graphing the PSWQ × MASQAD8 interaction illustrates that anxious apprehension's relationship with right frontal pole depends on the level of co-occurring anhedonic depression.

dominant tendency to read the color word). The fact that anxious apprehension and anxious arousal are not associated with error rate could reflect compensation by posterior DLPFC (inferred from greater activity). Despite its disrupting impact on efficiency, increased activity associated with anxious apprehension or worry may be adaptive under some circumstances. Anxious apprehension ameliorated a depression-related suppression of activity in DLPFC (again, only when anxious arousal was low; Engels et al., 2010). Types of anxiety and depression may thus interact to influence optimal levels of activity in brain regions associated with cognitive control, which in turn may affect the balance of goal maintenance vs. stimulus-driven or contextual processing.

A two-way interaction emerged for right MTG in which greater RT interference activity was associated with high anxious apprehension when anxious arousal was low and with decreased activity when anxious arousal was high. Additional examination of this interaction revealed one significant slope, such that brain activity increased as anxious arousal increased, but only when anxious apprehension was low. Right MTG is thought to interact with a network of regions involved in detecting and responding to threat (e.g., Compton et al., 2003; Corbetta et al., 2008). This region may be a part of a system that functions adaptively to switch between top-down attentional control and more stimulus-driven processing (Corbetta et al., 2008). Using an emotion-word Stroop task, Engels et al. (2007) demonstrated that negative emotion words elicited greater right middle-temporal/inferior-temporal activity in an anxious arousal group. Importantly, present results generalize Engels' et al. (2007, 2010) findings to non-emotional contexts, suggesting that anxiety-modulated increases in activity in this region interfere with an inhibition-related function for cognitive control. Additionally, in a non-overlapping sample, Engels et al. (2010) found that anxious arousal ameliorated depression-related suppression of activity in this region, in response to threatening words. Again, these findings suggest that under some circumstances anxiety-related activation has an adaptive function.

Similar to the pattern observed for right MTG, greater right frontal pole (BA10) activity was associated with high anxious apprehension when anxious arousal was low and with decreased activity when anxious arousal was high. Additionally, anxious apprehension diminished depression-related suppression of activity in this region. Rostral PFC (BA10) has been implicated in supporting a wide range of functions including prospective memory, multitasking, and "mentalizing" or reflecting on mental states (see Burgess et al., 2007, for review). According to the gateway hypothesis (Burgess et al., 2007), rostral PFC is part of a cognitive control system that biases the relative influence of stimulus-independent and stimulus-oriented thought. Lateral regions of rostral PFC are associated with stimulus-independent cognition, the mental processes that accompany self-generated or self-maintained thought that is not provoked by or directed toward an external stimulus (i.e., task-irrelevant thought). The right frontal pole region in the present study overlaps with the lateral area of rostral PFC identified by Burgess et al. (2007) as supporting stimulus-independent function. Anxious apprehension modulation of brain activity in this region (when anxious arousal is low) could reflect task-irrelevant thoughts such as worry, an example of stimulus-independent cognition, potentially interfering with task efficiency. However, anxious apprehension also interacted with depression in this same region, such that depression-related hypoactivity decreased as anxious apprehension increased. Findings suggest that whereas anxious apprehension could interfere with task efficiency when anxious arousal is low, worry could potentially be adaptive for task performance at high levels of depression.

Contrary to hypotheses, no significant moderation of anxiety, depression, or their interactions emerged with any of the ROIs associated with self-reported inhibition in everyday life. It is possible that the color-word Stroop task does not robustly engage inhibition-related neural mechanisms that implement the kind of everyday inhibitory control that is affected by anxiety or depression. Another possible explanation for the lack of significant findings is the general nature and range of everyday scenarios that the self-reported inhibition score indexes. Although the self-reported inhibition score may be sensitive to neural mechanisms supporting this function, the measure may not be specific enough to capture anxiety and depression deficits.

Maintenance of top-down attentional control is typically assumed to be the main function of DLPFC. However, present results suggest a more nuanced view of DLPFC in the context of cognitive control, as sub-regions were differentiated by two aspects of inhibition-related functions. Present results support an emerging view that areas within DLPFC (mid and posterior) may provide distinct contributions to cognitive control (Banich, 2009). Whereas mid-DLPFC has been associated with stimulus-driven attentional control (Crocker et al., 2012), posterior DLPFC imposes a top-down attentional set that maintains overall task goals. In combination, these regions are involved in preventing irrelevant information from entering working memory. In the context of the current study, present findings suggest that differing inhibition-related mechanisms may contribute to the efficiency in which information is maintained in working memory, as well as resistance to interference.

DLPFC dysfunction has been implicated as a source of cognitive impairment in a range of psychopathology, including depression and anxiety (Engels et al., 2007, 2010; Levin et al., 2007; Warren et al., 2008; Herrington et al., 2010; Silton et al., 2010). Although inhibitory functions are not the only factors that are associated with cognitive dysfunction in psychopathology, their differing neural mechanisms certainly have probative value. For example, theories of depression (Joormann et al., 2007) and anxiety (Eysenck et al., 2007) postulate inhibitory dysfunction as a source of symptom development and maintenance, although specific inhibitory functions are not addressed. Indeed, present findings demonstrate that only response inhibition-related brain activity (RT interference) was significantly moderated by psychopathology. Thus, assessing individual differences in specific inhibition-related functions and their neural mechanisms might be a profitable approach to understanding how "inhibition" contributes to cognitive and emotional disruptions in psychopathology.

Anxiety-modulated hyperactivity in brain regions associated with cognitive control suggests a vulnerability to distraction, even in conditions when there is no manipulated threat (e.g., color-word Stroop task). In the same vein, Silton et al. (2011) found that, as anxious apprehension increased, increased dACC activity (another key region associated with implementing cognitive control) was associated with greater Stroop interference (less efficient performance). Neuroimaging evidence and theories of anxiety (e.g., Eysenck et al., 2007; Eysenck and Derakshan, 2011) suggest that excessive anxiety manifests as hyperactivity in brain regions associated with attentional control during task performance, a pattern of activity that is thought to reflect compensation. However, there are limits to compensation, and it is important to determine when compensation may break down, such as when individuals with excessive anxiety are under stress. Under such conditions, it is likely that functional impairments become overtly apparent in the contexts in which they are most detrimental (e.g. during an exam or meeting an important deadline).

Present findings reveal specific inhibition-related neural mechanisms associated with PFC, particularly sub-regions of DLPFC, and MTG, as well as the modulating effects of specific combinations of anxious apprehension, anxious arousal, and anhedonic depression. Although these effects indicate potential sources of impaired or disrupted performance, under some circumstances they may function to ameliorate or compensate for imbalances in optimal levels of activity in systems of cognitive control.

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Indirect assessment of an interpretation bias in humans: neurophysiological and behavioral correlates

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Affective state can influence cognition leading to biased information processing, interpretation, attention, and memory. Such bias has been reported to be essential for the onset and maintenance of different psychopathologies, particularly affective disorders. However, empirical evidence has been very heterogeneous and little is known about the neurophysiological mechanisms underlying cognitive bias and its time-course. We therefore investigated the interpretation of ambiguous stimuli as indicators of biased information processing with an ambiguous cue-conditioning paradigm. In an acquisition phase, participants learned to discriminate two tones of different frequency, which acquired emotional and motivational value due to subsequent feedback (monetary gain or avoidance of monetary loss). In the test phase, three additional tones of intermediate frequencies were presented, whose interpretation as positive (approach of reward) or negative (avoidance of punishment), indicated by a button press, was used as an indicator of the bias. Twenty healthy volunteers participated in this paradigm while a 64-channel electroencephalogram was recorded. Participants also completed questionnaires assessing individual differences in depression and rumination. Overall, we found a small positive bias, which correlated negatively with reflective pondering, a type of rumination. As expected, reaction times were increased for intermediate tones. ERP amplitudes between 300 and 700 ms post-stimulus differed depending on the interpretation of the intermediate tones. A negative compared to a positive interpretation led to an amplitude increase over frontal electrodes. Our study provides evidence that in humans, as in animal research, the ambiguous cue-conditioning paradigm is a valid procedure for indirectly assessing ambiguous cue interpretation and a potential interpretation bias, which is sensitive to individual differences in affect-related traits.

Keywords: ERP, N200, LPP, cognitive bias, rumination, reflective pondering

INTRODUCTION

Affective states, including depression, can strongly affect cognitive processes, such as attention, memory, appraisal, and decision-making (Mathews and Macleod, 1994; Beck, 2008; Gotlib and Joormann, 2010; Disner et al., 2011). It has been proposed that a negatively biased interpretation of ambiguous situations results from facilitated attentional processes through emotions (affective priming theories; Bower, 1981; Isen and Daubman, 1984; Isen et al., 1987). This theoretical consideration originates from the semantic network theory, which assumes that associated memories are more easily accessible through a process of "spreading activation" (Anderson and Bower, 1973). In that respect, cognitive theories of depression posit that negative schemata, which are dysfunctional mental representations about the self, trigger a mood congruent interpretation of a distinct situation as good or bad, which itself has consequences on the emotional state of an individual (Beck, 1976). An enduring vicious circle of negative interpretation bias and negative emotional states might then lead to the development of psychopathological conditions, such as affective disorders (Mathews and Macleod, 2005). Indeed, some empirical evidence for negative attention, memory, and interpretation bias related to depression has been provided; however, the results are mixed, probably due to specifics in the selection of stimulus material and assessment of the bias. While studies using questionnaires with ambiguous stories were able to detect a negative interpretation bias in depression (Butler and Mathews, 1983; Berna et al., 2011), other studies that used measures like response latency or startle reflex were only in part successful. Lawson and Macleod (1999) studied the naming latency of words in positive or negative valence presented after an affective prime sentence and found no relation to scores in the Beck Depression Inventory (BDI; Beck et al., 1996). In contrast, participants with a higher BDI score showed larger startle reflex amplitudes elicited by ambiguous merge words compared to neutral stimuli (Lawson et al., 2002). This is in line with the hypotheses of a negative interpretation bias in depression as the startle reflex amplitude is

known to be increased after negative stimuli (Bradley et al., 1990; Lang et al., 1990).

Apart from clinical depression, individual coping style has been proposed to influence the interpretation of a situation as positive or negative. Lyubomirsky and Nolen-Hoeksema (1995) have shown that rumination, a coping style that refers to focusing one's attention and thoughts on negative aspects of a situation (Nolen-Hoeksema et al., 2008), leads to more negative interpretations of hypothetical situations. Using more explicit measures of cognitive bias, Kuehner and Huffziger (2012) showed that an induced ruminative self-focus after negative mood induction significantly increased dysfunctional depressiogenic attitudes in healthy individuals.

The heterogeneity of results in clinical as well as analogous samples (e.g., healthy individuals with elevated induced or naturally occurring negative mood), might, at least in part, result from methodological difficulties with experimental tasks that were used to assess biased information processing (see above). In the present study, we therefore adopted an ambiguous cue-conditioning paradigm from animal research that indirectly assesses biased information processing. In an acquisition phase, participants first learn to discriminate two tones of different frequency, which are followed by either a positive or a negative consequence. This part of the paradigm is similar to affective (or evaluative) conditioning which has been shown to be effective in various fields of research (De Houwer et al., 2001). Using a learning procedure similar to affective conditioning and pairing stimuli with reinforcers has repeatedly led to valence transfer as reported in the visual (Stolarova et al., 2006; Schacht et al., 2012) and auditory domain (Laufer and Paz, 2012). In a second phase of the paradigm participants are confronted with additional tones of intermediate frequency that are not reinforced. The response to these ambiguous tones is used as an indicator of an interpretation bias.

This experimental setup has several advantages. First, the auditory cues are indeed neutral in the beginning of the experimental procedure and have no negative or positive connotation. Also, as the intermediate tones are never followed by feedback, they are truly ambiguous which is essential for a cognitive bias to affect decision-making. This is in contrast to a study by Anderson et al. (2012), who applied a similar paradigm to assess emotional biases. In this study, however, the intermediate tones were also reinforced, which renders them non-ambiguous and, therefore, did not allow for the detection of an inherent interpretation bias. Second, this experimental setup was initially developed in rodents (e.g., Harding et al., 2004; Enkel et al., 2010). Its adaptation to human research paves the way for translational research that offers new possibilities for identifying neural and molecular mechanisms underlying biased information processing as well as the potential of developing new treatment strategies. Using such an ambiguous cue-conditioning paradigm, Enkel et al. (2010) successfully distinguished between congenitally non-helpless and helpless rats, which served as an animal model of depression. Moreover, Richter et al. (2012) showed that the negative bias of helpless rats was decreased after enrichment supporting the idea of using such bias as a measurement sensitive to depression treatment.

To also elucidate the neural time-course underlying biased information processing, we assessed event-related brain potentials (ERPs) of the EEG. Promising potentials include the N2 component, peaking around 200 ms post-stimulus over frontocentral electrode sites, which is associated with cognitive control and response conflict (Folstein and Van Petten, 2008). In the present study, ambiguous stimuli make demands on cognitive control processes (e.g., in cancelling a prepared response) and induce response conflict due to perceptual similarity and unclear response demands. N2 amplitude increases have been reported for increasing perceptual similarity (Folstein and Van Petten, 2004) and for increasing difficulty to discriminate ambiguous stimuli (Szmalec et al., 2008).

In addition, a positive deflection of the ERP starting around 300 ms post-stimulus has been consistently related to emotion and arousal (see Olofsson et al., 2008). As discussed by Kissler et al. (2009), this potential has been variously termed P3, late positive potential (LPP), or late positive complex (LPC). For the present study, we will use the term LPP for this positivity. There is evidence showing it to be increased for emotional stimuli (Foti et al., 2009; Hajcak et al., 2010; Kaestner and Polich, 2011) even when controlling for arousal (e.g., Rozenkrants and Polich, 2008; Kaestner and Polich, 2011; Feng et al., 2012) and it is also related to subjective intensity ratings of emotion (Cuthbert et al., 2000). Interestingly, it has also been reported to differentiate between negatively and positively conditioned stimuli (Schacht et al., 2012).

Late positive ERP components with a maximum over frontal electrode sites have also been associated with executive processes involved in categorization (Folstein and Van Petten, 2011) and there is evidence for an interaction between categorization and emotional valence modulating the LPP. In categorization tasks, negative stimuli have been found to elicit larger LPPs than either positive or neutral stimuli (Kanske and Kotz, 2007). Here again, the interpretation of the ambiguous tones may be reflected in the LPP amplitude. Therefore, in the present study, the LPP may be increased for reference tones because of their association with reward and punishment and could also reflect the differential processing of positively and negatively interpreted ambiguous tones.

In sum, the main goal of the present study was to test the described ambiguous cue-conditioning paradigm in humans. Therefore, we aimed at (1) establishing that the intermediate tones are perceived as ambiguous by comparing reference and intermediate tones, and (2) elucidating the processing of negatively and positively interpreted ambiguous stimuli. As pointed out above, interpretation of ambiguous stimuli is influenced by affective states and cognitive styles. We therefore assessed current affect, depression, and rumination. We hypothesized that ambiguity of the intermediate tones would be reflected in uncertain response choices, increased response times, and increased amplitudes of the N2 due to difficult discriminability and unclear response demands resulting in response conflict. We also expected LPP amplitudes to be increased for the non-ambiguous reference tones because of their greater behavioral relevance and associated affective salience. We further hypothesized the specific interpretation of ambiguous stimuli to be reflected in differential

ERP responses, specifically LPP amplitudes, which might show increases for negatively interpreted tones.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited via advertisements at the universities of Mannheim and Heidelberg. They received course credits and obtained the monetary gain from the ambiguous cue-conditioning task according to their task performance (see below for details). In total, 20 participants (10 women) with a mean age of 24.2 years ($SD = 9.1$) took part in the experiment. All had normal or corrected to normal vision and normal hearing. One participant reported to be left-handed. Since we had no lateralization hypotheses and as the results did not change, when excluding this participant, we report data with this participant included. None of the participants reported a history of head injuries, tinnitus, or mental disorders. After being informed about the experiment the participants gave written informed consent. The study was approved by the local Ethics Committee of Heidelberg University and was conducted in accordance with the Declaration of Helsinki.

MATERIALS

Stimuli consisted of five sinusoidal tones with a fundamental frequency between 1000 and 1164 Hz. They were selected so that all tones had a distance of 0.25 Bark ($f_1 = 1000$ Hz, $f_2 = 1038$ Hz, $f_3 = 1078$ Hz, $f_4 = 1120$ Hz, $f_5 = 1164$ Hz). The total duration of the tones was 250 ms with a linear ramp of 20 ms. For feedback a yellow smiley or a red frowney were presented (see **Figure 1**).

EXPERIMENTAL PROCEDURE

Participants were tested in an electrically shielded room in a single experimental session. They were seated in front of a monitor screen (1 m distance). To adjust the loudness of the tones to the individual hearing level, participants were presented a sinusoidal tone of 1000 Hz, which decreased in loudness, and pressed a button as long as they heard the tone. This procedure was repeated 10 times. The intensity of the test tones was then scaled according to the individual hearing level (Moore, 2003). The experimental task was to discriminate two reference tones (tone 1 and 5) by pressing one of two buttons with their right index or middle finger, respectively. One of the reference tones is referred to as "positive tone" (PT) as it acquired positive valence over the course of the experiment through positive feedback (smiley) and monetary gain (15 cents) after a correct button press. If participants responded incorrectly to this tone, they were informed that they had "missed the chance to win" money. In this case, a picture of a crossed smiley was shown. The other reference tone is referred to as "negative tone" (NT), as participants lost 15 cents when they pressed the incorrect button and negative feedback (frowney) was presented. By pressing the correct button to the NT, participants could prevent money loss and were presented with a crossed frowney and the information that loss of money had been avoided. If participants did not press any button within a response window of 1 s, they either lost money when the NT was presented or missed the chance to win money when the PT was presented. Each trial was comprised of a tone lasting 250 ms, a response window of 750 ms,

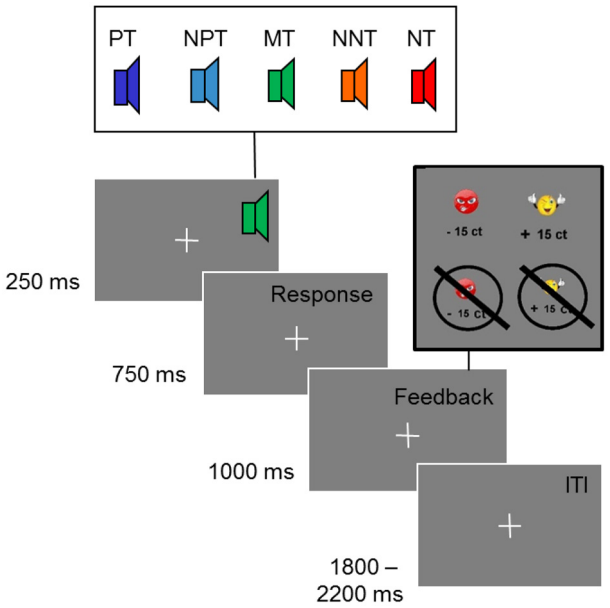

FIGURE 1 | Ambiguous cue-conditioning paradigm. PT, positive tone; NPT, near-positive tone; MT, middle tone; NNT, near-negative tone; NT, negative tone. Participants were instructed to press a button after each tone to obtain reward or avoid loss of reward (0.15 €). After the button press participants received a feedback. In case of a correct identification of the positive tone, they saw a smiley indicating a monetary gain. For a wrong button press or no response, they saw a crossed smiley indicating that they had missed the chance to earn money. A correct identification of the negative tone was followed by a picture of a crossed frowney indicating that they had successfully avoided loosing money; for a wrong button press, participants lost money and saw a frowney. No feedback was presented after intermediate tones (NPT, MT, NNT) and after 4% of the reference tones (PT, NT). The inter-trial-interval (ITI) was jittered between 1800 and 2200 ms.

the following feedback lasting 1 s and, finally, a jittered inter-trial interval of 2 s on average (randomly selected between 1800 and 2200 ms) (see **Figure 1**). Participants were randomly assigned to one of four counterbalanced conditions with respect to the finger used for button presses and the fundamental frequency of PT and NT.

During a brief learning and a training session, participants learned to discriminate PT and NTs. First, both tones were presented five times each and participants were told how to respond (learning session). Second, discrimination of reference tones was practiced with 40 randomized trials (training session). In the experimental test phase, three additional tones were presented (66 times each) in addition to the two reference tones (PT, NT; 282 times each). The three additional tones were intermediate in frequency (see section Materials) and labeled near-positive tone (NPT), middle tone (MT), and near-negative tone (NNT). The three intermediate tones were not followed by any feedback to render them fully ambiguous. All tones were presented in pseudo-randomized order. Furthermore, during the test phase 24 (4%) of the reference tones (12 PT, 12 NT) were also presented without feedback to cover the presence of intermediate tones. Thus, a total of 222 tones were presented without feedback, another 540 trials

(270 PT, 270 NT) were presented with positive or negative feedback. All tones without feedback were less frequent than reference tones with feedback to cover their presence and to keep the participants motivated. Participants were instructed to respond to each tone by pressing one of the two buttons and they were informed that not every trial would have a feedback. The test phase was divided into six blocks of 127 trials, each lasting about 8 min. At the end of each block participants had a break of 2 min in which they were informed about the total amount of money won up to that point.

QUESTIONNAIRES

Several questionnaires were used to explore inter-individual differences in emotional state and trait variables. We measured current depression with the German version of the Beck Depression Inventory II (Beck et al., 1996; Hautzinger et al., 2006), a 21 item self-report questionnaire. To investigate strategies for coping with depressive symptoms participants completed a German version of the Response Style Questionnaire (RSQ; Nolen-Hoeksema, 1991), which tests for two subcomponents of rumination: "reflective pondering" and "brooding" (10 items; Gonzalez et al., 2003; Kuehner and Huffziger, 2012). Furthermore, participants completed the Positive and Negative Affect Scale (20 Items; Watson et al., 1988) immediately before the ambiguous cue-conditioning task.

EEG RECORDING

During the ambiguous cue-conditioning task, a continuous 64 channel EEG was recorded using Ag/AgCl-electrodes positioned according to the international 10/20 system. The signals were amplified by Neuroscan Synamp amplifiers (Compumedics, Charlotte, NC, USA), digitized at a rate of 500 Hz and recorded by Neuroscan Scan 4 Acquire software (Compumedics, Charlotte, NC, USA). The right mastoid was used as on-line reference and an electrode positioned on the sternum was used as ground electrode. Another electrode was placed on the left mastoid (for offline re-referencing). Horizontal eye movements were recorded from two electrodes placed lateral to both eyes, while two electrodes placed above and below the right eye registered vertical eye movements. Impedances of all electrodes were kept below 15 kOhm.

DATA ANALYSIS

For the EEG data analyses, Brain Vision Analyzer software (Brain Products GmbH, Munich) was used. The pre-processing of the EEG data included re-referencing to the mean of the mastoids and down-sampling to 200 Hz. Then, the data were filtered (0.1–30 Hz) to remove high- and low-frequency waves and the data were visually inspected to check for artifacts. To correct for eye movement artifacts, we performed an independent component analysis (Comon, 1994). In a next step, segments of 1200 ms starting 200 ms pre-stimulus and ending 1000 ms after stimulus onset were created. Using the semiautomatic artifact rejection tool, segments were excluded if the minimum and maximum amplitude in a segment differed by more than 300 μV. To obtain event-related potentials (ERPs), the segments were averaged relative to a 200 ms pre-stimulus baseline.

For the statistical analyses of behavioral, questionnaire, and ERP data, SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA) was used. To test for effects of ambiguity we compared behavioral and ERP responses to the reference and to the intermediate tones. Because of the very low number of incorrect responses to the reference tones, only the correct response trials were included for analyses of reaction time and ERP data. To analyze the participants' response choice, a difference score between the frequencies of the two response options (positive, negative) was calculated, reflecting the degree of uncertainty in associating a tone with a response. This difference score was then compared between reference and intermediate tones.

To test for effects of interpretation biases, we analyzed the responses to the three intermediate tones since the participants' response reflects the categorization of the ambiguous tones as either predicting reward or punishment. Here, we calculated 3×2 repeated measures ANOVAs with the factors tone (NNT, MT, NPT) and response (positive, negative). Also, to obtain an overall measure of the cognitive bias, which can be correlated with questionnaire scores, we calculated a bias score defined as the mean of all responses to the three intermediate tones. A response to avoid punishment (negative response) was calculated as -1 while a response to obtain reward (positive response) counted $+1$. A positive bias score indicates more positive than negative responses, while a negative bias score indicates more negative than positive responses to the ambiguous tones. An independent sample t-test was computed to test for gender differences in the bias score. To test if the bias changed during the test phase, a One-Way ANOVA with the factor block (1–6) was calculated.

In this study, ERP analyses focused on N2 and LPP. Based on the literature (Folstein and Van Petten, 2008) we extracted the mean activity in the time window from 180 to 240 ms post-stimulus for analyzing the conflict-related N2 component. For LPP analyses, we first calculated an omnibus ANOVA of the mean activity with the factors tone (NNT, NPT, MT), response (positive, negative), and electrode for consecutive time windows of 100 ms up to 1000 ms. These analyses showed a significant response by electrode interaction in the time window from 300 to 700 ms. For the analyses of the ambiguity effect we chose a shorter time window from 0 to 500 ms for the omnibus ANOVA with the factor ambiguity (reference tones, intermediate tones) and electrode since analyses of the later time windows would be confounded by feedback-related activity that occurred on average 540 ms post-stimulus (as a feedback was only presented after reference tones, not after the intermediate tones). Based on the results obtained here we focused further analyses on the time window from 300 to 500 ms. We then exported mean activity in the time range 300–500 ms (early LPP) and 300–700 ms (late LPP) and performed analyses per electrode. Based on these analyses we defined two regions of interest (frontal: F1, Fz, F2, FC1, FCz, and FC2; posterior: P1, Pz, P2, PO3, POz, and PO4) that we included in further analyses.

To link behavioral data with ERP results and questionnaire data, we computed bivariate Spearman correlations. For all analyses significant thresholds of $p < 0.05$ were used and significant main effects and interactions were followed up

with Bonferroni corrected *post-hoc* paired comparisons or contrasts. A Greenhouse-Geisser correction was applied when necessary.

RESULTS

BEHAVIORAL FINDINGS

Response choice

Participants were well able to discriminate the two reference tones as indicated by 86.9% ($SD = 20$) correct responses in the training session. In the following test phase, the percentage of correct responses to the reference tones was similarly high (mean percentage of correct responses: 87.0%; $SD = 7$), despite the presentation of additional intermediate tones (see **Figure 2A**).

To test for the effects of ambiguity on response choice, we compared responses to the reference and to the intermediate tones. Specifically, we compared the absolute difference between the percentage of positive and negative button presses. For the reference tones, this yielded a mean difference score of 81.73% ($SD = 11.56$). For the intermediate tones the index was 45.68% ($SD = 13.70$), indicating a more undetermined response pattern. A repeated measures ANOVA with the factor ambiguity (reference tones, intermediate tones) was significant [$F_{(1)} = 143.73$; $p < 0.001$; partial $\eta^2 = 0.88$].

To check for effects of interpretation biases, we compared the number of negative and positive responses to the three intermediate tones. A repeated measures ANOVA with tones (NNT, MT, NPT) and responses (negative, positive) yielded a significant effect of tone [$F_{(1.07)} = 12.13$; $p < 0.01$; partial $\eta^2 = 0.39$], which points to differences between NNT and MT ($p < 0.001$), as well as NPT and MT ($p < 0.001$) as indicated by pairwise comparisons. A significant tone by response interaction [$F_{(1)} = 189.72$; $p < 0.001$; partial $\eta^2 = 0.91$] was driven by a higher percentage of positive responses to NPT and a higher percentage of negative responses to NNT [$F_{(1)} = 355.40$; $p < 0.001$; partial $\eta^2 = 0.95$].

Reaction time

Figure 2B displays the reaction time data for all tone and response combinations. To test for the effect of ambiguity on reaction times, we again compared reference and intermediate tones. This effect was significant indicating that participants responded faster to the reference compared to the intermediate tones [$F_{(1)} = 27.64$; $p < 0.001$; partial $\eta^2 = 0.59$].

To test for the effect of interpretation biases, the three intermediate tones were compared with repeated measures ANOVA with the factors tone (NPT, MT, NNT) and response (positive, negative). This analysis showed a significant tone by response interaction [$F_{(2)} = 18.45$; $p < 0.001$; partial $\eta^2 = 0.49$]. *Post-hoc* contrasts showed that this interaction was due to faster responses to obtain reward than to avoid punishment after NPT [$F_{(1)} = 19.44$; $p < 0.001$; partial $\eta^2 = 0.51$] and faster responses to avoid punishment than to obtain reward after NNT [$F_{(1)} = 11.85$; $p < 0.005$; partial $\eta^2 = 0.38$]. Positive and negative responses to MT were equally fast ($p > 0.90$).

Individual differences in bias score

In the current sample the bias score was slightly positive with a mean of 3.95 ($SD = 44.8$) but not significantly different from 0 [$t_{(19)} = 3.94$; $p = 0.70$]. To test if the bias changed throughout the experiment, we calculated a One-Way ANOVA with the factor block, which was not significant indicating constant interpretation of the intermediate tones across the six experimental blocks ($p > 0.5$). We also observed no gender differences ($p > 0.5$). Furthermore, there was no significant correlation of cognitive bias with current mood (PANAS) and depression (BDI; all $p > 0.5$). We did, however, observe a significant correlation between the bias score and the reflective pondering subscale of the RSQ, indicating that participants with a higher score in reflective pondering displayed a more negative bias ($\rho = -0.50$; $p = 0.025$; see **Figure 3**) while the brooding subscale did not correlate with the bias score ($p > 0.5$).

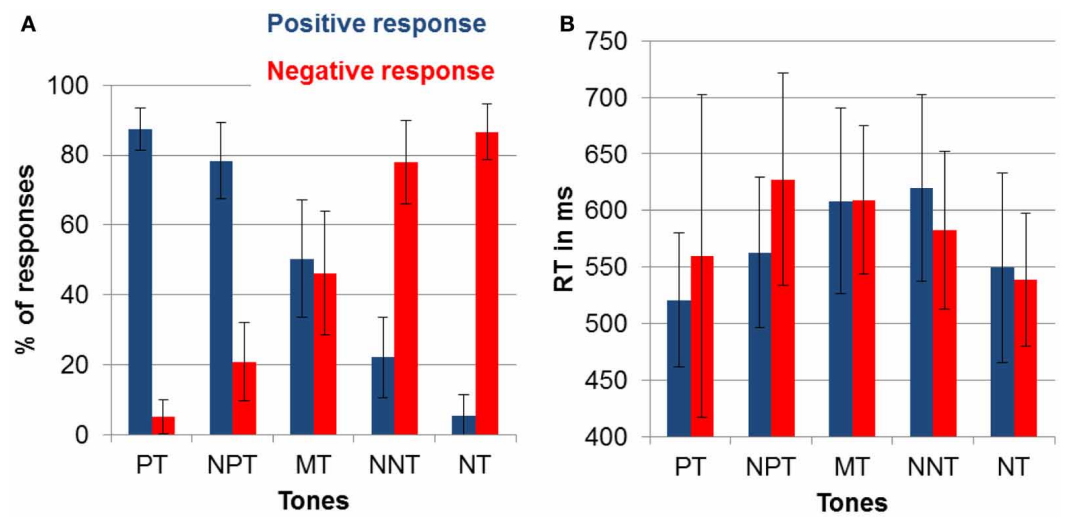

FIGURE 2 | (A) Percentage of chosen responses (and SD) to avoid punishment (negative response) and obtain reward (positive response) for each of the five tones. **(B)** Mean reaction times (and SD) to the five tones.

ERP RESULTS

Across conditions the following ERP components were detected: a negative deflection peaking around 200 ms after tone onset (N2) and a positive deflection starting around 300 ms after tone onset (LPP).

In order to define the latency range of these components we calculated several omnibus ANOVAs per electrode. Besides the effect for electrode in each time window, we obtained a significant effect for ambiguity from 400 to 500 ms [$F_{(60)} = 10.24$; $p < 0.01$; partial $\eta^2 = 0.39$] and significant interactions for ambiguity and electrode [300–400 ms: $F_{(60)} = 1.83$; $p < 0.001$; partial $\eta^2 = 0.1$; 400–500 ms: $F_{(60)} = 2.56$; $p < 0.001$; partial $\eta^2 = 0.14$]. Further analyses focused on the time window from 300 to 500 ms.

For the interpretation bias effect omnibus ANOVAs revealed main effects for electrode in each time window and in addition effects for response in the time window from 300 to 400 ms [$F_{(1)} = 4.4$; $p < 0.05$; partial $\eta^2 = 0.22$] and from 600 to 700 ms [$F_{(1)} = 11.76$; $p < 0.01$; partial $\eta^2 = 0.4$]. Further, the analyses showed a significant response by electrode interaction in the time windows from 300 to 400 ms [$F_{(60)} = 2.6$; $p < 0.001$; partial $\eta^2 = 0.14$], from 400 to 500 ms [$F_{(60)} = 2.0$; $p < 0.001$; partial $\eta^2 = 0.11$], from 500 to 600 ms [$F_{(60)} = 1.9$; $p < 0.001$; partial $\eta^2 = 0.11$] and from 600 to 700 ms [$F_{(60)} = 1.68$; $p < 0.001$; partial $\eta^2 = 0.1$]. Thus, analyses focused on the time window from 300 to 700 ms.

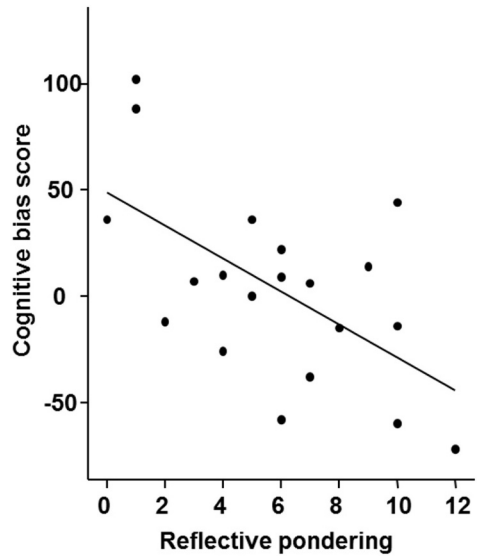

FIGURE 3 | Correlation of the cognitive bias score with the reflective pondering subscale of the Response Style Questionnaire ($p < 0.05$; $\rho = -0.501$).

Ambiguity effect

To test for the effects of ambiguity, we calculated an ANOVA with the factors ambiguity (reference tones, intermediate tones) and region (anterior, posterior). For the early LPP time window (300–500 ms), we identified significant main effects of ambiguity [$F_{(1)} = 6.0$; $p < 0.05$; partial $\eta^2 = 0.27$] and region [$F_{(1)} = 54.75$; $p < 0.001$; partial $\eta^2 = 0.78$]. As shown in **Figure 4**, early LPP amplitudes were larger for reference compared to ambiguous tones and over posterior compared to anterior electrodes. The interaction of ambiguity and region was not significant ($p > 0.1$). For the N2, only a significant effect of region [$F_{(1)} = 79.45$; $p < 0.001$; partial $\eta^2 = 0.82$] with larger N2 amplitudes over frontal

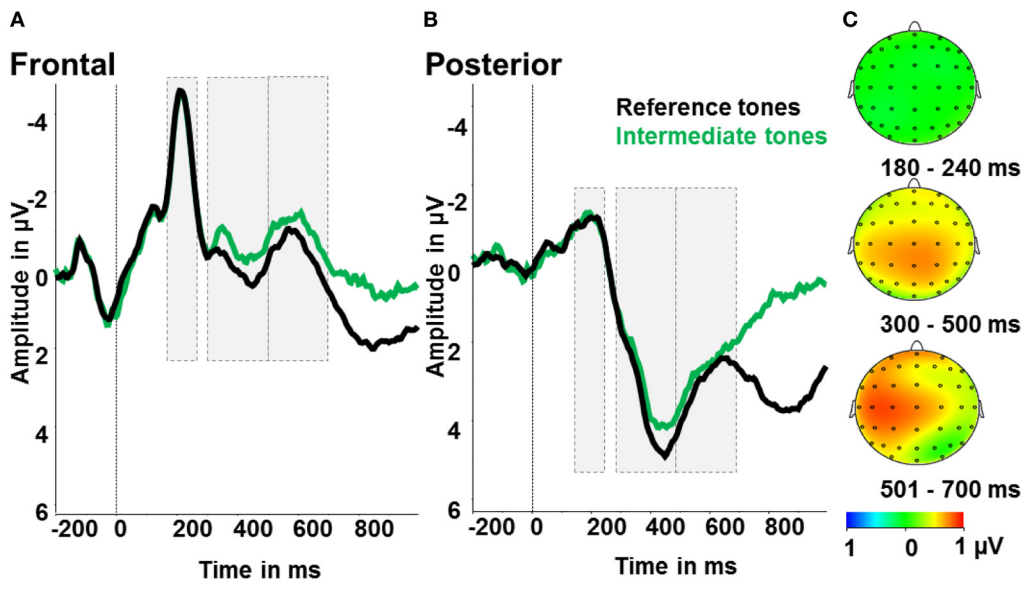

FIGURE 4 | Ambiguity effect: ERPs after reference tones (black) and intermediate tones (green). (A) Event-related activity averaged over frontal electrodes (F1, Fz, F2, FC1, FCz, FC2). **(B)** Event-related activity averaged over posterior electrodes (P1, Pz, P2, PO3, POz, PO4). **(C)** Maps display the activity difference of the reference tones and correct responses minus ambiguous tones and all responses in µV in the time windows 180–240 ms (N2), 300–500 ms (early LPP) and 501–700 ms (late LPP) post-stimulus.

compared to posterior electrodes was found. Further main effects or interactions were not significant (all $p > 0.5$, see **Figure 4**).

Interpretation bias effect

To test for indicators of different processing of positively or negatively interpreted stimuli, we compared intermediate tones with positive and negative responses. Therefore, we conducted repeated measures ANOVAs with the factors tone (NPT, MT, NNT), response (positive, negative), and region (frontal, posterior). For the LPP in the time window 300–700 ms post-stimulus there were significant effects of response [$F_{(1)} = 4.55$; $p < 0.05$; partial $\eta^2 = 0.22$] with larger amplitudes after negative responses and a main effect of region with larger amplitudes over posterior electrode sides [$F_{(1)} = 65.08$; $p < 0.001$; partial $\eta^2 = 0.80$]. Besides, there was a significant response by region interaction [$F_{(1)} = 11.21$; $p < 0.01$; partial $\eta^2 = 0.41$]. Over frontal electrodes, amplitudes were increased after negatively, as opposed to positively, categorized intermediate tones [$F_{(1)} = 11.11$; $p < 0.01$; partial $\eta^2 = 0.41$], while there were no effects over posterior electrode sites (all $p > 0.5$; see **Figure 5**). For the N2, a significant effect of region [$F_{(1)} = 63.29$; $p < 0.001$; partial $\eta^2 = 0.78$] with larger N2 amplitudes over frontal compared to posterior electrodes was found. Further main effects or interactions were not significant in this time range (all $p > 0.5$, see **Figure 5**).

DISCUSSION

The current study employed an ambiguous cue-conditioning paradigm for the indirect assessment of an affect-related interpretation bias and investigated the related neurophysiological correlates with EEG. In contrast to instrumental conditioning procedures, this paradigm comprised a second stage introducing additional stimuli intermediate in frequency to the learned ones. Ambiguity of these intermediate tones could be established with participants responding slower and with less certainty when confronted with the intermediate tones. In the current sample of healthy individuals, a small positive cognitive bias was observed which was associated with inter-individual differences in ruminative coping style, i.e., reflective pondering. Higher scores in reflective pondering were related to a more negative bias. Also, the data yield insight into the time-course of ambiguous stimulus interpretation showing decreases in LPP amplitudes after ambiguous tone presentation, but no N2 effect. Moreover, we observed differences in ERP amplitudes depending on the interpretation of the ambiguous stimuli: frontal LPP amplitudes were increased for negatively compared to positively interpreted intermediate tones.

AMBIGUITY EFFECT

For the validity of the present paradigm it is essential that the intermediate tones are perceived as ambiguous with regard to what potential outcome they predict. Evidence for this is the increased response uncertainty that participants showed by selecting positive and negative responses equally often after the intermediate tones, while the responses to the reference tones were either clearly positive or negative. Additionally, response times were longer for intermediate tones also indicating increased response uncertainty (Szmalec et al., 2008; Anderson et al., 2012).

The collected ERP data can shed light on the time-course of processing ambiguity in the intermediate tones. In contrast to our hypotheses, we observed no effect of ambiguity on the N2. As ambiguity has been conceptualized as representing a form of cognitive conflict (Szmalec et al., 2008), we would have expected to see increased N2 amplitudes for ambiguous vs. reference tones, analogous to incongruent vs. congruent stimuli in conflict tasks like the flanker or Stroop (van Veen and Carter, 2002). A critical

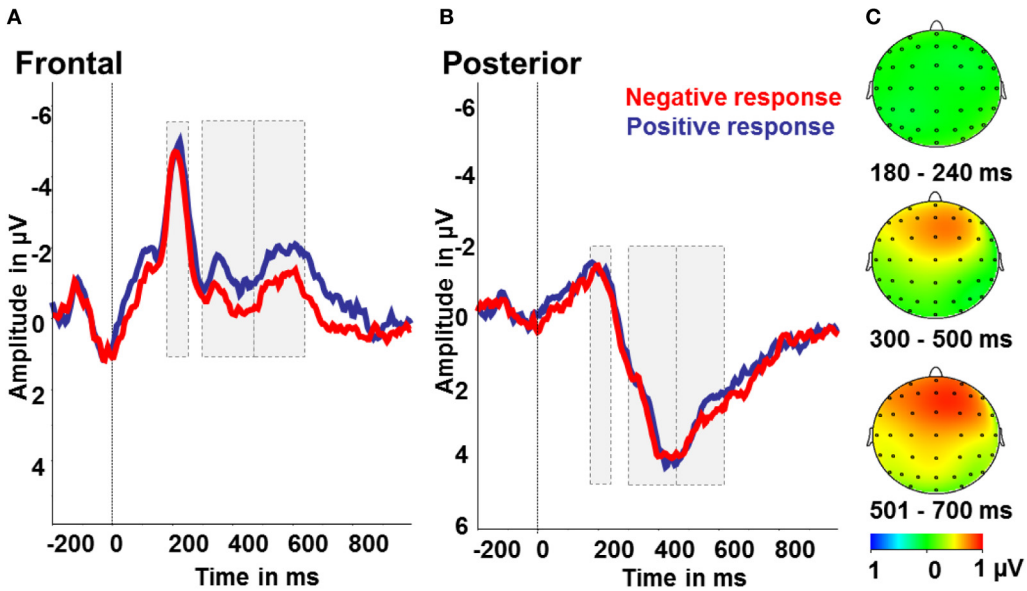

FIGURE 5 | Interpretation bias effect: ERP amplitudes for positive (blue) and negative responses (red) to the intermediate tones. (A) Frontal region of interest. **(B)** Posterior region of interest. **(C)** Activity difference of ambiguous tones and positive responses minus ambiguous tones and negative responses in µV in the time windows 180–240 ms (N2), 300–500 ms (early LPP) and 501–700 ms (late LPP) post-stimulus onset.

difference from previous reports of N2 increases for ambiguous stimuli (Szmalec et al., 2008) is the affective context in the present study. Szmalec et al. (2008) also had participants differentiate two tones of variably perceptual similarity, but responses were not associated with reward or punishment. Positive and negative emotional stimuli, however, have been shown to modulate processing of cognitive conflict and the related N2 amplitude (Kanske and Kotz, 2010, 2011). In particular, the N2 is enlarged for stimuli of greater emotionality, reflecting increased recruitment of cognitive control processes (for an overview see Kanske, 2012). In the present study, it could be argued that the reference tones possess more emotional salience due to their association with potential monetary gain or loss, thus recruiting more cognitive control resources. This may have raised N2 amplitudes to the level of the ambiguous tones. The pattern of LPP amplitude changes corroborates this explanation. We observed increased LPP amplitudes for the reference compared to the intermediate tones, which suggests that the reference tones were perceived as more salient. The LPP has been consistently found to be increased for emotional and arousing stimuli of different modalities (Cuthbert et al., 2000; Schupp et al., 2003; Foti et al., 2009; Schacht and Sommer, 2009; Hajcak et al., 2010). In addition, P3 which peaks in a similar time range has been associated with task relevance (for a review see Kok, 2001). In the present study, task relevance is arguably higher for the reference tones, as they are followed by monetary gains and losses, while the responses to the intermediate tones are without consequences.

In sum, the ERP data suggest that the reference tones in the present task were of higher salience than the intermediate tones, reflected in increased LPP amplitudes, which may have overridden an ambiguity effect in the N2 time window.

Since participants were presented with a visual feedback after the reference tones (which occurred on average 540 ms after stimulus onset), but not after the intermediate tones, the ERP cannot be meaningfully interpreted in the late LPP time window. The late positive deflection which is increased for reference compared to intermediate tones from 540 ms post-stimulus onwards is most likely due to this visual stimulation.

INTERPRETATION BIAS EFFECT

A second question we addressed concerned the differences in processing between positive and negative interpretations of the ambiguous intermediate tones. The absence of a strong overall bias means that about half of the intermediate tones were interpreted negatively and positively. This pattern varied, however, as NPT and NNTs were interpreted more often as positive and negative, respectively. Interpretations in the opposite direction (e.g., a negative response to a NPT) were also slowed down. The major question here was whether the decision to respond to a tone positively or negatively is associated with differential processing of the tones. The effect of tone interpretation on LPP amplitudes suggests that this is the case. The amplitudes were increased for tones that were subsequently responded to with a negative compared to a positive button press. This direction of the effect falls in line with several previous studies that showed enlarged positivities for different types of emotional stimuli (Kanske and Kotz, 2007; Rozenkrants and Polich, 2008; Kaestner and Polich, 2011; Feng et al., 2012). The present data, however, add to this evidence that the top-down interpretation of the affective value of a certain stimulus yields similar brain responses as when the affective value is inherent in the stimulus. Previously, Schacht et al. (2012) found increased LPP amplitudes for stimuli with learned positive valence. The authors suggest that this finding might be due to better learning for the positive compared to negative reinforcers. The present results show an effect on LPP amplitude due to the interpretation and association of the intermediate tones with a certain valence. The fact that we find enlarged LPP amplitudes for negatively interpreted tones might be explained by task differences. In our study, participants received feedback on their response and thus learned a tone—response association leading to one positive and one NT. In contrast, Schacht et al. (2012) used picture sets of different valence (as rated a priori) and participants had to classify the pictures in positive, neutral, or negative without feedback. Beyond that, the focus of our analyses was on intermediate tones that were not reinforced in the acquisition phase. Here, we find processing differences apparent already from around 300 ms post-stimulus in the LPP. Even though the more anterior distribution of this component is not typical, some variability in the topography of valence effects in the P3 time window has been reported (Rozenkrants and Polich, 2008; Feng et al., 2012). Principal components analyses of valence-related ERP effects corroborate this, showing a number of late positivities that might only partially share neural generators because of different scalp distribution (Foti et al., 2009). The exact role of these differentiable components still needs to be specified, however.

INTERPRETATION BIAS AND ITS RELATIONSHIP TO AFFECT-RELATED VARIABLES

We suggested that valence is ascribed to the intermediate tones on the basis of an individual interpretation preference that biases cognitive processing. However, here we observed no significant correlations between current positive or negative mood or depression and interpretation bias, although this has previously been reported (Eysenck et al., 1991; Mogg et al., 2006; Anderson et al., 2012). The lack of a relationship between current mood and depressive symptoms with the interpretation bias in the present study might result from a very limited variance in these affect-related variables in young healthy individuals (e.g., BDI ranging from 0 to 8 on a scale with a maximum score of 63, see **Table 1**). Nevertheless, we did observe a significant negative correlation between the bias score and reflective pondering, a subcomponent of rumination. This might indicate that individuals with a stronger ruminative coping style show a more negative bias and vice versa. Joormann et al. (2006) have also studied the relation between cognitive bias and rumination. Here, an attentional bias toward sad faces correlated significantly with brooding, a second subcomponent of rumination as measured with the RSQ, but not with reflective pondering. From this finding, the authors concluded that there might be functional as well as dysfunctional components of rumination. However, in depressed patients both rumination subscales (brooding and reflective pondering) were increased compared to healthy controls (Joormann et al., 2006). There are several explanations for the finding of a relationship between reflective pondering and a negative interpretation

Table 1 | Questionnaire data.

	Minimum	Maximum	Mean	*SD*
BDI	0	8	2.85	2.46
RSQ_R	0	12	5.80	3.40
RSQ_B	1	8	4.45	2.46
PA	18	39	28.65	6.72
NA	10	18	11.00	1.89

Range, mean, and standard deviation (SD) of participants' scores in the Beck Depression Inventory (BDI), Reflective pondering subscale (RSQ_R), and Brooding subscale (RSQ_B) of the Response Style Questionnaire, and positive (PA) and negative affect (NA) assessed before the measurement with the Positive and Negative Affect Scale (PANAS).

bias, while no such relationship was found between brooding and biased information processing. First, questionnaire data show that the variance for brooding was much smaller than for reflective pondering, limiting the potential to find a correlation. Second, whereas in clinical depression reflective pondering might represent the more adaptive ruminative coping style (in comparison to brooding), it still indicates a ruminative coping style that is maladaptive when compared to more adaptive cognitive coping strategies, such as positive reappraisal, positive refocusing, or focusing on planning. Our result of a negative correlation between reflective pondering and the interpretation bias is in line with previous studies relating cognitive bias and rumination (Gotlib and Joormann, 2010; Koster et al., 2011) and encourages further research with clinical samples using the described paradigm as it suggests that a maladaptive, depressive cognitive style is related to negative interpretation bias.

That, on a group level, we did not observe a significant interpretation bias may be plausible, given the fact that we investigated a group of healthy individuals that rather tend to show a positive bias (Deldin et al., 2001). Further, it is supposed that cognitive biases result from depressiogenic schemata and that they are not active until triggered by a negative event or a negative mood state (Scher et al., 2005). Thus, negative mood or thought induction may be necessary to elicit a negative cognitive bias in control participants. With the induction of self-focused thoughts which are similar to ruminative thinking, Hertel and El-Messidi (2006) observed more negative interpretations of ambiguous homographs in dysphoric students. Future research could combine mood induction procedures with the present paradigm to test for changes in the measured bias.

LIMITATIONS

Although the present study provides a validation of an animal experimental setup that allows the indirect assessment of an interpretation bias and gives new insights into the time-course of ambiguous cue processing, a number of limitations have to be pointed out. First, we did not assess other, more explicit measures of cognitive bias in addition to the ambiguous cue-conditioning task, which could have added some external validity to the present results. Second, we did not collect valence rating for the tones after the conditioning paradigm, which could have corroborated their acquired valence status. In a later yet unpublished study we included valence ratings. In this study participants ascribed more positive valence to the PT than to the NT and the intermediate tones. The NT did not differ in valence which might be due to the fact that only false responses to the NT had negative consequences. A direct loss after the NT would be a stronger negative feedback and more comparable to the punishing effect of an electric shock in the study by Enkel et al. (2010). Apart from the valence transfer to the intermediate tones their categorization might also be influenced by the sensory resemblance of the NPT to the PT and the NNT to the NT. Sensory similarity might facilitate the affective interpretation of these tones or affective interpretation might partly be a consequence of the sensory similarity. If sensory similarity was the only basis for decision-making then the responses would be identical to the ones after the corresponding reference tones. The present results indicate that responses to these tones are biased by both the frequency information of the tones and top-down interpretations. In case of the MT sensory resemblance plays no role since these tones resemble neither the PT nor the NT. Responses to these tones might therefore underlie a cognitive bias more strongly. In addition, the intermediate tones might differ in their degree of ambiguity. Although the lack of feedback after all three intermediate tones leads to uncertainty as seen by an increase in reaction time, the sensory resemblance of NPT and NNT might facilitate response selection. Thus, MT represents the highest level of ambiguity. In the present study the number of MT was too small for statistical analyses but further studies could increase the number by only presenting MT and no NNT or NPT. Another limitation of the paradigm might be that it lacks a neutral condition. Presenting another tone which is either followed by neutral feedback or where the participant does not need to respond would further corroborate the affective conditioning procedure. Finally, as the present study was designed to validate the employed experimental task and to delineate the neurophysiological mechanisms of ambiguous cue processing and biased interpretation of ambiguous cues, we were not able to detect a relation of the interpretation bias with depression measures. As this was probably due to the small variance in depression scores in the present sample, future studies should test clinical samples with the procedure. Although the correlational findings of the present study suggest an association between interpretation bias and rumination, our sample size was very small. Besides, we did not correct for multiple comparisons underlining the rather exploratory nature of our findings although it is under debate if Bonferroni corrections are appropriate (Perneger, 1998). To corroborate our findings mood or rumination inductions (e.g., Huffziger and Kuehner, 2009) would be necessary. But, we also have to point out that the literature on cognitive biases in depression is inconsistent (for reviews see Dalgleish and Watts, 1990; Gotlib and Joormann, 2010). Especially studies using implicit measures of cognitive bias fail to detect a negative interpretation bias (Lawson and Macleod, 1999) even after negative mood induction (Bisson and Sears, 2007).

CONCLUSION

The present study aimed at establishing an ambiguous cue-conditioning paradigm in humans. Such an approach has the

advantage that it assesses the interpretation bias indirectly, which yields it unaffected by demand effects or a priori connotations of the applied stimulus material (as is the case, for example, in words; Lawson and Macleod, 1999; or homophones; Mogg et al., 2006). Furthermore, it offers the possibility of testing for positive and negative biases by assigning affective significance (positive and negative, respectively) to two initially neutral tones through classical conditioning. After such an acquisition phase, the test phase introduced tones of intermediate frequency that served as a measure of interpretation bias since the response to these tones indicated the participants' expectation of a rewarding or potentially punishing event.

The results of the present study provide evidence that ambiguous cue processing and resulting interpretation bias is assessable by using the proposed ambiguous cue-conditioning task that has previously been established in animals. On a behavioral level, ambiguous stimuli led to uncertainty in their response options and longer reaction times. On a neurophysiological level, we observed no N2 differences, but increased LPP amplitudes for reference stimuli compared to ambiguous stimuli, suggesting greater task-relevance and emotional salience for the reward- and punishment-related stimuli. Interpretation of the ambiguous stimuli had an effect on LPP over frontal electrodes with increased amplitudes for a negative compared to a positive interpretation. This indicates early and prolonged differences in the activation of top-down interpretation mechanisms.

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Relationships among cognition, emotion, and motivation: implications for intervention and neuroplasticity in psychopathology

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Emotion-cognition and motivation-cognition relationships and related brain mechanisms are receiving increasing attention in the clinical research literature as a means of understanding diverse types of psychopathology and improving biological and psychological treatments. This paper reviews and integrates some of the growing evidence for cognitive biases and deficits in depression and anxiety, how these disruptions interact with emotional and motivational processes, and what brain mechanisms appear to be involved. This integration sets the stage for understanding the role of neuroplasticity in implementing change in cognitive, emotional, and motivational processes in psychopathology as a function of intervention.

Keywords: emotion, cognition, motivation, anxiety, depression, neuroplasticity, intervention

INTRODUCTION

Research on emotion and its relationship with cognition has garnered much attention in recent years (e.g., Phelps, 2006; Levin et al., 2007; Pessoa, 2008; Miller, 2010; Dolcos et al., 2011), evident in the increasing popularity of the term "emotion-cognition interactions" in the literature. This body of literature has come to appreciate the intimate and closely interacting nature of these processes and is expanding to understand the relationships between motivational and cognitive processes (Spielberg et al., 2008, 2011b; Pessoa, 2009; Pessoa and Engelmann, 2010; Chiew and Braver, 2011). We define emotion as a system of multiple related processes (including relevant thoughts, experiences, and preparations for action, manifesting in physiology, overt behavior, and language; Lang, 1968; Kozak and Miller, 1982; Roseman, 2008) that "attempt to promote adaptation by responding to the pursuit and attainment (or lack of attainment) of individuals' needs, goals, and concerns" (Berenbaum et al., 2003, pg. 208). Similar to cognition and emotion, emotion and motivation are related constructs but are not identical (for further discussion, see Chiew and Braver, 2011). Although emotions and motivations both have a hedonic component, motivations are typically conceptualized as processes that drive goal-directed behaviors aimed at achieving desired outcomes and avoiding undesired ones (Carver, 2006; Roseman, 2008). Pessoa (2009) described motivation as "what makes one work to obtain a reward or to avoid punishment."

Although some have argued that emotions and motivations cannot be separated (Buck, 2000; Laming, 2000), many argue that these constructs are related yet distinguishable, and differ in their effects on cognition and behavior (for a review, see Chiew and Braver, 2011). These psychological processes are implemented via both shared and distinct brain regions. Carver (2006) proposed that emotion is the affect that emerges from comparing the actual versus expected progress toward a goal, whereas motivation is what drives progress toward that goal. When there is a mismatch between actual and expected progress, changes in emotional states occur and alter subsequent motivations, impeding or promoting goal attainment. Further, changes in motivation may modify expectations about future events, which can then result in changes in emotions.

Accumulating evidence demonstrates that performance on tasks commonly considered nonemotional can be influenced by emotional and motivational states, more enduring emotion- and motivation-related traits, and the emotional qualities of situations. Cognitive processing is also an integral part of emotion and motivation and affects the degree to which they influence ongoing activities and behaviors. It has become increasingly clear that cognition, emotion, and motivation are intricately intertwined, and it is difficult to determine where to draw the line between them (Pessoa, 2008, 2009; Miller, 2010). Complex relationships among these psychological processes appear to play an important role in the development and maintenance of psychopathology and in treatment effectiveness. As demonstrated below, a review of the cognitive difficulties experienced by individuals with anxiety and depression makes clear that it is virtually impossible to separate these difficulties from their emotional and motivational influences. Conversely, the emotional and motivational disruptions that are characteristic of anxiety and depression are embedded in

abnormal cognitions, as has been well established for some time (e.g., Beck, 1976; Levin et al., 2007) and can be targeted effectively in treatment paradigms.

Recent years have also seen advances in elucidating the functional and structural brain mechanisms that support the effects of emotion and motivation on cognition and vice versa (for reviews, see Gray, 2004; Phelps, 2006; Pessoa, 2008, 2009; Chiew and Braver, 2011; Dolcos et al., 2011; Ochsner et al., 2012). Researchers have often used neuroimaging data to support the notion of functional specialization in the brain, carving it into distinct "cognitive," "affective," and "motivational" regions. Growing sophistication in theory and methodological approaches has led to empirical evidence suggesting that these processes are not only interdependent but effectively integrated in at least some areas of the brain (e.g., Gray, 2004; Pessoa, 2008, 2009; Miller, 2010). Cognitive, emotional, and motivational processes are implemented by overlapping networks of regions that play various roles depending on the task/context. These networks include prefrontal cortex (PFC), cingulate, amygdala, striatum, hypothalamus, hippocampus, insula, and parietal regions. Despite a growing body of research on this topic, much work remains to be done, especially to advance concepts and theories to guide the work (Miller, 1996, 2010). There continues to be enormous but unrealized potential to apply these findings to psychopathology and treatment (Miller et al., 2007; Carrig et al., 2009; Fu et al., 2012). A better understanding of the psychological and neural mechanisms involved in the complex relationships between cognition, emotion, and motivation can aid in advancing the development of such new applications.

The goals of this paper are (1) to integrate findings of studies exploring relationships between cognitive, emotional, and motivational processes, and their associated neural mechanisms in anxiety and depression and (2) to highlight psychological and biological processes implicated in emotion-cognition and motivation-cognition interactions that are amenable to ongoing modification and can be targeted with interventions. Thus, this review will convey the current state of the field and highlight the potential synergy between basic and treatment-related research that can move the field forward.

In the present review, neuroplasticity refers to functional and structural flexibility of brain systems, regions, and structures over time, such that a given system is able to change in response to input (which may include experience or other interventions) and does not harden into rigidity with maturation. In some cases a functional change might reflect alterations in dynamic neural processes as inferred by modifications in activity and metabolism or other aspects of physiology. In such cases there is no presumption that the altered physiology directly influences or reflects change in the structure of the neural tissue. In other cases, the neural tissue itself may be the substrate of neuroplasticity inasmuch as there is alteration in cellular and/or regional structure. The present review will focus on anxiety and depression, but manifestations of other types of psychopathology are also highly dependent on emotion-cognition and motivation-cognition interactions. For example, the clinical picture of schizophrenia is influenced significantly by emotional adjustment, motivational dynamics (e.g., reward responsivity, approach/avoidance coping style), and cognitive biases, each of which interacts with the other and the clinical course of the disorder (e.g., Rector and Beck, 2002). Explication of the dynamics of emotion-cognition and motivation-cognition processes in anxiety and depression may contribute to understanding similar dynamics in other disorders.

EMOTION-COGNITION INTERACTIONS IN ANXIETY AND DEPRESSION

Emotion-cognition interactions gone awry can lead to clinically significant levels of anxiety and depression. For example, anxiety and depression are characterized by information-processing biases and cognitive dysfunction, which appear to contribute to the onset and/or maintenance of symptoms, including persistent negative affect and poor emotion regulation. A pervasive finding in the anxiety literature is that anxious individuals exhibit an attentional bias, such that they preferentially process threat-related information (for reviews, see McNally, 1998; Bar-Haim et al., 2007). Anxious individuals display facilitated orientation toward threatening stimuli and have difficulty disengaging from it once their attention is captured (for reviews, see Cisler et al., 2009; Sass et al., 2010). This attentional bias appears to play a key role in the etiology and maintenance of anxiety disorders (MacLeod et al., 2002; Amir et al., 2009; Koster et al., 2009).

There is also some evidence that depressed individuals exhibit an attentional bias to negative material, though this literature is mixed (for reviews, see Levin et al., 2007; Gotlib and Joormann, 2010). When biased attention has been found in depression, it has often been the case that stimuli were presented for relatively longer durations (e.g., >500 ms, see Bradley et al., 1997; Gotlib et al., 2004) than is typical in the anxiety literature, in which stimuli are presented very briefly (e.g., <100 ms). Williams and colleagues (1997) proposed that the attentional biases for threat observed in studies of anxiety reflect earlier stages of processing (e.g., orienting), whereas biases in depression reflect later stages of processing (e.g., elaborative processing). However, some scalp event-related brain potential (ERP) findings have indicated a bias to attend to negative words as early as 200 ms post stimulus onset, as well as later enhanced processing in depression with comorbid anxiety (Sass et al., under review). Thus, evidence suggests that impairments in control of attention, particularly in the face of distracting emotional information, characterize both depression and anxiety, although potentially in different ways or on different time scales.

Hemodynamic neuroimaging work examining the successful implementation of control of attention in the context of emotional distractors has implicated several key areas, including dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC; Whalen et al., 1998; Compton et al., 2003; Mohanty et al., 2007; Banich et al., 2009; Herrington et al., 2010). Not surprisingly, these areas appear to function abnormally in anxiety and depression, such that dysfunction in DLPFC, as well as in dorsal ACC (dACC) and rostral ACC (rACC), has been associated with difficulty ignoring distracting emotional information (e.g., Engels et al., 2007, 2010; Bishop, 2008; Herrington et al., 2010). Additionally, various parts of the parietal cortex play a role in control of attention in both emotional and nonemotional contexts (Banich et al., 2000; Compton et al., 2003; Corbetta et al., 2008) and are disrupted in anxiety and depression (Bruder et al.,

1997; Engels et al., 2007; for reviews, see Heller, 1993; Heller et al., 2003). Together, these findings suggest that anxiety and depression are associated with abnormal cognition in the presence of emotional distractors, from earlier selective attention to later inhibition and response selection.

There is ample evidence that anxious individuals also exhibit an interpretation bias, in which ambiguous information and situations are interpreted negatively (Mathews and MacLeod, 2005; Zinbarg and Yoon, 2008). This bias is supported by two fMRI findings (for a review, see Bishop, 2007). First, responsivity of the amygdala to neutral stimuli increases as a function of anxiety, suggesting that anxious individuals overinterpret such stimuli as threatening (Somerville et al., 2004). Second, PFC is engaged when healthy individuals attempt to decrease the impact of negative information via emotion-regulation strategies, including generating new interpretations of situations. Individuals with anxiety exhibit decreased PFC recruitment during such tasks, suggesting that they have difficulty generating alternative meanings of such stimuli in order to alter their initial and ongoing emotional response (Goldin et al., 2009). This interpretation bias appears to play a causal role in anxiety and can lead to distortions in memory (Wilson et al., 2006; Hirsch et al., 2009; Hertel and Brozovich, 2010).

It is unclear whether depression is also associated with an interpretation bias, given mixed results in the literature (for discussion, see Gotlib and Joormann, 2010). However, there is consistent evidence that depression is characterized by a memory bias, such that depressed individuals preferentially recall negative over positive information (for review, see Mathews and MacLeod, 2005; Gotlib and Joormann, 2010). Depressed individuals also tend to retrieve overgeneral autobiographical memories that lack details, even when they are instructed to recall specific events (Williams et al., 2007). Consistent with these findings, hypoactivation of the hippocampus and parahippocampal gyrus has been observed in individuals diagnosed with major depressive disorder (MDD) during an autobiographical memory task (Young et al., 2012). Given deficits in DLPFC activation in depressed individuals, difficulty implementing strategies to recall detailed memories may be related to impaired connectivity between PFC and hippocampal regions. Overgeneral memory recall has been associated with longer depressive episodes (Raes et al., 2005), delayed recovery from affective disorders (Dalgleish et al., 2001), and less complete recovery from major depression (Brittlebank et al., 1993).

EXECUTIVE FUNCTION DEFICITS IN ANXIETY AND DEPRESSION

Anxiety and depression have been associated with deficits in executive function (EF; Levin et al., 2007; Snyder, 2013; Snyder et al., under review), which may contribute to the observed emotion-cognition problems reviewed above. EF can be defined as the "set of abilities required to effortfully guide behavior toward a goal, especially in nonroutine situations" (Banich, 2009, p. 89). Examples of EFs include planning and organizing, sequencing steps to accomplish a task, inhibiting prepotent responses, updating and manipulating information in working memory, shifting between strategies or tasks, and flexibly adjusting behavior to environmental demands. A pervasive view in the literature is that the EF deficits that characterize anxiety and depression are due to the symptoms of psychopathology (e.g., Williams et al., 2000; Eysenck et al., 2007) and hence resolve when symptoms remit. However, others have asserted that these deficits are not simply the result of current symptoms, and several studies have demonstrated that individuals in remission from depression still exhibit various EF deficits (Beats et al., 1996; Paradiso et al., 1997; Austin et al., 2001). Given that executive dysfunction persists even when symptoms improve, it is plausible that these EF deficits contribute to initial onset or relapse, rather than merely resulting from disorder.

There is evidence that anxiety is associated with deficits in shifting between mental sets (Airaksinen et al., 2005; Johnson, 2009), although others have failed to replicate this finding (Castaneda et al., 2010). In addition, anxiety has been linked to working memory problems (MacLeod and Donnelan, 1993; Derakshan and Eysenck, 1998; Eysenck et al., 2005), particularly under stressful conditions (Eysenck et al., 2007). An influential proposal, the attentional control theory, considers anxiety in relation to three EF components—inhibition, shifting, and updating of working memory—based on a model proposed by Miyake and colleagues (2000). This theory proposes that anxiety is characterized by an EF deficit in control of attention due to worry impairing the central executive of the working memory system (Eysenck et al., 2007). This impairment is accompanied by deficits in inhibition and shifting functions, as well as an imbalance in two attention systems. Specifically, anxiety decreases the influence of a goal-directed, top-down attention system and increases the influence of a stimulus-driven, bottom-up attention system. Little work has been conducted thus far investigating key aspects of this theory, but some support of its assertions is starting to accrue (for reviews, see Derakshan and Eysenck, 2009; Eysenck and Derakshan, 2011; Snyder et al., under review).

Using the three-component EF model developed by Miyake and colleagues (2000), Warren et al. (under review) found that the specificity of anxiety-related EF impairments depended on differentiating dimensions of anxiety, specifically anxious apprehension or worry from anxious arousal or sympathetic hyperarousal. Whereas anxious apprehension was associated with shifting impairments only, anxious arousal was associated with broad impairments in EF (shifting, updating, and inhibition), especially updating and inhibition. These findings are generally consistent with Eysenck et al.'s (2007) prediction that anxiety impairs shifting and inhibition, although they extend the attentional control theory to suggest that distinct dimensions of anxiety are associated with specific patterns of executive dysfunction (Warren et al., under review). Future work should examine these dimensions of psychopathology in relation to Miyake and Friedman's (2012) updated EF model in which the inhibition-specific component is subsumed by a common EF factor. This factor is what is common across all 3 EFs (inhibition, shifting, and updating) and may reflect the ability to "actively maintain task goals and goal-related information" (Miyake and Friedman, 2012, p.11).

Deficits in inhibition appear to be associated with the difficulties that depressed individuals have disengaging from

mood-congruent negative information, which leads to further elaboration of the negative information and contributes to the attentional bias described above (for a review, see Gotlib and Joormann, 2010). Some evidence suggests that this effect is valence-specific, such that depressed individuals demonstrate inhibition deficits selectively for negative information (e.g., Goeleven et al., 2006). In addition, depressed individuals have difficulty intentionally ignoring distracting information, whether it is emotional or nonemotional in nature (Gotlib and Joormann, 2010; Snyder, 2013). Depression therefore appears to be associated with an increased vulnerability to distracting information, but once attention has been captured, difficulties in disengaging are specific to information with negative valence.

Depression-related difficulty disengaging from information also appears to be related to deficits in other cognitive control mechanisms, specifically updating and removing previous task-relevant information, both emotional and nonemotional in nature, from working memory and flexibly switching attention to the task at hand (Joormann and Gotlib, 2008; Banich et al., 2009; Joormann, 2010; Warren et al., under review). These deficits likely also contribute to prolonged processing of negative aspects of stimuli, which in turn hinders emotion regulation processes and leads to the sustained negative affect and rumination observed during depressive episodes (Joormann, 2010). Further, depression has been associated with a variety of other EF deficits, including impairments in verbal fluency, verbal and visuospatial working memory, and planning (for reviews, see Yee, 1995; Levin et al., 2007; Snyder, 2013).

Studies of healthy individuals have consistently implicated several subregions of PFC across a variety of EFs. Specifically, DLPFC, ventrolateral PFC (VLPFC), and dACC are recruited during tasks involving inhibition, shifting, working memory, and planning (Wager and Smith, 2003; Wager et al., 2004; Collette et al., 2005, 2006; Nee et al., 2007). Depression and anxiety have both been associated with hypoactivation in these regions (Rogers et al., 2004; Levin et al., 2007; Fitzgerald et al., 2008; Bishop, 2009). Impaired recruitment of PFC regions appears to be associated with difficulty implementing various functions associated with EF tasks, including maintaining task goals and goal-related information. Further, activity in left DLPFC has been shown to depend on levels of both anxiety and depression. Specifically, comorbid anxious arousal and depression were associated with reduced left DLPFC activity during an EF task, but only when anxious apprehension was low (Engels et al., 2010). In addition, anxiety and depression are associated with altered activity in a DLPFC-dACC network, albeit in distinct ways (Silton et al., 2011).

MOTIVATION-COGNITION INTERACTIONS IN ANXIETY AND DEPRESSION

Numerous behavioral and psychophysiological studies have provided evidence that depression is associated with motivation-related deficits. These are reflected in decreased responsivity to positive or rewarding stimuli and reduced approach-related behaviors (for reviews, see Fernandes and Miller, 1995; Pizzagalli et al., 2011). Relative to healthy controls, individuals with MDD exhibit blunted responsiveness to pleasant films and scenes (Berenbaum and Oltmanns, 1992; Sloan et al., 1997), to cues signaling the potential for reward (Pizzagalli et al., 2009a), and to receipt of actual rewards (Henriques and Davidson, 2000; Pizzagalli et al., 2009a). Depressed individuals also fail to demonstrate the bias toward attending and responding to positive and rewarding stimuli that nondepressed controls show (McCabe and Gotlib, 1995; Pizzagalli et al., 2009b).

Hemodynamic neuroimaging studies of reward tasks have demonstrated that depression is associated with decreased activation in key brain areas associated with the processing of reward-related information, specifically nucleus accumbens and caudate, as well as decreased activation in left PFC, an area that has been associated with approach-related motivation and the processing of positive stimuli (Davidson and Henriques, 2000; Herrington et al., 2005, 2010; Pizzagalli et al., 2009a; Wacker et al., 2009; Miller et al., 2013). Decreased activation in striatal areas has been found during both anticipatory and consummatory phases of reward processing (Pizzagalli et al., 2009a; Smoski et al., 2009). Other brain areas display abnormally increased activation in relation to reward processing in depression, including orbitofrontal cortex (OFC), implicated in the assessment of risk and reward, and dACC, implicated in predicting response value (Knutson et al., 2008; Smoski et al., 2009).

In addition to deficits in processing reward and decreased approach behavior, depression appears to be associated with increased avoidance behavior and an enhanced sensitivity to negative cues and punishment, consistent with a bias toward negative information as reviewed above (see also Pizzagalli et al., 2011). Furthermore, depressed individuals exhibit abnormal responses to errors and perceived failure and demonstrate problems adjusting their behavior appropriately after making mistakes and receiving negative feedback (Elliott et al., 1996, 1997; Heller and Nitschke, 1997; Murphy et al., 2003; Holmes and Pizzagalli, 2007, 2008). Studies examining brain activation in relation to the anticipation of and response to negative cues, feedback, and making errors have found hyperactivity in several areas associated with threat-related processing, including amygdala, ACC, and medial PFC (mPFC) along with hypoactivity in lateral PFC (Tucker et al., 2003; Holmes and Pizzagalli, 2008).

Although the literature on motivation and approach/avoidance behavior in psychopathology has typically focused on depression, there is evidence of abnormality in anxiety as well. Anxious individuals appear to be hypersensitive to negative or punishment-related stimuli, consistent with being prone to interpret information as threatening (for reviews, see Gray, 1975, 1982; Sass et al., 2010). Further, anxious individuals exhibit increased activation in threat-related brain regions when responding to negative stimuli, including PFC, dACC, amygdala, and parietal and temporal areas (Heller et al., 2003; Engels et al., 2007, 2010; Bishop, 2008; Olvet and Hajcak, 2008). Similar to depression, anxiety is associated with enhanced avoidance motivation (Spielberg et al., 2011a), such that anxious individuals habitually avoid potentially threatening situations (Barlow, 2002). The tendency for anxious individuals to engage in risk-avoidant behavior is due in part to exaggerated perceptions of the likelihood and cost of negative outcomes (Maner and Schmidt, 2006). Anxiety has been associated with increased activity in the insula while making

risky decisions and learning to avoid monetary loss (Paulus et al., 2003; Samanez-Larkin et al., 2008; Damsa et al., 2009). The insula is a key brain area involved in both the experience and the anticipation of negative outcomes, as well as decision-making about risky behaviors (for a review, see Samanez-Larkin et al., 2008).

Furthermore, anxious individuals display hyper-reactivity to making errors, as evidenced by increased ACC activation and an enhancement in error-related negativity (ERN), an ERP component that indexes error processing (for a review, see Olvet and Hajcak, 2008). Anxiety also appears to be characterized by hypersensitivity to rewards, as it is associated with faster responses to potential rewards (Hardin et al., 2006) and increased activation in areas involved in reward processing (e.g., ventral striatum; Guyer et al., 2006, 2012; Bar-Haim et al., 2009). Thus, anxiety appears to be associated with exaggerated responses to both rewards and punishments, indicating enhanced sensitivity to incentives irrespective of valence.

It is likely that at least some of the observed motivation-related dysfunction associated with anxiety and depression is related to the EF deficits that also characterize these disorders. Adaptive motivational processing relies on intact EF, such that goals can be selected based on their predicted value, behaviors can be initiated to achieve these goals, and goal-directed action can be maintained across time, particularly in the face of distraction (Spielberg et al., 2012a,b). Many of the abnormal approach- and avoidance-related behaviors associated with anxiety and depression are likely due at least in part to dysfunction in specific EFs. For example, depressed individuals have difficulty sustaining reward responsiveness over time (Heller et al., 2009), which may be due to problems maintaining the contents of working memory, particularly when distractors are present (Yee and Miller, 1994). Heller and colleagues (2009) found that problems in reward responsiveness were linked to dysfunction in frontal and subcortical areas, which interact to implement goal-directed behavior.

Just as EFs appear to influence motivational processes, there is also evidence that motivation affects these cognitive processes in anxiety and depression. In healthy individuals, altering motivational processing via monetary incentives has been associated with enhancements of various EFs, including cognitive control, attention, set-shifting, and working memory (Pochon et al., 2002; Taylor et al., 2004; Engelmann and Pessoa, 2007; Engelmann et al., 2009; Jimura et al., 2010; Savine et al., 2010). In contrast, depressed adults and adolescents failed to adaptively adjust their performance during EF tasks in order to optimize their chances of winning money in rewarding and punishing contexts (Henriques and Davidson, 2000; Jazbec et al., 2005). Similarly, high trait-anxious individuals did not improve their performance during a demanding EF task when monetary incentives were offered, while low trait-anxious individuals demonstrated the expected enhanced performance in the reward condition (Eysenck, 1985). In a sample of anxious adolescents, incentive-related modulation of performance on a cognitive control task was significantly weaker than in healthy adolescents (Hardin et al., 2007).

The failure of motivational manipulations to appropriately modulate EFs in individuals with anxiety and depression is likely related to the observed dysfunction in brain networks associated with incentive processing and task-relevant cognitive processing. As reviewed above, anxiety and depression are associated with dysfunction in areas involved in processing both positive, rewarding stimuli and negative, punishing stimuli (e.g., putamen, caudate, and nucleus accumbens). Additionally, anxiety and depression have been associated with abnormal function in a network of brain regions involved in implementing EFs during various tasks, including DLPFC, dACC, rACC, and parietal cortex (Bruder et al., 1997; Heller et al., 2003; Engels et al., 2007, 2010; Bishop, 2008; Herrington et al., 2010). Furthermore, it is likely that networks involved in implementing motivation-related processes and EFs fail to interact appropriately in order to integrate various functions and successfully execute goal-driven behavior. Studies of healthy individuals have implicated several "hub" regions that link the two networks and integrate incentive-related processes with EFs: DLPFC, ACC, and posterior cingulate cortex (PCC; Pochon et al., 2002; Taylor et al., 2004; Locke and Braver, 2008; Pessoa, 2009; Jimura et al., 2010; Pessoa and Engelmann, 2010), all three of which have been associated with dysfunction in anxiety and depression (Bench et al., 1993; Mayberg, 1997; Mayberg et al., 1999; Engels et al., 2007, 2010; Bishop, 2008; Herrington et al., 2010).

RELATIONSHIPS AMONG EF, EMOTION, AND MOTIVATION

Evidence reviewed above establishes many interactions among cognition, emotion, and motivation and clearly indicates that these interactions contribute to psychopathology. However, the mechanisms remain mostly speculative, and a question of interest concerns whether deficits in one domain predict or cause deficits in another, so as to affect the onset and/or maintenance of psychopathology. Although it is generally assumed that deficits in cognition and EF are caused by emotional and motivational disturbances, it has also been postulated that deficits in specific EFs (e.g., inhibition, shifting) are at least partly responsible for key cognitive, emotional, and motivational features of psychopathology, including cognitive biases, motivation-related dysfunction, and impaired emotion-regulation abilities (Levin et al., 2007; Gotlib and Joormann, 2010). For example, a bias to attend to negative information in anxious and depressed individuals may be driven in part by difficulties inhibiting distracting information or shifting attention to relevant aspects of a task. EFs may affect motivational processes, such that they alter ability to evaluate potentially pleasurable stimuli or activities or implement approach-related behaviors. EF deficits make it difficult to select goals based on their anticipated benefits and to implement strategies aimed at achieving these goals, particularly when distractions are present in the environment (Banich, 2009). EF deficits could also make it challenging for individuals to initiate and/or maintain emotion-regulation strategies aimed at promoting pleasant emotion or engaging adaptive coping behaviors that would buffer against the effects of stress (Monroe and Reid, 2009).

Some support for EF deficits contributing to emotion-related symptoms of psychopathology has been provided by recent research. Bredemeier and Berenbaum (in press) found that, when controlling for initial levels of worry, reduced working memory capacity predicted worry levels several weeks later. Similarly, research in our laboratory found that self-reported working

memory difficulties predicted increases in symptoms of depression several months later, above and beyond the effects of initial depression (Letkiewicz et al., under review). Alexopoulos and colleagues (2000) found evidence that scores on measures of initiation and perseveration predicted early relapse, recurrence of depression, and the course of depressive symptoms post-remission. Interestingly, a treatment study of the response of depressed individuals to the antidepressant fluoxetine found that nonresponders performed significantly worse on pre-treatment measures of EF (Wisconsin Card Sorting Task, Stroop task; Dunkin et al., 2000). Determining which deficits come first, or understanding the causal and temporal mechanisms of the relationship between difficulties in EF and psychopathology, will depend in part on the availability of longitudinal data. It is likely that the relationships among EF, emotion, and motivation are bidirectional and/or multidirectional, such that deficits in one foster deficits in another, creating a snowball effect and in turn, exacerbating the initial deficits.

Regardless of the nature of causality among these psychological and biological processes (Miller, 2010), the relationships among EFs, emotion, and motivation in anxiety and depression are likely related to dysfunction in brain networks that are involved in integrating aspects of these processes, particularly DLPFC and ACC (Gray et al., 2002; Koechlin and Hyafil, 2007; Kouneiher et al., 2009; Pessoa, 2009). Evidence suggests that DLPFC and ACC merge input from various regions involved in subprocesses of cognition, emotion, and motivation (Gray et al., 2002; Gray, 2004; Pessoa, 2008, 2009; Spielberg et al., 2012a,b). DLPFC has substantial connectivity to regions involved in determining the emotional significance and motivational value of stimuli, including more medial PFC structures, such as pre-supplementary motor area (pre-SMA), dACC (Kouneiher et al., 2009), and frontopolar cortex (Koechlin and Hyafil, 2007). Further, research in our laboratory showed that DLPFC regions associated with approach and avoidance motivation demonstrated increased connectivity with OFC, ACC, amygdala, and basal ganglia during an EF task involving goal maintenance in the face of distraction (Spielberg et al., 2012a).

ACC also seems a likely candidate for integrating aspects of emotion, motivation, and EF, evidenced by its connectivity to both the amygdala and nucleus accumbens, as well as OFC and ventral striatum (Pessoa, 2009), key areas involved in emotion and motivation. Hence, subregions of ACC are involved in assessing events for their emotional and motivational relevance, error and conflict monitoring, and predicting value of potential rewards and punishments (Rushworth et al., 2004, 2007; Banich, 2009; Pessoa, 2009). In addition, DLPFC and ACC interact in order to utilize emotional and motivational information to develop and implement goal-directed strategies (Beckmann et al., 2009; Spielberg et al., 2012a). In anxiety and depression, DLPFC and ACC appear to be dysfunctional in integrating emotion- and motivated-related information when recruited to implement cognitive control/EFs and exhibit decreased connectivity (Silton et al., 2011).

Other research explicitly examining functional connectivity between regions also suggests that anxiety and depression are associated with dysfunctional communication between regions. For example, individuals with MDD exhibited decreased connectivity in a fronto-parietal network relative to healthy controls during a working memory task (Vasic et al., 2009). Individuals with social phobia displayed less functional connectivity between the amygdala, medial OFC, and PCC than healthy individuals during rest (Hahn et al., 2011), as well as altered connectivity between various regions (e.g., amygdala, mPFC, inferior parietal lobule) during a face perception task (Danti et al., 2010). Thus, it is likely that the dysfunction observed in individuals with anxiety and depression is related to problematic communication between regions, rather than just altered activity in isolated regions.

INTERVENTION AND NEUROPLASTICITY

Numerous interventions, both psychological and biological, have been developed to target disruptions in cognition, emotion, and motivation interactions associated with anxiety and depression. In addition, a growing body of research has aimed to elucidate the mechanisms of neuroplasticity by characterizing the experience-dependent functional and structural changes in the brain associated with these interventions. As reviewed above, anxiety and depression are associated with impaired executive control, dysfunctional relationships among cognitive, emotional, and motivational processes, and abnormal activity in brain regions that are part of networks implementing these processes. Psychological/behavioral, pharmacological, and direct physiological (e.g., electroconvulsive therapy [ECT]) interventions have been shown to reduce emotional symptoms, decrease negative thoughts and beliefs, and alter maladaptive motivational and behavioral styles (for reviews, see Mayberg, 2000; Mayberg et al., 2005; DeRubeis et al., 2008; Frewen et al., 2008; Clark and Beck, 2010). Importantly, they appear to normalize function and structure in the brain regions and networks that exhibit dysfunction prior to treatment in individuals who respond to treatment.

Although a large body of literature demonstrates improvements in psychological symptoms associated with various types of interventions, it should be noted that not everyone responds to one or more of these treatments. For example, Cognitive Therapy (CT), a type of psychotherapy with much empirical support, is effective for approximately 40-60% of individuals with depression (APA, 2000). Less than half of individuals with depression who receive either psychotherapy or pharmacotherapy are able to attain full remission (Casacalenda et al., 2002). Butler and colleagues (1991) found that only 32% of individuals with Generalized Anxiety Disorder (GAD) who received CT scored within the healthy range on three measures of anxiety immediately after treatment. Further, many individuals who respond initially to treatment ultimately relapse, regardless of the type of treatment received. However, there is evidence that psychotherapy leads to lower relapse rates than does pharmacotherapy (Gould et al., 1995, 1997; Hollon et al., 2006). There continues to be great room for improvement in treatments in order to increase recovery rates and prevent relapse. If we can better understand the psychological and neural mechanisms through which treatment is effective for responders, this knowledge can be used to improve treatments, as well as match specific treatments to those who are likely to benefit from it.

Cognitive behavioral therapy (CBT) is one of the most effective psychological treatments for anxiety and depression and addresses emotion-cognition and motivation-cognition interactions that are altered in these disorders. The cognitive component of CBT (and CT) emphasizes changing problematic patterns of thinking and maladaptive beliefs, which leads to improvements in emotional and motivational function and enhances approach behavior. The behavioral component of CBT and a related therapeutic approach, Behavioral Activation (BA), target problematic behavioral patterns (e.g., avoidance of negative stimuli/situations and punishment-related outcomes) and use positive reinforcement to facilitate engagement in pleasant, rewarding activities (Martell et al., 2001; Kuyken et al., 2005). In addition to increasing more adaptive, approach-related behaviors, these behavioral strategies lead to alterations in cognition and emotion. Thus, CBT and CT emphasize the interconnection of thoughts, emotions, and motivations.

Successful CBT/CT for anxiety and depression has consistently been shown to alter activity in several brain regions, including DLPFC, VLPFC, and ACC (for reviews, see Frewen et al., 2008; Clark and Beck, 2010; Miller, 2010). Some studies have found that CBT and CT for depression are associated with decreased amygdala activation and increased prefrontal activation during tasks that recruit various cognitive, emotional, and motivational processes relative to pre-treatment activation (see DeRubeis et al., 2008). Others have found that prefrontal activation decreased during a resting-state condition (e.g., Goldapple et al., 2004). It has been suggested that maintaining lower frontal resting-state activity is adaptive in that it allows for more flexible activity during EF task conditions, with the amount of activity depending on the context and task demands (DeRubeis et al., 2008).

Similar to CBT studies of depression, studies of successful CBT for anxiety disorders highlight the neuroplasticity of several brain regions that play key roles in cognition, emotion, and motivation. For example, individuals diagnosed with posttraumatic stress disorder (PTSD) were given treatment involving imaginal exposure to feared situations and cognitive restructuring, two key components of CBT for PTSD that target avoidance behaviors and distortions in thought patterns (Felmingham et al., 2007). Researchers found that treatment was associated with PTSD-symptom improvement, as well as increased rACC activation and decreased amygdala activation when viewing fearful versus neural faces. Thus, treatment normalized dysfunctional pre-treatment activity in regions involved in emotional experience and regulation.

Treatment for obsessive-compulsive disorder (OCD) that focused on changing maladaptive behavior patterns was associated with decreased caudate activity during rest (Schwartz et al., 1996; Nakatani et al., 2003) as well as alterations in functional connectivity between areas in the caudate-orbital-thalamic circuit for CBT treatment responders (Baxter et al., 1992; Schwartz et al., 1996). Individuals with spider phobia exhibited decreased symptoms post-CBT along with significant reductions of pre-treatment hyperactivity in insula and ACC (Straube et al., 2006) as well as DLPFC and parahippocampal gyrus (Paquette et al., 2003). Clark and Beck (2010) reviewed studies of CBT for anxiety disorders and reported that treatment leads to increased activity in ventral and dorsal ACC, mPFC, and VLPFC, regions that exhibit pre-treatment hypoactivity relative to controls, as well as decreased activity in amygdala, hippocampus, and anterior and medial temporal cortex, which show pre-treatment hyperactivity. Thus, CBT alters activity in regions involved in diverse cognitive, emotional, and motivational processes, including more bottom-up, stimulus-driven processing and top-down processing (Clark and Beck, 2010).

As with CBT/CT, numerous studies examining the effects of antidepressant medication treatment have found decreases in depressive symptoms with concomitant alterations in activation in several brain regions involved in a range of cognitive, emotional, and motivational processes. Successful antidepressant treatment has been associated with decreased activation in regions involved in threat and punishment-related responses such as the amygdala, subgenual cingulate, and striatum in response to affective stimuli (Mayberg et al., 2000; Sheline et al., 2001; Davidson et al., 2003; Fu et al., 2004). Prior to treatment, these regions appeared to be hyperactive relative to healthy individuals. In addition, antidepressant treatment has been shown to increase activation in several cognitive control regions that are typically hypoactive in depressed individuals, including prefrontal cortex and rACC (Mayberg et al., 2000; Davidson et al., 2003; Fu et al., 2004). Supporting these results, a meta-analysis of 9 studies found that antidepressant treatment for depression was associated with increased activation in DLPFC, VLPFC, and dorsomedial PFC, along with decreased activation in amygdala, hippocampus, parahippocampal gyrus, ACC, PCC, OFC, insula, and parietal regions (Delaveau et al., 2011). It has been proposed that antidepressant medication does not target prefrontal activity directly; rather, it targets amygdala activity, which in turn prompts prefrontal disinhibition (DeRubeis et al., 2008) with the effect of increasing activity supporting cognitive control. Further, antidepressant medication appears to enhance functional connectivity among brain regions in depressed individuals (Anand et al., 2007), shown in other work to be disrupted (e.g., Silton et al., 2011).

Antidepressant medication has been used to treat anxiety as well. Studies examining its effects on neural activity in individuals with anxiety disorders have found that it also appears to normalize activity in regions and networks that were dysfunctional prior to treatment in medication responders. For example, obsessive-compulsive disorder (OCD) has been associated with hyperactivity in frontal-subcortical circuits relative to healthy individuals, and antidepressant treatment has been shown to decrease activity in OFC and caudate nucleus (Saxena et al., 1999). In addition, antidepressant treatment has been associated with decreased activity in medial temporal cortex in individuals with PTSD (Seedat et al., 2004). Further, after antidepressant treatment, individuals with social phobia displayed attenuated activity in amygdala, hippocampus, and parahippocampal cortex during a public speaking task (Furmark et al., 2002, 2005).

These functional changes associated with successful medication and psychotherapy treatment are supported by structural changes. Antidepressants appear to reverse various structural abnormalities observed in depression and anxiety. For example, there is evidence that chronic antidepressant treatment enhances

neurogenesis, prevents neuronal atrophy, and promotes neuronal sprouting and dendritic branching (Vaidya and Duman, 2001; Pittenger and Duman, 2008). It also stimulates new synapse formation, strengthens synaptic connectivity, and alters neurotrophic signaling cascades (Manji et al., 2003; Pittenger and Duman, 2008; Andrade and Rao, 2010). These cellular and molecular changes are associated with more macro-level changes, including increased regional brain volume (e.g., hippocampus; Vermetten et al., 2003; Malykhin et al., 2010). There is little direct evidence of cellular and regional changes associated with psychotherapy specifically; however, such changes have been observed after various learning-related experiences similar to those involved in psychotherapy (Kolb and Whishaw, 1998; Liggan and Kay, 1999), and the neuroplastic effects of structured behavioral interventions more generally are well established (e.g., Elbert et al., 1995).

Studies examining the neurobiological effects of pharmacological versus psychological treatments have been inconsistent, with some reporting similar results (e.g., Baxter et al., 1992; Furmark et al., 2002), and others reporting diverging results (for reviews, see Mayberg, 2003; DeRubeis et al., 2008). Seminowicz and colleagues (2004) asserted that different types of treatment (e.g., CBT, medication) alter activity in some of the same regions, though in different ways (e.g., CBT increases or decreases activity in a region, whereas medication does the opposite). Regardless, psychotherapy and antidepressant medication appear to have at least some similar effects, though they likely have distinct mechanisms of change (e.g., Kumari, 2006; DeRubeis et al., 2008). It has been hypothesized that CBT/CT and antidepressant medication both ultimately affect prefrontal, limbic, and subcortical regions, though they differ in their "proximal mechanisms of action" and direct targets, such that CBT/CT directly enhances prefrontal function and top-down emotion regulation and cognitive control, whereas antidepressant medication alters amygdala activation and bottom-up, stimulus-driven processes (Linden, 2006; DeRubeis et al., 2008). This hypothesis is consistent with anecdotal reports that medication can be helpful in diminishing the intensity of emotional and motivational symptoms in a way that allows more intentional cognitive strategies to be deployed effectively. This may explain why the combination of antidepressants and CBT is more effective than either alone in difficult-to-treat cases of depression (Keller et al., 2000b). To our knowledge, no research has examined the neural changes associated with combined medication and psychotherapy treatment. Future research in this area will be useful to determine if pharmacotherapy and psychotherapy have additive or interactive effects on brain activation.

The studies reviewed above are limited in that they reflect neural changes in individuals who responded to treatment and showed at least some symptom improvement. However, as mentioned above, numerous individuals do not respond to medication and/or psychotherapy. Although uncommon, a few studies have examined neural patterns in treatment nonresponders. For example, Mayberg and colleagues (2000) found that, relative to responders, nonresponders showed an inverse activation pattern in some areas (e.g., hippocampus, PCC) as well as no change in subgenual cingulate and prefrontal cortex. In addition, an exciting line of research has begun to examine how findings from studies of neural mechanisms involved in psychological and pharmacological interventions can be used to inform treatment selection for individuals, given that not everyone responds. Numerous studies have found that pre-treatment activity in rACC and subgenual portions of ACC (sgACC) is consistently predictive of who will respond to treatment (for a review, see Mayberg, 2003). For example, Siegle and colleagues (2006) scanned depressed individuals prior to 16 sessions of CBT while they performed an emotional information processing task. They found that low pre-treatment sgACC and high amygdala activation in response to negative words were associated with increased response to CBT. The results regarding sgACC were replicated in two separate samples (Siegle et al., 2012), suggesting that baseline sgACC activity is a reliable measure that can be used to increase response rates by providing CBT to those individuals most likely to benefit from it. Such evidence of pretreatment psychophysiological reactivity predicting psychotherapy response adds to a long tradition of such literature (e.g., Lang et al., 1970).

Similar to CBT, several antidepressant studies have found that greater pre-treatment activity in rACC consistently predicted better response to antidepressant treatment in individuals with anxiety and depressive disorders (Mayberg et al., 1997; Pizzagalli et al., 2001; Davidson et al., 2003; Whalen et al., 2008; Nitschke et al., 2009). Activity in other regions, including OFC and amygdala, has also been found to predict greater improvement with treatment (Saxena et al., 1999; McClure et al., 2007). In addition, patterns of connectivity between regions in a network shown to be dysfunctional in depression (e.g., PFC, sgACC, OFC, hippocampus) have been used to distinguish antidepressant medication responders from nonresponders (Seminowicz et al., 2004). Measures of pre-treatment structural neuroanatomy, particularly rACC volume, have also been used to predict response to antidepressant medication and CBT in individuals with MDD and PTSD, respectively (Bryant et al., 2008; Costafreda et al., 2009). Although much work remains to be done before routinely applying such findings to clinical practice, matching individuals with treatments likely to be effective based on pretreatment psychophysiological and neuroantatomical characterization is a promising method that can be used in the future to enhance response rates.

COGNITIVE BIAS MODIFICATION

Another line of research has explored improving response rates with strategies other than treatment-matching. Some researchers have argued that using methods that more directly target cognitive processes, specifically the biases observed in anxiety and depression, will improve current treatment approaches. Thus far, evidence suggests that decreasing cognitive biases leads to enhanced emotional function (for review, see Koster et al., 2009; Hertel and Mathews, 2011). This literature developed in part to test the theory that cognitive biases play a role in the etiology of anxiety and depressive disorders and are an important target for therapeutic intervention. Numerous studies have now provided support that cognitive biases 1) play a causal role in psychopathology, 2) can be modified, and 3) lead to improvements in clinical symptoms and emotional reactivity to stress when these biases are reduced or alleviated. In fact, cognitive bias modification

(CBM) has received so much recent attention that a special section in *Journal of Abnormal Psychology* (Volume 118, Number 1) was devoted to it, numerous reviews have already been published (e.g., Beard, 2011; Hertel and Mathews, 2011; MacLeod, 2012), and meta-analyses have been conducted (e.g., Hakamata et al., 2010; Hallion and Ruscio, 2011; Beard et al., 2012). This literature encompasses a variety of experimental procedures, typically computerized, that are used to systematically alter cognitive processing styles.

Given the prolific research focusing on the role of attentional bias in anxiety, it is not surprising that there is also a large CBM literature investigating the alteration of this bias (for review, see Bar-Haim, 2010). For example, individuals with GAD exhibited reduced anxiety symptoms after undergoing a training procedure involving a probe task that induced a bias to orient attention away from threatening information toward neutral words (Amir et al., 2009). In fact, 50% of those individuals in the 8-session computer training condition no longer met criteria for a diagnosis of GAD after training versus 13% in the control condition. These results provide support for the assertion that an attentional bias to negative information plays a causal role in the development of GAD symptoms. Similarly, individuals who suffered from recurrent depression exhibited significant reductions in depression, anxiety, automatic negative thoughts, and rumination after undergoing attention training involving monitoring external auditory stimuli under conditions of selective attention, attention switching, and divided attention (Papageorgiou and Wells, 2000).

Research has also found that modifying attentional biases buffers against the negative effects of stressors in real-world contexts (Hakamata et al., 2010). For example, See and colleagues (2009) found that, in addition to reducing trait anxiety scores, an attentional bias modification procedure led to decreased state anxiety in response to the real-life stress associated with moving to a new country to start college. In a series of studies, Dandeneau and colleagues (2007) demonstrated that attentional training reduced a bias toward threatening social information and led to decreased stress responses in both school and work settings. Based on their meta-analysis, Hallion and Ruscio (2011) proposed that cognitive biases exert their influence on anxiety and depressive symptoms only after being activated by stressors.

In addition to targeting attention, cognitive bias modification procedures have also been developed to alter other types of biases, including the negative interpretation bias observed in anxious individuals and the overgeneral autobiographical memory bias that accompanies depression. Hirsch and colleagues (2009) implemented a procedure that allowed individuals high in worry to practice accessing benign instead of threatening meanings of homographs and emotionally ambiguous scenarios. These individuals reported fewer negative thought intrusions and less worry during a breathing focus task than participants in a control training condition. Further, individuals who underwent the benign-meaning training demonstrated greater residual working memory capacity despite being instructed to worry, suggesting that this intervention also enhances a key cognitive process that appears to play a role in anxiety development and exacerbation.

Several studies have demonstrated that interpretation biases contribute to observed distortions in memory (for review, see Hertel and Brozovich, 2010; Hertel and Mathews, 2011). Thus, alleviating this bias likely improves memory as well. As reviewed above, depression is associated with overgeneral autobiographical memory. Watkins and colleagues (2009) found that providing concreteness training to dysphoric individuals reduced their tendency to engage in abstract and overgeneral processing and decreased depressive symptoms, rumination, and self-criticism.

Little is known about the neural mechanisms associated with the psychological changes induced by CBM procedures. One study examining the effects of attentional training with healthy individuals found altered activity in lateral PFC spanning dorsolateral and ventrolateral regions during a novel attention task (Browning et al., 2010). Specifically, activity in lateral PFC increased when participants attended to faces that were the valence they were trained to avoid (i.e., fearful faces for those in the avoid-threat condition, neutral faces for those in the attend-threat condition). In addition, connectivity analyses indicated that lateral PFC influenced activity in visual sensory cortex, consistent with studies showing that both regions are part of a network involved in control of attention.

It has been suggested that the mechanisms through which CBM procedures exert their effects are distinct from those associated with CBT and pharmacological interventions, specifically that they operate at different stages of processing (e.g., Browning et al., 2010). However, conflicting theories exist about which stage of processing CBM affects. For example, Browning and colleagues (2010) suggested that, whereas pharmacological interventions affect the initial deployment of attention and involve a bottom-up, stimulus-driven system including the amygdala, CBM targets later stages of attentional processes involving PFC. In contrast, Hallion and Ruscio (2011) asserted that CBM targets earlier, more automatic cognitive processes, whereas CBT targets later stages. Future work will likely benefit from employing hemodynamic and electromagnetic neuroimaging methods to help determine which stages of processing are affected by various interventions.

There are numerous additional questions to address regarding CBM. For example, it is not clear how much training is needed (e.g., number and length of sessions), how long their effects last, how effective CBM techniques are relative to other treatments, or what factors moderate their effectiveness. The CBM literature has not explicitly considered the impact that such interventions may have on motivational processes, including real-life behavioral outcomes. However, it is likely that CBM-induced improvements in cognitive and emotional function translate into enhanced motivational function, such as decreasing avoidance and increasing pro-social behavior. Future work will need to test this hypothesis. In addition, several researchers have suggested that combining CBM with other therapies (e.g., CBT) may enhance their effectiveness (e.g., Bar-Haim, 2010; Browning et al., 2010; Hallion and Ruscio, 2011), but this has yet to be systematically assessed. To the extent that EF deficits actually drive biases associated with anxiety and depression, it may be that CBM procedures actually enhance EF processes (e.g., control of attention, working memory capacity) that in turn reduce biases. Thus, using interventions that more directly target specific EFs (e.g., inhibition, working memory) may be even more effective and lead to more long-lasting changes.

EXECUTIVE FUNCTION TRAINING

Evidence is accruing that EF can improve with training (e.g., Olesen et al., 2004; Erickson et al., 2007; Dahlin et al., 2008) and that interventions targeting specific EFs directly are associated with improvements in symptoms of psychopathology (e.g., Papageorgiou and Wells, 2000; Siegle et al., 2007). A small but growing number of studies demonstrate that training-related increases in working memory ability can yield improvements in a range of cognitive skills (Chein and Morrison, 2010; Jaeggi et al., 2011; Brehmer et al., 2012), improvements in cognitive function in clinical populations with known inhibitory impairment (e.g., Klingberg et al., 2005; Popov et al., 2011), and improvements in quality of life (e.g., Vogt et al., 2009). The generalizability of training-related increases in working memory ability to non-trained tasks is hypothesized to occur when the transfer task recruits overlapping cortical regions (e.g., Jonides, 2004; Olesen et al., 2004). Identifying specific EF deficits and their associated neural mechanisms in anxiety and depression could improve the focus of cognitive remediation interventions, as well as their transfer effects to real-world applications (e.g., promoting goal attainment, approach behavior, or emotion-regulation abilities).

Because of the importance of working memory in general cognition (Kane and Engle, 2002), many cognitive training programs have been developed to target it. The hope has been that related cognitive abilities (e.g., inhibition, updating, attention) will subsequently improve and lead to enhanced emotional and motivational function. Numerous studies have shown that frontal and parietal regions are key nodes in a network involved in implementing working memory (for a review, see D'Esposito, 2001). Working memory training with healthy individuals was associated with increases in activation in prefrontal and parietal regions, specifically middle frontal gyrus and superior, intraparietal and inferior parietal cortex (Olesen et al., 2004). Not surprisingly, research suggests that working memory capacity is correlated with the structural integrity of white matter connecting frontoparietal regions (Klingberg, 2006). Working memory training increased the white matter structural integrity of a region adjacent to intraparietal sulcus, which connects this region to frontal cortex, and a region adjacent to the body of the corpus collosum, which connects bilateral DLPFCs (Takeuchi et al., 2010). It was hypothesized that more effective communication of brain regions via increased myelination accounts for enhanced working memory post-training.

As interest in the potential role of EF as a target of intervention is increasing (Chein and Morrison, 2010; Jaeggi et al., 2011; Brehmer et al., 2012), identification of specific EF deficits and associated patterns of brain activity in psychopathology will likely serve the development and/or modification of effective interventions (such as "neurobehavioral interventions" as discussed in Siegle et al., 2007). In fact, difficulties with different aspects of EF may present barriers to current treatment methods. For example, an individual who has trouble shifting might need help planning strategies to transition more easily between daily tasks. It has been shown that the efficacy of current psychological treatments depends on adequate EF (Mohlman and Gorman, 2005). For example, CBT involves reappraisal, hypothesis generation, and self-monitoring, which all require EF (Mohlman and Gorman, 2005; Gotlib and Joormann, 2010). In addition, there is some evidence that EF training actually improves response to CBT (Mohlman, 2008), although research is needed to examine which aspects of EF are most crucial for the efficacy of these interventions and might benefit most from training. More research is clearly needed to explore how EF training might improve treatment outcomes.

Many individuals do not fully recover after receiving therapy or relapse after therapy has completed (Kendall and Sugarman, 1997; DeRubeis et al., 1999). It may be advantageous for these individuals to receive interventions that initially target and enhance EFs, which could allow them to engage in and benefit more from other components of the treatment. There is some preliminary data that adding EF training to treatment as usual (TAU) leads to better outcomes in depressed individuals (Siegle et al., 2007). Specifically, Siegle and colleagues added Cognitive Control Training (CCT) to enhance working memory and attention to TAU, which included group psychotherapy, case management, and psychotropic medication. They found that individuals who received CCT in addition to TAU displayed greater improvements in depressive symptoms than did those in the TAU alone condition, as well as normalization of activation in DLPFC and amygdala.

MINDFULNESS-BASED INTERVENTION

Not much research has been conducted examining the outcomes of specific EF training procedures utilizing EF tasks in individuals with anxiety and depression beyond the preliminary study described above. However, outcomes related to mindfulness are an area of increasing interest because it is considered an intervention that trains control of attention and other EFs. A large body of evidence has demonstrated that mindfulness-based stress reduction (MBSR) is an effective intervention for a range of psychological disorders, including anxiety and depression (Hofmann et al., 2010). It has been hypothesized that the improvement in emotional symptoms associated with mindfulness is due to the fact that it utilizes cognitive strategies that involve strengthening EFs, including sustaining attention, flexibly switching the focus of attention, and inhibiting elaborative processing (Bishop et al., 2004). Mindfulness interventions have been associated with significant improvements in performance on working memory and sustained attention tasks, as well as concomitant decreases in rumination, depressive symptoms, and negative affect relative to a control group (Chambers et al., 2008). Mindfulness also appears to decrease rates of relapse in individuals who have experienced several depressive episodes (Teasdale et al., 2000). Similar to CBM, the mindfulness literature has not directly assessed alterations in motivation-related processes and behaviors, though it is likely that the improvements in cognitive and emotional function enhance motivational processing.

The cognitive improvements and symptom reductions gained through mindfulness training are accompanied by mindfulness-induced neuroplasticity (for a review, see Holzel et al., 2011). Healthy adults who completed an 8-week MBSR training course and expert meditators exhibited reduced activation in brain areas associated with a visceral sense of self, including anterior

insula, ventral ACC, and mPFC during the act of meditation (Ives-Deliperi et al., 2011) and while processing emotional stimuli, which also corresponded with reduced amygdala activation (Desbordes et al., 2012). These effects suggest that experience with MBSR and other types of meditation results in reduced reactivity to both physical and emotional stimuli. In addition, there is evidence of increases in activity in brain regions associated with attention and executive control. Studies have observed increases in PCC during active meditation (Ives-Deliperi et al., 2011) and less activity in major nodes of the default-mode network, including mPFC and PCC, during periods of rest in experienced meditators (Brewer et al., 2011), suggesting decreased mind wandering. A study utilizing ERPs during a Stroop task found that individuals with MBSR experience displayed increased early-latency responses recorded over right posterior cortex to all stimuli, suggesting increased deployment of early attentional resources, and reduced later centro-parietal potentials to all stimuli but especially incongruent stimuli, indicating more efficient processing and control of these conflict stimuli (Moore et al., 2012). Although little research has examined these effects in clinical populations, one study found that individuals diagnosed with social anxiety disorder (SAD) who underwent MBSR training exhibited reduced amygdala activation and increased dorsomedial PFC, ventromedial PFC, mPFC, and PCC activation in response to negative stimuli (Goldin and Gross, 2010). These effects suggest that these individuals were better able to control their emotional response to negative stimuli via reduced bottom-up, stimulus-driven reactivity and/or increased top-down control.

Other noteworthy neuroimaging effects observed in individuals with MBSR experience comes from research employing techniques that examine structural changes in the brain. Increased cortical thickness has been observed in several regions in individuals with MBSR experience, including PFC, PCC, OFC, hippocampus, and anterior insula (Lazar et al., 2005; Luders et al., 2009; Holzel et al., 2011). These increases in gray matter density were found to positively correlate with meditation experience (Lazar et al., 2005). Individuals with MBSR experience have been shown to exhibit increased connectivity among major fiber tracts in the brain, including whole brain fiber tracts, major tracts in both hemispheres, and the two largest interhemispheric fiber tracts than did healthy controls (Luders et al., 2011). Brewer et al. (2011) found increased connectivity among DLPFC, dACC, and PCC in experienced meditators, which again suggests increased self-monitoring ability and enhanced cognitive control. Finally, increased gyrification, or an increase in cortical gray matter and synaptogenesis, has been observed in precentral gyrus, fusiform gyrus, cuneus, and dorsal insula in individuals with MBSR experience (Luders et al., 2012). Among these areas showing increased gyrification, only dorsal anterior insula was correlated with meditation experience. This area is involved in integrating aspects of autonomic, affective, and cognitive processes and may contribute to decreased mind wandering, daydreaming, and ruminating, which are all key aspects of successful meditation.

Although the study by Goldin and Gross (2010) appears to be the only one to directly examine the neural effects of MSBR in individuals diagnosed with an anxiety or depressive disorder thus far, the growing body of research on brain changes associated with MBSR in healthy populations has implications for how it may mitigate or prevent anxiety or depression. Some of the neuroplastic effects observed in healthy individuals with MBSR experience occur in areas exhibiting dysfunction in anxiety and depression, as reviewed above. Thus, it is likely that MBSR practice in individuals with anxiety and depression normalizes activity in these regions, in addition to reducing symptoms and increasing control over rumination and worry.

LIMITATIONS AND FUTURE DIRECTIONS

In terms of neuroplasticity, many of the structural changes have been examined in relation to medication. Much less work has been done to understand the structural changes associated with psychological interventions. In fact, a pervasive premise, and not only among the general public, is that biological abnormalities should be treated with biological interventions. Yet there is now abundant evidence that psychological treatments alter biology, just as biological treatments alter psychology (Miller, 1996, 2010). Further, despite a large body of research examining the functional changes associated with various types of psychological and biological interventions, there is much we do not yet know because of the limited contexts in which these changes have been assessed. These functional changes have been assessed almost entirely using tasks tapping basic emotional processing (e.g., viewing negative versus neutral faces). Understanding of the neural changes associated with such interventions would be greatly enhanced by examining changes across a variety of tasks and contexts recruiting a range of cognitive, emotional, and motivational processes. This would permit testing whether interventions lead to greater flexibility and dynamic range of neural activity, such that the degree of activation depends on the context and task demands rather than being habitually high or low, or whether interventions lead to consistently moderate responses.

In addition to research that examines a broader range of contexts, interventions would greatly benefit from future work that is informed by the psychological and biological research reviewed in the present paper. Current treatments (e.g., CBT, medication) may be enhanced by the initial implementation of targeted strategies that more directly boost activity in EF-related regions (e.g., cognitive control/working memory training) and/or decrease activity regions that play key roles in initial reactivity to stimuli (e.g., mindfulness). Although these strategies may not be sufficient alone, they could potentially address specific deficits that in turn allow individuals to more fully engage in challenging treatment techniques. Further, research on shared brain mechanisms that contribute to various forms of psychopathology (e.g., connectivity between DLPFC and ACC) could inform nonspecific treatment strategies that address symptoms present in a range of disorders (Siegle et al., 2007).

Several other methodological and theoretical limitations that are pervasive in the field also need to be addressed. The vast majority of the treatment studies reviewed reported results at the level of individual areas. However, the field is moving towards

a network approach in order to better understand interactions among cognitive, emotional, and motivational processes, which involve a complex array of operations that engage distributed networks of brain regions. There is some, albeit minimal evidence starting to accrue that treatment normalizes functional communication between regions in individuals with anxiety and depression. Anand et al. (2005) found that after 6 weeks of antidepressant treatment, individuals with depression exhibited increased connectivity between ACC and various regions (amygdala, thalamus, and striatum) at rest and after viewing neutral and positive but not negative pictures. Further, measures of pre-treatment connectivity, rather than just the activity of a single region, may also be useful for predicting who will respond to treatment. Salvadore and colleagues (2010) found that less functional connectivity between pregenual/subgenual ACC and left amygdala during a working memory task prior to antidepressant treatment was associated with greater symptom improvement post-treatment. Thus, the field would greatly benefit from future studies that utilize a network perspective in order to better understand the mechanisms through which various treatments exert their effects.

As reviewed above, various antidepressant and psychological treatments appear to target processes that rely heavily on top-down EF (e.g., interpretation of negative information), as well as dampen reactivity to emotional stimuli. This is reflected in treatment-related enhancements of activity in regions involved more in top-down processing and decrements in activity in regions involved more in bottom-up, stimulus-driven processing. Although some researchers have theorized that a specific type of treatment primarily targets one or the other type of processing, it is likely that ultimately both are affected, given the functional connectivity and interactive nature of the systems/networks that implement these processes. Future work explicitly examining functional connectivity should directly test this hypothesis.

In addition, very few studies take into account the frequency at which anxiety and depression co-occur (Sanderson et al., 1990; Kessler et al., 1994; Brown et al., 2001). Comorbidity is present in at least one-half of those diagnosed with an anxiety or depressive disorder (for reviews, see Gersh and Fowles, 1979; Breier et al., 1985; Clark, 1989) and leads to a greater impact than either disorder alone. Comorbidity is associated with greater impairments in psychosocial function, greater severity of disorder, elevated rates of suicidality and morbidity, increased health service use, increased treatment resistance, and poorer short- and long-term outcomes (Judd et al., 1998; Lydiard and Brawman-Mintzer, 1998). Without taking comormidity into account, it is unclear whether patterns of brain activity are specific to depression or anxiety or if instead they reflect their co-occurrence. Some evidence indicates that co-occurring anxiety and depression have additive and interactive effects on brain function (e.g., Bruder et al., 1997; Keller et al., 2000a; Kentgen et al., 2000; Pizzagalli et al., 2002; Engels et al., 2010). Much work needs to be done to better understand how co-occurring levels of anxiety and depression alter brain network function during tasks involving a range of cognitive, emotional, and motivational processes as well as how treatment alters these patterns.

Another issue that warrants consideration in the hemodynamic neuroimaging treatment literature is the reliability of the blood-oxygen-dependant-level (BOLD) signal across time, given that various factors that can affect it (e.g., caffeine, nicotine, movement, breathing rate; MacDonald and Jones, 2009). Carrig and colleagues (2009) reviewed research investigating the test-retest reliability of fMRI and determined that studies examining intraclass correlation coefficients (ICC) have found good to excellent reliabilities. However, Plichta and colleagues (2012) found that the stability of within-subject amplitude varied depending on the specific task being examined (emotional vs. motivational and cognitive). Little work has been done in examining the reliability of the BOLD signal specifically in patients, an issue that is particularly relevant for the treatment literature. One study found that individuals with schizophrenia exhibited low reliability (ICC = 0.2) in DLPFC, whereas control participants exhibited excellent reliability (ICC = 0.81; Manoach et al., 2001). Thus, future research would benefit from examining reliability of the BOLD signal in individuals with anxiety and depression prior to treatment.

CONCLUSION

It has become clear just how interconnected the cognitive, emotional, and motivational deficits in anxiety and depression are, such that it is difficult to distinguish their influences. The present review has demonstrated how basic research on the relationships among cognition, emotion, and motivation in psychopathology and related neural mechanisms has been used to inform treatment-related research. In fact, there continues to be rich potential for the synergy between these literatures. Despite numerous advances, we do not fully understand the mechanisms that lead to psychopathology, or how to harness these mechanisms most effectively for successful interventions.

This review has highlighted numerous gaps in the literature. It is clear that motivation is related to the cognitive and emotional symptoms observed in psychopathology, but little work has been done to understand exactly how motivation interacts with and affects emotion and cognition. Additionally, much of the treatment-related research has focused on emotion-cognition interactions and neglected to examine how interventions may lead to alterations in motivational processes. This work could lead to the development and refinement of treatments that better target the motivational deficits observed in psychopathology. Further, there is much excitement about the application of CBM procedures and EF training to better treat psychopathology, but much research remains to be done before these methods are used in common practice. For example, it is not clear how their effects translate to everyday performance or how long they last. If it is determined that they are as effective as current treatment methods or useful in improving the effectiveness of current methods, these training paradigms could likely be employed easily at home, via internet or computer software, for little cost. There is much promise in capitalizing on the synergy between neuroscience and intervention research to better prevent and treat psychological disorders.

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Neural signatures of the response to emotional distraction: a review of evidence from brain imaging investigations

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Prompt responses to emotional, potentially threatening, stimuli are supported by neural mechanisms that allow for privileged access of emotional information to processing resources. The existence of these mechanisms can also make emotional stimuli potent distracters, particularly when task-irrelevant. The ability to deploy cognitive control in order to cope with emotional distraction is essential for adaptive behavior, while reduced control may lead to enhanced emotional distractibility, which is often a hallmark of affective disorders. Evidence suggests that increased susceptibility to emotional distraction is linked to changes in the processing of emotional information that affect both the basic response to and coping with emotional distraction, but the neural correlates of these phenomena are not clear. The present review discusses emerging evidence from brain imaging studies addressing these issues, and highlights the following three aspects. First, the response to emotional distraction is associated with opposing patterns of activity in a ventral "hot" affective system (*HotEmo*, showing *in*creased activity) and a dorsal "cold" executive system (*ColdEx*, showing *de*creased activity). Second, coping with emotional distraction involves *top–down* control in order to counteract the *bottom-up* influence of emotional distraction, and involves interactions between the amygdala and the prefrontal cortex. Third, both the response to and coping with emotional distraction are influenced by individual differences affecting emotional sensitivity and distractibility, which are linked to alterations of both *HotEmo* and *ColdEx* neural systems. Collectively, the available evidence identifies specific neural signatures of the response to emotional challenge, which are fundamental to understanding the mechanisms of emotion-cognition interactions in healthy functioning, and the changes linked to individual variation in emotional distractibility and susceptibility to affective disorders.

Keywords: emotional interference, affective-cognitive interactions, amygdala, prefrontal cortex, working memory, neural circuitry, functional magnetic resonance imaging

INTRODUCTION

Emotion and cognition are two complexly intertwined, yet distinct facets of human behavior. Emotion has often been compared to a "double-edged sword," as it can exert both beneficial and deleterious influences on our cognition and behavior. For example, we may experience enhanced memory for emotional events, but could also be more distracted by emotional stimuli that interfere with our goals. These effects have been linked to prioritization of emotional information, possibly due to its enhanced evolutionary value, as at a basic level these phenomena depend on neural mechanisms that allow timely detection, identification, and privileged processing of stimuli and situations that are important for survival (e.g., finding food, avoiding predators; Hansen and Hansen, 1988; Ledoux, 1996; Whalen et al., 1998b; Ohman et al., 2000, 2001; Anderson and Phelps, 2001).

Although the enhancing effects of emotion on cognitive functions such as memory, where emotion tends to be task-relevant, have been the focus of extensive research (see Dolcos et al., 2011, 2012 for comprehensive reviews), the detrimental effects of task-irrelevant emotion on cognitive functions have started to be the focus of research more recently (Johnson et al., 2005; Most et al., 2005; but see Seibert and Ellis, 1991; Oaksford et al., 1996; Shackman et al., 2006). An important factor modulating the impairing effect of emotion is the capacity to engage coping mechanisms in order to resist emotional distraction. Importantly, emotional distraction does not impact everybody in the same way, as people vary in their response to and the ability to cope with emotional distraction. This, in turn, influences the susceptibility to affective disorders, such as depression and anxiety, which are characterized by increased emotional distractibility. Thus, understanding the mechanisms underlying the response to and coping with emotional distraction is critical for understanding fundamentals of healthy functioning, as well as of changes associated with emotional disorders.

The present review discusses emerging evidence from brain imaging studies investigating the neural correlates of the detrimental impact of transient emotional distraction on goal-oriented processing and the neural correlates of coping with

such distraction. The discussion focuses primarily on findings from studies using delayed-response working memory (WM) tasks and similar dual-task paradigms with emotional distraction, which allowed a clear dissociation of the fMRI signal in brain regions involved in cognitive and emotional processing. Although, overall, the focus in the present review is on the effect of transiently-induced emotional responses, in some cases investigations identified more complex combinations of effects, involving transient emotional responses, longer-lasting states, and trait-like aspects. For matters of conciseness, the present paper does not provide an in-depth discussion of evidence from studies employing perceptual, conflict resolution, and emotion regulation paradigms, which are also methodologically different (see Banich et al., 2009; Etkin et al., 2011; Shackman et al., 2011; Ochsner et al., 2012; Ray and Zald, 2012 for recent reviews and meta-analyses).

The focus will be on the following three main aspects: (1) We will first discuss evidence concerning the neural circuitry underlying the impact of emotional distraction, focusing on the interplay between two major neural systems: a ventral system associated with "hot" emotional processing (*HotEmo* system) and a dorsal system associated with "cold" executive processing (*ColdEx* system); (2) We will then discuss evidence concerning the neural mechanisms of coping with emotional distraction, focusing on the interaction between brain structures involved in basic emotional response (amygdala [AMY]) and brain structures involved in coping with irrelevant emotions (prefrontal [PFC] and anterior cingulate [ACC] cortices); (3) Finally, we will also discuss evidence concerning the role of individual differences in the response to and coping with emotional distraction in healthy participants, with a focus on personality and sex-related differences. The review will conclude with identification of outstanding issues emerging from the extant literature and discussion of future directions.

NEURAL CORRELATES OF THE RESPONSE TO EMOTIONAL DISTRACTION—BASIC FINDINGS

NEURAL CORRELATES OF THE DETRIMENTAL IMPACT OF EMOTIONAL DISTRACTION

Investigations of the neural circuitry underlying the detrimental impact of emotional distraction complement the research investigating the neural correlates of the enhancing effect of emotion (reviewed in Dolcos et al., 2011, 2012). Studies investigating synergistic emotion-cognition interactions have revealed that the memory-enhancing effect of emotion is associated with *increased* activity in and interactions between emotion-based systems, involving AMY, and memory-based systems, involving medial-temporal lobe (MTL) and PFC regions (Dolcos et al., 2004; Kensinger and Corkin, 2004; see also Dolcos et al., 2011, 2012 for reviews). Based on the findings regarding the memory-enhancing effect of emotion, a default assumption concerning the impairing effect is that the detrimental impact of emotional distraction on cognitive functions may be linked to *reduced* activity in brain regions subserving the functions impaired by emotion. This assumption is supported by evidence from both clinical and non-clinical groups (Mayberg, 1997, 2006; Drevets and Raichle, 1998; Yamasaki et al., 2002; Price and Drevets, 2010, 2012).

Models of affective-cognitive interactions inspired by clinical studies point to dysfunctional interactions between a dorsal executive neural system (*ColdEx*) and a ventral emotional system (*HotEmo*), and propose that impaired executive control and enhanced emotional distractibility observed in depression are linked to *hypo*function of the *ColdEx* and *hyper*function of the ventral *HotEmo* neural systems (Mayberg, 1997, 2006; Drevets and Raichle, 1998; Price and Drevets, 2010, 2012) (**Figure 1**). The dorsal *ColdEx* system includes brain regions typically associated with executive functions, such as the dorsolateral prefrontal cortex (dlPFC) and the lateral parietal cortex (LPC), which are critical to active maintenance of goal-relevant information in working memory (WM). Increased activity in these regions during WM tasks is typically associated with increased performance (Smith and Jonides, 1999; D'Esposito et al., 2000; Miller and Cohen, 2001; Nee et al., 2012; Niendam et al., 2012; Rottschy et al., 2012). The ventral *HotEmo* system includes brain regions involved in emotion processing, such as the AMY, the ventrolateral PFC (vlPFC), and the medial PFC (i.e., the medial aspect of the frontal lobe, excluding the ACC; Davidson and Irwin, 1999;

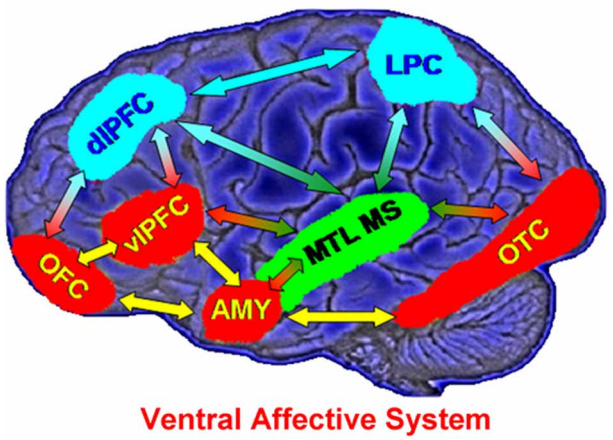

FIGURE 1 | Neural systems involved in cognitive/executive (dorsal) vs. emotional (ventral) processing. The dorsal system includes brain regions typically associated with "cold" executive (*ColdEx*; color-coded in blue) functions, such as the dorsolateral prefrontal cortex (dlPFC) and the lateral parietal cortex (LPC), which are critical to the active maintenance of goal-relevant information in working memory (WM). The ventral system includes brain regions involved in "hot" emotional (*HotEmo*; color-coded in red) processing, such as the amygdala (AMY), the ventrolateral PFC (vlPFC), and the medial PFC. Other brain regions that these systems interact with (MTL MS, OTC) are also illustrated. MTL MS, medial temporal lobe memory system; OFC, orbitofrontal cortex; OTC, occipitotemporal cortex. Note that this diagram does not include all regions that are part of the two systems, as in its present format it does not include medial brain regions. Also, even though the visual cortical areas illustrated here (OTC) are not technically part of the *HotEmo* system, they are colored in red because they are susceptible to influences from emotion processing regions. Monochromatic arrows represent connections within the same system, whereas bichromatic arrows represent connections across systems. Adapted from figure courtesy of Dr. Lihong Wang and Dr. Aysenil Belger. Reproduced from Dolcos et al. (2011), with permission.

Davis and Whalen, 2001; Phan et al., 2002; Kober et al., 2008; Vytal and Hamann, 2010; Lindquist et al., 2012).

Findings from recent studies investigating the neural correlates of cognitive interference by emotional distraction in healthy participants provide evidence that interactions between the *ColdEx* and *HotEmo* systems are not only reflected in longer-lasting altered states, as observed in clinical conditions such as depression, but can also occur transiently, in response to on-going task irrelevant emotional distracters. A series of studies by Dolcos and colleagues, investigating the neural correlates of the response to emotional distraction, identified dissociable patterns of brain activity in *ColdEx* vs. *HotEmo* systems, which were specific to transient distracting emotions (Dolcos and McCarthy, 2006; Dolcos et al., 2007, 2008). The basic approach involved recording of brain activity using fMRI, while participants performed a delayed-response working memory (WM) task with emotional distraction (**Figure 2**; see also Wong et al., 2012 for a detailed presentation of the experimental protocol). The WM task involved keeping in mind a set of human faces (Memoranda) for the duration of a short delay, and then answering whether a single face (Probe) was part of the initial set or not. During the delay interval between the memoranda and the probe, high-arousing negative pictures, selected from the International Affective Picture System (IAPS; Lang et al., 2008), were presented as task-irrelevant distracters. The subjects were instructed to look at the distracters but maintain focus on the memoranda, and to make quick and accurate responses to the probes. Importantly, this task allowed clear dissociations of the time-course of response to emotional distraction in the *HotEmo* and *ColdEx* systems as well as an objective quantification of the impact of emotional distraction on WM performance.

Using this paradigm, the study by Dolcos and McCarthy (2006) provided initial brain imaging evidence that impaired WM performance in the presence of emotional distraction is linked to increased activity in ventral system structures involved in emotional processing (e.g., AMY, vlPFC) while disrupting delay interval activity in dorsal brain regions implicated in attentional processes and active maintenance of task-relevant information in WM (e.g., dlPFC, LPC) (**Figure 3**). This opposing pattern of changes in *HotEmo* and *ColdEx* regions was confirmed by significant region × condition interactions (Dolcos and McCarthy, 2006). Importantly, the disruption of dorsal system activation was associated with impaired WM performance. The results of this study are consistent with the idea that activity in the affective and executive neural systems is interconnected, such that increased activity in the ventral affective regions in the presence of transient emotional distracters temporarily takes off-line the dorsal executive system and results in WM impairment, possibly as a result of a re-allocation of processing resources by emotional distraction (Dolcos and McCarthy, 2006).

Follow-up investigations (Dolcos et al., 2007, 2008; Denkova et al., 2010; Iordan et al., 2013b) provided additional evidence that these patterns of neural activity are specific to emotional distraction, and further explored the specificity of this response to different types of distracters. For instance, an investigation by Dolcos et al. (2008) directly compared the effects of novel non-emotional distracters that were highly similar to the memoranda (i.e., memoranda-confusable distracters) with those of emotional distracters, and showed that the two types of distracters were associated with opposing changes in dlPFC activity (i.e., increased vs. decreased, respectively), in conditions where both types of distracters produced similar effects on WM performance (see the activation cluster in the right hemisphere and the associated time course graph, in **Figure 4** below). This provided support for the idea that dlPFC *de*activation is specific to emotional distraction (Dolcos et al., 2008).

Another recent study investigating the effects of more specific emotional distracters (i.e., anxiety-inducing angry faces),

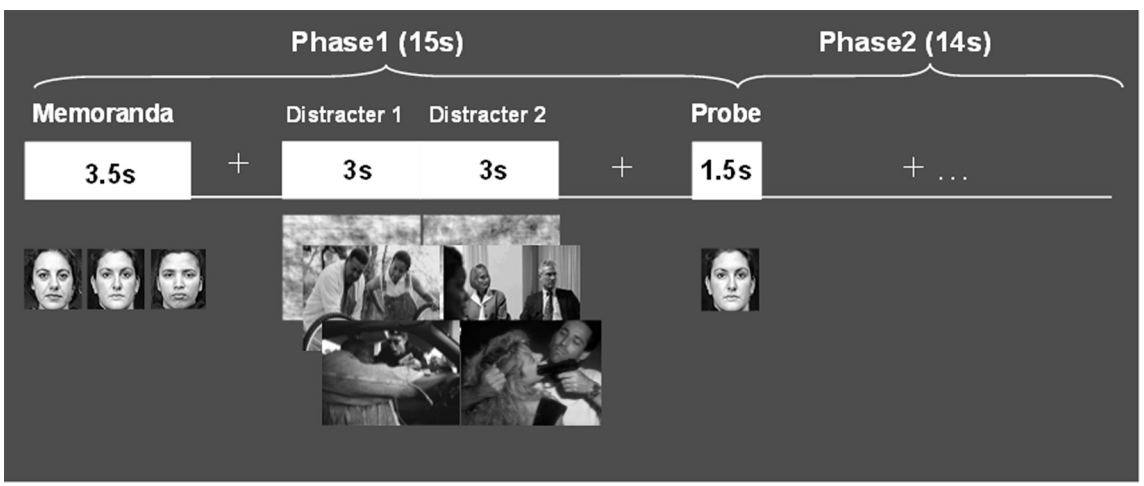

FIGURE 2 | Delayed-response WM task with emotional distraction. The memoranda consisted of human faces, which participants encoded and maintained into WM. After a short delay, a probe was presented and subjects had to decide whether it was part of the memoranda or not. During the delay between the memoranda and the probes, meaningful (emotional and neutral) and meaningless (scrambled) novel pictures were presented on the screen, and subjects were instructed to maintain focus on the WM task while looking at the pictures. Reproduced from Dolcos and McCarthy (2006), with permission.

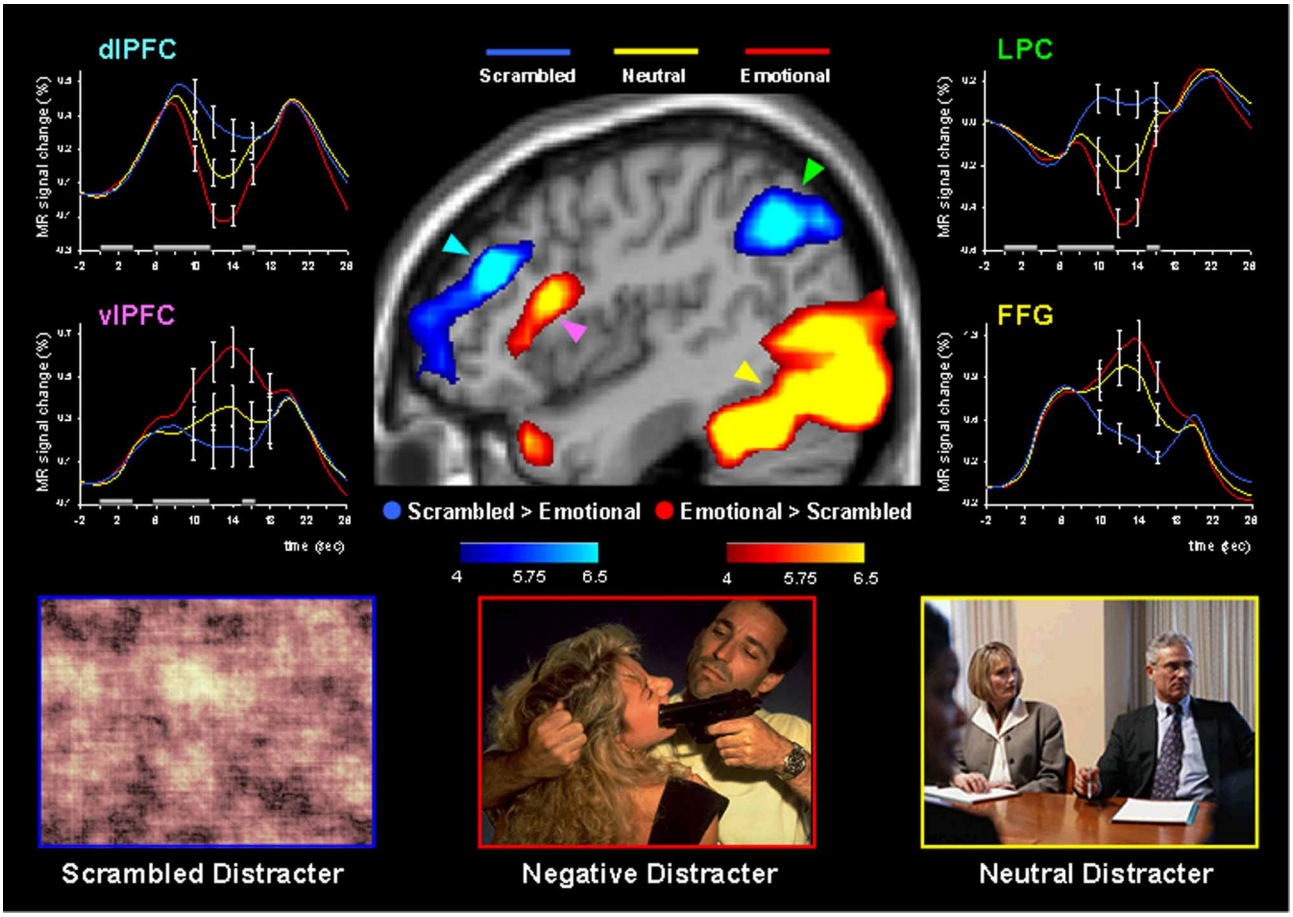

FIGURE 3 | Dissociable patterns of brain activity in the dorsal *ColdEx* and ventral *HotEmo* systems linked to impaired working memory performance in the presence of emotional distraction. Emotional distracters produced the most disrupting effect on the activity during the delay period of a working memory task in a set of dorsal brain regions associated with executive processes (the blue clusters) while producing the most enhancing effect on activity in a set of ventral brain regions associated with emotion processing (the red clusters). The central image shows activation maps of the direct contrasts between the most versus least distracting conditions (i.e., emotional vs. scrambled pictures), superimposed on a high-resolution brain image displayed in a lateral view of the right hemisphere. The colored horizontal bars at the bottom of the brain image indicate the gradients of the t values for the activation maps displayed. The line graphs show the time courses of activity in representative dorsal and ventral brain regions (indicated by color-coded arrows). The gray rectangular boxes above the *x*-axes indicate the onset and duration of the different phases of the working memory task: presentation of the memoranda, distracters, and probes, respectively. PFC, Prefrontal Cortex; dlPFC, Dorsolateral PFC; LPC, Lateral Parietal Cortex; vlPFC, Ventrolateral PFC; FFG, Fusiform Gyrus. Reproduced from Dolcos and McCarthy (2006), with permission.

as opposed to those inducing a general emotional distraction involved in previous studies (i.e., IAPS pictures), found similar brain imaging effects (Denkova et al., 2010). Confirming that the manipulation worked in inducing anxiety, participants had significantly higher levels of state anxiety after the completion of the task compared to the beginning of the study. These findings show that similar dissociable patterns of activity in the *ColdEx* and *HotEmo* systems are also produced by relatively mild distracters (negative facial expressions) inducing specific emotions (anxiety; see also Grillon and Charney, 2011). Moreover, preliminary findings from an investigation that manipulated other emotional properties of task-irrelevant distracters (arousal: high vs. low, and valence: positive vs. negative) suggest that similar brain activity effects may also be observed in the case of positive distraction (Iordan et al., 2013b). Finally, other investigations using similar (Anticevic et al., 2010; Diaz et al., 2011; Oei et al., 2012) or different tasks (e.g., "emotional odd-ball task," Yamasaki et al., 2002; Wang et al., 2005; "emotional interrupt task," Mitchell et al., 2008), and evidence from clinical research (Morey et al., 2009; Anticevic et al., 2011) also support this dorso-ventral dissociation in response to emotional distraction, thus pointing to the replicability and generalizability of these findings (see **Table 1** and **Figure 10**).

Collectively, these findings are consistent with the idea that the outcome of task-irrelevant emotional distraction depends on dynamic interactions between neural systems that allow the ability to stay focused on task-relevant information and systems involved in the processing of emotional information that may compete with the available processing resources. Possibly as a result of their salience, emotional distracters may produce

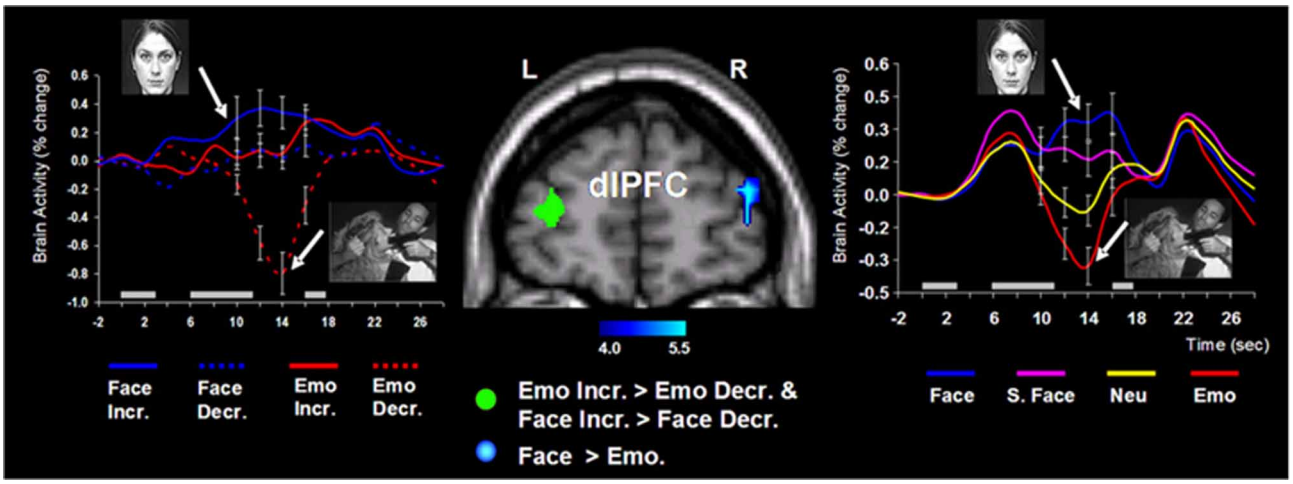

FIGURE 4 | Opposing dorsolateral prefrontal cortex (dlPFC) modulation linked to the nature of distraction. Specific areas of the right dlPFC (e.g., BA 10/46) showed opposing modulation linked to the nature of distraction (i.e., *in*creased activity to memoranda-confusable face distracters, and *de*creased activity to emotional scene distracters). These findings were also confirmed when faces and emotional scene distracters were compared to their corresponding control conditions (i.e., scrambled faces and neutral scene distracters, respectively). The blue cluster on the middle panel shows the activation map of the direct contrast between delay activity to face and emotional distracters, superimposed on a high-resolution brain image displayed in a coronal view. The colored horizontal bar at the bottom of the brain image indicates the gradient of the t values. The line graph on the right side shows the time courses of activity in the right dlPFC region of interest (ROI). As described in section II below, specific dlPFC areas in the left hemisphere (i.e., the green cluster on the middle panel) showed similar modulation to face and emotional distraction linked to WM performance. The line graph on the left side shows the time courses of activity at peak voxels from overlapping areas of the left dlPFC (BAs 9/10) identified by analyses examining differences in brain activity associated with individual differences in performance in the presence of memoranda-confusable and memoranda-nonconfusable emotional distraction. For simplicity, the left-side graph is plotting the time courses of the face and emotional distracters alone (i.e., with the scrambled face and neutral conditions omitted). The gray rectangular boxes above the *x*-axes indicate the onset and duration of the memoranda, distracters, and the probes, respectively. Face, face distracters; S. Face, scrambled face distracters; Emo, emotional scene distracters; Neu, neutral scene distracters; Incr., increase group; Decr., decrease group; L, left; R, right; BA, Brodman area. In all graphs, error bars represent the standard errors of means. Reproduced from Dolcos et al. (2008), with permission.

a *bottom-up* impact on processing of goal-relevant information by re-allocating processing resources (Vuilleumier et al., 2001) and impairing performance. Although the exact nature of these resources is not clear, one possible interpretation is along the lines of Desimone and Duncan's (1995) biased competition model of selective attention, consistent with the idea that processing of emotional stimuli requires attentional resources, and that emotional stimuli compete for neural representation with all the other stimuli. Hence, the emotional distracters tap into the same resources necessary to process the task-relevant information, and impair WM performance. It is possible, however, that processing of emotional, especially threatening, information is prioritized, and hence it occurs automatically, without being limited by the availability of attentional resources (e.g., Morris et al., 1999; Anderson et al., 2003). A potential reconciliation of these opposing views, in the perceptual domain, may be suggested by the results of a recent investigation from our group (Shafer et al., 2012), which showed that task-irrelevant emotion processing is subjective to both the emotional content of distraction and the level of attentional demand. Importantly, Shafer's et al. results showed that the interaction between emotion and cognition emerges only when finer assessments of emotional charge (comparison of most vs. least emotional conditions) along with manipulations of processing load (high vs. low) are taken into account, suggesting a more nuanced interplay between automatic and controlled processes involved in emotion processing (see also Van Dillen et al., 2009 and Vytal et al., 2012 for complementary approaches).

The opposing responses observed in the *HotEmo* and *ColdEx* systems in response to emotional distraction have proven to be robust and replicable results, demonstrated with different tasks, and also replicated by others. Similar bottom-up effects, consistent with the idea that emotional stimuli can "hijack" attention, have also been demonstrated using emotional variants of other cognitive tasks, tapping into perceptual and attentional domains (Williams et al., 1996; Bradley et al., 1999; Fox et al., 2001; Vuilleumier et al., 2001; Bradley, 2009; Cohen et al., 2011; Shafer et al., 2012). It should be noted that these studies have typically used emotional stimuli inducing transient emotions, such as emotional pictures and faces, and that these stimuli may have distinct characteristics compared to those typically employed in emotion-induction studies involving longer-lasting emotional responses (e.g., video clips and conditioned stimuli; see Okon-Singer et al., 2012 for a discussion). Moreover, as we will see in the next sections, further investigations also showed that this pattern of response to emotional distraction is sensitive to personality and sex-related differences (Denkova et al., 2010; Iordan et al., 2013a), affected by sleep deprivation (Chuah et al., 2010), and altered in clinical conditions, such as PTSD (Morey et al., 2009) and schizophrenia (Anticevic et al., 2011). Importantly, as

Table 1 | Relevant studies investigating the impact of emotional distraction, targeted in the present review.

Study	Subjects	Task	Memoranda	Type of emotional distracters	Behavioral results	Dorsal-ventral dissociation identified?	Additional areas	Coping with emotional distraction	Additional results
Dolcos and McCarthy (2006)	F	WM with distraction	Faces	IAPS pictures	Decreased WM performance for Emo	Yes	Dorsal: PCC Ventral: sgACC, Ins, HC	Incr vlPFC activity associated with lower distractibility index	N/A
Dolcos et al. (2006)*	F	WM with distraction	Faces	IAPS pictures	Decreased WM performance for Emo	Yes	N/A	Incr AMY-IFC/vlPFC coupling Incr L IFC/vlPFC for correct trials	N/A
Dolcos et al. (2008)	F	WM with distraction	Faces	IAPS pictures	Subset of subjects showing decreased WM performance for Emo	Yes	Dorsal: SPC Ventral: sgACC, MFC, HC	Incr L dlPFC for subjects showing increased performance	Incr dlPFC for Face distracters
Morey et al. (2009)	F + M, PTSD vs. CON	WM with distraction	Faces	Combat-related pictures	Decreased WM performance for PTSD group	Yes	Ventral: TP	N/A	Incr AMY, vlPFC, FG for Combat in PTSD group Decr dlPFC for Combat and Neu in PTSD group
Chuah et al. (2010)	F + M	WM with distraction	Faces	IAPS pictures	Decreased WM performance for Emo Decreased WM performance after sleep deprivation	Yes	Dorsal: dACC Ventral: Ins	Incr AMY-mPFC and AMY-dlPFC connectivity associated with better WM performance	Incr AMY associated with lower WM performance for Emo
Denkova et al. (2010)	F	WM with distraction	Faces	Morphed angry faces	Decreased WM performance for Emo	Yes**	Dorsal: dmPFC Ventral: vmPFC	Incr L vlPFC and dmPFC associated with increased WM performance	Incr L FG associated with increased social anxiety Incr R FG associated with lower WM performance for Emo
Iordan et al. (2013a)	F + M	WM with distraction	Faces	Morphed angry faces	Decreased WM performance for Emo in F	Yes**	Dorsal: dmPFC Ventral: vmPFC	Incr L vlPFC associated with increased WM performance in F Incr R dlPFC associated with increased WM performance in M	Incr L FG to Emo in F, associated with lower WM performance Incr sgACC in F
Dolcos et al. (2013)	F	WM with distraction	Faces	IAPS pictures	Subset of subjects showing decreased WM performance to Emo	Yes	Dorsal: SPL Ventral: mPFC, Ins, HC	Incr L vlPFC for correct trials Incr R vlPFC associated with WM success for subsequently remembered Emo distracters	Incr AMY and decr dlPFC in subjects showing impaired WM to Emo Incr AMY associated with higher AI scores Incr dlPFC associated with lower AI scores

(Continued)

Table 1 | Continued

Study	Subjects	Task	Memoranda	Type of emotional distracters	Behavioral results	Dorsal-ventral dissociation identified?	Additional areas	Coping with emotional distraction	Additional results
Anticevic et al. (2010)	F + M	WM with distraction	Shapes	IAPS pictures	Decreased WM performance for Emo	Yes	Dorsal: aPFC Ventral: OFC	Incr R aPFC and R vlPFC for correct trials	Decr aPFC and dlPFC associated with increased WM performance Incr AMY associated with decreased WM performance for all distracter types Incr AMY-dlPFC negative coupling during task, compared to rest-state
Oei et al. (2012)	M	WM with distraction	Letters	IAPS pictures	Decreased WM performance and slower RT for Emo	Yes	Dorsal: aPFC Ventral: Ins, TP	N/A	Incr ventral regions for stressed group
Yamasaki et al. (2002)***	F + M	Emotional odd-ball	N/A	IAPS pictures	Slower RT to Emo	Yes	N/A	N/A	Incr rACC to both Emo and targets
Wang et al. (2008b)***	F + M, MDD vs. CON	Emotional odd-ball	N/A	Commercial and in-house pictures	Slower RT to target-after-Emo Slower RT for MDD, esp. to target-after-Emo	Yes	Dorsal: dACC, PCC Ventral: Ins, sub-regional specificity in IFC	Incr ACC to target-after-Emo and incr R IFC to target-after-Neu in CON Incr R IFC associated with faster RT in MDD	Decr executive regions in MDD

The identification of the dorsal-ventral dissociation in the response to emotional distraction (column 7) was based on indexing brain regions typically showing decreased activity (dorsolateral prefrontal cortex [dlPFC] and lateral parietal cortex [LPC]) and brain regions typically showing increased activity (amygdala [AMY], ventrolateral prefrontal cortex [vlPFC], and fusiform gyrus [FG]) in response to emotional distraction. Of note, the ventral areas also included regions that are susceptible to emotion modulation (i.e., FG), that are not part of the emotional system per se.

**Same subject sample as in the Dolcos and McCarthy (2006) study.*

***There was no vlPFC activation identified in female participants, in this study.*

****Although these studies have not used the delayed WM task with distraction, they are based on a similar task (i.e., 'emotional odd-ball'; introduced by the Yamasaki et al., 2002 study), which involves both executive and emotional processing components and dissociates between the dorsal and ventral networks (see also Wang et al., 2005, 2008a, 2012, for studies using similar tasks).*

Legend: F, female subjects; M, male subjects; PTSD, post-traumatic stress disorder clinical sample; MDD, major depressive disorder clinical sample; CON, healthy controls; WM, working memory, IAPS, International Affective Picture System (Lang et al., 2008); Emo, emotion; Neu, neutral; RT, reaction time; aPFC, anterior PFC; OFC, orbitofrontal cortex; IFC, inferior frontal cortex; mPFC, medial PFC; dmPFC, dorsomedial PFC; vmPFC, ventromedial PFC; MFC, medial frontal cortex; ACC, anterior cingulate cortex; rACC, rostral ACC; dACC, dorsal ACC; sgACC, subgenual ACC; PCC, posterior cingulate cortex, SPC, superior parietal cortex; SPL, superior parietal lobule; TP, temporal pole; Ins, insula; HC, hippocampus; Incr, increased activity; Decr, decreased activity; AI, attentional impulsiveness.

described below, the disadvantageous outcomes of this bottom-up impact of emotional distraction can be mitigated by *top–down* interventions from cognitive control regions, engaged to regulate emotional responses and cope with emotional distraction (Gray et al., 2002; Dolcos et al., 2006, 2008; Pessoa, 2008; Chuah et al., 2010; Denkova et al., 2010; reviewed in Dolcos et al., 2011).

The dorsal-ventral dissociation in the neural response to emotional distraction has been observed not only in the larger neural systems (i.e., *ColdEx* and *HotEmo*), as discussed above, but also in more restricted brain areas, such as the ACC, which has been consistently associated with emotion-cognition integrations (Bush et al., 2000; Etkin et al., 2011; Shackman et al., 2011). A number of studies investigating conflict resolution by using emotional adaptations of cognitive conflict tasks (e.g., Stroop) point to a similar dorsal/ventral dissociation in the ACC, with the midcingulate cortex ("dorsal" ACC) responding mainly to cognitive conflict and perigenual-subgenual ACC ("rostral" ACC) responding mainly to emotional conflict (Whalen et al., 1998a; Etkin et al., 2006; Mohanty et al., 2007; also see Bush et al., 2000 for a review). However, other investigations have not fully supported this dissociation, offering a rather different picture, in which the dorsal ACC is engaged irrespective of the emotional content of the information to be ignored, whereas the ventral ACC remains selective for emotional information (Haas et al., 2006; Egner et al., 2008; Ochsner et al., 2009; Kanske and Kotz, 2011a,b). It should be noted that there are conceptual and methodological differences between studies employing delayed WM tasks with emotional distraction and studies involving cognitive-emotional conflict resolution (see Banich et al., 2009 for a discussion). Although it is beyond the scope of the present paper to discuss the latter type in detail, more in-depth discussions are provided in other recent reviews (Banich et al., 2009; Etkin et al., 2011; Shackman et al., 2011).

Noteworthy, the dorsal-ventral distinction is primarily a functional dissociation based on the opposing response to emotional distraction in identified typical cognitive/executive and emotion processing regions. In addition to this general dissociation, there are also exceptions, reflecting sub-regional specificity. For example, certain dorsal sub-regions show an increased response to emotional distraction (e.g., BA6/9; Dolcos et al., 2008). Also, as we will see in the next section, the increased response to emotional distraction in specific vlPFC areas has been linked to coping with emotional distraction (e.g., Dolcos et al., 2006). In other words, although consistent with its inclusion in the *HotEmo* system, vlPFC/inferior frontal cortex (IFC) shows overall increased activity to emotional distraction, consistent with evidence regarding its role in top–down control (Aron et al., 2004; Aron, 2007), specific areas within this larger region have proven to be involved in coping with emotional distraction. These results are consistent with other investigations that have implicated the dorsal PFC in emotion processing and the vlPFC in inhibition and affect regulation, respectively (see Aron, 2007; Kober et al., 2008; Vytal and Hamann, 2010; Ochsner et al., 2012 for recent reviews and meta-analyses).

In summary, studies investigating the neural correlates of the basic response to emotional distraction point to an interplay between two major neural systems: a ventral system, associated with "hot" emotional processing (*HotEmo* system), showing *in*creased activity, and a dorsal system, associated with "cold" executive processing (*ColdEx* system), showing *de*creased activity. The impact of task-irrelevant emotional distraction is chiefly supported by *bottom-up* mechanisms that may redirect processing resources away from the main cognitive task and toward stimuli with enhanced relevance for survival. As we will see in the next section, in response to this effect of task-irrelevant emotions, *top–down* mechanisms are engaged in order to cope with emotional distraction.

NEURAL CORRELATES OF COPING WITH EMOTIONAL DISTRACTION

Brain imaging studies in which emotional information was presented as task-irrelevant distraction also provided evidence regarding the neural correlates of coping with distracting emotions. A series of investigations from our group and from others (Dolcos and McCarthy, 2006; Dolcos et al., 2006, 2008; Anticevic et al., 2010; Chuah et al., 2010; Denkova et al., 2010; Henckens et al., 2012; Oei et al., 2012) provided evidence that coping with task-irrelevant emotional distraction entails increased activity in and interactions between brain regions involved in basic emotion processing (AMY) and brain regions associated with cognitive control (particularly lateral and medial PFC). In this section we will discuss basic evidence concerning the role of the lateral PFC (mostly vlPFC) in coping with emotional distraction (see **Table 1** and **Figure 10**), but the role of other regions (e.g., ACC) will also be emphasized. Complementary evidence concerning the neural correlates of coping with emotional distraction will be further elaborated in the section on individual differences. It is important to note that we operate a distinction between successful coping with emotional distraction and explicit manipulation of emotion regulation strategies, based on the different type of processing that is assessed in studies investigating the two aspects. Specifically, studies employing the delayed WM approach measure successful coping with emotional distraction *objectively*, in relation to performance in a cognitive task, whereas typical studies of explicit emotion regulation assess the effect of emotion regulation manipulation *subjectively,* in relation to emotional ratings. While here we discuss both objective and subjective aspects of coping with distraction, more in-depth discussions of the latter can be found in other sources (Gross, 2002; Gross and John, 2003; Ochsner et al., 2012; Ray and Zald, 2012).

Evidence of enhanced AMY-PFC coupling during processing of transient emotional distraction

Functional connectivity analyses of data from the Dolcos and McCarthy study provided evidence for enhanced positive coupling between AMY and vlPFC/IFC during processing of emotional distraction (**Figure 5A**). In turn, the engagement of IFC leads to successful coping with emotional distraction, as reflected in greater activity to correct vs. incorrect trials in the WM task, despite the presence of emotional distraction (Dolcos et al., 2006). Further investigation of activity in these PFC regions provided evidence clarifying the consequences of their engagement in coping with emotional distraction (**Figure 5B**). The engagement of the AMY can be seen as having the role of an "emotional detector"

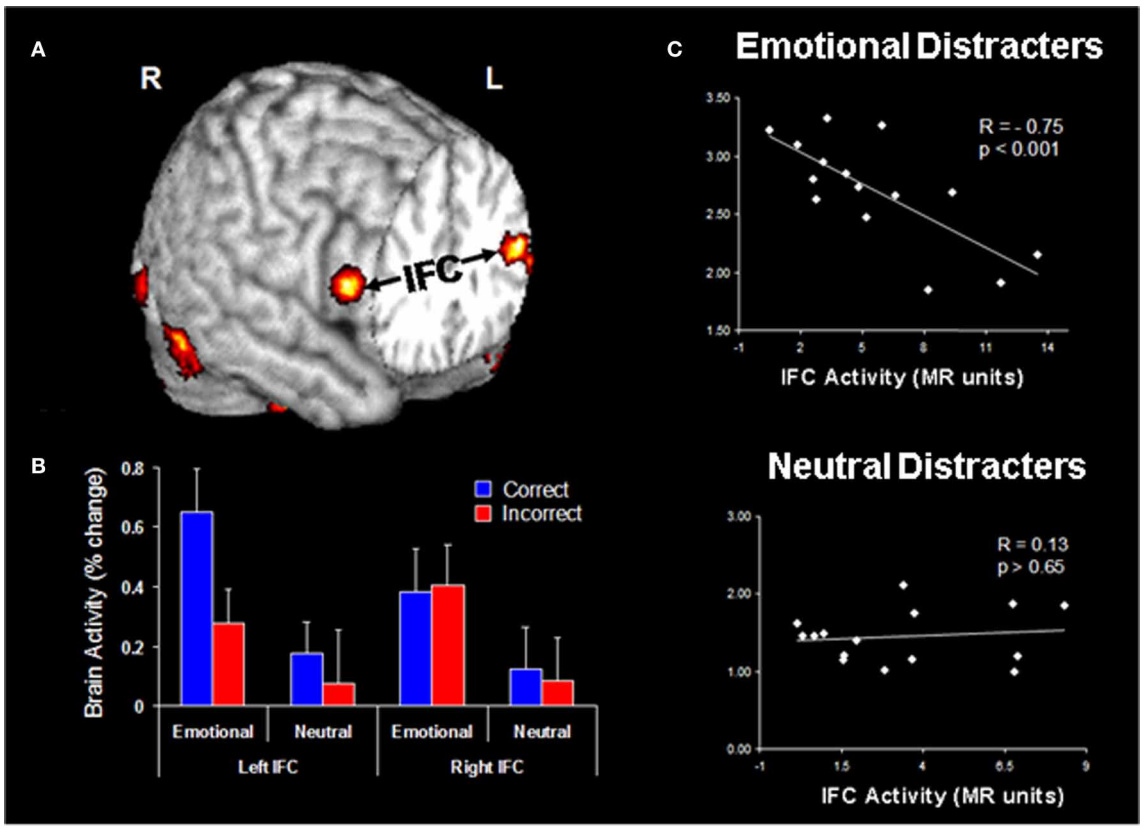

FIGURE 5 | Evidence for the role of lateral PFC in coping with distracting emotions. (A) Brain regions showing enhanced functional coupling with the amygdala during processing of emotional distraction—ventrolateral prefrontal cortex (vlPFC)/inferior frontal cortex (IFC) highlighted. **(B)** Hemispheric asymmetry in the vlPFC/IFC during successful coping with emotional distraction. **(C)** Enhanced correlation between vlPFC activity and subjective emotional distractibility scores. Taken together, these findings suggest a hemispheric asymmetry in the IFC with respect to its role in actually coping with distraction (left vlPFC/IFC) vs. coping with the subjective feeling of being distracted (right vlPFC/IFC). Correct/Incorrect, Remembered/Forgotten items in the WM task; R, Right; L, Left. Adapted from Dolcos and McCarthy (2006) and Dolcos et al. (2006), with permission.

that signals the PFC about the presence of emotional, potentially distracting, stimuli and thus the need to control their possible detrimental effects on cognitive performance (Dolcos et al., 2006). Anatomical evidence of substantial AMY–vlPFC connections (Amaral et al., 1992) supports this interpretation, and hence it is reasonable to posit that enhanced functional connectivity between the AMY and IFC reflects processing that originates in the AMY. Of all the lateral PFC regions, which are generally sparsely connected to the AMY, the IFC/vlPFC provides the most substantial connections, thus making it the best candidate among the lateral PFC regions to potentially exert direct control over AMY (Ray and Zald, 2012; see also Pessoa, 2010). Our interpretation is consistent with the idea that AMY is signaling the emotional relevance of the stimuli to PFC regions, such as ventrolateral and ventromedial PFC, which are integrating and interpreting them according to the current goals, and "taking" context-appropriate decisions which may dampen the emotional experience and benefit WM processing (Wager et al., 2008; Chuah et al., 2010; Denkova et al., under review). As described below, investigation of IFC activity in response to task-irrelevant emotional distraction provided further evidence consistent with this idea. These findings complement the results of emotion regulation studies typically identifying negative correlations between the levels of activity in PFC and AMY regions (e.g., Ochsner et al., 2004; see also Ray and Zald, 2012 for a review).

Evidence for the role of vlPFC/IFC in the inhibition of distracting emotions

Investigation of vlPFC/IFC activity in the two areas showing increased coupling with AMY in response to emotional distraction revealed a hemispheric asymmetry in this region, concerning its involvement in *objective* (left vlPFC) vs. *subjective* (right vlPFC) coping with emotional distraction. Specifically, activity in the left vlPFC distinguished between successful and unsuccessful WM trials in the presence of emotional distracters, by showing increased activity to trials associated with correct vs. incorrect responses. This finding suggests that this left vlPFC/IFC region is involved in successful coping with emotional distraction, by controlling the *objective* impact of emotional distraction on WM performance (Dolcos et al., 2006; **Figure 5B**). On the other hand, activity in the right vlPFC/IFC did not distinguish between correct and incorrect trials, but showed a negative correlation with subjective

ratings of distractibility, for emotional but not for neutral distracters (**Figure 5C**). In other words, participants engaging this region during processing of emotional distracters perceived them as less distracting and less emotional, possibly as a result of engaging inhibitory processes that diminished the subjective experience of being distracted, thus pointing to a role of this region in coping with the *subjective* "feeling of being distracted" (Dolcos and McCarthy, 2006).

Overall, these findings are consistent with evidence pointing to vlPFC as a site of cross-modal inhibition, generally associated with inhibitory processes (Aron et al., 2004; Aron, 2007; Berkman et al., 2009) and with evidence associating vlPFC/IFC with the inhibition of negative emotions (Petrovic et al., 2002; Ochsner et al., 2004), in addition to ventromedial PFC (Diekhof et al., 2011). Also, as discussed in the section on the role of individual differences, subsequent investigations have further supported the role of the left PFC in coping with distracting stimuli conveying general (Dolcos et al., 2008) and specific (Denkova et al., 2010) negative emotions. Although the exact mechanism of interaction between these structures is not clear, a potential explanation for the dlPFC deactivation in response to emotional distraction could be based on AMY-driven bottom-up effects. By virtue of their salience, emotional distracters may trigger automatic reallocation of processing resources from the main cognitive task and impair WM performance (Anticevic et al., 2010; Chuah et al., 2010). Alternatively, it is possible that the actual mechanisms engaged in order to cope with emotional distraction (e.g., vlPFC-dependent) could trigger dlPFC deactivation, by tapping into a common regional pool of resources (Ray and Zald, 2012). This issue should be investigated in future studies.

Noteworthy, other investigations also point to the involvement of other brain regions, such as the ACC and dlPFC, in coping with emotional distraction. Regarding the ACC, the evidence consistent with the involvement of the ventral/rostral ACC in emotional conflict resolution also supports a role for this region in coping with irrelevant emotions (Bush et al., 2000; Etkin et al., 2006; Egner et al., 2008; Ochsner et al., 2009; Kanske and Kotz, 2011a,b). Regarding the dlPFC, other studies using adaptations of the Stroop task have rather emphasized the involvement of this region in coping with distraction (Compton et al., 2003; Herrington et al., 2005), consistent with a more generic role of the dlPFC in biasing processing toward task-relevant information and away from task-irrelevant information, irrespective of the emotional content of the information to be ignored (Banich et al., 2009).

In summary, the extant evidence concerning the neural correlates of coping with distracting emotion highlights the role of lateral PFC regions, particularly the left ventrolateral PFC, in diminishing the *objective* negative impact of irrelevant emotions on goal-oriented processing. The engagement of the ventrolateral PFC involves functional coupling with the AMY, which can be seen as an "emotional detector" signaling frontal regions about the need to control potentially distracting emotions. Other brain regions, such as the ventral ACC and the dlPFC, have also been linked to coping with emotional distraction, in the context of tasks requiring resolution of emotional conflict. As we will see in the next section, both the basic response to and coping with emotional distraction are influenced by individual differences, the investigation of which allows for a more refined understanding of the associated neural correlates.

THE ROLE OF INDIVIDUAL DIFFERENCES IN THE RESPONSE TO EMOTIONAL DISTRACTION

Investigation of individual differences is an important topic in the corpus of research examining emotion-cognition interactions (see Dolcos et al., 2011 for a review). Earlier investigations have linked various personality traits to differences in brain activity reflecting general and specific (e.g., anxiety) emotion processing (Canli et al., 2002b; Bishop et al., 2004; see also Hamann and Canli, 2004; Bishop, 2007 for reviews). Other studies identified sex differences in emotion processing, and pointed to specific differences in brain activity associated with enhanced emotional reactivity and emotional memory in women compared to men (Lang et al., 1993; Canli et al., 2002a; Cahill et al., 2004; see also Andreano and Cahill, 2009; Kret and De Gelder, 2012 for reviews). In the present section, we will review fMRI findings from studies investigating the role of individual differences linked to general aspects of cognitive/executive and affective domains (Dolcos et al., 2013), specific aspects of affective processing (i.e., anxiety; Denkova et al., 2010), and sex differences in both the basic response to and successful coping with transient emotional distraction (Iordan et al., 2013a). This line of investigation has been triggered by the Dolcos et al. (2008) study, which provided initial evidence for individual variation in the susceptibility to emotional distraction. Subsequent investigations further addressing this issue are discussed below. Investigation of these aspects is important for understanding emotion-cognition interactions in healthy functioning, as well as the changes linked to individual variation in emotional distractibility and susceptibility or resilience to affective disorders.

INDIVIDUAL DIFFERENCES LINKED TO GENERAL ASPECTS OF COGNITIVE/EXECUTIVE AND AFFECTIVE DOMAINS

The same study that identified the specificity of dlPFC engagement in response to emotional distraction (Dolcos et al., 2008) discussed above (see **Figure 4**) also provided evidence for the role of dlPFC in coping with distracting emotions. Results of this investigation revealed that, while in most participants emotional distraction impaired WM performance, in some subjects it did not have a detrimental effect. Analyses performed to examine the brain activity associated with individual differences in WM performance identified increased dlPFC activity in subjects whose performance was not impaired by the presence of emotional distraction (see **Figure 4** above). However, given the lack of additional measures that could have further clarified the link between the observed behavioral and fMRI results in that study, it was difficult to assess what other factors may influence the differential sensitivity to emotional distraction. These issues were specifically targeted in a follow-up investigation (Dolcos et al., 2013), which in addition to fMRI data collected during the WM task with emotional distraction also assessed individual differences related to other aspects of general functioning in both cognitive/executive and affective domains, such as trait attentional impulsiveness and basic emotional sensitivity.

Regarding the basic response to emotional distraction, Dolcos et al. (2013) identified increased impact of irrelevant emotional distraction, affecting both *ColdEx* and *HotEmo* neural systems, in those subjects who showed increased susceptibility to emotional distraction. Specifically, participants who were more susceptible to the WM impairing effect of emotion showed greater *HotEmo* activations and greater *ColdEx* deactivations. For instance, the results identified increased AMY activation in subjects who were impaired by emotional distraction relative to those who were not (see **Figure 6**, the red cluster in the bottom panel depicting left AMY). These findings complement the results of the Dolcos et al. (2008) study, by showing that individual differences in the susceptibility to emotional distraction are associated not only with differences in top–down *ColdEx* regions (dlPFC), but also in ventral/bottom-up regions (AMY). Moreover, activity in both *HotEmo* and *ColdEx* regions was modulated by attentional impulsiveness. Specifically, trait attentional impulsiveness (AI), as assessed by the Barratt Impulsiveness Scale (Spinella, 2007), was associated with increased activity in the AMY and decreased activity in the dlPFC (**Figure 6**). Given the evidence that AI is characterized by increased distractibility and reduced ability to focus attention (Stanford et al., 2009), and the link between increased AI and impaired executive performance (Enticott et al., 2006; Pietrzak et al., 2008; Kam et al., 2012), this evidence points to AI as a potential general executive factor that contributes to increased sensitivity to emotional distraction.

Results from the same investigation also provided further support for the role of the left vlPFC/IFC in successful coping with emotional distraction, and revealed an interesting hemispheric dissociation between brain activity linked to the short-term vs.

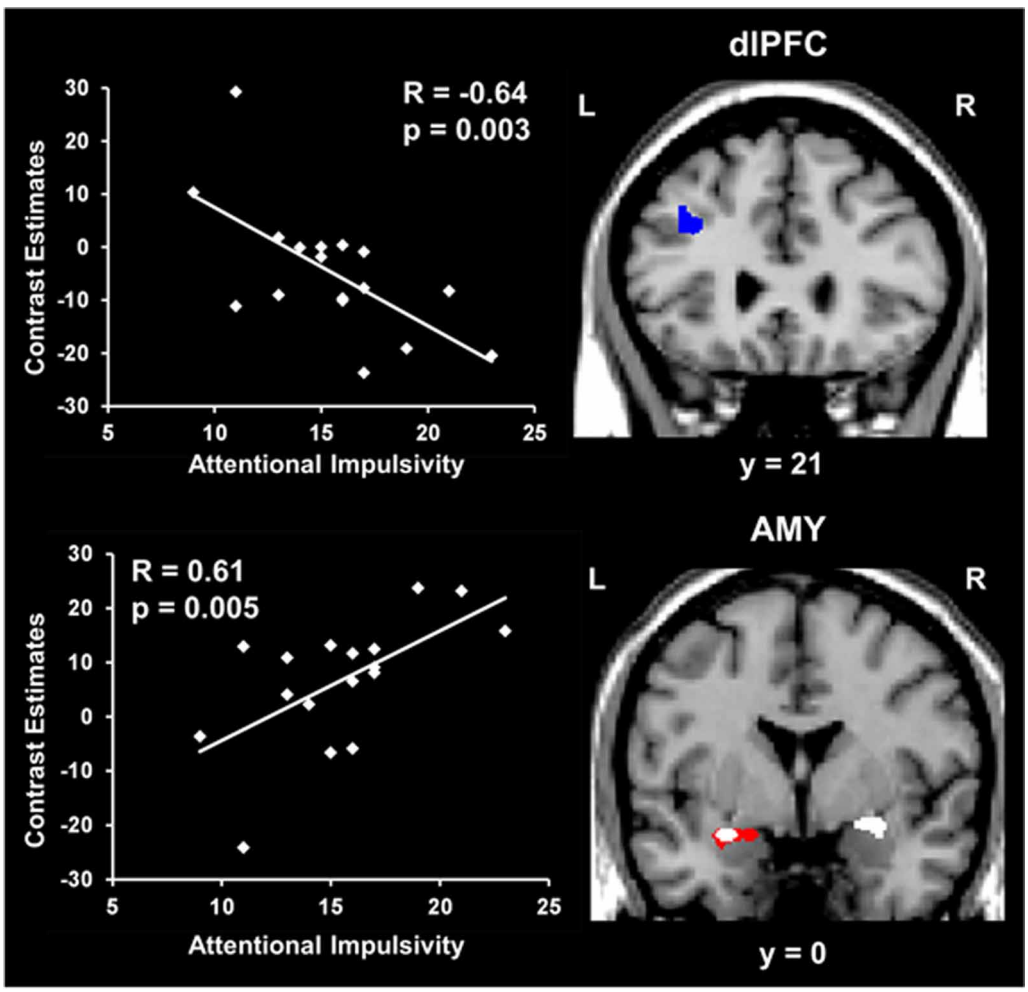

FIGURE 6 | Opposing co-variation of activity in *HotEmo* (AMY) and *ColdEx* (dlPFC) regions with individual differences in Attentional Impulsiveness. Bilateral AMY activity increased (white clusters) and left dlPFC activity (BA 8/9) decreased (blue cluster) with individual scores of attentional impulsivity (AI). Interestingly, the positive correlation and the difference in activity overlapped in a left AMY area also showing increased activation in subjects showing impaired WM performance to emotional distraction (red cluster). Also, the positive co-variation identified at the group level in the right AMY was driven by the subjects showing impaired WM performance. The scatterplots illustrate the co-variation between brain activity in AMY and dlPFC to emotional vs. neutral distraction and AI scores. The activation maps are superimposed on a high resolution brain image displayed in coronal view (y indicates the Talairach coordinates on the anterior-posterior axis of the brain). AMY, Amygdala; dlPFC, Dorsolateral prefrontal cortex; L, Left; R, Right. Reproduced from Dolcos et al. (2013), with permission.

long-term impact of emotional distraction on WM and episodic memory (EM), respectively (Dolcos et al., 2013). Analyses of the fMRI data associated with WM success (by comparing the trials with correct vs. incorrect WM responses) identified increased left IFC activity, which provide further support for a role of this area in controlling the objective impact of emotional distraction (Dolcos et al., 2006). In contrast, analyses performed only on trials corresponding to distracters associated with WM success and which were later remembered during a subsequent EM task identified a similar pattern of increased response and a positive correlation with WM performance in the right vlPFC/IFC, suggesting a specific role of this area in linking the initial coping with emotional distraction with enhanced memory for the distracters themselves (Dolcos et al., 2013).

INDIVIDUAL DIFFERENCES LINKED TO SPECIFIC ASPECTS OF AFFECTIVE PROCESSING: THE ROLE OF ANXIETY

Relationships between brain activity and personality-related differences were identified not only for traits reflecting general aspects of cognitive/executive and affective processing, but also for traits reflecting differences in processing and experiencing of specific emotions, such as anxiety. Complementing previous evidence showing that anxiety modulates the response to threat conveyed by social stimuli (e.g., angry faces) in primary emotion processing regions (AMY; e.g., Evans et al., 2008; Ewbank et al., 2009; see also Bishop et al., 2007), a recent study in healthy participants (Denkova et al., 2010) identified individual differences in brain activity linked to both the basic response to and coping with anxiety-inducing distraction (i.e., angry faces); for complementary approaches, see also Bishop (2009) and Ladouceur et al. (2009). Regarding the basic response to emotional distraction, the study by Denkova et al. (2010) identified a hemispheric asymmetry in the bottom-up impact of emotional distraction. Specifically, results pointed to a dissociation between the left and right fusiform gyrus (FG, BA 37), a perceptual region susceptible to emotion modulation (Kanwisher and Yovel, 2006), with the left FG showing positive correlation with anxiety scores and the right FG showing negative correlation with WM performance (**Figure 7**). This suggests a potential dissociation in the bottom-up impact of emotional distraction in the two hemispheres, with the left FG being involved in the subjective impact and experiencing of anxiety-inducing distraction and the right FG being involved in the actual/objective impact on WM performance.

In addition, medial prefrontal regions associated with experiencing of emotion (e.g., ventromedial PFC—vmPFC) showed increased overall activity and positive correlations with trait

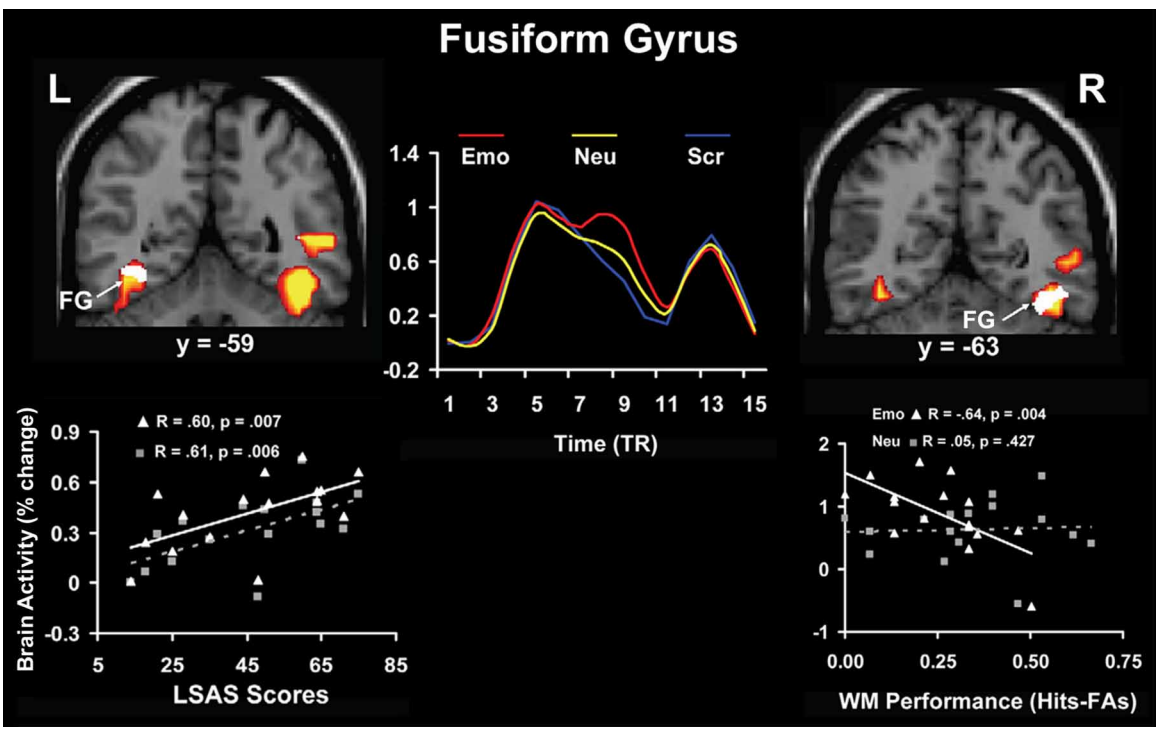

FIGURE 7 | Hemispheric asymmetry linked to bottom-up impact of emotional distraction in the fusiform gyrus (FG). Although these perceptual areas showed bilateral increased activity in response to anxiety-inducing distraction (red clusters and middle time course graph), a dissociation in the bottom-up response could be observed, linked to individual differences in trait anxiety and cognitive performance. Specifically, the left FG showed positive correlation with trait anxiety (white cluster in the left panel), whereas right FG showed negative correlation with working memory (WM) performance (white cluster in the right panel), consistent with a dissocation of subjective (left) and objective (right) effects. The middle panel illustrates the time course of activity in the FG, which was similar in both hemispheres. The scatterplots on the left and right panels are based on the corresponding correlations of the signal extracted from the FG with the social anxiety (LSAS) and WM scores, respectively. L, Left; R, Right; TR, Repetition Time. Adapted from Denkova et al. (2010), with permission.

anxiety scores, whereas lateral regions associated with executive functions (e.g., dlPFC) showed decreased overall activity and negative correlations with trait anxiety scores (Denkova et al., 2010). Denkova et al. (2010) also found that activity in the same ventral and dorsal regions showing opposing changes to transient anxiety-inducing distraction (i.e., *in*creased vs. *de*creased activity) also showed opposing correlations with behavioral indices of trait anxiety and WM performance. Specifically, ventral regions showed patterns of positive correlation with trait anxiety and negative correlation with WM performance, whereas dorsal regions showed patterns of negative correlation with trait anxiety and positive correlation with WM performance. Although it is unclear how these regions interact with each other, these effects demonstrate that individual variations in trait anxiety and WM performance modulate the response to anxiety-inducing distraction in both ventral and dorsal regions. This complements previous evidence regarding the impact of task-irrelevant emotional distraction and points to more complex effects involving transiently-induced emotional responses and trait-like components, such as trait social anxiety. Finally, Denkova et al. (2010) also identified individual differences in coping with anxiety-inducing distraction. Consistent with the role of the left vlPFC in successful coping with task-irrelevant emotional distraction, results identified a positive correlation between activity in this region and WM performance, suggesting that participants showing less reduction in the left vlPFC activity (and hence, overall greater activity), also performed better in the WM task (see **Figure 9** in the next subsection, left panel).

Overall, the results of these investigations suggest that individual differences in general cognitive/executive control (e.g., attentional impulsivity) and general and specific emotional sensitivity (e.g., anxiety) are linked to neural changes indexing increased sensitivity to emotional distraction, reflected in exacerbated activity in *HotEmo* regions and reduced activity in *ColdEx* regions, which affect both the basic response to and coping with distracting emotions. Given that previous investigations have revealed sex differences in the processing of emotional information (reviewed in Wager and Smith, 2003; Hamann and Canli, 2004; Stevens and Hamann, 2012), it was important to establish whether similar or different patterns of response would also be observed in women and men, in the context of delayed WM tasks with emotional distraction. A follow-up study using the same female subjects and methodology as in the Denkova et al. (2010) study, and adding a male sample, addressed these issues. The study by Iordan et al. (2013a) identified dissociable patterns of activity in the *HotEmo* and *ColdEx* networks in women and men, in the context of similar overall patterns of response to emotional distraction in the two sexes. Regarding commonly engaged areas, results showed that men and women display similar patterns of activation and deactivation in a host of brain regions associated with the ventral *HotEmo* (e.g., AMY, vmPFC, and FG) and dorsal *ColdEx* (e.g., dlPFC) neural systems, consistent with the idea of a generalizable pattern of response to emotional distraction across sexes. However, the study also identified differences in brain activity linked to differential impacts of and coping with emotional distraction in women and men. These results are featured in the next section.

SEX DIFFERENCES IN THE RESPONSE TO EMOTIONAL DISTRACTION

Available evidence has shown that in addition to enhanced emotional competence (Kring and Gordon, 1998; Seidlitz and Diener, 1998; Barrett et al., 2000), women also show enhanced reactivity to emotional challenge (Shields, 1991; Lang et al., 1993; Hamann and Canli, 2004), specificity in the deployment of emotion regulation strategies (Thayer et al., 2003; Matud, 2004; McRae et al., 2008; Mak et al., 2009; Domes et al., 2010; Denkova et al., 2012), and increased susceptibility to affective disorders (i.e., nearly two times higher lifetime prevalence of mood and anxiety disorders than men; Kessler, 2003; Bekker and Van Mens-Verhulst, 2007). Given the possibility that the same mechanisms that help generate the enhanced emotional experience in women could also be partially responsible for enhanced sensitivity to emotional factors, in a recent investigation (Iordan et al., 2013a) we examined whether sex-related differences in basic emotional reactivity are associated with differences in emotional distractibility, and identified neural mechanisms that implement differences in emotional distractibility between women and men.

The study by Iordan et al. (2013a) identified sex differences in the basic response to emotional distraction, consistent with the idea of increased bottom-up impact of emotional distraction in women relative to men. Specifically, women showed increased sensitivity to emotional distraction in regions associated with the *HotEmo* system, such as FG, AMY, and subgenual ACC. Supporting the idea of enhanced bottom-up effects in female participants, the left FG, a perceptual area susceptible to modulation by emotion, showed a pattern of increased activity in response to angry-face distracters in women relative to men and negative correlation with WM performance in women only. These results complement the findings of our previous investigation in women (Denkova et al., 2010), in which a pattern of increased activity and negative correlation with WM performance was observed in the right FG (BA 37). Activity in the same right FG area, however, was not different and did not co-vary with WM performance in men. Given that FG is a region known to be selectively responsive to faces, the possibility that this effect might be more specific to emotional faces or to other emotional stimuli depicting human presence could not be excluded. An increased response to emotional distraction in women relative to men was also identified in the subgenual ACC (**Figure 8**), a higher-level emotion integration region, which has been linked to the experience of negative emotion, in both healthy and clinical samples (Gotlib et al., 2005; Mobbs et al., 2009; Baeken et al., 2010; Ball et al., 2012).

Interestingly, a specific pattern of sensitivity to emotional distraction was also revealed in men, who showed increased sensitivity in regions of the *ColdEx* system, including polar and dorsal PFC, and dorsal ACC, and in brain regions associated with the default mode network. However, overall WM performance was not affected by emotional distracters in the male participants, and overall they also had higher WM performance than the female subjects. Overall, these sex-related dissociations in the basic response to emotional distraction are consistent with increased sensitivity in "bottom-up" responses in women, linked to impaired WM performance, and increased sensitivity in

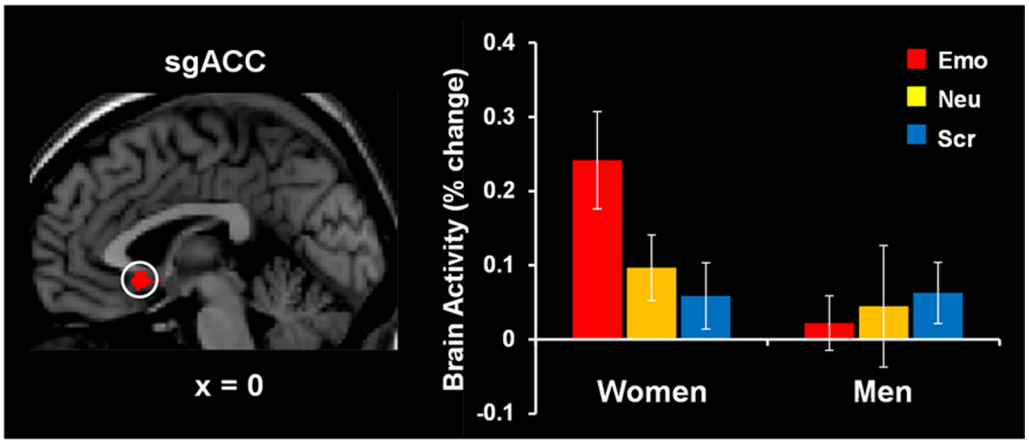

FIGURE 8 | Increased subgenual anterior cingulate cortex (sgACC) activity to emotional distraction, in women. The area indicated by the white circle (BA 25), showing a difference in activation in response to angry faces in women versus men, was masked with a map identifying a main effect of emotion relative to baseline in women. The bar graph illustrates the fMRI signal, as extracted from the region of interest corresponding to the difference in activation between women and men. The activation map is superimposed on a high-resolution brain image displayed in sagittal view (with *x* indicating the Talairach coordinate on the left-right axis of the brain). Error bars represent standard errors of means. Emo, Emotional distracters; Neu, Neutral distracters; Scr, Scrambled distracters. Reproduced from Iordan et al. (2013a), with permission.

"top–down" responses in men, linked to increased performance, in the face of emotional distraction. Noteworthy, these differences were identified in the context of overall similar response to emotional distraction in women and men, suggesting that, at a more general level, men and women also deploy similar mechanisms in response to transient emotional distraction.

The same investigation also identified sex differences linked to the engagement of mechanisms to cope with emotional distraction. Results revealed a dorsal-ventral hemispheric dissociation within the lateral PFC, with the left ventral PFC being linked to individual differences in WM performance in women, and the right dorsal PFC being linked to individual differences in men (**Figure 9**). Interestingly, the same left vlPFC region showing enhanced activation in the female participants who performed better in the WM task (Denkova et al., 2010) showed "by default" an overall increased level of activity in males, who also had higher levels of WM performance. A similar pattern was observed in the right lateral PFC in men—although as a group they showed reduced activity in this region, compared to women, those who had increased activity also coped successfully with emotional distraction. The vlPFC results also bear relevance for the generalizability of the role of this region in coping with emotional distraction. Specifically, vlPFC's involvement in coping with emotional distraction has been supported mostly by results from studies with female participants (see **Table 1** and **Figure 10**), and thus its role should be further clarified by future investigations comparing female and male participants. Overall, results of the two studies discussed above support the idea that enhanced emotional competence in women may have the side-effect of increased emotional reactivity, which in turn may lead to enhanced emotional distractibility. This phenomenon is reflected in different patterns of activity in response to emotional distraction in women relative to men, mainly consistent with an increased bottom-up effect of distracting emotions in women.

In summary, available evidence points to the role of individual differences in both the basic response to and coping with task-irrelevant emotions, suggesting that increased sensitivity to emotional distraction is associated with a pattern of activity characterized by both greater *HotEmo* activations and greater *ColdEx* reductions. Moreover, evidence also suggests that individual differences linked to general and specific aspects of cognitive/executive control and affective processing, such as trait attentional impulsiveness and anxiety, modulate the response to emotional distraction by increasing bottom-up *HotEmo* responses and diminishing top–down *ColdEx* engagement. Additionally, evidence points to sex differences in both bottom-up and top–down effects of emotional distraction, by linking increased recruitment of emotion processing areas with decreased cognitive performance in women and revealing dissociations in coping with distraction mechanisms between women and men. Finally, asymmetries between the left and right hemispheres linked to subjective vs. objective impact of emotional distraction on WM, resisting emotional distraction vs. coping and facilitation of long-term retention, and sex differences in coping with emotional distraction point to potential dissociations in their engagement in specific processes. Taking into account all these findings, it becomes clear that investigation of the role of individual differences that mediate the basic response to and the ability to cope with emotional challenge offers a promising path for better understanding of the susceptibility to affective disorders.

CONCLUSIONS, OPEN ISSUES, AND FUTURE DIRECTIONS

The present review discussed evidence regarding the neural correlates of the response to emotional distraction, as provided by fMRI studies focusing on three main topics: (1) the neural circuitry underlying the basic response linked to a detrimental impact of emotional distraction, (2) the neural mechanisms of

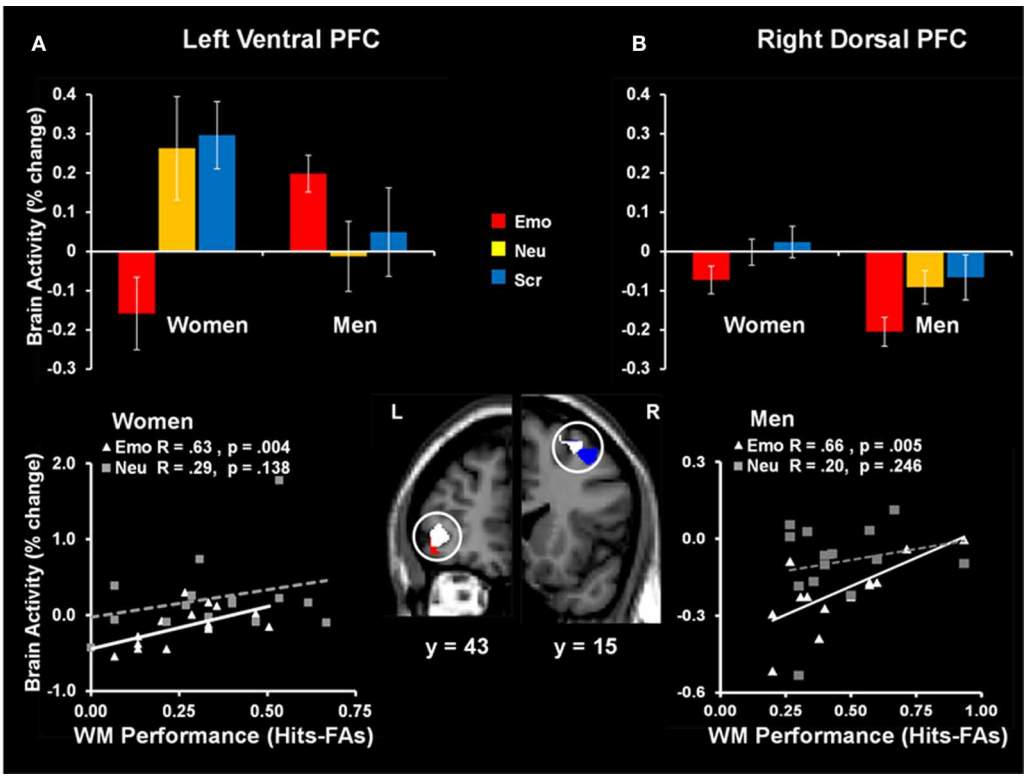

FIGURE 9 | Sex-related dorso-ventral dissociation in the lateral prefrontal cortex (PFC) in response to emotional distraction, linked to WM performance. The left ventral PFC (BA 47) had overall reduced activity in women but showed increased activity in those women who coped successfully with emotional distraction **(A)**; a similar pattern was observed in the right dorsal PFC (BA 8/6) in men—although as a group they showed reduced activity in this region, compared to women, those who had increased activity also coped successfully with emotional distraction **(B)**. The bar graphs illustrate the fMRI signal, as extracted from regions of interest (ROI) corresponding to the differences in activation between women and men. The red and blue activation maps illustrate differences in the response to emotional distraction between women and men: men > women (red cluster) and women > men (blue cluster). The white activation maps illustrate the positive correlation between brain activity in response to emotional stimuli and WM performance in women (left ventral PFC) and men (right dorsal PFC). Scatterplots depicting these co-variations are presented in the bottom panels. The activation maps are superimposed on a high-resolution brain image displayed in coronal view (with y indicating the Talairach coordinates on the anterior- posterior axis of the brain). Error bars represent standard errors of means. Emo, Emotional distracters; Neu, Neutral distracters; Scr, Scrambled distracters; L, left; R, Right. Reproduced from Iordan et al. (2013a), with permission.

coping with emotional distraction, and (3) the role of individual differences in these phenomena. Overall, the extant evidence points to specific neural signatures of the response to emotional challenge (summarized in **Table 1** and **Figure 10**), which are fundamental to understanding the mechanisms underlying emotion-cognition interactions in healthy functioning, and the changes linked to individual variation in emotional distractibility and susceptibility or resilience to affective disorders. Regarding (1), the impact of task-irrelevant emotional distraction is associated with opposing patterns of activity in two major neural systems: a ventral system associated with "*hot*" emotional processing (*HotEmo system*), comprising regions such as AMY and vlPFC, which shows *in*creased activity, and a dorsal system associated with "*cold*" executive processing (*ColdEx system*), comprising regions such as dlPFC and LPC, which shows simultaneous *de*creased activity to emotional distraction. The reviewed evidence demonstrates that this is a robust pattern of activity, which has been systematically replicated using different types of tasks and stimuli. Moreover, this evidence suggests that the detrimental impact of task-irrelevant emotional distraction on goal-oriented processing is linked to *bottom-up* mechanisms, which are able to "hijack" processing resources and divert attention from the ongoing task to processing emotional information, which in turn leads to impaired cognitive performance.

Regarding (2), *top–down* control mechanisms are engaged in order to counteract the bottom-up influence produced by emotional distraction, cope with distracting emotions, and maintain cognitive performance. This interplay is supported by converging functional and anatomical evidence identifying specific roles for the involved structures, such as the AMY, acting as an "emotion detector," and the PFC, particularly the vlPFC, acting as "top–down controller"; other regions, such as the ACC and medial PFC, are also involved. Noteworthy, recent evidence points to sex differences in the involvement of PFC in coping with emotional distraction, and further investigations are required to clarify whether the results based on female participants also generalize to males. Regarding (3), the behavioral responses linked to

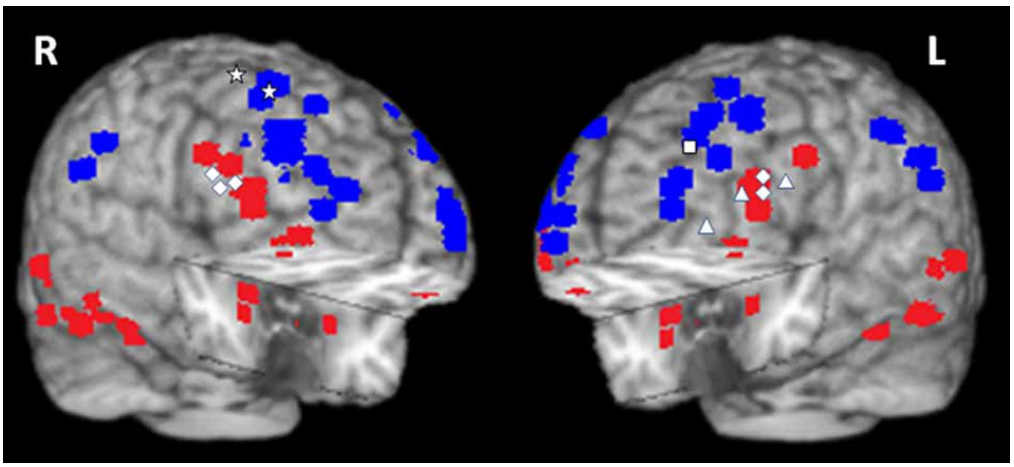

FIGURE 10 | Summary of activations in brain regions associated with the ventral *HotEmo* system (red) and the dorsal *ColdEx* system (blue). The figure shows peak activation voxels from areas showing increased (red) and decreased (blue) activity to emotional distraction, as identified by the studies featured in **Table 1**. The white geometric shapes identify peak voxels from regions associated with coping with emotional distraction, in women and men. Specifically, for the female subjects, the rhombi identify peak activation voxels from bilateral inferior frontal areas controlling for the subjective "feeling of being distracted" (Dolcos and McCarthy, 2006). The triangles identify peak activation voxels from left inferior frontal areas controlling for the objective impact of emotional distraction (Dolcos et al., 2006, 2013; Denkova et al., 2010); and the square identifies the peak activation voxel from a left dlPFC area linked to increased performance in the presence of emotional distraction (Dolcos et al., 2008). For the male subjects, the stars identify peak activation voxels in right dorsal frontal areas linked to increased performance in the presence of emotional distraction (Iordan et al., 2013a). The peak activation voxels are superimposed on a high resolution brain image displayed in a tridimensional view using MRIcro (www.mccauslandcenter.sc.edu/mricro/mricro/). R, Right; L, Left.

both the basic response to and coping with emotional distraction are influenced by individual differences, such as increased emotional sensitivity and distractibility, which are associated with greater *HotEmo* activations and greater *ColdEx* deactivations. Individual differences linked to both general and specific aspects of cognitive/executive and emotion processing, along with sex differences, also modulate activity in *HotEmo* and *ColdEx* systems. Overall, the findings regarding the role of individual differences point to a link between increased sensitivity to task-irrelevant emotional distraction and increased bottom-up effects. Finally, the reviewed evidence also points to hemispheric asymmetries seemingly linked to individual differences regarding specific processes, such as the experiencing of and coping with emotional distraction.

Despite a rapidly-growing body of literature providing clarification into the neural correlates of the response to emotional distraction, a number of issues are still unclear. Below, we briefly introduce them in relation to the topics covered in the present review.

1. An important open question refers to the role of emotional valence and arousal in the impact of emotional distraction. For instance, the majority of studies investigating the impact of task-irrelevant emotional distraction on performance in short-term/working memory tasks have used high-arousing negative distracters, and hence it is not known whether similar effects are also produced by positive distracters, or further dissociations linked to emotional arousal and valence exist. Given that positive and negative emotions have evolved to subserve different functions, it is reasonable to expect that their impact as distracters may be associated with different neural mechanisms, which may partially overlap with the mechanisms underlying the more general effect of emotional arousal. Only a limited number of studies have used stimuli with different emotional properties (i.e., arousal and valence) as task-irrelevant distracters, and the results so far have been mixed (Erk et al., 2007; Straube et al., 2008, 2011; Jasinska et al., 2012b). Preliminary findings from a recent investigation from our group (Iordan et al., 2013b) suggest that while "bottom-up" responses to emotional distraction engage mechanisms jointly sensitive to both arousal and valence (e.g., AMY), "top–down" responses are more specialized, with clearer dissociations between brain regions sensitive to arousal or valence.
2. Regarding the neural correlates of coping with emotional distraction, an important open question refers to understanding the role of different types of emotional control and their associated neural correlates. Although evidence from studies investigating the response to emotional distraction shows that the impact of task-irrelevant emotions is modulated by inhibitory mechanisms deployed in order to cope with distracting emotions (Dolcos and McCarthy, 2006; Dolcos et al., 2006), it has not been clear what type of coping with distraction strategies participants are using and whether there is a link between individual differences in coping with distraction and differences in emotion regulation strategies (Gross, 1998). Task manipulations emphasizing either the cognitive aspect of the task (consistent with an automatic engagement of coping mechanisms) or the engagement of more elaborate emotion regulation strategies (e.g., reappraisal) could potentially

disentangle the outcomes of engaging automatic and controlled inhibitory processes on both emotional experience and cognitive performance.

3. Another open question refers to the role of individual differences in the impact of emotional distraction on different cognitive processes, other than WM. Although recent evidence reconciled a long-standing debate regarding whether the processing of emotional stimuli is automatic or depends on available attentional resources (Shafer et al., 2012; also see Lavie, 2005; Pessoa, 2005; Vuilleumier, 2005), by showing that task-irrelevant emotion processing is subjective to both the emotional content of distraction and the level of attentional demand, the role of individual differences in the impact of emotional distraction on lower-level perceptual processing has been less investigated (but see Bishop et al., 2004, 2007).
4. Investigations of the role of individual differences in the response to emotional distraction may prove informative not only for understanding features of individual variation in healthy subjects, but also changes associated with clinical conditions. Recent evidence suggests that dysfunctional alterations in factors influencing emotional sensitivity and susceptibility to emotional distraction, along with changes in the associated neural correlates, could play an important role in mental disorders affecting both emotional and cognitive domains, such as post-traumatic stress disorder (PTSD; Morey et al., 2009, 2011), depression (Wang et al., 2008a,b), and schizophrenia (Anticevic et al., 2011). For example, consistent with PTSD symptoms of hypervigilance and general distractibility during goal-directed cognitive processing, a recent investigation in PTSD patients (Morey et al., 2009) has identified increased activity in ventral processing regions related to trauma-related distracters and greater disruptions in cognitive processing regions. Also, combined behavioral-genetics (e.g., Jasinska et al., 2012a) and imaging-genetics investigations (Bishop et al., 2006; Morey et al., 2011; Qin et al., 2012) have highlighted the role of genetic differences in the response to emotional challenge. One such investigation in PTSD patients (Morey et al., 2011) identified increased responses to combat-related distracters in emotional processing regions, in the short allele carriers of the serotonin transporter gene. This evidence points to specific neural signatures of the response to emotional challenge, which may be used as neurobiological markers to enhance diagnostic accuracy and treatment efficacy.
5. Regarding the larger context of the impact of emotion on cognition, although a substantial corpus of research (reviewed in Dolcos et al., 2011) provides compelling evidence that emotion can produce both enhancing and impairing effects on cognition, the link between these two effects has been scarcely investigated (but see Shafer and Dolcos, 2012; Dolcos et al., 2013). Investigation of these effects within the same subjects is critical, as these opposing effects tend to co-occur not only in normal conditions but also in clinical disorders, such as PTSD and depression, characterized by alterations in both short- and long-term responses to emotional challenge. One of the few investigations of this issue (Dolcos et al., 2013) has examined the link between the short-term/impairing and long-term/enhancing effects of emotion in healthy subjects using a combined WM–EM paradigm, and identified dissociable bottom-up and top–down mechanisms of EM enhancement, linked to differences in the initial impact of emotional distraction on WM (i.e., WM impairment vs. successful coping with distraction). Further investigations of these phenomena should also include clinical samples (Dolcos, 2013).
6. Finally, manipulations involving other types of distraction, emerging from the engagement of other systems, such as long-term memory, could complement present evidence emphasizing the impact of transient visual distracters. This could also expand our present understanding of the role of individual differences in order to include a greater repertoire of responses and establish further links with changes occurring in clinical disorders. For example, clinical research has linked increased susceptibility to recollecting negative events with both symptom severity and cognitive impairment in emotional disorders such as depression and PTSD (e.g., Davis and Nolen-Hoeksema, 2000; Rubin et al., 2008). Hence, distressing thoughts related to personal events from the past and/or learned associations involving aversive stimuli could also act as powerful distracters even in healthy individuals, but it is not clear whether they engage the same neural systems as those associated with the response to visual emotional distraction.

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Visual avoidance in phobia: particularities in neural activity, autonomic responding, and cognitive risk evaluations

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We investigated the neural mechanisms and the autonomic and cognitive responses associated with visual avoidance behavior in spider phobia. Spider phobic and control participants imagined visiting different forest locations with the possibility of encountering spiders, snakes, or birds (neutral reference category). In each experimental trial, participants saw a picture of a forest location followed by a picture of a spider, snake, or bird, and then rated their personal risk of encountering these animals in this context, as well as their fear. The greater the visual avoidance of spiders that a phobic participant demonstrated (as measured by eye tracking), the higher were her autonomic arousal and neural activity in the amygdala, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and precuneus at picture onset. Visual avoidance of spiders in phobics also went hand in hand with subsequently reduced cognitive risk of encounters. Control participants, in contrast, displayed a positive relationship between gaze duration toward spiders, on the one hand, and autonomic responding, as well as OFC, ACC, and precuneus activity, on the other hand. In addition, they showed reduced encounter risk estimates when they looked longer at the animal pictures. Our data are consistent with the idea that one reason for phobics to avoid phobic information may be grounded in heightened activity in the fear circuit, which signals potential threat. Because of the absence of alternative efficient regulation strategies, visual avoidance may then function to down-regulate cognitive risk evaluations for threatening information about the phobic stimuli. Control participants, in contrast, may be characterized by a different coping style, whereby paying visual attention to potentially threatening information may help them to actively down-regulate cognitive evaluations of risk.

Keywords: phobia, fear, cognitive risk, visual attention, vigilance-avoidance, fMRI, autonomic nervous system activity, eye tracking

INTRODUCTION

Fear is an emotion that influences what is in the focus of attention and what is ignored. According to Öhman and Mineka (2001), evolution has formed highly conserved fear circuits that ensure rapid focusing of attention on potential threat sources in order to prioritize the processing of fear- or survival-relevant situations. Research has distinguished between early, automatic, and later, more controlled mechanisms of attention deployment. The most prominent view is that phobic and anxious individuals are characterized by a so-called vigilance-avoidance pattern, implying an early enhanced automatic direction of attention toward a threat source, but subsequent diversion of attention away from the threat, when more controlled processes come into play (e.g., Mogg et al., 1997; Amir et al., 1998; Rinck and Becker, 2006).

In an exemplary study, Hermans et al. (1999) simultaneously presented images of spiders and flowers to spider fearful and non-spider fearful individuals. During the first 500 ms of stimulus presentation, spider fearful and non-spider fearful individuals did not differ in their fixation times on spiders; both looked longer at spiders than they did at flowers. However, afterward, spider fearful participants avoided looking at the spiders. Thus, this study speaks to differences in later, more controlled attention deployment between the two groups of participants, but, contrary to the conceptions of Öhman and collaborators (e.g., Öhman et al., 2001), not to differences in initial vigilance. Whether speeded automatic threat detection occurs or not may depend on task characteristics (Rinck et al., 2005).

The hypothesis of avoidance during controlled processing of fear-related stimuli in highly fearful or phobic individuals is corroborated by other studies that used free viewing time (e.g., Hamm et al., 1991; Tolin et al., 1999). However, the reasons for and consequences of such viewing behavior are still unclear. Among other things, the exact conditions under which visual avoidance sets in remain to be identified. In some situations, a phobic individual visually ignores phobic stimuli, but in other situations does not. Likewise, not every phobic individual displays a similar degree of visual avoidance in a given situation.

Better knowledge of brain responses and peripheral physiology might help to uncover important mechanisms at the basis of phobic visual avoidance and thus help to refine hypotheses about the

origin and function of such behavior [for the promise and limitations of functional magnetic resonance imaging (fMRI) in the study of psychological phenomena, see (Aue et al., 2009)]. Visual avoidance is often considered as a sign of a fear regulation deficit (i.e., individuals are unable to actively cope with the perceived threat because they feel their own resources do not match the situational demands; Helbig-Lang and Petermann, 2010). Such viewing behavior may be part of a de-escalation strategy that prevents the fear response from completely unfolding, thus being beneficial in the short run[1].

We therefore hypothesized that visual avoidance tends to arise when phobic individuals feel particularly threatened and fearful. If this really were the case, we would expect visual avoidance in phobia to vary as a positive function of initial activity in the fear circuit. This would imply, among other things, increased activity within the amygdala (for the implication of the amygdala in animal phobia, see Carlsson et al., 2004; Åhs et al., 2009) and increased autonomic arousal (Sarlo et al., 2002; Mühlberger et al., 2006; Wendt et al., 2008). Such heightened amygdala and autonomic activity could be associated with the perception of increased cognitive conflict, thus enhancing the need for regulatory actions (e.g., visual avoidance).

Alternatively, it is also conceivable that avoidance behavior is negatively associated with fear level (and concomitant amygdala and autonomic activity). In fact, phobic individuals do not need to experience fear at all if they know that a threatening situation can be successfully avoided (for a discussion on emotion avoidance strategies as opposed to emotion-driven behavior, see Barlow et al., 2004). In that case, the initiation of rapid visual avoidance could prevent fear from setting in. Therefore, phobic individuals who avoid looking at potentially threatening scenes might be more successful in preventing the fear response from unfolding than those who do not.

Other brain regions that could play an important role in visual avoidance are located in the orbitofrontal cortex (OFC). Bishop (2007), for instance, suggested that altered coupling of the amygdala-prefrontal (including medial and lateral OFC) circuitry underlies fear and anxiety. Along these lines, an influential view on the regulation of negative affect sees the prefrontal cortex as a crucial site for the down-regulation of amygdala activity (Rosenkranz et al., 2003; Quirk and Beer, 2006). Contrary to the latter view, however, more recent research suggests OFC-amygdala co-activation to be responsible for successful down-regulation of negative affect (Banks et al., 2007). Although opposing, these two views point to the importance of interactions between the amygdala and the OFC in the evolvement of negative emotions such as fear.

Consistent with this observation several findings from human brain imaging studies indicate that anxiety disorders are characterized by elevated amygdala activity, on the one hand, and abnormal activity in the ventromedial prefrontal cortex (vmPFC) and/or the ventrolateral prefrontal cortex (vlPFC), on the other (for supportive evidence in animal fear, see Rauch et al., 1995; Carlsson et al., 2004; Schienle et al., 2007; Straube et al., 2007; Åhs et al., 2009). Although there is great inconsistency regarding the direction of effects in the prefrontal cortex, deviating prefrontal changes have most often been assumed to reflect fear regulation difficulties (e.g., Hermann et al., 2009). Because visual avoidance can be seen as a specific form of regulation, it can be hypothesized that the OFC (possibly in conjunction with the amygdala) is implicated in visual avoidance as well.

In the current study, we aimed to uncover both central and autonomic mechanisms at the basis of visual avoidance in spider phobia. We also wanted to determine whether eye gaze behavior (i.e., duration of fixations on spider stimuli as recorded by eye tracking) is directly related to cognitive evaluations of risk and subjective feelings of fear. We thereby hoped to shed light on the function of visual avoidance. It is, for instance, conceivable that visual avoidance of a threat source corresponds with cognitive avoidance (according to the principle "out of sight, out of mind") and therefore leads to a reduction in risk estimation for threat encounter, as well as diminished experience of fear. However, direct evidence demonstrating such links is still missing.

While undergoing fMRI, spider phobic and non-spider phobic participants viewed pictures of spiders, snakes, and birds; estimated the risk that they would encounter these animals at different forest locations (cognitive evaluation); and rated their fear intensity (subjective feeling). During task performance, the participants' eye fixations as well as their central and autonomic nervous system responses (heart rate and skin conductance) were recorded.

In sum, we hypothesized that (1) spider phobic participants would be characterized by visual avoidance of spiders; (2) such avoidance would vary as a positive function of activity in the fear circuit (with characteristic central and autonomic activations); and (3) these increases would be accompanied by altered activity in the OFC. We further predicted that greater visual avoidance in spider phobia would be associated with lowering of the generally increased (4) cognitive evaluations of personal risk, and (5) subjective fear levels (Aue and Hoeppli, 2012). Moreover, we expected these predicted associations (points 2–5) to be qualitatively different from those observed for spiders in the control group (i.e., to be specific for spider phobia). We further investigated this idea of phobia-specific associations by including responses to snakes (that neither spider phobics nor controls feared) in statistical testing; no differences in associations between the two groups were expected for these animals.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited via advertisements placed in university buildings and on regional advertisement websites. Individuals interested in the study were interviewed by telephone and assessed with the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text revision; American Psychiatric Association, 2000) and the *International Classification of Diseases* (10th revision; World Health Organization, 1992) criteria for the presence or absence of spider phobia and comparably low fear of snakes (adapted from Mühlberger et al., 2006). Thirty-six right-handed

[1]Despite positive short-term effects, it is also evident that such avoidance behavior is likely to prevent the experience of habituation processes and, in the long run, a realistic evaluation of the situation.

individuals (all female, 18 spider phobics), aged between 19 and 44 years ($M = 25.8$, $SD = 5.79$), without history of neurological illness and use of neuroleptics, anxiolytics, or antidepressants, took part in the study. One participant in the phobic group was excluded because of problems with eye gaze acquisition, resulting in an insufficient number of valid eye-tracking data samples (<30%). An additional participant in the control group was exempted because she had not performed the task correctly.

During the telephone interview, participants rated their fear of spiders and snakes on a scale from 0 (*no fear at all*) to 100 (*maximal or extreme fear*). Spider phobic participants rated their fear of spiders higher than did control participants, $t_{(32)} = 14.76$, $p < 0.000001$ (Ms = 83.5 and 16.4). The two groups did not differ with respect to their (low) ratings for fear of snakes, $t_{(32)} = -0.27$, *ns* (Ms = 11.5 and 12.4). Fear of spiders and snakes was also assessed after the experiment by the use of the fear of spiders questionnaire (Szymanski and O'Donohue, 1995), $t_{(32)} = 8.95$, $p < 0.000001$ (Ms = 86.4 and 23.5), and the Snake Questionnaire (Klorman et al., 1974), $t_{(32)} = 0.74$, *ns* (Ms = 4.1 and 3.2). Participants in the two groups did not differ in age, $t_{(32)} = -0.42$, *ns* (Ms = 25.1 and 25.9).

STIMULI

Stimuli consisted of 30 pictures displaying spiders and 30 pictures displaying snakes (taken from the Geneva Affective PicturE Database; Dan-Glauser and Scherer, 2011). Spider and snake pictures were matched for valence, $t_{(58)} = 0.08$, *ns* (Ms = 3.1 and 3.1; SDs = 0.94 and 0.95, for spiders and snakes, respectively; scale range: 1 [*very unpleasant*]—9 [*very pleasant*]); and arousal ratings, $t_{(58)} = 0.03$, *ns* (Ms = 6.1 and 6.1; SDs = 0.88 and 0.75, for spiders and snakes, respectively; scale range: 1 [*not arousing at all*]—9 [*very arousing*]), as assessed in an earlier study (Dan-Glauser and Scherer, 2011) with an unselected group of undergraduate students. Thirty additional pictures displaying birds were collected from the Internet. Pictures of 10 neutral animals (e.g., goats and frogs) were included for use in 10 practice trials.

SETTING AND APPARATUS

MRI data were acquired from a 3T scanner (Trio TIM, Siemens, Germany) with the product 12-channel head coil. Autonomic nervous system activity was acquired continuously with the Biopac MP150 System (Goleta, CA, USA). There were different settings for the electrocardiogram and skin conductance channels (see section Autonomic Nervous System Data, for details)[2]. Autonomic signals were transferred from the experimental room to the MP150 Acquisition Unit (16 bit A/D conversion) in the control room and stored on computer hard disk. A digital channel received inputs from the presentation computer and recorded on- and offset of the presented stimuli.

Visual stimuli were presented on a back projection screen inside the scanner bore using an LCD projector (CP-SX1350, Hitachi, Tokyo, Japan). Participants' eye movements were monitored continuously at a sampling rate of 60 Hz with the EyeTrac6 Eye Tracking System (Applied Sciences Laboratories, Bedford, MA, USA). The eye camera is characterized by easily accessible focus and iris adjustments. The illuminator source is an FCR lamp (12 VDC power supply; non-coherent illumination). Eye irradiance was less than 0.5 mW/cm^3.

Behavioral responses were recorded with a response button box (HH-1 × 4-CR, Current Designs, Inc., Philadelphia, PA, USA). Experimental control was performed by E-Prime 2 Professional (Psychology Software Tools, Sharpsburg, PA, USA).

PROCEDURE

Upon the participants' arrival at the laboratory, the nature of the experiment was explained and written informed consent was obtained in accordance with the Helsinki Declaration of Human Rights (World Medical Association, 1999) and regulations of the local ethics committee. Before the start of the experiment, participants performed 10 practice trials and a standardized calibration procedure for eye movements was undertaken. During this procedure, participants looked at 9 dots appearing at different locations on the computer screen.

In the experimental task, they imagined visiting different forest locations at which two forest officials had encountered specific animals before. Specifically, in each trial, participants saw a fixation cross (500 ms), followed by a picture of a forest location (1 s), followed by a picture of an animal (spider, snake, or bird; 4 s; see **Figure 1**). At the time they saw the animal (covering ∼40% of the screen), participants simultaneously received background information about (1) the number of times the first forest official had encountered a specific animal out of the number of times he had visited the location (e.g., 2/9); and (2) the number of times the second forest official had encountered this animal out of the number of times he had visited the same location (e.g., 0/9). This background information was displayed below the pictures. Importantly, the objective probabilities (i.e., the average of the two likelihoods given as background information) were equal across the three animal categories.

From the background information, participants rated the risk that they would encounter the animal if they were themselves at that same forest location, and the fear they experienced when imagining this scenario [17-point scale ranging from 0% (*no risk of encounter at all; no fear at all*) to 100% (*absolute certainty of encounter; extreme, paralyzing fear*)]. Responses were given by pressing two buttons of a button box, which moved a slider across the scales. The time for a response was limited to 4 s for each rating.

The 90 experimental trials were presented in random order in two runs of 23 trials and two runs of 22 trials, separated by short pauses. In addition, the whole sequence was presented in a jittered manner (two jitters/random time intervals ranging between 1 and 2 s, inserted between animal/background

[2]Respiration rate and muscle activity over the cheek and brow regions (measured over the M. Zygomaticus major and the M. Corrugator supercilii, respectively) had also been assessed. Because of space limitations and because they are not of central importance for the current investigation, these variables will not be specified. For further details, see Aue et al. (2012).

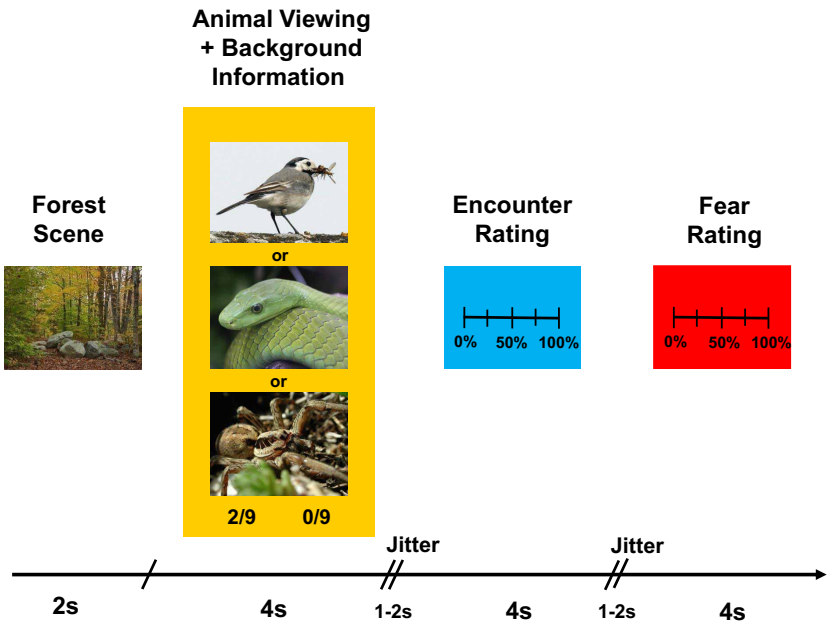

FIGURE 1 | Timeline of an experimental trial. See text for more details.

presentation and encounter risk rating, and between encounter risk rating and fear rating), making an intertrial interval of ∼15–16 s (**Figure 1**).

VARIABLES

Gaze duration

Participants' eye movements (i.e., gaze durations on different locations of the back projection screen) were acquired in the animal viewing/background presentation phase (see **Figure 1**).

Central nervous system data (fMRI)

Structural images were acquired with a T_1-weighted 3D sequence (MPRAGE, TR/TI/TE = 1900/900/2.27 ms, flip angle = 9°, PAT factor = 2, voxel dimensions: 1 mm isotropic, 256 × 256 × 192 voxels). Functional images were acquired with a T_{2^*}-weighted EPI sequence (TR/TE = 2000/30 ms, flip angle = 80°, PAT factor = 2, 64 × 64 pixels, 3.2 × 3.2 mm, 36 slices, 3.2-mm slice thickness, 20% slice gap). An automatic shimming procedure was performed to minimize inhomogeneities of the static magnetic field. At the beginning of each session, image acquisition started after the recording of three dummy volumes to avoid T_1 saturation effects.

MRI data were preprocessed and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional images were reoriented to the AC-PC line, spatially realigned to the first volume by rigid body transformation, corrected for time differences in slice acquisition using the middle slice in time as reference, spatially normalized to the standard Montreal Neurological Institute EPI template, resampled to an isotropic voxel size of 3 mm, and spatially smoothed with an isotropic 8-mm full width at half-maximum (FWHM) Gaussian kernel (Friston et al., 1995).

Autonomic nervous system data

Autonomic signals were recorded continuously with a sampling rate of 10000 Hz and pre-processed with AcqKnowledge 4.1 (Biopac, Santa Barbara, CA, USA) and PPP 7.12 (Extra Quality Measurement Systems, Frankfurt am Main, Germany).

Heart rate. Heart rate (in beats per minute) was recorded with ConMed Cleartrace (ConMed Corporation, Utica, NY, USA) pre-gelled disposable Ag/AgCl electrodes, fixed according to Einthoven II. Amplification: 500, online high-pass filter: 0.5 Hz, offline comb band stop filter: 17.5 Hz (with all harmonics out to Nyquist; to eliminate scanner noise).

Skin conductance. Electrodermal activity was measured with a constant voltage of 0.5 V, using MR-compatible ConMed Cleartrace pre-gelled disposable Ag/AgCl electrodes. The transducers were placed at the volar surfaces of the medial phalanges of the index and middle fingers of the left hand. Amplification: 5 μS/V, online filters: DC and 10 Hz, offline low-pass filter: 1 Hz.

Rating data

Participants' encounter risk and fear ratings were registered for each experimental trial.

DATA ANALYSIS

Gaze duration

Missing signals in the eye-tracking data were eliminated (10–15% of all samples, due to eye blinks and signal loss). The percentage of samples spent in the region of the screen where the picture was displayed relative to the overall number of samples acquired was calculated for each participant and trial. Participants' gaze

duration was then subjected to an analysis of variance with the factors Animal (spider, snake, bird) and Group (spider phobic, control). In order to investigate shifts in visual attention over time, we added the factor Time for gaze duration analyses (8 0.5 s intervals, corresponding to the 4 s of animal/background presentation time).

Link between gaze duration and neural responses (fMRI)

Statistical analysis was performed using the general linear model for event-related designs in SPM8. Hemodynamic response functions with 10 regressors were estimated for the whole time series: one regressor for the forest picture onset, three different regressors for the animal/background presentation onset (spider, snake, bird), three regressors for the encounter risk rating phase (same event categories as for animal/background presentation phase), and another three regressors for the fear rating phase (same event categories). Six motion-correction parameters were also added to the model. A high-pass filter of 128 s was applied to account for low-frequency noise of the scanner and first-order autoregressive corrections for autocorrelation between scans. Effects at each brain voxel were estimated using a least squares algorithm. Our analysis focused on activation patterns correlating with gaze duration to spiders (and snakes) in the two groups of participants (see below)[3].

Whole-brain analysis. We performed a parametric analysis to identify brain mechanisms associated with visual avoidance in spider phobia. Because we considered birds as a neutral reference category, mean gaze duration for birds was subtracted from mean gaze duration for spiders (snakes) in each participant. The so-calculated behavioral gaze duration contrast variable was then used as a between-subjects covariate for the prediction of the BOLD contrast "spider–bird" ("snake–bird") in a second-level group analysis. Specifically, we identified group differences in covariation effects with a second-level t-test. In order to avoid alpha inflation, we report only significant clusters containing at least 22 contiguous voxels at $p < 0.001$. This minimum cluster size was calculated by a Monte Carlo simulation with 10,000 iterations, assuming some interdependence between voxels (8-mm FWHM), resulting in a corrected whole-brain p-value of 0.01.

For the so-identified clusters, mean individual activations for spiders (snakes) and birds were extracted and the BOLD contrast "spider-bird" ("snake-bird") was calculated. Next, correlations of the BOLD contrast and the behavioral gaze duration contrast variable were calculated separately for each group and each cluster. These group Pearson product-moment correlations were then transformed into Fisher's Z-values. Finally, we performed a t-test for independent groups to determine the significance of the observed group differences. All parametric maps were rendered on sections of the average T_1-weighted template brain of the entire group (all participants).

[3]Analyses for snakes were included to test the idea that associations between gaze duration and neural activations/deactivations for spiders in spider phobics are phobia specific. In contrast to the analyses for spiders, no differences in associations between spider phobics and controls were expected for snakes.

Regions of interest (ROIs). From earlier literature (e.g., Bishop, 2007), we hypothesized altered activity in the amygdala-prefrontal (more specifically OFC) circuitry to be implicated in phobic visual avoidance. Parameter estimates for amygdala and OFC—describing the mean activity change provoked by the animal picture presentation—were extracted for each participant by applying masks according to the automated anatomical labeling approach of activations (Tzourio-Mazoyer et al., 2002). The BOLD contrast "spider–bird" ("snake–bird") was then calculated and correlated with the behavioral gaze duration contrast variable "spider–bird" ("snake–bird"), both within the phobic group and within the control group. Next, these group Pearson correlations were transformed into Fisher's Z-values. Finally, we performed a t-test for independent groups to test whether the relationship between neural activity in the ROIs and gaze duration varied as a function of experimental group (phobic vs. control).

Link between gaze duration and autonomic responses

We hypothesized phobic visual avoidance to vary as a positive function of autonomic arousal. Outliers [>3 *SD* from the mean value of a given participant in a given autonomic measure (heart rate; skin conductance)] and artifacts were eliminated ($\sim$1%). To obtain autonomic changes resulting from the presentation of the different stimuli, baseline scores (2-s interval before animal/background presentation phase) were subtracted from task scores in the animal/background presentation phase [heart rate: animal picture onset to picture offset; skin conductance: animal picture onset $+1$ s to picture offset $+1$ s (because skin conductance changes only slowly)].

Because of data recording problems, one phobic participant was excluded from all autonomic analyses. Because of changes in module calibration, two other participants (one phobic and one control) were excluded from skin conductance analyses. Finally, given the difficulty in obtaining a high-quality electrocardiogram in an MRI scanner, four phobic and three control participants were excluded from heart rate analyses.

For both measures (heart rate and skin conductance), the contrast "spider–bird" ("snake–bird") was calculated and correlated with the behavioral gaze duration contrast variable "spider–bird" ("snake–bird"), both within the phobic group and within the control group. Subsequent steps were similar to those described for fMRI analyses.

Link between gaze duration, encounter risk ratings, and fear ratings

We wanted to know whether phobic visual avoidance would impact (i.e., decrease) behavioral ratings of encounter risk for and fear of spiders and whether this relationship would be specific for spiders in spider phobics (i.e., not present in controls and not observable for snakes in the phobic group). For the phobic and the control group, we therefore separately calculated paired Pearson product-moment correlation coefficients between the behavioral gaze duration contrast variable "spider–bird" ("snake–bird"), on the one hand, and "spider–bird" ("snake–bird") difference scores for both encounter risk and fear ratings, on the other. Subsequent steps were similar to those described for fMRI analyses.

RESULTS

GAZE DURATION

Spider phobics were characterized by a visual avoidance pattern for spiders, whereas the non-fearful controls displayed a vigilance pattern (**Figure 2**), interaction Animal × Group, $F_{(2, 64)} = 5.71$, $p < 0.01$ [main effect of Group, $F_{(1, 32)} = 0.15$, *ns*; main effect of Animal, $F_{(2, 64)} = 1.75$, *ns*]. When the two groups were analyzed separately, the main effect of Animal failed to reach significance in the spider phobic group, $F_{(2, 32)} = 2.18$, *ns*, but the interaction Time × Animal was significant, $F_{(14, 224)} = 1.92$, $p < 0.05$. The avoidance pattern in phobics arose between 2 and 3 s following stimulus onset, as indicated by analyses of variance with the factor Animal conducted separately for each time interval, $Fs_{(2, 32)} = 3.44$ and 3.05, $ps < 0.05$ and 0.07, for 2–2.5 s and 2.5–3 s, respectively. *Post-hoc* Tukey tests revealed that, in both cases, gaze durations for spiders were (marginally) shorter than gaze durations for both snakes and birds (all *p*s for corresponding pairwise comparisons <0.11). At the same time, no difference in gaze duration for snakes vs. birds was observed in this group (*p*s > 0.99). For controls, the main effect of Animal turned out to be significant, $F_{(2, 32)} = 7.67$, $p < 0.005$, but not the interaction Time × Animal, $F_{(14, 224)} = 0.59$, *ns*. They consistently looked longer at spiders than at birds ($p < 0.005$; remaining pairwise comparisons: *p*s > 0.11)[4].

LINK BETWEEN GAZE DURATION AND NEURAL RESPONSES

Whole-brain analysis

The whole-brain parametric analyses based on gaze duration yielded six clusters, whose activation pattern for spiders (vs. birds) was differently related to gaze duration (difference in gaze duration for spiders vs. birds) in the two experimental groups. Two clusters were located in the anterior cingulate cortex (ACC), and others were in the precuneus/cuneus, the medial postcentral gyrus/precuneus, the caudate, and the middle temporal gyrus. In all cases, phobics demonstrated a negative association between gaze duration and activation, whereas it was the reverse for controls (see **Figure 3**; **Table 1**). A similar whole-brain analysis conducted for snakes (vs. birds) did not yield any group difference, thus showing that the above-described associations in spider phobics were specific to phobogenic stimulus material.

ROI analysis

In accordance with our hypotheses, phobics demonstrated a negative association between gaze duration for spiders (difference in gaze duration for spider vs. bird) and BOLD activation to spiders (vs. birds) in bilateral amygdala (**Figure 3**). The same association was observed in the OFC. Controls, on the other hand, did not show any significant association between gaze duration for spiders and BOLD activity in any of the investigated ROIs (**Table 2**). Again, these associations originated from phobia-specific responses to spiders in spider phobics; we did not find any group difference when contrasting associations for snakes vs. birds.

LINK BETWEEN GAZE DURATION AND AUTONOMIC RESPONSES

Shorter gaze duration for spiders in spider phobics was associated with increased autonomic arousal, and the opposite association was observed in controls (**Table 3**). Both the associations for heart rate and skin conductance show phobia specificity[5].

[4]In both spider phobics and controls, the extent of visual avoidance/vigilance was unrelated to the extent of spider fear, as indicated in the Spider Fear Screening (telephone interview) and the Fear of Spiders Questionnaire (after completion of the experimental task).

[5]Three participants (two phobic, one control) were excluded from skin conductance analyses because their difference scores (spider-bird) deviated more than 3 SD from the group mean.

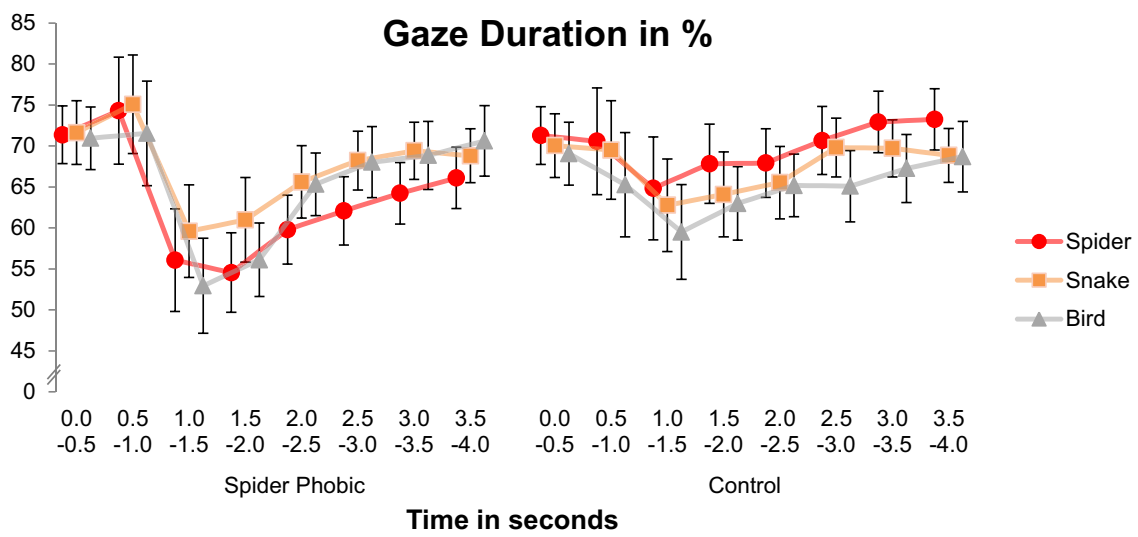

FIGURE 2 | Gaze duration on the pictures presented as a function of animal, time, and group. Error bars depict standard errors.

origin and function of such behavior [for the promise and limitations of functional magnetic resonance imaging (fMRI) in the study of psychological phenomena, see (Aue et al., 2009)]. Visual avoidance is often considered as a sign of a fear regulation deficit (i.e., individuals are unable to actively cope with the perceived threat because they feel their own resources do not match the situational demands; Helbig-Lang and Petermann, 2010). Such viewing behavior may be part of a de-escalation strategy that prevents the fear response from completely unfolding, thus being beneficial in the short run[1].

We therefore hypothesized that visual avoidance tends to arise when phobic individuals feel particularly threatened and fearful. If this really were the case, we would expect visual avoidance in phobia to vary as a positive function of initial activity in the fear circuit. This would imply, among other things, increased activity within the amygdala (for the implication of the amygdala in animal phobia, see Carlsson et al., 2004; Åhs et al., 2009) and increased autonomic arousal (Sarlo et al., 2002; Mühlberger et al., 2006; Wendt et al., 2008). Such heightened amygdala and autonomic activity could be associated with the perception of increased cognitive conflict, thus enhancing the need for regulatory actions (e.g., visual avoidance).

Alternatively, it is also conceivable that avoidance behavior is negatively associated with fear level (and concomitant amygdala and autonomic activity). In fact, phobic individuals do not need to experience fear at all if they know that a threatening situation can be successfully avoided (for a discussion on emotion avoidance strategies as opposed to emotion-driven behavior, see Barlow et al., 2004). In that case, the initiation of rapid visual avoidance could prevent fear from setting in. Therefore, phobic individuals who avoid looking at potentially threatening scenes might be more successful in preventing the fear response from unfolding than those who do not.

Other brain regions that could play an important role in visual avoidance are located in the orbitofrontal cortex (OFC). Bishop (2007), for instance, suggested that altered coupling of the amygdala-prefrontal (including medial and lateral OFC) circuitry underlies fear and anxiety. Along these lines, an influential view on the regulation of negative affect sees the prefrontal cortex as a crucial site for the down-regulation of amygdala activity (Rosenkranz et al., 2003; Quirk and Beer, 2006). Contrary to the latter view, however, more recent research suggests OFC-amygdala co-activation to be responsible for successful down-regulation of negative affect (Banks et al., 2007). Although opposing, these two views point to the importance of interactions between the amygdala and the OFC in the evolvement of negative emotions such as fear.

Consistent with this observation several findings from human brain imaging studies indicate that anxiety disorders are characterized by elevated amygdala activity, on the one hand, and abnormal activity in the ventromedial prefrontal cortex (vmPFC) and/or the ventrolateral prefrontal cortex (vlPFC), on the other (for supportive evidence in animal fear, see Rauch et al., 1995; Carlsson et al., 2004; Schienle et al., 2007; Straube et al., 2007; Åhs et al., 2009). Although there is great inconsistency regarding the direction of effects in the prefrontal cortex, deviating prefrontal changes have most often been assumed to reflect fear regulation difficulties (e.g., Hermann et al., 2009). Because visual avoidance can be seen as a specific form of regulation, it can be hypothesized that the OFC (possibly in conjunction with the amygdala) is implicated in visual avoidance as well.

In the current study, we aimed to uncover both central and autonomic mechanisms at the basis of visual avoidance in spider phobia. We also wanted to determine whether eye gaze behavior (i.e., duration of fixations on spider stimuli as recorded by eye tracking) is directly related to cognitive evaluations of risk and subjective feelings of fear. We thereby hoped to shed light on the function of visual avoidance. It is, for instance, conceivable that visual avoidance of a threat source corresponds with cognitive avoidance (according to the principle "out of sight, out of mind") and therefore leads to a reduction in risk estimation for threat encounter, as well as diminished experience of fear. However, direct evidence demonstrating such links is still missing.

While undergoing fMRI, spider phobic and non-spider phobic participants viewed pictures of spiders, snakes, and birds; estimated the risk that they would encounter these animals at different forest locations (cognitive evaluation); and rated their fear intensity (subjective feeling). During task performance, the participants' eye fixations as well as their central and autonomic nervous system responses (heart rate and skin conductance) were recorded.

In sum, we hypothesized that (1) spider phobic participants would be characterized by visual avoidance of spiders; (2) such avoidance would vary as a positive function of activity in the fear circuit (with characteristic central and autonomic activations); and (3) these increases would be accompanied by altered activity in the OFC. We further predicted that greater visual avoidance in spider phobia would be associated with lowering of the generally increased (4) cognitive evaluations of personal risk, and (5) subjective fear levels (Aue and Hoeppli, 2012). Moreover, we expected these predicted associations (points 2–5) to be qualitatively different from those observed for spiders in the control group (i.e., to be specific for spider phobia). We further investigated this idea of phobia-specific associations by including responses to snakes (that neither spider phobics nor controls feared) in statistical testing; no differences in associations between the two groups were expected for these animals.

MATERIALS AND METHODS

PARTICIPANTS

Participants were recruited via advertisements placed in university buildings and on regional advertisement websites. Individuals interested in the study were interviewed by telephone and assessed with the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text revision; American Psychiatric Association, 2000) and the *International Classification of Diseases* (10th revision; World Health Organization, 1992) criteria for the presence or absence of spider phobia and comparably low fear of snakes (adapted from Mühlberger et al., 2006). Thirty-six right-handed

[1]Despite positive short-term effects, it is also evident that such avoidance behavior is likely to prevent the experience of habituation processes and, in the long run, a realistic evaluation of the situation.

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Visual avoidance in phobia: particularities in neural activity, autonomic responding, and cognitive risk evaluations

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We investigated the neural mechanisms and the autonomic and cognitive responses associated with visual avoidance behavior in spider phobia. Spider phobic and control participants imagined visiting different forest locations with the possibility of encountering spiders, snakes, or birds (neutral reference category). In each experimental trial, participants saw a picture of a forest location followed by a picture of a spider, snake, or bird, and then rated their personal risk of encountering these animals in this context, as well as their fear. The greater the visual avoidance of spiders that a phobic participant demonstrated (as measured by eye tracking), the higher were her autonomic arousal and neural activity in the amygdala, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and precuneus at picture onset. Visual avoidance of spiders in phobics also went hand in hand with subsequently reduced cognitive risk of encounters. Control participants, in contrast, displayed a positive relationship between gaze duration toward spiders, on the one hand, and autonomic responding, as well as OFC, ACC, and precuneus activity, on the other hand. In addition, they showed reduced encounter risk estimates when they looked longer at the animal pictures. Our data are consistent with the idea that one reason for phobics to avoid phobic information may be grounded in heightened activity in the fear circuit, which signals potential threat. Because of the absence of alternative efficient regulation strategies, visual avoidance may then function to down-regulate cognitive risk evaluations for threatening information about the phobic stimuli. Control participants, in contrast, may be characterized by a different coping style, whereby paying visual attention to potentially threatening information may help them to actively down-regulate cognitive evaluations of risk.

Keywords: phobia, fear, cognitive risk, visual attention, vigilance-avoidance, fMRI, autonomic nervous system activity, eye tracking

INTRODUCTION

Fear is an emotion that influences what is in the focus of attention and what is ignored. According to Öhman and Mineka (2001), evolution has formed highly conserved fear circuits that ensure rapid focusing of attention on potential threat sources in order to prioritize the processing of fear- or survival-relevant situations. Research has distinguished between early, automatic, and later, more controlled mechanisms of attention deployment. The most prominent view is that phobic and anxious individuals are characterized by a so-called vigilance-avoidance pattern, implying an early enhanced automatic direction of attention toward a threat source, but subsequent diversion of attention away from the threat, when more controlled processes come into play (e.g., Mogg et al., 1997; Amir et al., 1998; Rinck and Becker, 2006).

In an exemplary study, Hermans et al. (1999) simultaneously presented images of spiders and flowers to spider fearful and non-spider fearful individuals. During the first 500 ms of stimulus presentation, spider fearful and non-spider fearful individuals did not differ in their fixation times on spiders; both looked longer at spiders than they did at flowers. However, afterward, spider fearful participants avoided looking at the spiders. Thus, this study speaks to differences in later, more controlled attention deployment between the two groups of participants, but, contrary to the conceptions of Öhman and collaborators (e.g., Öhman et al., 2001), not to differences in initial vigilance. Whether speeded automatic threat detection occurs or not may depend on task characteristics (Rinck et al., 2005).

The hypothesis of avoidance during controlled processing of fear-related stimuli in highly fearful or phobic individuals is corroborated by other studies that used free viewing time (e.g., Hamm et al., 1991; Tolin et al., 1999). However, the reasons for and consequences of such viewing behavior are still unclear. Among other things, the exact conditions under which visual avoidance sets in remain to be identified. In some situations, a phobic individual visually ignores phobic stimuli, but in other situations does not. Likewise, not every phobic individual displays a similar degree of visual avoidance in a given situation.

Better knowledge of brain responses and peripheral physiology might help to uncover important mechanisms at the basis of phobic visual avoidance and thus help to refine hypotheses about the

Table 4 | Correlations between gaze duration and participants' encounter risk and fear ratings.

	Gaze duration								
	Spider vs. Bird			Spider			Bird		
	r_{Phobic}	$r_{Control}$	Z	r_{Phobic}	$r_{Control}$	Z	r_{Phobic}	$r_{Control}$	Z
ENCOUNTER RISK RATING									
Spider vs. Bird	0.29	−0.08	1.00						
Spider				*0.46*	**0.74**	**3.83**			
Bird							*0.43*	**0.61**	**3.09**
FEAR RATING									
Spider vs. Bird	−0.02	0.40	1.17						
Spider				0.29	0.01	0.76			
Bird							0.03	0.03	0.00
	Snake vs. Bird			**Snake**					
	r_{Phobic}	$r_{Control}$	Z	r_{Phobic}	$r_{Control}$	Z			
ENCOUNTER RISK RATING									
Snake vs. Bird	0.24	−0.09	0.89						
Snake				*0.45*	**0.76**	**3.92**			
FEAR RATING									
Snake vs. Bird	0.15	0.11	0.11						
Snake				0.16	0.12	−0.75			

N = 17 in each group. Bold: $p < 0.05$ (two-tailed); italics: $p < 0.10$ (two-tailed). Z, Fisher's Z transformation, testing the difference between the two group correlations.

spider phobics (but increased vigilance in controls). A recent neuroimaging study related threat anticipation in humans to elevated caudate activity (Choi et al., 2012). Mogenson et al. (1980) proposed that the caudate is an important structure in the translation of motivational states into behavioral action. Support for such an interpretation comes from studies demonstrating that lesions to the caudate prevent avoidance learning or the initiation of avoidance behavior in animals (e.g., Winocur and Mills, 1969) and that activity in this area is related to the personality trait, behavioral inhibition (Helfinstein et al., 2012). What is more, the head of the caudate nucleus is intimately linked to neural pathways connecting prefrontal cortical areas that control eye movements (e.g., frontal eye fields) with subcortical oculomotor centers, such as the superior colliculus (e.g., Petit et al., 1996; Lynch and Tian, 2006; Harsay et al., 2011). Thus, the initiation of gaze avoidance in spider phobia may emanate from increased activity in the caudate and subsequent projections to oculomotor pathways.

Taken together, these observations converge to suggest that visual avoidance in phobia (and vigilance in less fearful individuals) sets in *after* the fear circuit has already been activated, and not *before*. Therefore, it is likely that visual avoidance, in our case, did not prevent the emergence of the fear response altogether. Rather, our findings may indicate that greater fear leads to stronger avoidance.

Other differences between the two groups of participants were found in a number of brain regions that have been related to (attempts at) emotion regulation in earlier research, namely, the OFC, ACC, and precuneus (e.g., Botvinick et al., 2001; Cavanna and Trimble, 2006; for activations with respect to animal phobia, see Rauch et al., 1995; Carlsson et al., 2004; Schienle et al., 2007; Straube et al., 2007; Hermann et al., 2009; for an implication of these areas in anxiety disorders, in general, see Charney, 2003). Whereas phobics displayed a negative association between activity in the ACC and precuneus, on the one hand, and gaze duration to pictures of spiders, on the other, controls displayed a positive association. In addition, the OFC was also negatively related to gaze duration for spiders in phobics but unrelated to gazing behavior in controls.

In line with their supposed importance for emotion regulation processes, the OFC, ACC, and precuneus have also been found to be implicated to various degrees in stimulus-driven orienting, attention, salience, and self-relevance (Botvinick et al., 2001; Cavanna and Trimble, 2006; Sturm et al., 2006), as well as in interoception and control of autonomic arousal (Critchley et al., 2004). In sum, our brain data therefore add support to the idea that the more fear-evoking and personally salient the phobia-related material is experienced, the more the phobic participants will feel themselves unable to actively cope with the situation and thus unable to continue looking at the spiders. This may in turn trigger regulatory actions (i.e., visual avoidance) with immediate adaptive benefits.

Interestingly, though, Hermann et al. (2009) and Schienle et al. (2007) related reduced activity in the vmPFC, including the medial OFC, to *reduced* automatic regulation capacities in spider phobia[8]. In addition, Hermann et al. (2009) found rostral ACC activity to be reduced in effortful down-regulation of fear of

[8]This inconsistency can be related to incongruent findings regarding the amygdala-OFC interplay for the regulation of emotion (Rosenkranz et al., 2003; Quirk and Beer, 2006); vs. (Banks et al., 2007).

duration was then subjected to an analysis of variance with the factors Animal (spider, snake, bird) and Group (spider phobic, control). In order to investigate shifts in visual attention over time, we added the factor Time for gaze duration analyses (8 0.5 s intervals, corresponding to the 4 s of animal/background presentation time).

Link between gaze duration and neural responses (fMRI)

Statistical analysis was performed using the general linear model for event-related designs in SPM8. Hemodynamic response functions with 10 regressors were estimated for the whole time series: one regressor for the forest picture onset, three different regressors for the animal/background presentation onset (spider, snake, bird), three regressors for the encounter risk rating phase (same event categories as for animal/background presentation phase), and another three regressors for the fear rating phase (same event categories). Six motion-correction parameters were also added to the model. A high-pass filter of 128 s was applied to account for low-frequency noise of the scanner and first-order autoregressive corrections for autocorrelation between scans. Effects at each brain voxel were estimated using a least squares algorithm. Our analysis focused on activation patterns correlating with gaze duration to spiders (and snakes) in the two groups of participants (see below)[3].

Whole-brain analysis. We performed a parametric analysis to identify brain mechanisms associated with visual avoidance in spider phobia. Because we considered birds as a neutral reference category, mean gaze duration for birds was subtracted from mean gaze duration for spiders (snakes) in each participant. The so-calculated behavioral gaze duration contrast variable was then used as a between-subjects covariate for the prediction of the BOLD contrast "spider–bird" ("snake–bird") in a second-level group analysis. Specifically, we identified group differences in covariation effects with a second-level t-test. In order to avoid alpha inflation, we report only significant clusters containing at least 22 contiguous voxels at $p < 0.001$. This minimum cluster size was calculated by a Monte Carlo simulation with 10,000 iterations, assuming some interdependence between voxels (8-mm FWHM), resulting in a corrected whole-brain p-value of 0.01.

For the so-identified clusters, mean individual activations for spiders (snakes) and birds were extracted and the BOLD contrast "spider-bird" ("snake-bird") was calculated. Next, correlations of the BOLD contrast and the behavioral gaze duration contrast variable were calculated separately for each group and each cluster. These group Pearson product-moment correlations were then transformed into Fisher's Z-values. Finally, we performed a t-test for independent groups to determine the significance of the observed group differences. All parametric maps were rendered on sections of the average T_1-weighted template brain of the entire group (all participants).

[3]Analyses for snakes were included to test the idea that associations between gaze duration and neural activations/deactivations for spiders in spider phobics are phobia specific. In contrast to the analyses for spiders, no differences in associations between spider phobics and controls were expected for snakes.

Regions of interest (ROIs). From earlier literature (e.g., Bishop, 2007), we hypothesized altered activity in the amygdala-prefrontal (more specifically OFC) circuitry to be implicated in phobic visual avoidance. Parameter estimates for amygdala and OFC—describing the mean activity change provoked by the animal picture presentation—were extracted for each participant by applying masks according to the automated anatomical labeling approach of activations (Tzourio-Mazoyer et al., 2002). The BOLD contrast "spider–bird" ("snake–bird") was then calculated and correlated with the behavioral gaze duration contrast variable "spider–bird" ("snake–bird"), both within the phobic group and within the control group. Next, these group Pearson correlations were transformed into Fisher's Z-values. Finally, we performed a t-test for independent groups to test whether the relationship between neural activity in the ROIs and gaze duration varied as a function of experimental group (phobic vs. control).

Link between gaze duration and autonomic responses

We hypothesized phobic visual avoidance to vary as a positive function of autonomic arousal. Outliers [>3 *SD* from the mean value of a given participant in a given autonomic measure (heart rate; skin conductance)] and artifacts were eliminated (∼1%). To obtain autonomic changes resulting from the presentation of the different stimuli, baseline scores (2-s interval before animal/background presentation phase) were subtracted from task scores in the animal/background presentation phase [heart rate: animal picture onset to picture offset; skin conductance: animal picture onset +1 s to picture offset +1 s (because skin conductance changes only slowly)].

Because of data recording problems, one phobic participant was excluded from all autonomic analyses. Because of changes in module calibration, two other participants (one phobic and one control) were excluded from skin conductance analyses. Finally, given the difficulty in obtaining a high-quality electrocardiogram in an MRI scanner, four phobic and three control participants were excluded from heart rate analyses.

For both measures (heart rate and skin conductance), the contrast "spider–bird" ("snake–bird") was calculated and correlated with the behavioral gaze duration contrast variable "spider–bird" ("snake–bird"), both within the phobic group and within the control group. Subsequent steps were similar to those described for fMRI analyses.

Link between gaze duration, encounter risk ratings, and fear ratings

We wanted to know whether phobic visual avoidance would impact (i.e., decrease) behavioral ratings of encounter risk for and fear of spiders and whether this relationship would be specific for spiders in spider phobics (i.e., not present in controls and not observable for snakes in the phobic group). For the phobic and the control group, we therefore separately calculated paired Pearson product-moment correlation coefficients between the behavioral gaze duration contrast variable "spider–bird" ("snake–bird"), on the one hand, and "spider–bird" ("snake–bird") difference scores for both encounter risk and fear ratings, on the other. Subsequent steps were similar to those described for fMRI analyses.

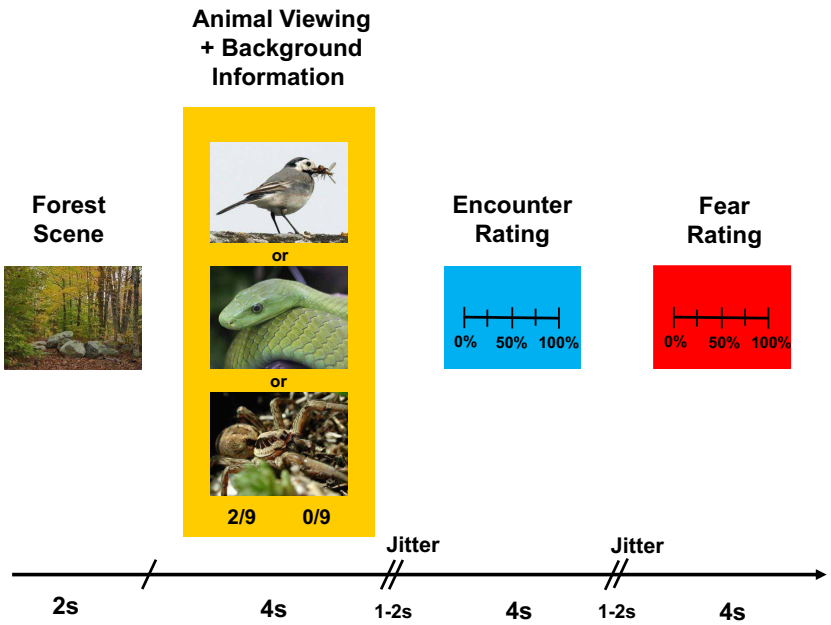

FIGURE 1 | Timeline of an experimental trial. See text for more details.

presentation and encounter risk rating, and between encounter risk rating and fear rating), making an intertrial interval of ∼15–16 s (**Figure 1**).

VARIABLES

Gaze duration

Participants' eye movements (i.e., gaze durations on different locations of the back projection screen) were acquired in the animal viewing/background presentation phase (see **Figure 1**).

Central nervous system data (fMRI)

Structural images were acquired with a T_1-weighted 3D sequence (MPRAGE, TR/TI/TE = 1900/900/2.27 ms, flip angle = 9°, PAT factor = 2, voxel dimensions: 1 mm isotropic, 256 × 256 × 192 voxels). Functional images were acquired with a T_{2^*}-weighted EPI sequence (TR/TE = 2000/30 ms, flip angle = 80°, PAT factor = 2, 64 × 64 pixels, 3.2 × 3.2 mm, 36 slices, 3.2-mm slice thickness, 20% slice gap). An automatic shimming procedure was performed to minimize inhomogeneities of the static magnetic field. At the beginning of each session, image acquisition started after the recording of three dummy volumes to avoid T_1 saturation effects.

MRI data were preprocessed and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional images were reoriented to the AC-PC line, spatially realigned to the first volume by rigid body transformation, corrected for time differences in slice acquisition using the middle slice in time as reference, spatially normalized to the standard Montreal Neurological Institute EPI template, resampled to an isotropic voxel size of 3 mm, and spatially smoothed with an isotropic 8-mm full width at half-maximum (FWHM) Gaussian kernel (Friston et al., 1995).

Autonomic nervous system data

Autonomic signals were recorded continuously with a sampling rate of 10000 Hz and pre-processed with AcqKnowledge 4.1 (Biopac, Santa Barbara, CA, USA) and PPP 7.12 (Extra Quality Measurement Systems, Frankfurt am Main, Germany).

Heart rate. Heart rate (in beats per minute) was recorded with ConMed Cleartrace (ConMed Corporation, Utica, NY, USA) pre-gelled disposable Ag/AgCl electrodes, fixed according to Einthoven II. Amplification: 500, online high-pass filter: 0.5 Hz, offline comb band stop filter: 17.5 Hz (with all harmonics out to Nyquist; to eliminate scanner noise).

Skin conductance. Electrodermal activity was measured with a constant voltage of 0.5 V, using MR-compatible ConMed Cleartrace pre-gelled disposable Ag/AgCl electrodes. The transducers were placed at the volar surfaces of the medial phalanges of the index and middle fingers of the left hand. Amplification: 5 μS/V, online filters: DC and 10 Hz, offline low-pass filter: 1 Hz.

Rating data

Participants' encounter risk and fear ratings were registered for each experimental trial.

DATA ANALYSIS

Gaze duration

Missing signals in the eye-tracking data were eliminated (10–15% of all samples, due to eye blinks and signal loss). The percentage of samples spent in the region of the screen where the picture was displayed relative to the overall number of samples acquired was calculated for each participant and trial. Participants' gaze

individuals (all female, 18 spider phobics), aged between 19 and 44 years ($M = 25.8$, $SD = 5.79$), without history of neurological illness and use of neuroleptics, anxiolytics, or antidepressants, took part in the study. One participant in the phobic group was excluded because of problems with eye gaze acquisition, resulting in an insufficient number of valid eye-tracking data samples (<30%). An additional participant in the control group was exempted because she had not performed the task correctly.

During the telephone interview, participants rated their fear of spiders and snakes on a scale from 0 (*no fear at all*) to 100 (*maximal or extreme fear*). Spider phobic participants rated their fear of spiders higher than did control participants, $t_{(32)} = 14.76$, $p < 0.000001$ (Ms = 83.5 and 16.4). The two groups did not differ with respect to their (low) ratings for fear of snakes, $t_{(32)} = -0.27$, *ns* (Ms = 11.5 and 12.4). Fear of spiders and snakes was also assessed after the experiment by the use of the fear of spiders questionnaire (Szymanski and O'Donohue, 1995), $t_{(32)} = 8.95$, $p < 0.000001$ (Ms = 86.4 and 23.5), and the Snake Questionnaire (Klorman et al., 1974), $t_{(32)} = 0.74$, *ns* (Ms = 4.1 and 3.2). Participants in the two groups did not differ in age, $t_{(32)} = -0.42$, *ns* (Ms = 25.1 and 25.9).

STIMULI

Stimuli consisted of 30 pictures displaying spiders and 30 pictures displaying snakes (taken from the Geneva Affective PicturE Database; Dan-Glauser and Scherer, 2011). Spider and snake pictures were matched for valence, $t_{(58)} = 0.08$, *ns* (Ms = 3.1 and 3.1; SDs = 0.94 and 0.95, for spiders and snakes, respectively; scale range: 1 [*very unpleasant*]—9 [*very pleasant*]); and arousal ratings, $t_{(58)} = 0.03$, *ns* (Ms = 6.1 and 6.1; SDs = 0.88 and 0.75, for spiders and snakes, respectively; scale range: 1 [*not arousing at all*]—9 [*very arousing*]), as assessed in an earlier study (Dan-Glauser and Scherer, 2011) with an unselected group of undergraduate students. Thirty additional pictures displaying birds were collected from the Internet. Pictures of 10 neutral animals (e.g., goats and frogs) were included for use in 10 practice trials.

SETTING AND APPARATUS

MRI data were acquired from a 3T scanner (Trio TIM, Siemens, Germany) with the product 12-channel head coil. Autonomic nervous system activity was acquired continuously with the Biopac MP150 System (Goleta, CA, USA). There were different settings for the electrocardiogram and skin conductance channels (see section Autonomic Nervous System Data, for details)[2]. Autonomic signals were transferred from the experimental room to the MP150 Acquisition Unit (16 bit A/D conversion) in the control room and stored on computer hard disk. A digital channel received inputs from the presentation computer and recorded on- and offset of the presented stimuli.

Visual stimuli were presented on a back projection screen inside the scanner bore using an LCD projector (CP-SX1350, Hitachi, Tokyo, Japan). Participants' eye movements were monitored continuously at a sampling rate of 60 Hz with the EyeTrac6 Eye Tracking System (Applied Sciences Laboratories, Bedford, MA, USA). The eye camera is characterized by easily accessible focus and iris adjustments. The illuminator source is an FCR lamp (12 VDC power supply; non-coherent illumination). Eye irradiance was less than 0.5 mW/cm^3.

Behavioral responses were recorded with a response button box (HH-1 × 4-CR, Current Designs, Inc., Philadelphia, PA, USA). Experimental control was performed by E-Prime 2 Professional (Psychology Software Tools, Sharpsburg, PA, USA).

PROCEDURE

Upon the participants' arrival at the laboratory, the nature of the experiment was explained and written informed consent was obtained in accordance with the Helsinki Declaration of Human Rights (World Medical Association, 1999) and regulations of the local ethics committee. Before the start of the experiment, participants performed 10 practice trials and a standardized calibration procedure for eye movements was undertaken. During this procedure, participants looked at 9 dots appearing at different locations on the computer screen.

In the experimental task, they imagined visiting different forest locations at which two forest officials had encountered specific animals before. Specifically, in each trial, participants saw a fixation cross (500 ms), followed by a picture of a forest location (1 s), followed by a picture of an animal (spider, snake, or bird; 4 s; see **Figure 1**). At the time they saw the animal (covering ∼40% of the screen), participants simultaneously received background information about (1) the number of times the first forest official had encountered a specific animal out of the number of times he had visited the location (e.g., 2/9); and (2) the number of times the second forest official had encountered this animal out of the number of times he had visited the same location (e.g., 0/9). This background information was displayed below the pictures. Importantly, the objective probabilities (i.e., the average of the two likelihoods given as background information) were equal across the three animal categories.

From the background information, participants rated the risk that they would encounter the animal if they were themselves at that same forest location, and the fear they experienced when imagining this scenario [17-point scale ranging from 0% (*no risk of encounter at all; no fear at all*) to 100% (*absolute certainty of encounter; extreme, paralyzing fear*)]. Responses were given by pressing two buttons of a button box, which moved a slider across the scales. The time for a response was limited to 4 s for each rating.

The 90 experimental trials were presented in random order in two runs of 23 trials and two runs of 22 trials, separated by short pauses. In addition, the whole sequence was presented in a jittered manner (two jitters/random time intervals ranging between 1 and 2 s, inserted between animal/background

[2]Respiration rate and muscle activity over the cheek and brow regions (measured over the M. Zygomaticus major and the M. Corrugator supercilii, respectively) had also been assessed. Because of space limitations and because they are not of central importance for the current investigation, these variables will not be specified. For further details, see Aue et al. (2012).

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Prefrontal inhibition of threat processing reduces working memory interference

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Bottom-up processes can interrupt ongoing cognitive processing in order to adaptively respond to emotional stimuli of high potential significance, such as those that threaten wellbeing. However it is vital that this interference can be modulated in certain contexts to focus on current tasks. Deficits in the ability to maintain the appropriate balance between cognitive and emotional demands can severely impact on day-to-day activities. This fMRI study examined this interaction between threat processing and cognition; 18 adult participants performed a visuospatial working memory (WM) task with two load conditions, in the presence and absence of anxiety induction by threat of electric shock. Threat of shock interfered with performance in the low cognitive load condition; however interference was eradicated under high load, consistent with engagement of emotion regulation mechanisms. Under low load the amygdala showed significant activation to threat of shock that was modulated by high cognitive load. A directed top-down control contrast identified two regions associated with top-down control; ventrolateral PFC and dorsal ACC. Dynamic causal modeling provided further evidence that under high cognitive load, top-down inhibition is exerted on the amygdala and its outputs to prefrontal regions. Additionally, we hypothesized that individual differences in a separate, non-emotional top-down control task would predict the recruitment of dorsal ACC and ventrolateral PFC during top-down control of threat. Consistent with this, performance on a separate dichotic listening task predicted dorsal ACC and ventrolateral PFC activation during high WM load under threat of shock, though activation in these regions did not directly correlate with WM performance. Together, the findings suggest that under high cognitive load and threat, top-down control is exerted by dACC and vlPFC to inhibit threat processing, thus enabling WM performance without threat-related interference.

Keywords: emotion, emotion regulation, top-down control, prefrontal cortex (PFC), amygdala, anterior cingulate cortex, anxiety, DCM

PREFRONTAL INHIBITION OF THREAT PROCESSING REDUCES WORKING MEMORY INTERFERENCE

In daily life we regulate our emotions continuously and automatically in order to remain focused on current thoughts and actions. There must be a balance between the ability to detect and attend to potentially significant, sometimes threatening emotional stimuli, and the ability to focus on current goals without unnecessary interruptions. In typical situations this balance is likely to be maintained automatically with little need for individuals to employ deliberate emotion regulation strategies (Mauss et al., 2007). However, anxiety is associated with reduced top-down control over threat related distractors (Bishop et al., 2004) and deficits in maintaining this balance are apparent in cases of highly anxious individuals where intrusive threat-related perceptions and thoughts severely impact day-to-day activities (Etkin et al., 2010). Interference by emotions and emotional stimuli may be overcome by top-down control mechanisms that either facilitate and protect task-related processing, inhibit the interfering emotional effects or a combination of the two. It is not clear whether overcoming emotional interference occurs with a concomitant regulation of subjective emotion, with the majority of studies using emotional stimuli as opposed to induced emotions *per se*. Here, we examined the interplay between bottom-up threat detection systems and top-down control mechanisms using a spatial WM task performed under threat of electric shock. We also investigated whether individual differences in a completely independent non-emotional attentional control task predict the recruitment of top-down control mechanisms in an emotional control task.

The neural basis of emotion regulation has been primarily studied by explicitly instructing participants to reappraise emotional stimuli (Ochsner et al., 2002; Schaefer et al., 2002; Ochsner and Gross, 2008), implicating a brain network including lateral and ventral prefrontal and cingulate regions. Fewer studies have used tasks in which regulating emotion is required but not explicitly instructed. An example is cognitive tasks performed in the context of emotional distractors or some form of emotion induction, for example anxiety (Dolcos and McCarthy, 2006; Shackman et al., 2006), which can impair task performance (Dolcos and McCarthy, 2006; Shackman et al., 2006; Blair et al., 2007; Oei et al., 2012), particularly for anxious individuals (Fales et al., 2008; Cisler and Koster, 2010). There is some evidence that

this interference is reduced when the cognitive load of the task increases (Erthal et al., 2005; Van Dillen and Koole, 2009; Vytal et al., 2012), possibly through the automatic engagement of lateral prefrontal top-down control mechanisms that inhibit subcortical regions involved in emotional responding such as the amygdala (Blair et al., 2007; Van Dillen et al., 2009). However, results are not consistent with other studies reporting greater interference with increasing load (Eysenck et al., 2007).

Lavie's load model (Lavie et al., 2004) attempts to reconcile similar incongruences that exist in the non-emotional cognition and attention domain. Under this framework a distinction between perceptual and cognitive load determines whether distracting stimuli produce interference; under increasing perceptual load fewer resources are available to process the distracting stimuli and so interference is reduced whilst with increasing cognitive load there are fewer cognitive resources available to exert top-down control and so interference increases. It is not clear how such a system may operate for emotional distractors. A straightforward translation of Lavie's model would posit that tasks involving high perceptual load might deplete perceptual resources to such an extent that potentially significant emotional stimuli escape processing, and therefore such tasks do not show effects of interference from emotional stimuli, whereas tasks with high cognitive load will. Indeed, the perceptual load model can account for some results, for example the diminished emotional interference in Erthal et al. (2005) where increased load is perceptual (comparing the orientation of peripherally presented bars) as are the emotional stimuli (negative images). A direct translation of Lavie's model cannot account, however, for a number of studies where emotional interference is diminished by high cognitive load (e.g., Van Dillen and Koole, 2009; Vytal et al., 2012). In addition, emotional stimuli gain preferential processing compared to non-emotional stimuli (Dolan and Vuilleumier, 2003; Alpers and Gerdes, 2007; Stout et al., 2013), and automatic processing of threatening stimuli can lead to increased emotional responding outside of awareness (Whalen et al., 1998; Vuilleumier et al., 2002; Dolan and Vuilleumier, 2003). Therefore, it is unclear whether high perceptual load could reduce perceptual resources to such an extent that emotional stimuli, particularly threatening stimuli, are no longer processed. On the other hand, a model that includes active top-down control allows for the processing and subsequent control of emotional, potentially threatening stimuli.

Many studies suggest top-down control of emotion shares common mechanisms with top-down mechanisms for (non-emotional) attentional control and response inhibition (e.g., Pessoa et al., 2003; Ridderinkhof et al., 2004b; Stevens et al., 2007; Etkin et al., 2011; Shackman et al., 2011). Two specific brain regions, the ventrolateral prefrontal cortex (vlPFC) and dorsal anterior cingulate cortex (dACC) implicated in emotion regulation (Blair et al., 2007; Ochsner and Gross, 2008; Van Dillen et al., 2009) overlap with regions commonly identified in studies of cognitive control (e.g., Herath et al., 2001; Dux et al., 2006). Dorsal ACC is implicated in performance monitoring and detecting when control is necessary (MacDonald et al., 2000; Ridderinkhof et al., 2004a) possibly by conflict monitoring (Botvinick et al., 2001, 2004; Kerns et al., 2004; Kerns, 2006; Botvinick, 2007; Kim et al., 2011) or by comparing actual and predicted outcomes (Alexander and Brown, 2011), whilst lateral PFC regions including vlPFC are posited to be involved in implementing the appropriate attentional or behavioral adjustments (Ridderinkhof et al., 2004a; King et al., 2010). In one study of healthy adolescents using versions of a counting Stroop task, emotion control activated vlPFC, cognitive control activated dlPFC and both conditions activated an area in between, Brodmann Area (BA) 45 (inferior frontal gyrus), with higher activation in faster responders (Mincic, 2010). The authors suggested BA 45 serves as a common mechanism for top-down attentional control in cognitive and emotional contexts. Ochsner et al. (2008) used different versions of the Erkisen flanker task to examine response and affective conflict, observing common dACC and dlPFC activity but rostral medial PFC and left vlPFC were differentially activated by affective versus cognitive conflict. Similarly Krug and Carter (2010) used emotional and non-emotional versions of a facial Stroop task showing commonalities in dlPFC and dACC activity in both tasks.

One aspect of previous studies of top-down control of emotion that might explain discrepant findings is the nature of the emotional stimuli. Most previous research on top-down control of emotion has used emotional stimuli designed to distract from the cognitive task due to the salience of the stimulus, rather than due to any actual induced emotion. In this study we were interested in the mechanisms of emotional control that allow an individual to overcome the detrimental effects of an *experienced* emotion—induced anxiety—in order to perform a completely unrelated cognitive task.

We conducted an fMRI study of an emotional control task where anticipatory anxiety was induced by threat of shock whilst participants performed a visuospatial WM task under two load conditions (based on Shackman et al., 2006). We hypothesized that high WM load would reduce interference from threatening stimuli via an active top-down control mechanism, and that this effect would correspond to increased lateral PFC and dACC activation and decreased amygdala activation. We also aimed to test two possible active mechanisms by which interference from irrelevant stimuli can be overcome; facilitating task-related processing and inhibiting threat processing. Dynamic causal modeling was employed to compare the evidence for cognitive facilitation versus threat inhibition. We further predicted that an index of non-emotional top-down control taken from participant's performance on a dichotic listening task would predict activation in the same brain regions as emotional top-down control, pointing to a possible overlap in the neural circuitry underlying general adaptive top-down control.

MATERIALS AND METHODS

PARTICIPANTS

Nineteen volunteers (13 female) took part in the study. One participant was excluded from all analyses due to performing at chance on the emotional control task leaving 18 participants (13 Female) aged between 21 and 40 (mean = 25, $S.D = 5$) with normal or corrected to normal vision and hearing. All participants were right-handed and did not report any history of neurological or psychiatric problems. Participants were scanned at the University of Reading Centre for Integrative Neuroscience and

Neurodynamics (CINN). Participants gave fully informed consent and the research was approved by the University of Reading Research Ethics Committee. All participants received images of their brain as compensation for their time.

PROCEDURE

There were two components to this study. The task used to directly assess spontaneous top-down regulation of emotion was a visuospatial WM task with threat of shock to induce anxiety. A directed dichotic listening task was used as an index of non-emotional top-down attentional control.

VISUOSPATIAL WM TASK

This n-back WM task was based on the study by Shackman et al. (2006) and consisted of a 2 (WM Load: Low Load/High Load) by 2 (Threat: Safe/Threat) within-subjects factorial design, with trials presented in blocks corresponding to the 4 experimental conditions (Low Load/Safe, Low Load/Threat, High Load/Safe and High Load/Threat. The structure of the task is shown in **Figure 1**. Each trial presentation consisted of a box containing one of six letters in one of eight locations; the remaining area of the display was occupied by a random array of letters. The box was presented for 350 ms, followed by an inter-trial interval (1500 ms) where the box disappeared but the background array of letters remained, following which the box reappeared. On 2-back trials participants judged whether the box displayed on the current trial occurred in the same spatial location two trials previously (and responded accordingly with a button press), whilst on 3-back trials they indicated whether the box appeared in the same location three trials previously. As in Shackman et al. (2006), the boxes appeared in overlapping, asymmetric, non-cardinal locations to encourage the use of visuospatial WM as opposed to verbal strategies. The task was presented using E-Prime 2 software (Psychological Software Tools Inc.) and a Nordic Neuro Labs goggle visual display system displaying the stimuli at 60 Hz on an 800 × 600 pixel screen, with a field of view of 30 × 23°. The goggles included a built in infrared camera for recording relative pupil dilation (recorded using 60 Hz sample rate).

The possibility of receiving an unpleasant electrical shock to the index finger of the non-dominant hand was used to induce anxiety. Blocks were either Safe or Threat as indicated before the block began and throughout by the background color (counterbalanced across participants). In Safe blocks, participants were told that there was no possibility of shock whilst in Threat blocks

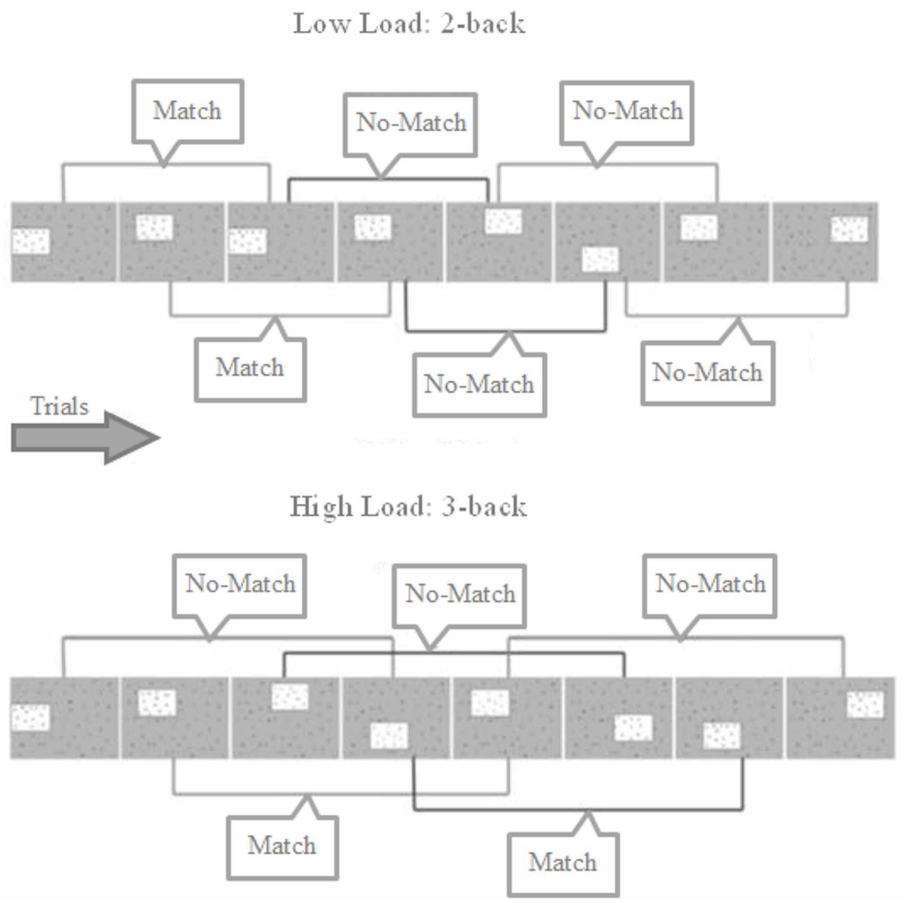

FIGURE 1 | Trial structure for 2- and 3-back blocks showing match and no-match trials. Participants must indicate whether the box is located in the same position as 2 or 3 trials previously. Each box was presented for 350 ms, separated by 1500 ms where only the background array of random letters is shown. Participants could answer any time from the box first appearing to the next box being shown.

participants were told that they may receive one or more electric shocks. Each block began with a 4 s display indicating the type of block (2- or 3-back) with the background color representing the threat level.

During a training phase in which the visuospatial WM task was performed outside the scanner, electric shocks were delivered via an ADInstruments ML856 PowerLab 26T Isolated Stimulator using an MLADDF30 stimulating bar electrode with 30 mm spacing of 9 mm contacts. Each participant's stimulation level was set by first exposing them to an electric stimulation of 1 mA (10 pulses at 50 Hz, with a pulse duration of 200 μs) and increasing the current in steps of 0.5 mA, up to a maximum of 10 mA, until a suitable participant-specific threshold was found that was uncomfortable and unpleasant but not painful. This level was then used throughout the task for that subject (subject-specific levels ranged between 3 mA and 10 mA). Participants were told they would receive between one and 20 random shocks throughout the course of the experiment, and that the intensity of stimulation would vary. In fact, during the training WM task prior to scanning, shocks were delivered during 50% of Threat blocks. This setup allowed practice in the task, ensured that experience of the electric shock was unpleasant and that the threat of shock was capable of inducing anxiety. During the scan sham electrodes were used meaning that the scan was free from contamination by shocks, though identical instructions were given. At the end of each block, participants rated their level of anxiety in the preceding block on a sliding scale ranging from 0 (not at all anxious) to 10 (extremely anxious) moving in steps of 0.25. After the scan participants were asked whether they did in fact believe during the scan that there was a chance of receiving any electric shocks.

Each block contained 18 response trials and lasted 45 s, with 4 blocks of each of the 4 experimental conditions. As the task was repetitive in nature and required continuous concentration from the participant, the task was divided into two scan runs of eight blocks with a break period in between. The order of conditions was counterbalanced across participants.

DICHOTIC LISTENING TASK

The dichotic listening task (Hugdahl et al., 2009) was carried out prior to scanning on the same day as the visuospatial WM task. This involved the auditory presentation of stimuli simultaneously to the right and left ears. The stimuli consisted of six syllables comprising the stop-consonants b, d, g, p, t, and k combined with the vowel a (/ba/, /pa/, etc.). These six syllables were combined into 36 pairs (including the homonyms) with one being played to the left and the other to the right ear. Each syllable had a duration of approximately 350 ms, with an interval between presentations of 4 s. Participants repeated back the sound they heard and this was then marked down by the researcher. There were three conditions; non-forced, forced right and forced left. In the non-forced condition there was no special instruction to direct attention towards either ear, whilst in the forced right and forced left conditions participants were instructed to listen only to the right or left ear respectively and ignore any sound they heard through the other ear. Each condition composed a full run of the 36 syllable combinations. The non-forced condition was always carried out first and participants were advised not to spend too long thinking about their answer and if they believed they had heard more than one sound to indicate which sound they heard most clearly. The orders of the forced right and left conditions were counterbalanced across participants. The procedure and stimuli used have been used elsewhere (e.g., Hugdahl, 1995) and the ability to direct attention to either ear in dichotic listening tasks has been proposed as an index of top-down control (Hugdahl et al., 2009).

Participants' responses were recorded as they performed the task. These were later classified as correctly producing the syllable presented to the left ear (Correct Left), correctly producing the syllable presented to the right ear (Correct Right), or incorrect. Trials where identical sounds were presented to both ears were not scored but used to ensure typical hearing. An index of top-down control was calculated for each participant; this was taken as the sum of Correct Right in the forced right condition minus Correct Right in the non-forced condition and Correct Left in the forced left condition minus Correct Left in the non-forced condition. Higher scores represent a greater ability to direct attention to either ear compared to the control condition. The demeaned scores were used to perform a regression analysis to identify regions where activation in the emotional control task correlated with non-emotional attentional control.

MRI ACQUISITION

Two identical T2*-weighted echo planar imaging (EPI) functional scans lasting 7 min and 44 s were acquired (TR = 2 s, TE = 30 ms, flip angle = 90°, FOV = 192 × 192 mm, 3 × 3 mm voxels, slice thickness 4 mm with an interslice gap of 1 mm, 30 axial slices), separated by a short break and recalibration of the eye tracking system. Participants held an MRI-compatible response box in their dominant right hand, with the sham stimulating electrodes attached to the index finger of the left hand. Following completion of the functional scans, a high-resolution T1-weighted anatomical scan was acquired (MPRAGE, 1 × 1 mm in-plane resolution, 256 × 256 mm FOV, axial slices with 1 mm slice thickness).

MRI DATA PROCESSING

fMRI analyses were carried out in Feat version 5.98 part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Brain extraction was carried out using the FSL Brain Extraction Tool (BET; Smith, 2002). Motion correction using MCFLIRT (Jenkinson et al., 2002), Gaussian smoothing (FWHM 5 mm) and a 200 s high pass temporal filter were employed. First-level GLM analysis was carried out for each functional scan run and then the two runs of each participant were combined using a fixed effects analysis. Separate regressors were specified for each of the four experimental conditions (Low Load/Safe, Low Load/Threat, High Load/Safe, and High Load/Threat) by convolving a binary boxcar function with an ideal haemodynamic response. A regressor for the anxiety rating period was included, as were six motion parameters to model residual signal changes due to participant motion.

Two main effect contrasts were defined; the first to reveal WM Load-related activity by identifying regions more active in High Load compared to Low Load trials (High Load/Safe +

High Load/Threat − Low Load/Safe − Low Load/Threat) and the second to reveal regions more active under threat than safety (Low Load/Threat + High Load/Threat − Low Load/Safe − High Load/Safe).

In addition to these main effect analyses, directed contrasts were set to address specific questions of this study. Firstly, a contrast was defined to identify top-down control activity by looking for areas with activation greater in the condition posited to engender top-down control (High Load/Threat) compared to all others. Secondly, a contrast to identify areas more active in the Low Load/Threat condition versus all others was defined to identify regions associated with emotional responding to threat that is reduced under high cognitive load. Given the strong a priori evidence for the role of the amygdala in negative emotions including anxiety (LeDoux, 2003; Kalin et al., 2004; Etkin and Wager, 2007; Etkin et al., 2009), a region of interest analysis was carried out with a bilateral amygdala mask (threshold 25% of the Harvard-Oxford subcortical atlas (FMRIB Software Library). Furthermore, a regression analysis with each participant's index of top-down control taken from the dichotic listening task was performed to identify how individual differences in top-down control of attention in a non-emotional task may predict individual differences in engagement of particular brain regions in the emotional control task.

Contrast images were registered to a standard space template (MNI152_T1_2 mm_brain) with FLIRT (Jenkinson and Smith, 2001; Jenkinson et al., 2002) using a two stage linear registration (functional-structural-template). Higher-level mixed effect analysis using OLS consisted of regressors for the group mean, demeaned dichotic listening scores and demeaned belief in receiving a shock (coded with 1 for expressing no doubt and −1 for expressing any). Whole-brain analysis was carried out using cluster thresholding based on Random Field Theory (Worsley, 2001) to ensure a corrected $p < 0.05$.

RESULTS

BEHAVIORAL RESULTS

Anxiety induction

In order to reduce the effect of response biases (e.g., participants tending to cluster around one part of the scale) anxiety ratings were standardized using each participant's average rating and standard deviation across all conditions. A 2 × 2 within subject ANOVA with anxiety rating as the dependent variable revealed a significant main effect of threat of shock [$F_{(1, 17)} = 9.697$, $p = 0.006$] with a greater anxiety rating in Threat compared to Safe blocks. Neither WM Load [$F_{(1, 18)} = 2.208$, $p = 0.155$] nor the interaction [$F_{(1, 18)} = 0.109$, $p = 0.745$] reached significance. Whilst the absolute ratings of anxiety [scaled from 0 ('not at all anxious') to 10 ('extremely anxious')] were low (threat = 4.3, $S.D = 1.33$; safety = 3.6, $S.D = 1.48$), the significant main effect supports the conclusion that threat of shock successfully induced anxiety.

Visuospatial WM Performance

In order to make decisive inferences about the differential effects of anxiety at both WM loads it is important to demonstrate psychometric equivalence. Discriminating power (Chapman and Chapman, 2001) was calculated by multiplying reliability in Safe conditions (measured by Cronbach's alpha) by the accuracy variance. This indicates the sensitivity of a test to detect an experimental manipulation. There was no significant difference in discriminating power in Low Load compared to High Load [$t_{(17)} = -0.367$, $p = 0.718$] conditions suggesting the sensitivity to detect an effect of threat was the same at both loads.

A within-subject ANOVA revealed a main effect of WM Load [$F_{(1, 17)} = 15.865$, $p = 0.001$], with significantly better performance on 2-back (86.8%, $S.D = 10.24$) than 3-back (81.8%, $S.D = 12.21$) trials. There was no main effect of Threat [$F_{(1, 17)} = 0.422$, $p = 0.525$] but a significant WM Load × Threat interaction effect [$F_{(1, 17)} = 17.480$, $p = 0.001$]. Under the Low Load condition threat of shock significantly interfered with performance [Low Load/Safe vs. Low Load/Threat; mean difference = +3.8%, $S.D = 4.8$; $t_{(17)} = 3.370$, $p = 0.004$] whereas under increased cognitive load there was no significant interference from threat of shock, in fact there was a trend for an improvement in performance [High Load/Safe vs. High Load/Threat; mean difference = −2.5%, $S.D = 5.8$; $t_{(17)} = -1.792$, $p = 0.091$] (see **Figure 2**).

This interference effect was not the result of a speed-accuracy trade-off; reaction times were slower in Threat (733 ms, $S.D = 151.7$) than Safe conditions (703 ms, $S.D = 154.6$) [$F_{(1, 17)} = 14.254$, $p = 0.002$] with no significant interaction effect [$F_{(1, 17)} = 0.074$, $p = 0.789$]. As expected there was a main effect of WM Load [$F_{(1, 17)} = 4.825$, $p = 0.042$] with faster responses in the 2-back (706 ms, $S.D = 139$) than 3-back (730 ms, $S.D = 168$) conditions.

PUPIL DILATION

Pupil dilation has been shown to be a reliable index of cognitive effort (Beatty, 1982; Steinhauer and Hakerem, 1992) as well as reflecting emotional arousal (Bradley et al., 2008). Whilst completing the WM task in the scanner pupil width was recorded via

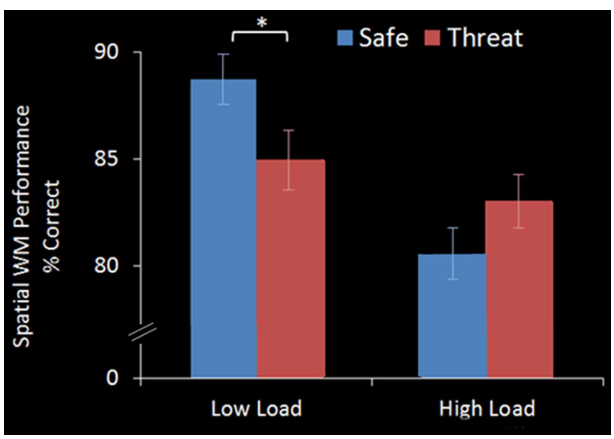

FIGURE 2 | WM accuracy in the emotional top-down control task. In the Low Load condition (2-back) threat significantly interfered with performance, whilst in the High Load condition (3-back) there was no interference from threat. Error bars display within-subject standard error (Morey, 2008). *$p < 0.05$ (two-tailed).

the in-built monocular eye tracker. Due to technical issues data could only be analysed from 13 of the 19 participants. Percentage changes from the participant's mean pupil diameter were calculated for each condition and displayed a significant main effect of WM Load [$F_{(1,\ 14.406)} = 10.448$, $p = 0.006$] and a borderline significant WM Load × Threat interaction [$F_{(1,\ 18.644)} = 4.689$, $p = 0.073$]. Greatest pupil dilation was observed in the High Load/Threat condition, which drove the interaction effect. This was significantly greater than Low Load/Threat [$F_{(1,\ 14.864)} = 12.429$, $p = 0.003$] with no significant difference between High Load/Safe and Low Load/Safe [$F_{(1,\ 16.467)} = 2.536$, $p = 0.130$]. These results suggest that the greatest cognitive effort was employed under High Load/Threat conditions. Whilst pupil dilation has also been associated with emotional arousal there was no main effect of Threat [$F_{(1,\ 11.536)} = 1.493$, $p = 0.130$] suggesting the observed effects were not due to the additive effects of cognitive effort and arousal/pain but specifically to the increased cognitive effort in the High Load/Threat condition. This result is consistent with recent findings, for example Urry et al. (2009) demonstrated that pupil diameter increased both when increasing and decreasing an emotional response compared to maintaining it, suggesting that pupil dilation is more sensitive to modulation of cognitive demand than to small changes in emotional arousal.

MAIN EFFECT IMAGING RESULTS

Main effect of WM load: high load—low load

No regions survived whole-brain cluster corrected thresholding, however at an uncorrected z-threshold of 2.3 a cluster located in the right dlPFC was found to be significantly more active in High Load compared to Low Load blocks (see **Table 1** and **Figure 3**). This region has been previously associated with visuospatial WM (e.g., Manoach et al., 2004), and also overlaps with frontal eye field regions suggested to be important in maintaining spatial location information during retention intervals in WM tasks (e.g., Postle, 2006; Ikkai and Curtis, 2011). There was also activation in left dlPFC as well as right parietal regions which have been implicated in working memory (Wager and Smith, 2003) and spatial cognition (Sack, 2009) and occipital regions involved in visual processing (Courtney and Ungerleider, 1997; Essen and Drury, 1997), again consistent with engagement in this spatial WM task.

Using a mask of regions involved in WM [constrained by inference meta-analysis map based on the term "Working Memory" generated on neurosynth.org (Yarkoni et al., 2011)]. Two separate clusters were extracted from the uncorrected data; a cluster in right dlPFC and a small cluster in the angular gyrus of the right parietal cortex. Activation in the right dlPFC cluster under the High Load versus Low Load contrast displayed a positive correlation with performance on the WM task under each condition and with WM accuracy overall ($r = 0.558$, $n = 18$, $p = 0.016$). However there was no correlation with WM performance under the same WM Load contrast ($r = 0.321$, $n = 18$, $p = 0.194$). This supports the role of this region in this task and suggests that people who are able to engage this region more under High Load than Low Load conditions perform better in general on this task. The parietal cluster was equivalent to less than five voxels in native space and so further analysis was not conducted.

Main effect of threat: threat—safe

This contrast identified areas more active under threat of shock than safety. Such a contrast is sensitive to areas involved in anxiety but would also reveal brain regions responsible for down-regulating emotion regardless of WM Load. Two significant clusters of activation were revealed in the middle frontal gyrus bilaterally, extending from a dorsal to a more ventral lateral region in the left hemisphere, as well as the medial PFC and anterior cingulate (see **Table 1** and **Figure 4**).

Top-down control contrast: high load/threat > others

This contrast identified regions more active under the condition proposed to engage top-down control (High Load/Threat) compared to all others. Consistent with our hypotheses we identified a significant cluster in the anterior cingulate and paracingulate gyrus as well as bilateral vlPFC activation (see **Table 1** and **Figure 5**). Whilst activation in these clusters under the top-down control contrast did not correlate with task performance general activation in these clusters correlated with overall task performance in both the right vlPFC and the dACC cluster ($r = 0.629$, $n = 18$, $p = 0.005$; $r = 0.615$, $n = 18$, $p = 0.006$, respectively) suggesting that participants who generally display greater recruitment of these regions whilst performing the task perform better at the task.

Emotion modulation contrast: low load/threat > others

This region of interest analysis using an amygdala mask identified significant bilateral amygdala activation in Low Load/Threat conditions compared to all others (see **Figure 6**). Activation in this cluster was significantly higher under Low Load/Threat than Low Load/Safe [mean difference = 0.17%, $S.D = 0.17$; $t_{(17)} = 4.191$, $p = 0.001$] with no significant difference between High Load/Threat and High Load/Safe [mean difference = −0.02%, $S.D = 0.25$; $t_{(17)} = 0.294$, $p = 0.772$]. Activation in this cluster under this emotion modulation contrast correlated positively with overall task performance ($r = 0.541$, $n = 18$, $p = 0.021$). This correlation remained significant after controlling for Low Load/Threat—Low Load/Safe activity in this amygdala cluster ($r = 0.518$, $n = 18$, $p = 0.033$). Thus the correlation is not driven by greater amygdala reactivity to threat under Low Load, but rather suggests that general task performance in this emotional control task was related to individual differences in the load-dependent reduction of amygdala activity. However, it should be noted that activation under this contrast did not correlate with anxiety ratings ($r = 0.130$, $n = 18$, $p = 0.606$).

DYNAMIC CAUSAL MODELLING (DCM)

Based on the proposed mechanism of top-down control of subcortical emotional regions, we employed dynamic causal modeling (DCM) (Friston et al., 2003) to probe potential connectivity in the network of regions identified in the prior analyses. All models included the right dlPFC region identified in the High Load—Low Load contrast posited to represent working memory task-related activity, left vlPFC and dACC from the top-down control contrast representing top-down control modules, and bilateral amygdala from the emotion modulation contrast. No constraints were placed on the models, permitting full bidirectional connectivity between all four nodes. Both High Load

Table 1 | Summary of imaging results for the main effect of WM Load, Threat, and the directed contrasts to investigate top-down control and emotion modulation.

Contrast		Local maxima (mm)				Cluster size (mm^3)
		Z score	*x*	*y*	*z*	
High Load > Low Load Uncorrected	r. Superior frontal gyrus	3.77	24	8	46	7056
	r. Middle frontal gyrus	3.33	30	4	50	
	r. Angular gyrus	3.55	48	−50	56	5868
	r. Lateral occipital cortex, superior division	3.18	40	−64	56	
	r. Superior parietal lobule	2.63	32	−70	56	
	l. Superior frontal gyrus	3.33	−24	10	58	2988
	r. Postcentral gyrus	2.47	53	70	64	1764
Threat > Safety	Cingulate gyrus, anterior division	5.03	0	22	26	62676
	r. Frontal pole	4.67	24	58	24	
	Superior frontal gyrus	4.12	6	48	40	
	l. Inferior frontal gyrus, pars opercularis	4.78	−50	14	18	48024
	l. Inferior frontal gyrus, pars triangularis	4.39	−50	32	2	
	l. Middle frontal gyrus	4.22	−50	20	30	
	l. Frontal pole	4.21	−28	64	16	
Top-down control contrast: WM Load/Threat > Others	l. Middle frontal gyrus	3.67	−50	18	36	20952
	l. Inferior frontal gyrus, pars opercularis	3.63	−58	14	16	
	l. Inferior frontal gyrus, pars triangularis	3.57	−48	34	14	
	r. Inferior frontal gyrus, pars triangularis	4.1	54	34	12	18144
	Frontal pole	3.67	38	95	48	
	Paracingulate gyrus	3.97	−8	30	28	16740
	Cingulate gyrus, anterior division	3.61	−10	30	24	
Emotion modulation: Low Load/Threat > Others (bilateral amygdala mask)	l. Amygdala	3.24	−22	−4	−18	2268
	r. Amygdala	3.67	24	−6	−18	1836

Displaying the coordinates and Z-score of non-redundant local maxima for each cluster. Unless otherwise stated data was thresholded at $z = 2.3$ with cluster thresholding (Worsley, 2001) to ensure a corrected $p < 0.05$.

conditions provided a driving input to the right dlPFC and both Threat conditions to the amygdalae.

We were motivated to investigate the route by which top-down control may act, hypothesizing that the modulation of the detrimental effect of induced anxiety could proceed by inhibiting some level of emotion processing, by facilitating task related activity, or some combination of the two. To test this, we used family inference, whereby families of models that differ only on specific features of interest are contrasted in order to provide evidence for or against this specific characteristic (Penny et al., 2010). In such inference, individual models in each family are modeled as random samples from the total possible model space, in much the same way as participants in an experiment are modeled as random samples from a population. Accordingly, we constructed three families with the same basic architecture described above but differing in the target of top-down control: Emotion Modulation—30 models representing inhibition of emotion processing where all possible combinations of connections between the amygdala and the two top-down nodes were modulated by either High Load/Threat conditions or dACC activation, Working Memory Modulation—30 models representing facilitation of task processing where all possible combinations of connections between the right dlPFC and the top-down control nodes were modulated, and Combined—30 models representing both emotional control and task-related control constrained such that in each model the equivalent connections between the top-down nodes and emotion and task nodes were modulated, resulting in the same number of models in each family.

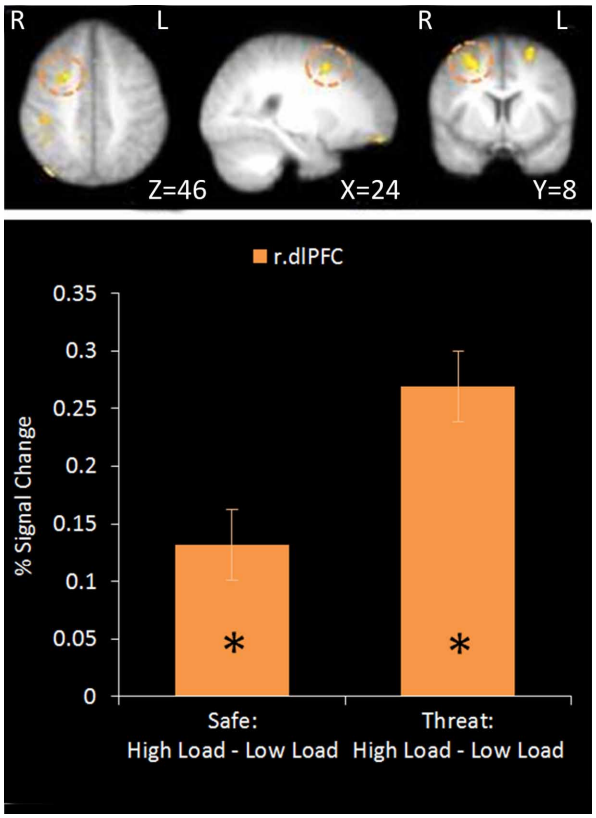

FIGURE 3 | Top: High Load—Low Load contrast imaging results. Threshold of $z = 2.3$ uncorrected. Bottom: A right dorsolateral cluster displayed greater activation under High Load compared to Low Load in both Safe and Threat trials [High Load/Safe—Low Load/Safe: mean difference = 0.121%, $S.D = 0.178$, $t_{(17)} = 2.880$, $p = 0.010$; High Load/Threat—Low Load/Threat: mean difference = 0.162%, $S.D = 0.188$, $t_{(17)} = 3.656$, $p = 0.002$]. Error bars display within-subject standard error (Morey, 2008). $^*p < 0.05$ (two-tailed).

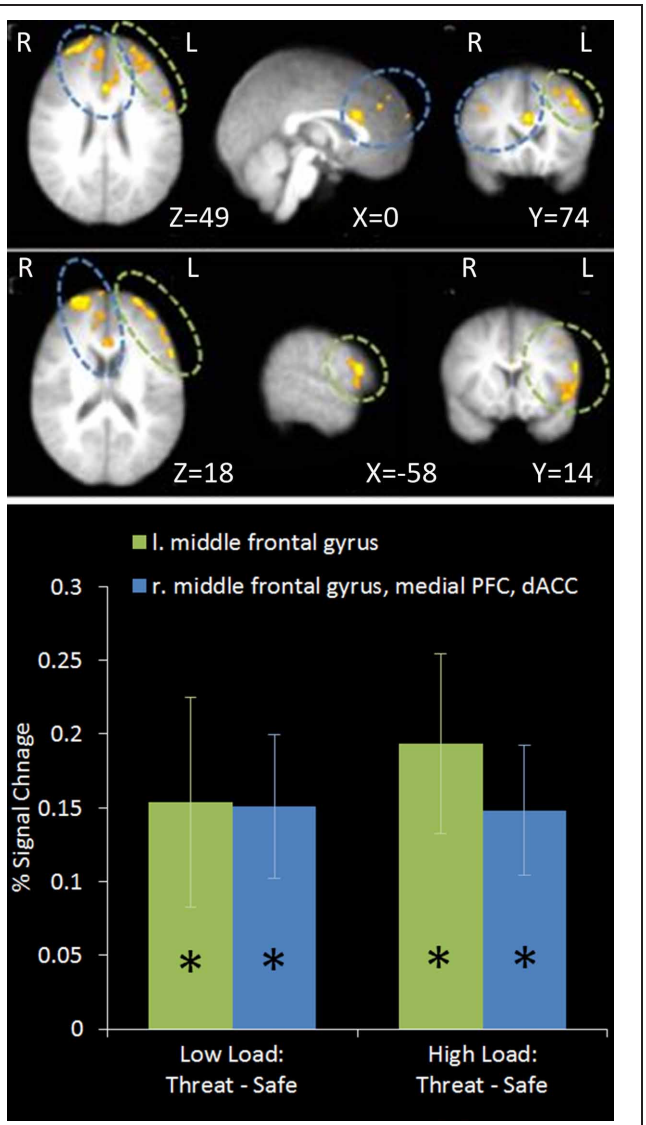

FIGURE 4 | Top: Threat—Safety contrast imaging results. Two significant clusters were identified revealing significant bilateral middle frontal gyrus, medial PFC and dACC activation under Threat compared to Safe conditions. **Bottom:** Pairwise comparisons of the signal change in the clusters identified. Activation in both clusters was significantly greater under Threat than Safety at both Low and High Load [left middle frontal gyrus: Low Load/Threat—Low Load/Safe: mean difference = 0.153%, $S.D = 0.213$, $t_{(17)} = 3.043$, $p = 0.007$; High Load/Threat—High Load/Safe: mean difference = 0.192%, $S.D = 0.183$, $t_{(17)} = 4.468$, $p < 0.001$; right middle frontal gyrus, medial PFC and dACC cluster: Low Load/Threat—Low Load/Safe: mean difference = 0.149%, $S.D = 0.146$, $t_{(17)} = 4.335$, $p < 0.001$; High Load/Threat—High Load/Safe: mean difference = 0.147%, $S.D = 0.132$, $t_{(17)} = 4.729$, $p < 0.001$]. Error bars display within-subject standard error (Morey, 2008). $^*p < 0.05$ (two-tailed).

The observed data were fit to each model, and random effect Bayesian model selection was used to estimate the posterior probabilities of each model given the data. A random effects analysis was used to permit different participants to favor different models as may be the case if individual differences determine the predominance of an inhibitory or facilitative route. Based on this the exceedance probability can be computed for each family, this represents the probability that one family is more likely than any other given the group data. **Figure 7** displays the exceedance probabilities for each family; this identified the winning family as Emotion Modulation; the exceedance probability for this family was 0.653 meaning we can be 65.3% confident that it has a greater posterior probability than any other family. The exceedance probability for the Working Memory Modulation family was 0.263 and 0.085 for Combined (though it must be noted that this family had the arbitrary constraint of only including equivalent modulations of Emotion and Working Memory connections). This result favors inhibition of emotional processing as the most probable route by which top-down control acts in this specific task.

Classical inference on the parameter estimates across participants (weighted by the evidence of each model for each participant) was conducted with a Bonferonni corrected p-threshold of 0.0018 (see **Figure 8** for model architecture and parameter estimates). This revealed a significant decrease in both the amygdalae to dACC connection [$t_{(17)} = -6.273$, $p = 0.00009$] and

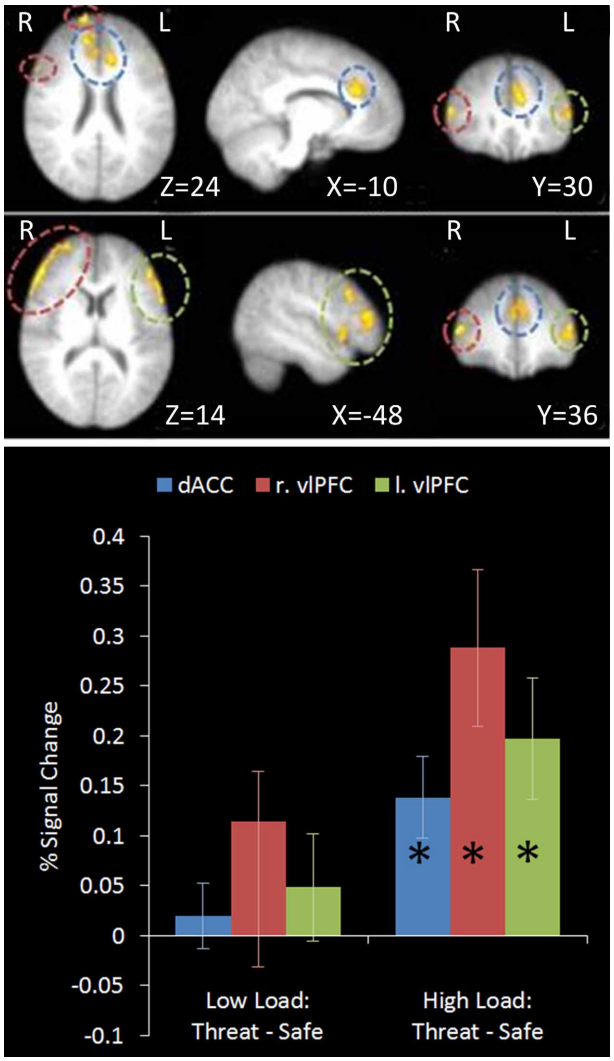

FIGURE 5 | Top: Top-down control contrast imaging results. This contrast revealed areas where activation was greater under High Load/Threat conditions compared to all others. Three clusters were identified: Dorsal ACC as well as bilateral PFC. Medial (upper panel) and lateral (lower panel) views are displayed. **Bottom:** Pairwise comparisons of the signal change in the regions identified. Activation in all three clusters was greater under threat compared to safety under the equivalent working memory loads, however this increase was only significant under High Load [cingulate: High Load/Threat—High Load/Safe: mean difference = 0.139%, $S.D = 0.122$, $t_{(17)} = 4.838$, $p < 0.001$; left vlPFC: High Load/Threat—High Load/Safe: mean difference = 0.197%, $S.D = 0.181$, $t_{(17)} = 4.614$, $p < 0.001$; right vlPFC: High Load/Threat—High Load/Safe: mean difference = 0.288%, $S.D = 0.236$, $t_{(17)} = 5.176$, $p < 0.001$]. Error bars display within-subject standard error (Morey, 2008). *$p < 0.05$ (two-tailed).

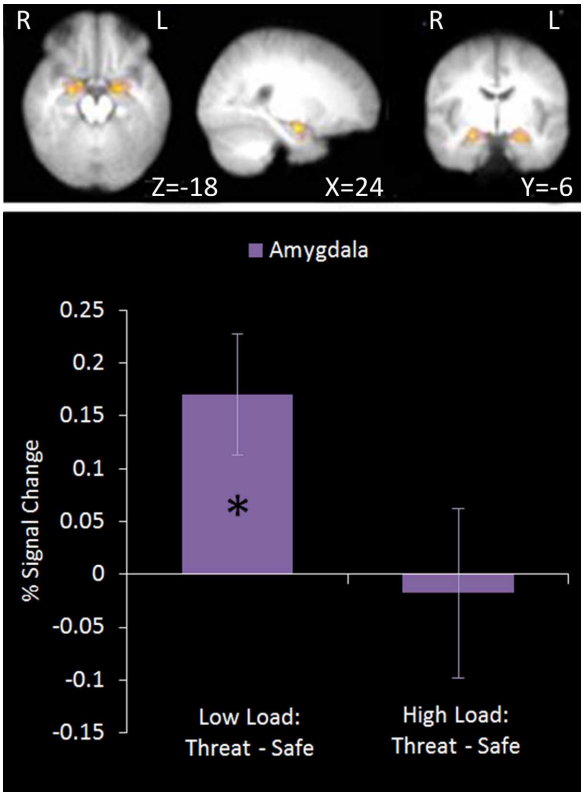

FIGURE 6 | Top: Emotion modulation contrast imaging results. This contrast revealed areas where activation was greater under Low Load/Threat conditions compared to all others. A ROI analysis was carried out using a bilateral amygdala mask (red). **Bottom:** Pairwise comparisons of the signal change. Activation in the amygdala cluster displayed a load-dependent modulation by threat with increased amygdala activation under threat compared to safety in Low Load but not High Load conditions [Low Load/Threat—Low Load/Safe: mean difference = 0.170%, $S.D = 0.172$, $t_{(17)} = 4.191$, $p = 0.001$; High Load/Threat—High Load/Safe: mean difference = 0.018%, $S.D = 0.254$, $t_{(17)} = 0.294$, $p < 0.772$]. Error bars display within-subject standard error (Morey, 2008). *$p < 0.05$ (two-tailed).

amygdalae to vlPFC connection [$t_{(17)} = -6.297$, $p < 0.00008$] under High Load/Threat conditions. The modulation of the connection from the dACC to amygdalae displayed only a trend to decrease [$t_{(17)} = -2.449$, $p = 0.025$] and the vlPFC to amygdalae connection did not display significant modulation under High Load/Threat conditions [$t_{(17)} = -0.855$, $p = 0.404$]. Additionally, the dlPFC to vlPFC connections were significantly increased by High Load/Threat [$t_{(17)} = 5.351$, $p = 0.000053$] whilst the dlPFC to dACC connection displayed a borderline significant modulation[$t_{(17)} = 3.168$, $p = 0.0056$].

Taken together these results suggest that whilst the family inference favors inhibition of emotion, there is also some evidence (in the dlPFC to vlPFC connection) for facilitation of WM-related activity. Furthermore, there is stronger evidence that this mechanism acts by suppressing the output of the amygdala in the case of inhibition of emotional processing and by boosting the output of the dlPFC in the case of facilitating task activity than by modulating the activity of these regions directly. Additionally, we found significant negative bidirectional connectivity between the amygdala and right dlPFC [amygdala to dlPFC: $t_{(17)} = -7.573$, $p = 0.000001$; dlPFC to amygdala: $t_{(17)} = -11.543$, $p < 0.000001$], consistent with interacting inhibitory emotional and cognitive networks (Dolcos and McCarthy, 2006; Dolcos et al., 2008; Dichter et al., 2010). Given that amygdala and dlPFC have few

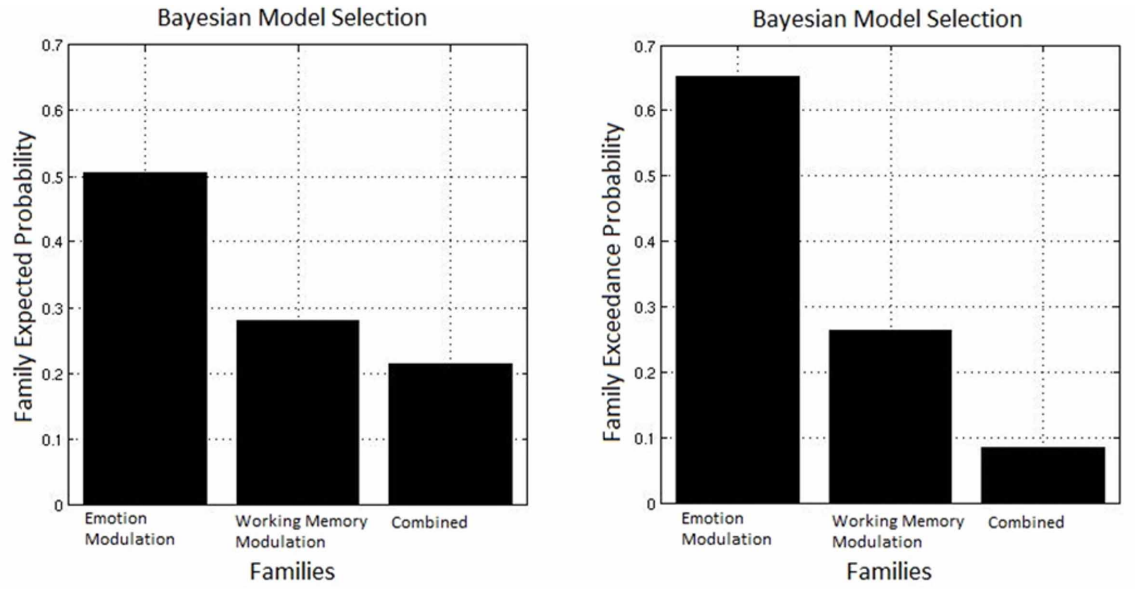

FIGURE 7 | Bayesian model selection for families. The Emotion Modulation family displayed the greatest exceedance probability, favoring models where connections between top-down nodes and the amygdala were modulated over ones with modulation of connections between top-down and task-related nodes.

if any direct structural connections (Porrino et al., 1981; Barbas and De Olmos, 1990; Ghashghaei and Barbas, 2002; Freese and Amaral, 2009), this last result suggests that a mutually inhibitory cognitive-emotional connection cannot be adequately explained by indirect pathways through the vlPFC or dACC, implying the existence of another indirect pathway.

REGRESSION ANALYSIS OF NON-EMOTIONAL TOP-DOWN CONTROL SCORES

We hypothesized that individual differences in people's performance on a non-emotional top-down control task would predict their recruitment of regions implicated in top-down control of emotion. To address this issue a regression analysis was performed using the index of non-emotional top-down control taken from the behavioral dichotic listening task as a regressor in the between subjects GLM of the emotional top-down control contrast. This would reveal brain regions for which non-emotional top-down control ability predicts activation associated with emotional top-down control.

A number of regions displayed this relationship (see **Table 2**). As hypothesized both the left vlPFC and dACC showed greater activation under this top-down control contrast in subjects who were better at the unrelated non-emotional attentional control task (left vlPFC: $r = 0.927$, $n = 18$, $p < 0.001$; cingulate: $r = 0.825$, $n = 18$, $p < 0.001$) (see **Figure 9**).

In addition to prefrontal regions implicated in top-down control widespread activation related to visual processing was discovered by this analysis, including a large cluster covering right lateral and mid occipital cortex, V1 and V2 as well as a smaller cluster in left lateral occipital cortex. This finding was not hypothesized but is consistent with individual differences in the ability to direct attention in the dichotic listening correlating with the ability to direct attention to the visual domain in this spatial WM task. Clusters were also identified bilaterally in the postcentral gyrus of the parietal cortex, relating to primary somatosensory cortex.

Activity in these regions specifically under the top-down control contrast correlated with performance on the dichotic listening task; general activity in these regions did not (with the exception of the left somatosensory cluster ($r = -0.548$, $n = 18$, $p = 0.019$). Thus the index of top-down attentional control predicts the recruitment of these regions under the conditions posited to require top-down emotional control, and not their general recruitment across all conditions. Furthermore, there was no direct correlation between the index of top-down control on the dichotic listening task and WM performance on the emotional control task ($r = 0.191$, $n = 18$, $p = 0.447$).

In the emotional control task, error rates differed across conditions and so present a potential confound for the results since dACC has been shown to be sensitive to errors (Kiehl et al., 2000; Menon et al., 2001). However activity under the top-down control contrast in both the cingulate cluster identified in the main effect analysis and in the regression analysis did not show any correlation with errors made in the WM task ($r = 0.366$, $n = 18$, $p = 0.135$; $r = 0.239$, $n = 18$, $p = 0.341$), meaning that activity observed in this contrast cannot be attributed to higher error rates.

DISCUSSION

The current study investigated how interfering effects of threat induced anxiety can be modulated in order to focus on current tasks. We demonstrated how threat-related interference can be overcome by increasing the load of a cognitive task; in this case interference of anxiety under threat of shock on a visual spatial WM task was eradicated when the WM load was increased.

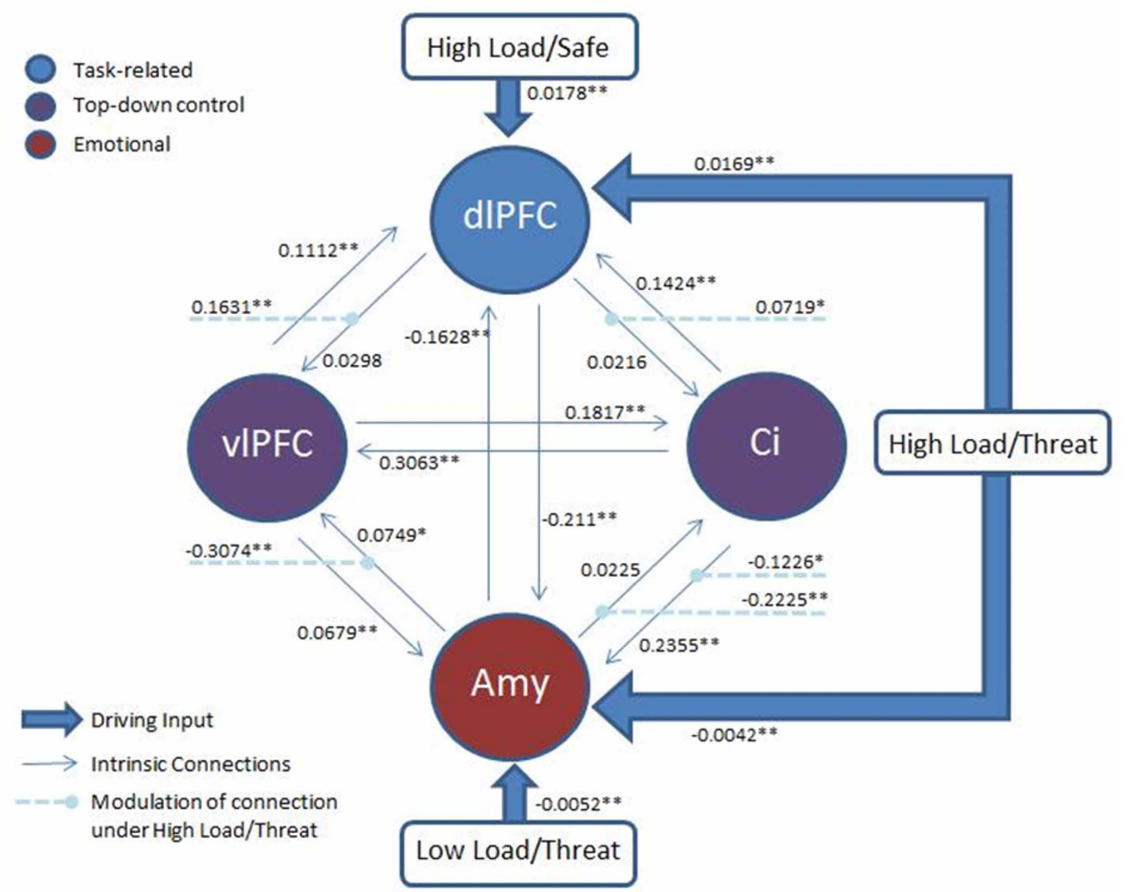

FIGURE 8 | Architecture of the model: Two top-down control nodes, left vlPFC and cingulate, from the top-down control contrast, a task-related node, right dlPFC, from the uncorrected High Load—Low Load contrast and an emotion node from the emotion modulation contrast. All threatening conditions had a driving input to the amygdala and all High Load conditions to the right dlPFC. Modulation of connections by High Load/Threat are also displayed. Full connectivity was permitted between all nodes. Average parameter estimates for each intrinsic connection, driving input and modulation are displayed. *$p < 0.05$ (two-tailed; uncorrected). **$p < 0.05$(two-tailed, Bonferonni correction applied).

Activation in dorsal ACC and ventrolateral PFC under high working memory load with threat of shock was consistent with their hypothesized roles in top-down control, suggesting they are recruited to modulate the interfering effects of emotion. Furthermore, a bilateral amygdala cluster displayed significantly greater activation under threat of shock compared to safety at low load but no effect of threat at a higher WM load, providing evidence that cognitive load can modulate threat-related amygdala activity. Dynamical Causal Modeling further suggested that this top-down control might be achieved through inhibition of ascending outputs from the amygdala to the prefrontal cortex.

The interaction between anxiety and cognition is not straightforward; anxiety is an adaptive mechanism that plays a vital role in warning of potential threats which might occur at any time, including when we are occupied with other activities. Accordingly, anxiety increases sensitivity to potential threats even when people are engaged in highly demanding perceptual tasks (Cornwell et al., 2007, 2011). Anxiety can disrupt ongoing cognitive processing due to competition for limited capacity WM resources (e.g., Lavie et al., 2004), for visuospatial attention resources (Shackman et al., 2006), by disrupting the functioning of the goal-directed attentional system (Eysenck et al., 2007), or via an automatic reciprocal interaction between ventral 'limbic' regions and dorsal executive areas (e.g., Dolcos and McCarthy, 2006; Dolcos et al., 2008; Dichter et al., 2010). Despite its privileged role in alerting us of danger, however, it is clear that interference by anxiety can be overcome in certain situations. Our results are consistent with a number of studies that suggest that increasing cognitive or attentional load reduces processing in emotion response regions such as the amygdala. For example, Taylor et al. (2003) and Northoff et al. (2004) found that even relatively simple tasks can affect neural activation in emotion-associated regions, and Van Dillen et al. (2009) demonstrated that activation in the amygdala is reduced by increasing cognitive load even when the emotional stimuli precede the task.

These results highlight a potential difference between top-down control of emotional versus non-emotional interference. In the non-emotional domain, for example, evidence exists that

Table 2 | Summary of imaging results for regression analysis under the top-down control contrast.

Contrast		Local maxima (mm)				Cluster size (mm^3)	Pearson's r. $N = 18$
		Z score	*x*	*y*	*z*		
Dichotic listening: Top-down control contrast regression analysis	Visual cortex V1	4.46	2	−80	12	50220	0.843**
	r. Lateral occipital cortex, inferior division	4.07	30	−88	0		
	l. Inferior frontal gyrus, pars opercularis	4.25	−54	16	0	33048	0.928**
	l. Inferior frontal gyrus, pars triangularis	3.74	−52	26	14		
	l. Precentral gyrus	4.42	−42	−16	56	22932	0.606**
	l. Postcentral gyrus	3.9	−42	−34	56		
	r. Inferior parietal lobule	3.5	60	−30	44	15012	0.709**
	r. Postcentral gyrus	3.41	36	−30	48		
	Paracingulate gyrus	4.11	4	48	20	13536	0.828**
	Cingulate gyrus, anterior division	3.69	0	22	22		
	l. Lateral occipital cortex, superior division	4.01	−34	−80	18	13212	0.714**
	l. Lateral occipital cortex, inferior division	3.41	−46	−78	−6		

*This identifies regions whose activation under the top-down control contrast (High Load/Threat > Others) correlates with dichotic listening scores; Pearson's r are displayed. ** indicates significance at 01 (two-tailed). Data were thresholded at z = 2.3 with cluster thresholding (Worsley, 2001) to ensure a corrected p < 0.05.*

when cognitive/executive load is increased, interference from task-irrelevant information is exacerbated, as explained by the load theory of attention and cognitive control proposed by Lavie et al. (2004). It is possible, however, that at least partially separate mechanisms exist for the top-down control of emotion. Emotional stimuli are a special case of distractors; although they might be irrelevant to the explicit task, they signal events with high potential significance to wellbeing and are preferentially and automatically processed (e.g., Dolan and Vuilleumier, 2003; Alpers and Gerdes, 2007; Stout et al., 2013). This might particularly be the case when the interference comes from an induced emotion as opposed to perception of an emotional stimulus (which may or may not elicit an emotional response). If emotional information can be automatically processed, there is no reason why it should necessarily interfere with cognitive processing—whether or not it does so might therefore be dependent on the nature of the ongoing task and the strength of top-down control. Although Shackman et al. (2006), observed interference from threat of shock in a 3-back condition, we only observed this interference at a lower WM load (2-back) using a very similar task. However, differences in task difficulty might explain this apparent discrepancy; Shackman et al. (2006) employed 6 different locations with the stimuli presented for 500 ms with 2500 ms intervals between presentations. In contrast, the current study, based on piloting evidence, employed 8 locations [differing in position and extent of overlap to Shackman et al. (2006)] and the stimuli were present for just 350 ms with 1500 ms intervals. Future psychophysical studies will be needed to characterize under exactly what WM load or task difficulty conditions top-down control reduces threat-related interference.

If threat cannot be processed entirely automatically, however, an alternative explanation to an active top-down control theory that could account for the reduced interference of threat under greater cognitive task demands must be acknowledged. Depletion of cognitive or attentional resources might prevent emotional stimuli from being processed sufficiently to interfere with the task (the latter case would be similar to how Lavie et al. (2004) explain the lack of interference from perceptual distractors under high perceptual load). In this experiment, we used threat of shock, rather than shock itself or other unpleasant stimuli such as pictures presented concurrent with the WM task, so that there was no overt emotional stimulus to be processed during task performance. However, it is still possible that emotional information such as heightened anxiety, even in the absence of a stimulus, might not be processed under high WM load due to WM capacity limits. Despite evidence from a large number of studies suggesting that affective stimuli can be at least partially processed automatically without the need for attention (e.g., Morris et al., 1998, 2001; Dolan and Vuilleumier, 2003), some studies suggest that this is not always the case (e.g., Pessoa et al., 2002). However, although

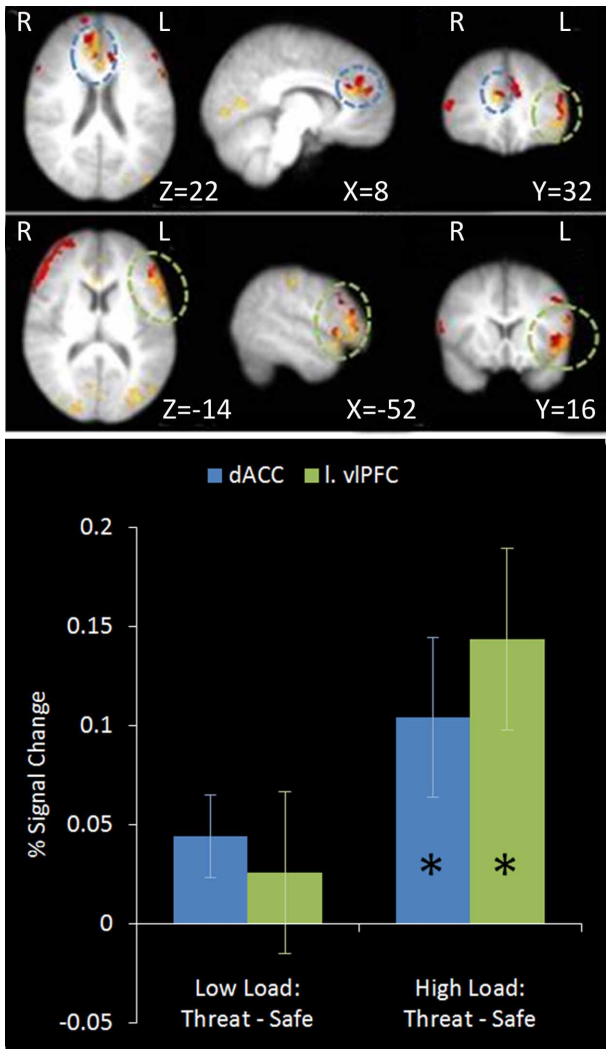

FIGURE 9 | Top: Top-down control regression imaging results overlaid on main effect top-down control (red). This identified regions where activation under the top-down control contrast in the emotional control task correlated with the index of attentional control from the dichotic listening task. Medial (upper panel) and lateral (lower panel) views are displayed. Dorsal ACC and left vlPFC identified by this analysis displayed some overlap with the main effect top-down control results. Bottom: Pairwise comparisons of the signal change in the regions identified. Both regions displayed a significant increase in activation under threat compared to safety in High Load conditions [Cingulate: High Load/Threat—High Load/Safe: mean difference = 0.104%, $S.D = 0.170$, $t_{(17)} = 2.585$, $p = 0.019$; left vlPFC: High Load/Threat—High Load/Safe: mean difference = 0.143%, $S.D = 0.194$, $t_{(17)} = 3.133$, $p = 0.006$]. The cingulate also displayed a borderline significant increase under threat in Low Load conditions [mean difference = 0.044%, $S.D = 0.089$, $t_{(17)} = 2.094$, $p = 0.052$]. Error bars display within-subject standard error (Morey, 2008). $^*p < 0.05$ (two-tailed).

the finding of a load dependent modulation of amygdala activity in the current study is consistent with both an active control mechanism and a resource depletion account, regions implicated in top-down control were recruited under High Load/Threat conditions and a Threat × WM Load interaction was observed in the pupil data, with greatest dilation under High Load/Threat. Both these results suggest that there was increased cognitive load in the High Load/Threat condition (Beatty, 1982; Steinhauer and Hakerem, 1992; Johnstone et al., 2007), which would not be expected if threat information was not being processed. It seems likely, then, that in the high cognitive load condition, threat information was processed but was actively prevented from interfering with WM performance.

The proposed active control mechanism could act by facilitating the task at hand, inhibiting the interfering effect of the emotion or a combination of the two. Some studies suggest there are dissociable neural systems implementing top-down control in emotional and non-emotional contexts (Ochsner et al., 2008; Mincic, 2010), with the distinction being that non-emotional interference is overcome with facilitation of task-related activity whilst emotional interference is overcome by active inhibition (Egner et al., 2008). In the current study there was greater support for the active inhibition of emotional processing; amygdala activation under Threat displayed a load-dependent modulation, with no activation to threat of shock at High Load. Under the High Load condition, however, there was also a trend for improvement in WM accuracy under Threat compared to Safe conditions, which might suggest some role of facilitation of task performance under High Load and Threat. Additionally, the increased cognitive effort in High Load/Threat trials indicated by the pupil dilation data may represent either the additional engagement of top-down regulatory mechanisms of the emotional interference or increased cognitive effort in the WM task.

Dynamic causal modeling was exploited to further probe the proposed circuitry. Models were partitioned into distinct families dependent on whether the pattern of modulation of connections was consistent with an emotion inhibition or WM task facilitation account. Family level inference found greater evidence that emotional interference is overcome by inhibition of emotional processing. Interestingly, the DCM analysis provided evidence that top-down control acts via the modulation of amygdala output, in addition to direct reduction of amygdala activity. The current results relate only to estimates of effective connectivity. Determining the precise anatomical routes and physiological mechanisms by which this control is implemented is a challenge for future studies, perhaps making use of diffusion tensor imaging to characterize the white matter pathways and pharmacological manipulations and/or magnetic resonance spectroscopy to understand the neurotransmitters involved.

A related issue is that although the ability to modulate interfering effects of emotion is significant in itself, it is not clear whether this requires a concomitant regulation in emotional experience. This highlights the multifactorial nature of emotions, which are made up of subjective feelings, physiological and neurological responses, as well as cognitive processes and action tendencies (Scherer, 2000). Whilst these components are related, their interaction with ongoing cognitive task demands may be somewhat distinct. For example, Dvorak-Bertsch et al. (2007) demonstrated that fear-potentiated startle can be modulated by working memory load and Vytal et al. (2012) observed eradication of interference from anxiety and diminished fear-potentiated startle with increasing WM load. In contrast, the current study observed a

load-dependent modulation of emotional interference in the WM task along with a load-dependent modulation of amygdala activation, but failed to regulate subjective ratings of anxiety. This may reflect the relative lack of sensitivity of the self-report measure and/or demand characteristics, or that the top-down control required to focus on the task does not reduce the subjective experience of anxiety. It should be noted that the current study is limited by the lack of additional valence sensitive online measures of emotion, such as facial EMG, or skin conductance measures.

We also examined whether individual differences in the performance of a completely non-emotional attentional control task (a dichotic listening task) would predict the recruitment of brain regions involved in the top-down control of threat. A regression analysis identified a number of such brain regions including both dACC and left vlPFC. Dorsal ACC and vlPFC have been associated with both emotion regulation (Blair et al., 2007; Ochsner and Gross, 2008; Van Dillen et al., 2009) and cognitive control (Herath et al., 2001; Dux et al., 2006). We propose that this correlation reflects these brain regions' common roles in both top-down control during a WM task in the presence of threat-provoked anxiety as well as during an auditory task with the need to selectively ignore irrelevant, non-emotional auditory information. The two tasks, as well as the type of distracting information, were deliberately chosen to be very different, making it unlikely that findings common to both tasks are due to the specifics of the stimuli or of task-specific processing demands.

Several studies have implicated regions of the cingulate in different types of cognitive control (see Vogt et al., 1992; Carter et al., 1999; Bush et al., 2000; Shackman et al., 2011 for reviews). Specifically, studies posit a role in monitoring when top-down control is required and recruiting the appropriate regions to implement this control (Ridderinkhof et al., 2004a,b). Many studies suggest the cingulate monitors conflict including studies of the Stroop task (Kerns et al., 2004), Simon task (Peterson et al., 2002; Kerns, 2006), and go/no-go paradigms (Braver et al., 2001), with evidence suggesting this conflict indicates the need for top-down control. Detection of conflict by the cingulate leads to recruitment of prefrontal regions necessary to implement this control (Kerns et al., 2004; Kerns, 2006). Similar regions of ACC have also been implicated in the processing of pain and affect. A recent meta-analysis of 192 imaging studies of cognitive control, negative affect and pain (Shackman et al., 2011) identified a region of the cingulate largely overlapping the region we found in the regression on dichotic listening scores (see **Figure 9**). Shackman et al. (2011) propose that this region of cingulate serves a general role in adaptive control, defined as being 'to bias responding in situations where the optimal course of action is uncertain or entails competition between alternative courses' (Shackman et al., 2011, p. 161). The connections of this region of cingulate cortex with other brain regions would support different types of adaptive control depending on the specific context. Connections with pre-motor and motor regions make dACC a suitable candidate for modifying, initiating or potentiating task-relevant motor actions. Connections with dorsal and lateral prefrontal cortex would enable biasing of attention and WM resources towards task-relevant information while connections with ventral prefrontal areas and limbic regions would allow for direct modulation of emotional responses. Thus whilst the dACC may serve an important role in emotion regulation, viewing its function in a broader context could help to elucidate more fully the role it plays. Whilst the current results are consistent with this domain general view of dACC function the conclusions that can be drawn from such regression analyses are limited and the correlation between recruitment of these regions and dichotic listening performance could be mediated by other factors. In order to fully address this it is necessary to perform functional imaging on the same participants completing both emotional and non-emotional top-down control tasks in future studies.

A further point is that although we hypothesize the existence of domain-general top-down control mechanisms which can be recruited in different contexts, they do not preclude the existence of neural circuitry involved in emotion regulation more specifically. For example, in the case of more voluntary emotion regulation such as that engaged in studies of emotion reappraisal, there is substantial evidence for the involvement of neural regions such as the orbitofrontal cortex (Lévesque et al., 2003; Goldin et al., 2008) that assign, or reassign, affective meaning or hedonic value to stimuli. In such situations then, one might expect domain-general mechanisms to interact with more emotion-specific or process-specific mechanisms.

The precise mechanisms by which top-down control can maintain task performance in the presence of threat or other sources of emotional interference, and the conditions under which such control mechanisms are effective or break down is highly clinically relevant. For example dysfunction in the neural circuitry that supports the top-down regulation of emotion has been demonstrated in several psychological disorders including bipolar disorder (Foland et al., 2008), schizophrenia (Blasi et al., 2009), depression (Johnstone et al., 2007; Joormann et al., 2007), PTSD (Shin et al., 2001) and several anxiety disorders (Campbell-Sills et al., 2011; Blair et al., 2012). Indeed, the wide range of psychopathologies linked to deficits in emotion regulation has been recognized in several recent reviews (Phillips et al., 2003; Taylor and Liberzon, 2007; Amstadter, 2008; Dillon et al., 2011; Berking and Wupperman, 2012). Studies of these psychopathologies have understandably focused on the affective nature of any deficits, however a relationship between emotional cognitive control and non-affective cognitive control suggests that deficits in other domains may also be apparent. For example, trait anxiety is linked to a diminished recruitment of prefrontal attentional control mechanisms to inhibit the processing of non-emotional distractors (Bishop, 2009) and deficits in executive functions have been observed in a number of psychological disorders including depression (Paelecke-Habermann et al., 2005; Siegle et al., 2007), obsessive-compulsive disorder, and schizophrenia (Moritz et al., 2002). It is possible that specific combinations of dysfunction in emotion-specific versus domain-general adaptive control will correspond to distinct symptoms or sub-categories of mood and affective disorders, though this speculative proposal has yet to be tested.

The current study demonstrates a load-dependent modulation of the interfering effects of induced anxiety and provides evidence that this occurs by an active mechanism favoring inhibition of emotional processing over task facilitation, though the

predominance of either route under different contexts requires further study. We also show that the ability to exert attentional control on a completely independent non-emotional task predicts the recruitment of vlPFC and dACC in this emotional control task, consistent with a proposed role in domain general top-down control, of which emotion regulation is just one example. The interaction between these emotional and cognitive networks is relevant to the understanding of a range of psychopathologies and further elucidation of how these networks interact as well as how they are modulated under different contexts is crucial.

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Still feeling it: the time course of emotional recovery from an attentional perspective

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Emotional reactivity and the time taken to recover, particularly from negative, stressful, events, are inextricably linked, and both are crucial for maintaining well-being. It is unclear, however, to what extent emotional reactivity during stimulus onset predicts the time course of recovery after stimulus offset. To address this question, 25 participants viewed arousing (negative and positive) and neutral pictures from the International Affective Picture System (IAPS) followed by task-relevant face targets, which were to be gender categorized. Faces were presented early (400–1500 ms) or late (2400–3500 ms) after picture offset to capture the time course of recovery from emotional stimuli. Measures of reaction time (RT), as well as face-locked N170 and P3 components were taken as indicators of the impact of lingering emotion on attentional facilitation or interference. Electrophysiological effects revealed negative and positive images to facilitate face-target processing on the P3 component, regardless of temporal interval. At the individual level, increased reactivity to: (1) negative pictures, quantified as the IAPS picture-locked Late Positive Potential (LPP), predicted larger attentional interference on the face-locked P3 component to faces presented in the late time window after picture offset. (2) Positive pictures, denoted by the LPP, predicted larger facilitation on the face-locked P3 component to faces presented in the earlier time window after picture offset. These results suggest that subsequent processing is still impacted up to 3500 ms after the offset of negative pictures and 1500 ms after the offset of positive pictures for individuals reacting more strongly to these pictures, respectively. Such findings emphasize the importance of individual differences in reactivity when predicting the temporality of emotional recovery. The current experimental model provides a novel basis for future research aiming to identify profiles of adaptive and maladaptive recovery.

Keywords: emotion, attention, reactivity, recovery, face, late positive potential, P3, N170

INTRODUCTION

Emotional events that bear relevance to an organisms' well-being, demand center stage in selective attention, and initiate a cascade of typical behavioral and psychophysiological response tendencies (Frijda, 1986; Davidson, 1998; Lang and Bradley, 2010). These responses can be considered to originate from an adaptive *emotional auto-regulation* process (Kappas, 2011); that is, modification of the intensity in emotional responding, or termination of emotional responding, is instigated without motivation, in order to avoid negative stimuli, approach positive stimuli, or return to a steady emotional state. Whilst the majority of research in the field examines affective responding upon the onset of an emotional stimulus, few studies have investigated the extent to which emotional responding continues after stimulus offset (Jackson et al., 2003; Hajcak and Olvet, 2008). Examining the time course of auto-regulation after the offset of an emotional event may provide crucial information to understand adaptive *recovery time*, which is described in the *affective chronometry* model, as the speed of return to a baseline state in a response system after an emotion eliciting stimulus (Davidson, 1998). A landmark study by Jackson et al. (2003) tested this notion by collecting electroencephalography (EEG) frontal asymmetry data to serve as a metric of individual differences in affective style, which was then used to predict outcomes on physiological markers of recovery such as eye-blink startle in an emotional task. The task in this study consisted of presenting International Affective Picture System (IAPS) pictures for 6 s, with audio probes presented either 2.5 or 4.5 s during the picture or 1 s after picture offset. Jackson and colleagues found individuals with right electrical frontal-asymmetry to have larger eye-blink startle magnitude to an audio probe presented 1 s after a negative picture, compared to a neutral picture. Furthermore, with a similar paradigm Larson et al. (2007) found healthy participants exhibiting depressive and anxiety symptoms to have different profiles of emotional recovery. For example, those with depressive symptoms had shown a blunted startle response to audio probes presented 1.5 s after positive pictures, compared to controls. In addition, individuals high in anxious apprehension showed potentiated startle to audio probes presented 1.5 s after unpleasant and pleasant pictures, relative to controls. Importantly, unraveling how adaptive

emotional recovery functions in the healthy population could serve as a useful comparison when recovery is compromised in clinical populations. A wealth of literature indeed demonstrates patients with depression and anxiety to ruminate and worry over past emotional events (for review Nolen-Hoeksema et al., 2008), which may be linked to the dysfunction of recovery mechanisms. For example, recovery from negative events in depressed patients may be stifled because of the sustainment of negative affect (Siegle et al., 2002), as well as the difficulty in maintaining positive affect (Heller et al., 2009).

One way to gage emotional recovery is through attentional paradigms. Attention and emotion have been shown to be strongly interconnected, with affective stimuli taking precedence over competing stimuli, regardless of task relevance (for review see Yiend, 2010). This effect has been well documented by means of an event-related potential (ERP) component known as the Late Positive Potential (LPP), which is located over centro-parietal sites at approximately 300 ms after stimulus onset, and is thought to reflect the process of sustained attention (Olofsson et al., 2008; Hajcak et al., 2010; Lang and Bradley, 2010). In emotional contexts, the LPP component is typically enhanced for arousing negative and positive pictures, relative to neutral, both during passive viewing (Cuthbert et al., 1999; Schupp et al., 2000), and concurrent task performance (Hajcak et al., 2007). This enlargement of the LPP for arousing stimuli, relative to neutral stimuli, has been postulated to signify the global inhibition of competing stimuli in the environment, permitting motivationally relevant stimuli to be selectively processed (Schupp et al., 2004; Brown et al., 2012). To test this notion, Schupp et al. (2004) presented emotional images in tandem with acoustic startle probes. Their results indicated negative and positive images to reliably inhibit the processing of secondary acoustic startle probes, denoted by larger LPPs to the arousing images and smaller P3 components to the probes. In addition, sustained attention as measured through the magnitude of the LPP has also been shown to extend beyond the offset of an emotional stimulus and to disrupt the processing of subsequent stimuli. For instance, the LPP has been shown to continue for up to 800 ms after pleasant pictures and for up to 1000 ms after unpleasant pictures (Hajcak and Olvet, 2008). Furthermore, Weinberg and Hajcak (2011) found pictures that elicited larger LPPs within individuals to predict slower reaction times (RTs) and reduced P300 amplitudes over parietal areas to subsequent categorization of shape targets. Given the temporality of attentional-emotional processes, represented through the LPP, these findings suggest that the LPP may serve as: (1) an important indicator of individual differences in the intensity of emotional reactivity, (2) a useful predictor of recovery outcomes e.g., a predictor of attentional interference on subsequent task-relevant stimuli.

Quantifying emotional recovery via the level of attentional modulation on task-relevant targets that appear after emotional stimuli may be useful in determining the lingering effect of emotion after offset. For instance, attentional interference or facilitation upon a following target can be considered a marker of continued processing of task-irrelevant emotional stimuli, with the former disrupting attention to following targets, whilst the latter widens attention to following targets. Furthermore, a recent body of behavioral research using rapid serial visual presentation tasks has provided ample evidence that viewing emotional stimuli can both interfere and facilitate the attentional processing of following targets, depending on the temporal proximity between stimuli (Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010). Bocanegra and Zeelenberg (2009) found emotional words impaired accuracy on subsequent neutral word targets when distances in time were as small as 50 ms and 500 ms, whilst longer time intervals of 1000 ms improved accuracy. Similarly, Ciesielski et al. (2010) observed that emotional picture distracters, particularly those exhibiting erotic and disgusting content, only reduced the participants' accuracy on a subsequent task during smaller distracter-target lags, e.g., 200 ms, 400 ms, and 600 ms. Longer lags, i.e., 800 ms, however, produced facilitation effects in accuracy. In addition, studies using target detection tasks have found comparable behavioral results. For example, Weinberg and Hajcak (2011) found interference, denoted as slower RTs on shape targets presented directly after emotional images (e.g., 0 ms).

Given the extent to which differential effects of attentional facilitation and interference appear dependent upon temporal aspects, as evidenced above, it can be postulated that several distinct mechanisms are at work during the recovery of an emotional stimulus. Indeed, support for this argument can be found from recent ERP studies, which demonstrate emotional pictures to modulate specific target ERP waveform components over time, thus indicating emotional stimuli to impact upon various stages of subsequent target processing (Ihssen et al., 2007; Weinberg and Hajcak, 2011; Brown et al., 2012). For example, Ihssen et al. (2007) found arousing images to disrupt processing of lexical targets as shown by slower RT and reduced amplitude on two ERP components: (1) the early attention-specific N1, observed over occipital sites, and time locked to 184–284 ms, and (2) the later LPP, observed over parieto-central regions and time locked to 412–712 ms. These effects occurred over three different temporal intervals between the emotional image and target, i.e., 80 ms, 200 ms, and 440 ms. Likewise, Brown et al. (2012) found that briefly presented negative images (e.g., 200 ms) disrupt processing on the early N1 to flashed probes, but not the N1 to Gabor patches, over short intervals of 570 ms between negative images and targets. Furthermore, Weinberg and Hajcak (2011) revealed emotional images to slow RTs and to attenuate subsequent P300 amplitude to shape targets which directly followed the images. The disparity between valence specificity in these studies may be due to differences in task type, specific state induced by the emotional images (positive vs. negative), as well as timing of the target stimuli presented. Despite this, it is important to note that these ERP studies are coherent in showing distraction from emotional stimuli on early ERP components locked to subsequent targets. In addition, the electrophysiological findings from these studies overlap with the behavioral research presented above, whereby shorter temporal proximities between an emotional prime and target result in interference effects. Yet, it remains unclear whether longer time intervals yield similar patterns of attentional interference or perhaps facilitation for electrophysiological and behavioral metrics.

In the study reported here, we used behavioral and ERP methodology in conjunction with an attentional paradigm to

investigate: (1) the extent of recovery from arousing negative and positive stimuli, relative to neutral stimuli; (2) the impact of individual differences in emotional reactivity upon recovery speed. The experimental task consisted of presenting emotional images for 3 s, followed by a probe stimulus of 500 ms consisting of a neutral face-target controlled with FACSGen and validated in a previous study (Roesch et al., 2011). Participants were instructed to identify the gender of the face and respond accordingly. In addition, we manipulated the inter-stimulus interval (ISI) between the picture and face-target in the form of a fixation cross presented for a random period of time in two conditions, varying between 400–1500 ms and 2400–3500 ms, respectively. We used IAPS images (Lang et al., 2005) as emotional stimuli because they have been shown to induce emotion (Lang and Bradley, 2010), reliably modulate the LPP component (Olofsson et al., 2008; Hajcak et al., 2010) and impact subsequent task processing (Ihssen et al., 2007; Weinberg and Hajcak, 2011; Brown et al., 2012). Our subset of IAPS pictures consisted of negative and positive emotional pictures that were matched in arousal, as well as neutral pictures, to assess the influence of valence and arousal upon recovery outcomes. The LPP component to the emotional images was recorded, to serve as a metric of individual differences in emotional reactivity and a predictor of individual differences in emotional recovery, quantified as the level of interference on subsequent face-targets. Face stimuli were used as probes for a number of reasons. Firstly, we aimed to expand the line of behavioral research that had previously used categorization tasks to assess the extent of attentional capture by emotional stimuli after offset more generally (Ihssen et al., 2007) and within individuals (Weinberg and Hajcak, 2011). Secondly, we wanted to capture ERPs that have been shown to be modulated by attention, such as: (1) the face-specific N170, which is a negative potential occurring around 150–200 ms over occipito-temporal sites, and is thought to reflect early perceptual and holistic encoding (Bentin et al., 1996). (2) The P3 component, a positive deflection found over parieto-occipital areas around 300–400 ms, which has been associated with target detection (Schupp et al., 2004; Weinberg and Hajcak, 2011). Isolating those stages of processing that may show effects of preceding emotion-laden stimuli may be important for understanding mechanisms relevant to emotional reactivity and regulation. An advantage of using the FACSGen stimuli, compared to other face stimuli, is that the expressions are computer generated based upon parametrically controlled facial action units, which means that the expressions portrayed on our stimuli set are as intrinsically neutral as possible and are exactly the same across the set. Lastly, temporal intervals were included in experiment to examine how valence and arousal would impact the temporality of emotional recovery speed. We opted for shorter and longer temporal intervals because of the paucity of ERP research examining the impact of preceding emotion-laden stimuli on attention over a timescale of several seconds within groups and individuals.

Our main hypotheses were fourfold. Firstly, we expected negative and positive images to elicit more sustained attention than neutral images, indexed by larger LPP amplitudes for negative and positive images, relative to neutral (Lang and Bradley, 2010). Secondly, we expected arousing pictures to interfere with the subsequent processing of face-targets, as shown by slower RTs and smaller N170/P3 amplitudes on following face stimuli, compared to neutral pictures (Ihssen et al., 2007; Weinberg and Hajcak, 2011). Thirdly, modulation of RT and N170/P3 amplitude would be contingent upon the temporal interval between the arousing picture and target. We proposed that attentional interference between an arousing image and target will occur over shorter temporal intervals due to increased competition between the image and target, thus suggesting a slower recovery speed to emotional images, relative to neutral images (Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010). We expected this to be shown by slower RTs and smaller N170/P3 amplitudes to face-targets (Weinberg and Hajcak, 2011). Based on the behavioral findings of Bocanegra and Zeelenberg (2009) and Ciesielski et al. (2010), we predict that attentional facilitation will ensue when the temporal interval between an arousing picture and target is longer, as the competition between the image and target will be reduced but with a lingering effect of emotional image on attentional focus. We anticipated this to be evidenced by faster RTs and larger N170/P3 amplitudes to face-targets. Lastly, we examined how individual differences in emotional reactivity could predict speed of emotional recovery, by correlating IAPS-locked LPP values to RTs and N170/P3 amplitudes on subsequent early and late face-targets. We expected higher LPP values for arousing images to predict a more sustained impact on the face targets, reflected in larger differences between RTs and ERP amplitudes on following face-targets after arousing vs. neutral images. Given previous work showing interference by the LPP upon the visual P3 of subsequent targets specifically (see Weinberg and Hajcak, 2011), we predicted this relationship to be stronger for the P3 component than the N170.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-five right-handed students from the University of Reading Psychology Department were recruited for this study (mean age = 20.2 years, 18 females and 7 males). All participants had normal or corrected to normal vision. Students provided written informed consent and received partial course credit for their participation. The procedure was approved by the University of Reading Ethics Committee.

STIMULI

We selected 216 pictures from the IAPS (Lang et al., 2005), depicting seventy-two events from each valence category (see **Table 1**); negative, positive, and neutral. Mean (*SD*) normative ratings of valence across the negative pictures was 2.61 (1.57); for positive 7.41 (1.57); and for neutral, 5.00 (1.25). Mean valence ratings for each picture category were significantly different to the other picture categories, $p < 0.001$. For arousal, mean (*SD*) negative, and positive picture ratings were matched, negative 5.66 (2.22); positive 5.61 (2.28); neutral 3.20 (1.93). Negative and positive arousal ratings did not significantly differ, $p = 0.6$. Both negative and positive arousal ratings significantly differed from neutral, $p < 0.001$. The mean (*SD*) complexity and luminance of the images selected were matched across categories by using the scores of complexity and luminance (see also van Reekum et al., 2007):

Table 1 | Reference numbers to images taken from the International Affective Picture System (IAPS; Lang et al., 2005).

Negative		Neutral		Positive	
1052	9040	2038	2594	1463	7200
1111	9050	2102	2595	1710	7230
1220	9140	2104	2749	1722	7260
1274	9180	2191	2830	1811	7270
1301	9181	2210	2840	2058	7330
2095	9250	2214	4605	2071	7350
2141	9253	2215	5130	2150	7400
2683	9300	2235	5410	2160	7430
2688	9301	2271	5534	2208	7470
2691	9320	2272	5740	2209	7502
2710	9340	2280	5875	2216	7508
2751	9373	2305	7020	2224	8030
2981	9400	2357	7030	2340	8034
3015	9419	2381	7034	2345	8080
3051	9420	2383	7036	2346	8090
3061	9421	2385	7038	2352.1	8170
3160	9423	2393	7040	4599	8180
3181	9424	2396	7050	4603	8185
3215	9425	2397	7053	4610	8186
3220	9428	2440	7055	4623	8200
3230	9429	2441	7059	4626	8210
3350	9430	2446	7110	4640	8300
5971	9433	2480	7150	4641	8350
5973	9470	2485	7160	5260	8370
6213	9495	2491	7161	5270	8380
6242	9520	2493	7180	5450	8400
6243	9560	2506	7185	5470	8420
6244	9570	2512	7234	5480	8461
6540	9584	2513	7491	5600	8470
6570.1	9592	2514	7493	5621	8490
6571	9620	2515	7595	5623	8496
6821	9621	2516	7705	5629	8499
6830	9630	2518	7950	5700	8503
7359	9901	2570	8311	5830	8510
7380	9911	2579	9070	5833	8531
8485	9925	2593	9210	5910	8540

Complexity, negative 124606.40 (40955.07); positive 121928.66 (31956.27); neutral 126801.65 (45579.57), and luminance, negative 0.37 (0.13); positive 0.38 (0.13); neutral 0.37 (0.16). Mean complexity and luminance did not significantly differ across categories, $p > 0.4$.

Pictures of thirty-six synthetic 3-dimensional neutral face stimuli (18 male and 18 female) were selected (see **Table 2**) from the stimuli used in the validation procedures for the FACSGen software (Roesch et al., 2011). As part of this validation procedure, 44 students from the University of Geneva were instructed to rate synthetic faces created with FaceGen Modeller (Singular Inversion Inc., 2012) on three continuous dimensions spanning 0–100: gender (anchored male-female), believability (anchored synthetic-believable), and intrinsic emotionality (anchored positive-neutral-negative). We selected thirty-six faces

Table 2 | Reference numbers to faces taken from the Facial Action Coding System Generator (FACSGen: Roesch et al., 2011).

Male	Female
95	7
96	23
102	30
109	45
111	49
119	56
136	59
139	60
141	70
143	72
145	75
146	77
147	86
157	87
163	88
164	92
166	176
171	178

(18 male; 18 female) for being the most unambiguous gender-wise, the most believable, and the most emotionally neutral faces as possible. Mean (*SD*) normative ratings of gender for the seventy-two faces were; female 78.61 (5.895) and male 4.655 (3.46), where ratings of male and female gender significantly differed, $p < 0.001$. In addition, male and female faces were matched for mean (*SD*) ratings of neutral emotional expression and credibility of the face: Neutral expression, female 47.41 (6.46); male 48.16 (5.77), and credibility, female 52.21 (11.33); male 55.65 (9.6). Mean neutral expression or credibility ratings of male and female categories did not significantly differ, $p > 0.2$.

TASK DESIGN

All of the tasks were administered using E-Prime 2.0 (Psychology Software Tools Ltd, Pittsburgh, PA). Within each task, the experimental trials were randomized and the response button press on the mouse for the gender task was counterbalanced across participants. Tasks were presented on a Viewsonic 22 inch monitor with a 60 Hertz refresh rate. Screen resolution was set at 1024 × 768 pixels. For both the emotional recovery task and IAPS rating task, participants sat at approximately 60 cm from the screen. The resulting visual angles were: 19° × 15° for FACSGen faces and 35.6° × 22.5° for IAPS images.

Emotional recovery task

Participants were required to passively view emotional pictures and identify the gender of following neutral face-targets, by pressing the appropriate button on the mouse. Participants were instructed to focus on a fixation cross displayed between the picture and the face-target, to minimize noise from eye and muscle movement on the EEG. The face target was presented at a random time between either 400–1500 ms or 2400–3500 ms, in order to assess the temporality of emotional recovery, demonstrated as the

degree of attentional spill-over from the previous emotional picture upon a subsequent face-target. The emotional recovery task consisted of 216 trials: 3 Valence (negative, neutral, positive) × 2 Temporal Interval (early: 400–1500 ms, late: 2400–3500 ms) × 36 Neutral Faces. Each IAPS picture was presented once; each neutral face was repeated six times and paired with a specific valence, which was counterbalanced across time and gender. A trial thus consisted of a 1000 ms fixation cross, 3000 ms IAPS picture presentation, 400–1500 ms or 2400–3500 ms fixation cross, 500 ms neutral face-target, and a 1500–3000 ms response window (see **Figure 1**).

IAPS rating task

Upon completion of the main experiment, all IAPS pictures were presented again to the participants, in a random order for 2 s. Participants were instructed to provide ratings on two dimensions, valence and arousal. The next trial started after participants completed both ratings using the keyboard. Each rating was provided on a nine point Likert scale, where participants were given instructions to rate valence, i.e., "how positive or negative you felt in response to the picture" and arousal, i.e., "the extent to which you felt calm or excited in response to the pictures." For the valence ratings, a response of 9 represented "very pleasant" and 1 "very unpleasant," while for arousal 1 represented "very calm" and 9 represented "very excited" (cf. Lang et al., 2005).

PROCEDURE

The current study was assessed and conducted in line with the ethics procedures in place at the University of Reading. Upon arrival, participants were informed of the experimental procedure and asked to complete a consent form. Participants were seated in a RF-shielded, sound-attenuated room for the EEG setup and experimental testing. Firstly, the participant's head was measured, in order to identify the correct size EEG cap. Secondly, once the cap was attached, the skin was cleaned with alcohol and a conductive gel was used to obtain sufficient impedance between the electrodes and scalp. When the EEG was stable and the participant was ready, the emotional recovery task was started on the computer. After completing the emotional recovery task, the EEG cap was removed. Next, participants performed the picture rating task. Lastly, participants were thanked for their participation and debriefed about the details of the study.

DATA COLLECTION AND REDUCTION

For EEG recording we used an MR compatible, 32-channel, powerpack operated amplifier (Brain Products, GmBH, Germany). Thirty-two Ag/AgCl pellet pin electrodes were positioned on an elastic cap according to the standard 10/20 system. There were three midline electrodes (Fz/Cz/Pz) and 14 electrodes over each hemisphere (FP1/FP2, F3/F4, F7/F8, FC1/FC2, FC5/FC6, FT9/FT10, C3/C4, CP1/CP2, CP5/CP6, T7/T8, TP9/TP10, P3/P4, P7/P8, and O1/O2). Electrode FCz served as the reference point and electrode AFz the ground. One electrode (IO) was placed on the outer canthi of the right eye for horizontal eye movement recordings. Electrode impedance was kept below 5 kΩ. EEG signals were recorded using Brain Vision Recorder Version 2.01 (Brain Products). Off-line EEG analysis was performed with Brain Vision Analyzer Version 2.01 (Brain Products). Firstly, the raw data were inspected for electromyographic (EMG) artifacts and other noise that could distort the EEG signal. These artifacts were highlighted and removed from the data. Secondly, data were filtered with a low cutoff of 0.1 Hz (Hajcak and Olvet, 2008) and a high cutoff of 40 Hz. Thirdly, to identify and remove eye movement artifacts, an ocular Independent Component Analysis was performed on the data. We used the IO electrode to identify horizontal eye movements and FP1 to identify vertical eye movements. Lastly, a semi-automated visual inspection for remaining physiological artifacts was made on each channel within each trial. Trials were rejected if there was: (1) a voltage step of more than 50 μV between sample points, (2) a voltage difference of 300 μV within a trial, and (3) a maximum voltage difference

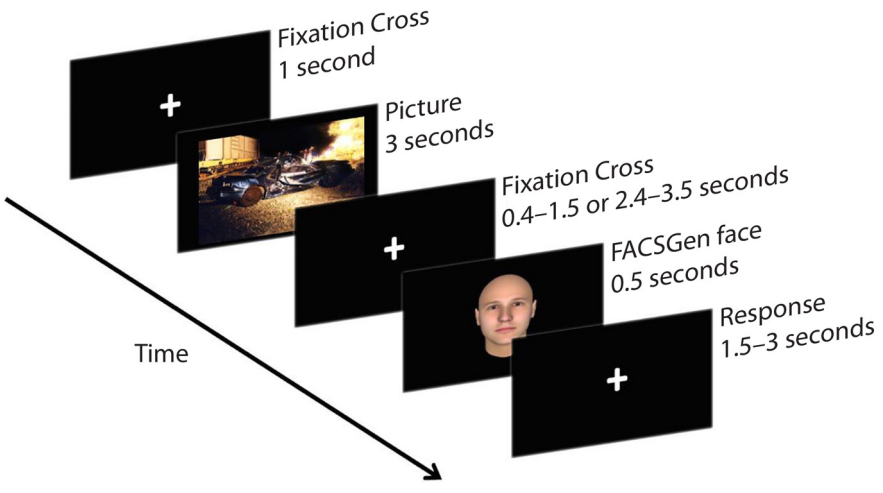

FIGURE 1 | A sample trial from the emotional recovery task: a fixation cross was presented at the center of the screen to direct participants' attention. Next, an IAPS image was presented, followed by a variable temporal interval. Lastly, a face-target was briefly presented. Participants were instructed to watch each picture and identify the gender of the following face-target as quickly and as accurately as possible.

of less than 0.50 μV within 100 ms intervals (Hajcak and Olvet, 2008).

EEG data from the emotional pictures and face-targets were only segmented if the emotional picture and face-targets were followed by a correct response (95% of trials). After completion of these artifact rejection steps, 74% of emotional picture trials and 70% of face trials were included in the segmentation and averaging process. The percentage of picture trials across participants for each condition were: Negative Early = 75%; Negative Late = 71%; Neutral Early = 75%; Neutral Late = 74%; Positive Early = 75%; Positive Late = 71%. The percentage of face trials across participants for each condition were: Negative Early = 70%; Negative Late = 72%; Neutral Early = 71%; Neutral Late = 66%; Positive Early = 72%; Positive Late = 71%.

For emotional picture stimuli, segments were extracted from −200 ms before the image and 3000 ms after image onset. The remaining trials were −200 to 0 ms baseline corrected and averaged. The average voltage ∗ ms from 300–1200 ms, 1200–2100 ms, and 2100–3000 ms post image onset was calculated for three electrodes associated with the LPP: Fz/Cz/Pz. The average voltage ∗ ms values were then collapsed individually for Fz/Cz/Pz, for each subject and experimental condition.

Epochs around the face stimuli were extracted from −100 ms before the face-target and 600 ms after face-target onset. The remaining trials were then −100 to 0 ms baseline corrected and averaged. A peak detection method was used to locate the negative polarity of the N170 in TP9/TP10, and to identify the positive polarity of the P3 in P7/P8/Pz/O1/O2. The time parameters for finding the peaks were 140–220 ms for the N170 and 300–390 ms for the P3. Average amplitude values were then collapsed across each subject and condition: independently for TP9/TP10 electrodes for the N170 and across P7/P8/Pz/O1/O2 electrodes for the P3.

RTs in the emotional recovery task were scored for correct responses and only those RTs above 300 ms were retained (95% of trials). Accuracy scores from the emotional recovery task were expressed as the proportion of correct trials to total trials included.

The data of one participant was excluded from analyses due to loss of signal over the temporal electrode sites, thus leaving a total of 24 participants for statistical analyses.

RESULTS

MAIN EFFECTS ANALYSIS

To test the extent to which IAPS stimuli modulate subsequent processing of neutral face information over time, we conducted a 3 Valence (negative, neutral, positive) × 2 Temporal Interval (early: 400–1500 ms, late: 2400–3500 ms) repeated measures analysis of variance (ANOVA) for RT, accuracy, and P3 amplitude. In addition, a 3 Valence (negative, neutral, positive) × 2 Temporal Interval (early: 400–1500 ms, late: 2400–3500 ms) × 2 Hemisphere (right, left) repeated measures ANOVA was conducted on N170 amplitude. The additional factor of hemisphere was included to assess the laterality of the N170, where N170 amplitudes are found to be typically larger over the right hemisphere sites, compared to left (Bentin et al., 1996). To examine LPP amplitude, we utilized a 3 Valence (negative, neutral, positive) × 2 Temporal Interval (early: 400–1500 ms, late: 2400–3500 ms) × 3 LPP Window (early: 300–1200 ms, middle: 1200–2100 ms, late: 2100–3000 ms) × 3 Lead (Fz, Cz, Pz) repeated measures ANOVA. Furthermore, to assess whether our participants' ratings of IAPS reflected the normative ratings, we used a 3 Picture (negative, neutral, positive) repeated ANOVA for IAPS ratings. Significant predicted effects in the omnibus tests were followed up with pairwise comparisons. All analyses were conducted using SPSS 17.0 (IBM Ltd).

IAPS ratings

The IAPS ratings produced a significant main effect of Valence, $F_{(2,\ 46)} = 156.664$, $p < 0.001$. Participants reported negative pictures ($M = 2.52$, $SD = 0.88$) to be the most unpleasant, positive pictures ($M = 6.50$, $SD = 0.81$) as the most pleasant and neutral ratings ($M = 4.83$, $SD = 0.75$) as neither unpleasant nor pleasant, $p < 0.001$. The ANOVA revealed arousal ratings to have a main effect of Valence, $F_{(2,\ 46)} = 2.545$, $p < 0.001$. Both negative ($M = 5.31$, $SD = 1.58$) and positive ($M = 4.66$, $SD = 1.75$) arousal ratings significantly differed from neutral ($M = 3.29$, $SD = 1.50$), $p < 0.001$. Although the arousal ratings were higher for negative than positive pictures in our sample, negative arousal ratings were not significantly different from arousal ratings of positive pictures, $p = 0.087$. The spread of arousal ratings of the positive pictures was higher in our sample relative to the normative ratings (see **Figure 2**).

IAPS-elicited LPP

As expected, a significant main effect of Valence was found, $F_{(2,\ 46)} = 7.492$, $p = 0.002$. Findings were partially in line with predictions, as LPP amplitudes were larger for negative pictures, relative to neutral pictures, at trend level, $p = 0.056$ (see **Figure 3**). Reflecting the (non-significant) effect observed in the IAPS ratings, negative pictures evoked larger LPPs than positive pictures, $p < 0.001$. Moreover, the LPP amplitude to positive pictures and neutral pictures did not significantly differ, $p = 0.163$ (see **Figure 3** and **Table 3**).

To test that the LPP waveforms' temporality and topography was comparable to previous research (e.g., Olofsson et al., 2008; Hajcak et al., 2010; Lang and Bradley, 2010) we split the LPP into three windows and assessed the LPP at each lead. As expected, the analysis yielded significant interactions between Lead × Valence × LPP Window, $F_{(8,\ 184)} = 2.059$, $p = 0.042$, Lead × Valence, $F_{(4,\ 92)} = 12.235$, $p < 0.001$, and Lead × LPP Window, $F_{(4,\ 92)} = 124.989$, $p < 0.001$. The results were in accordance with previous studies that have examined the LPP (see **Figure 3** and **Table 4**), as negative images had the largest centro-parietal activation and the smallest frontal activation during the early portion of the LPP, compared to neutral and positive images. In addition, within the middle portion of the LPP, negative images were found to elicit the strongest activity in central areas, relative to positive and neutral images. Furthermore, in the late portion of the LPP, negative images elicited more activity in centro-parietal regions than neutral and positive images. The LPP for neutral images were larger than positive images during middle and late windows, but only over parietal regions. The ANOVA also revealed a main effect of Lead, $F_{(2,46)} = 4.897$, $p < 0.012$, and

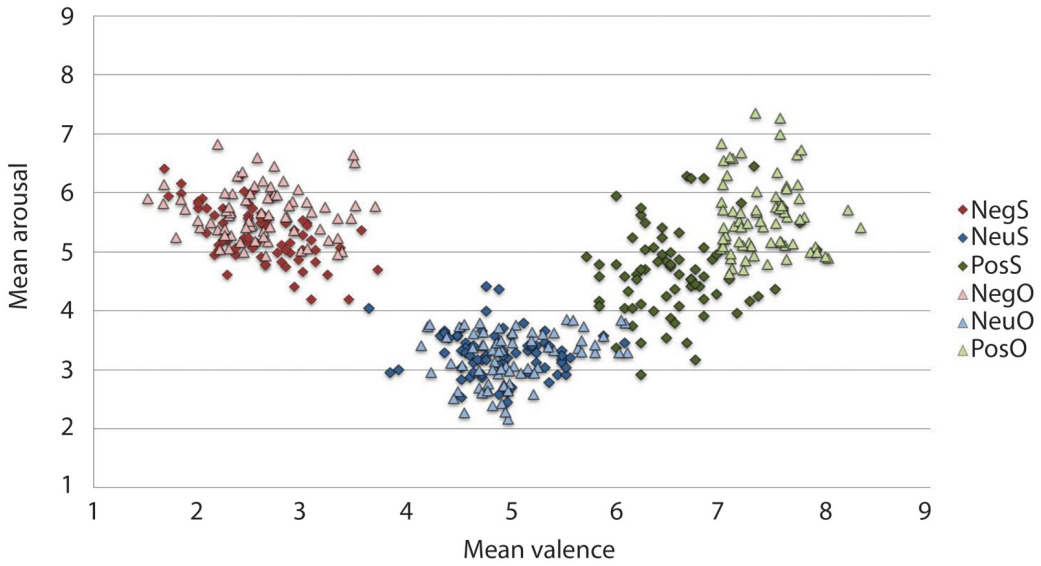

FIGURE 2 | Mean IAPS valence and arousal ratings from the current study sample and the original sample for the 216 pictures selected. On the valence scale, lower numbers denote negative valence, whilst higher numbers reflect positive valence. Similarly, in the arousal scale, high arousal is reflected by higher figures and lower arousal by lower figures. As expected, the current sample rated negative images as high arousing and unpleasant, and neutral images as low in arousal and neither pleasant or unpleasant. Positive images, however, have more variation in arousal ratings, particularly when comparing them to the original sample. The current experimental sample ratings may be typical for a young British sample, given that the images selected were controlled for arousal and valence based upon the original ratings that came with IAPS set (Lang et al., 2005). Neg, Negative; Neu, Neutral; Pos, Positive; S, current study sample ratings; O, original IAPS sample ratings.

Window, $F_{(2,46)} = 115.590$, $p < 0.001$, where the LPP was maximal: (1) at the Pz electrode, followed by Cz, and Fz electrodes. (2) In the early window, followed by the middle and late windows. No significant interaction between Valence × LPP Window was found, $F_{(4,\ 92)} = 0.387$, $p = 0.817$.

As a control, we tested for random differences in LPP values for the pictures preceding early vs. late face-targets. There was no Valence × Temporal Interval interaction, $F_{(2,\ 46)} = 0.192$, $p = 0.826$, for the LPP. Thus, while negative pictures elicited a higher LPP than positive and neutral pictures, no significant difference between LPP values from valence × early vs. late face conditions was found (see **Table 3**). No other interaction effects with Time were found, largest $F = 2.18$, *n.s.*

RT

While the average RT to faces following negative pictures were faster than those following positive and neutral pictures in the late interval, we found no significant main effect of Valence for RT, $F_{(2,\ 46)} = 0.974$, $p = 0.385$, nor Valence × Temporal Interval for RT, $F_{(2,\ 46)} = 0.331$, $p = 0.720$. As anticipated, however, RT was faster for later face-targets, compared to earlier face-targets, as reflected in a main effect of Temporal Interval, $F_{(1,\ 23)} = 43.250$, $p < 0.001$ (see **Table 3**).

Accuracy

Accuracy scores in emotional recovery task were relatively high across conditions, with on average 95% correct responses (see **Table 3**). Picture valence did not impact target-face Accuracy scores, $F_{(2,\ 46)} = 0.247$, $p = 0.782$, nor was there an effect of Valence × Temporal Interval, $F_{(2,\ 46)} = 1.369$, $p = 0.265$ or main effect of Temporal Interval, $F_{(1,\ 23)} = 0.919$, $p = 0.348$.

The face-locked N170 component

The N170 amplitudes revealed no main effect of Valence, $F_{(2,\ 46)} = 1.444$, $p = 0.247$, or Valence × Temporal Interval interaction, $F_{(2,\ 46)} = 0.002$, $p = 0.998$. Reflecting the behavioral effect observed for RT, the results yielded a significant main effect of Temporal Interval on N170 amplitude, $F_{(1,\ 23)} = 24.684$, $p < 0.001$ (see **Table 3**), whereby N170 amplitudes were potentiated for the late face-targets, relative to the early face-targets, $p < 0.001$. While larger N170 amplitudes were exhibited on the right TP10 electrode ($M = -10.46\,\mu V$, $SD = 5.43\,\mu V$), relative to the left TP9 electrode ($M = -9.88$, $SD = 5.10\,\mu V$), this difference was not significant, $F_{(1,\ 23)} = 0.638$, $p = 0.433$. No other interaction effects with Hemisphere were found, largest $F = 1.21$, *n.s.*

The face-locked P3 component

As predicted, P3 amplitudes revealed a main effect of Valence, $F_{(2,\ 46)} = 4.024$, $p = 0.025$, where P3 amplitudes were accentuated for faces that had followed negative, $p = 0.012$, and positive pictures, $p = 0.010$, relative to neutral (see **Table 3** and **Figure 4**). However, there was no significant difference in P3 amplitude between faces that had followed negative vs. positive pictures, $p = 0.890$. We did not find support for the prediction that the impact of picture valence on the face-locked P3 would dissipate over time, however; Valence × Temporal Interval, $F_{(2,\ 46)} = 0.224$, $p = 0.800$. Similar to N170, the ANOVA revealed a significant main

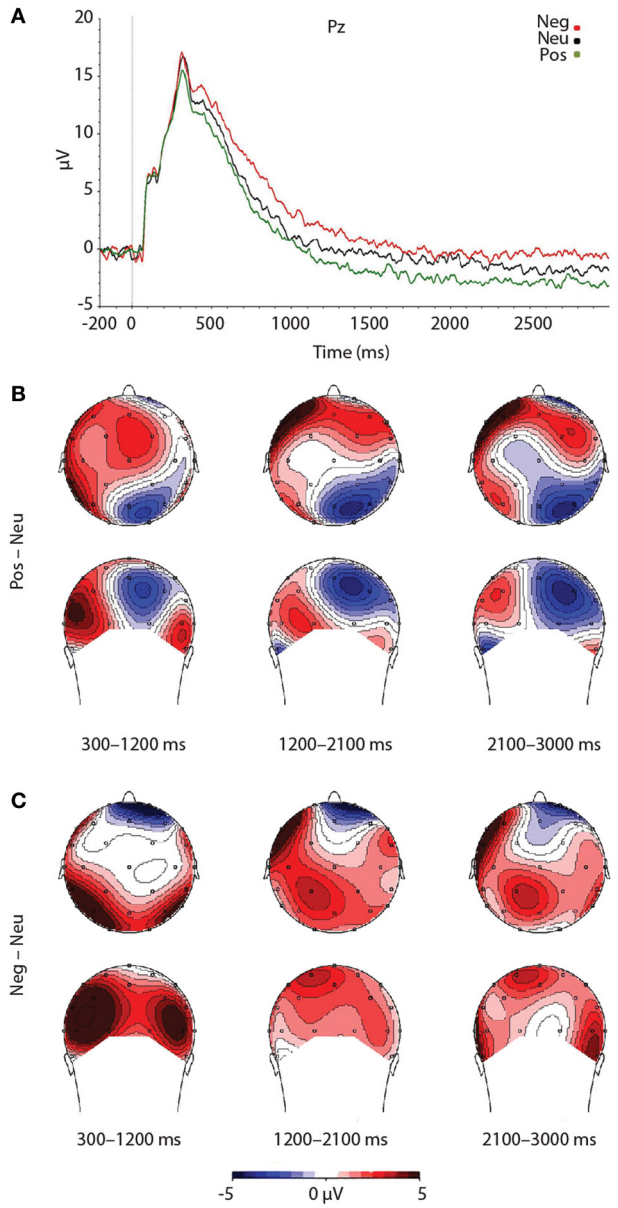

FIGURE 3 | Figure demonstrating: (A) Grand-averaged ERP waveforms of subjects during emotional picture presentation for each valence. The Pz sensor was selected for representing the LPP component over parietal regions, where the LPP was maximal. **(B)** Voltage difference maps across the LPP for negative images, relative to neutral images. **(C)** Voltage difference maps across the LPP for positive images, relative to neutral images. Neg, Negative; Neu, Neutral; Pos, Positive; μV, microvolts; ms, milliseconds.

effect of Temporal Interval on P3 amplitude, $F_{(1,\ 23)} = 17.384$, $p < 0.001$, where P3 amplitudes were larger for early face-targets, relative to late face-targets, $p < 0.001$. The same analyses, ran on the area metric data instead of the amplitudes at peak, yielded comparable results: Main effect of Valence, $F_{(2,\ 46)} = 4.749$, $p = 0.013$; and individual differences in the negative late—neutral late condition, $r = -0.498$, $p = 0.013$.

INDIVIDUAL DIFFERENCES ANALYSIS

To investigate what impact the reactivity to emotional pictures had upon an individuals' recovery speed, we correlated difference scores for the LPP and P3 components in negative and positive conditions, relative to neutral, for both temporal interval conditions. We considered correlations to be significant if the *p*-value was lower than 0.0125 (i.e., $p < 0.05$, Bonferroni corrected for the four conditions of interest: negative early—neutral early, positive early—neutral early, negative late—neutral late, and positive late—neutral late). Temporal specificity was assessed by conducting a test of significant difference between the two correlation coefficients, if a significant correlation was found for one temporal interval condition but not the other (e.g., for negative early—neutral early but not for negative late—neutral late).

We focused our individual difference analyses on the LPP and P3 because both measures yielded a main effect of Valence in the ANOVA. Nevertheless, we conducted the same correlations between the LPP and RT/N170 as a control, despite finding no main effect of Valence in these measures. For the individual difference analysis, we collapsed the LPP across windows (300–3000 ms) and centro-parietal (Cz, Pz) electrodes, in order to increase predictive power, given that only subtle changes in Cz and Pz electrodes were found when the LPP was split into windows, and that the Fz electrode showed little valence modulation.

Relationship between reactivity and recovery

LPP amplitude significantly correlated with P3 amplitude in the negative late—neutral late comparison, $r = -0.611$, $p = 0.002$, thus demonstrating individuals who had larger LPP amplitudes to negative pictures to show reduced P3 facilitation, even interference (i.e., a negative difference score) P3 amplitude on later face-targets presented after these negative images, relative to neutral images (see **Figure 5**). Additionally, temporal interval specificity was found for the negative—neutral LPP-P3 relationship, whereby the two correlation coefficients of negative early—neutral early ($r = -0.017$, $p = 0.937$) and negative late—neutral late significantly differed, $p = 0.0069$. Furthermore, we also found LPP amplitude to significantly correlate with P3 amplitude in the positive early—neutral early comparison, $r = 0.503$, $p = 0.012$. Individuals with larger LPP amplitudes to positive pictures showed an enhanced P3, denoting facilitation (i.e., a positive difference score) on earlier face-targets presented after these positive images, relative to neutral images (see **Figure 6**). This effect was temporally specific for the positive-neutral LPP-P3 relationship, as we found the two correlation coefficients of positive early—neutral early and positive late—neutral late ($r = -0.216$, $p = 0.310$) to significantly differ, $p = 0.0037$. However, the LPP did not predict any other dependent measures of recovery, such as RT or N170 (correlations did not survive Bonferonni correction).

DISCUSSION

In the current study, we found negative pictures to consistently evoke larger LPPs, relative to positive and neutral pictures. Both negative and positive images facilitated target detection of following face-targets, as indexed by increased face-locked P3 amplitudes. This relationship was found for both temporal interval

Table 3 | Summary of means (SD) for each dependent measure as a function of picture valence, separately for early and late temporal interval face-targets.

Measure	Early			Late		
	Negative	Neutral	Positive	Negative	Neutral	Positive
BEHAVIORAL						
RT (ms)	666.06 (139.98)	668.84 (138.55)	667.24 (150.35)	631.73 (128.06)	647.42 (131.51)	641.09 (120.62)
ACC	0.94 (0.04)	0.96 (0.03)	0.95 (0.04)	0.96 (0.04)	0.95 (0.05)	0.95 (0.05)
FACE-LOCKED ERPs						
N170 (μV)	−8.36 (5.21)	−9.35 (5.24)	−8.74 (5.45)	−11.10 (5.81)	−12.03 (5.97)	−11.44 (5.70)
P3 (μV)	19.26 (5.55)	17.46 (5.64)	18.99 (6.49)	15.99 (6.98)	14.89 (7.31)	16.07 (8.00)
IAPS-LOCKED ERPs						
LPP (μV * ms)	2843.84 (4114.14)	1611.45 (3200.67)	535.69 (2636.49)	3259.33 (3327.15)	1808.66 (3186.92)	1248.49 (3779.14)

*IAPS, International Affective Picture System; ERPs, Event-related potentials; N170 and P3 amplitude measured in microvolts; LPP, late positive potential amplitude measured in microvolts * milliseconds; RT, reaction time measured in milliseconds; ACC, proportion accuracy score.*

Table 4 | Summary of means (SD) for the LPP as a function of picture valence, window, and lead.

IAPS-locked LPP at each lead (μV * ms)	Early			Middle			Late		
	Negative	Neutral	Positive	Negative	Neutral	Positive	Negative	Neutral	Positive
Fz	-1855.85_{a} (3346.85)	-770.30_{b} (2883.90)	-904.33_{bc} (3129.23)	-791.99_{a} (2825.47)	-56.04_{ab} (2436.742)	834.71_{b} (2082.33)	-297.19_{a} (3232.13)	231.76_{ab} (2595.35)	1067.98_{b} (2442.37)
Cz	4089.91_{a} (2036.926)	3032.69_{b} (2013.362)	2874.85_{bc} (1808.24)	1694.53_{s} (2307.81)	519.18_{b} (2071.53)	110.99_{b} (1918.96)	1396.79_{a} (2632.48)	-159.69_{b} (2259.08)	-527.82_{b} (2305.09)
Pz	12829.49_{a} (6865.04)	10142.60_{b} (5783.34)	8563.41_{bc} (6241.78)	1285.88_{a} (6958.60)	-474.70_{a} (4963.65)	-2729.79_{b} (5546.25)	-42.03_{a} (6284.98)	-2205.13_{ab} (4582.51)	-3937.41_{b} (5262.74)

*IAPS, International Affective Picture System; LPP, late positive potential amplitude measured in microvolts * milliseconds. Means that do not share subscripts within rows from the same window condition are significantly different at the $p < 0.05$ based on Fisher's LSD post-hoc paired comparisons.*

delays between emotional image offset and face-target onset. However, individual differences in emotional reactivity to negative images and positive images, as demonstrated by the LPP, predicted the extent of interference and facilitation on subsequent face-targets after image offset: (1) The stronger the LPP to a negative image the smaller the P3 amplitude to a subsequent late face-target, thus suggesting a slower emotional recovery in those individuals who responded more strongly to the negative information. (2) The stronger the LPP to a positive image, the larger the P3 amplitude to a subsequent early face-target, therefore indicating a (short-lived) widening of attention in those individuals who responded more strongly to the positive information. No other metrics of emotional recovery (e.g., RT and the N170 component) were shown to be modulated by preceding emotional pictures at the group or individual difference level.

Our findings suggest preceding negative and positive stimuli to reliably modulate attentional processes, as indexed in our study by subsequent face-locked P3 amplitude, similarly to other ERP components (Ihssen et al., 2007; Weinberg and Hajcak, 2011; Brown et al., 2012) and other metrics of attention such as defense startle reflex (Jackson et al., 2003; Larson et al., 2007). Such findings are in line with past behavioral experiments which suggest emotional stimuli to increase attentional vigilance toward following task-relevant stimuli, when the temporal intervals between stimuli are longer (Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010). The main effect of valence was in part not in the predicted direction however, as we expected interference in the early time window, denoted as smaller P3 amplitudes after a negative and positive picture, similar to that reported by Ihssen et al. (2007). In addition, we did not find a valence by temporal interval interaction on P3 amplitude. These findings may reflect the current study design, as we incorporated longer temporal intervals between emotional pictures and face-targets compared to other studies, which have used either immediate presentation (Weinberg and Hajcak, 2011) or shorter temporal intervals (Ihssen et al., 2007; Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010).

Importantly, we found the P3 component to exhibit facilitation, or even interference effects based on valence and temporal interval in the individual difference data, as: (1) larger LPPs to negative relative to neutral pictures significantly predicted smaller P3 amplitudes to faces that were presented later in time, and (2) larger LPPs to positive relative to neutral pictures significantly predicted larger P3 amplitudes to faces that were presented earlier in time. Such effects suggest heightened reactivity to negative and positive stimuli to disrupt or facilitate the processing of following face-targets, dependent on the temporal interval between emotional stimuli and subsequent face-targets. These P3 results,

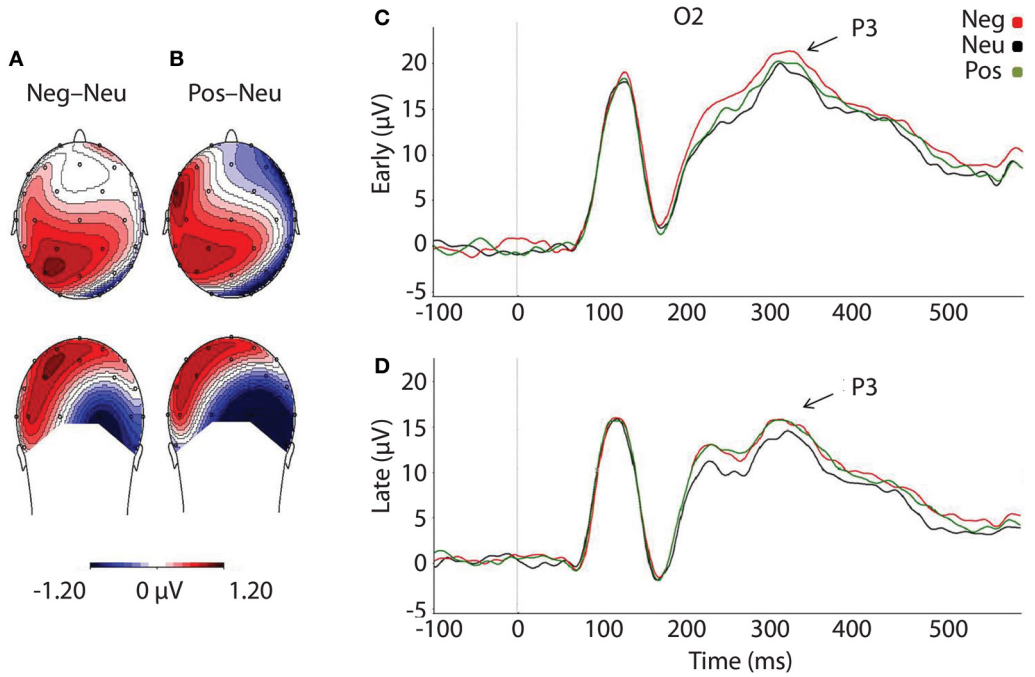

FIGURE 4 | Illustration depicting: (A) Voltage difference map for the P3 component (350 ms) when faces followed negative images, relative to neutral. (B) Voltage difference map for the P3 component (350 ms) when positive images preceded faces, relative to neutral images. **(C)** Grand-averaged ERP waveforms of subjects during face-targets in each valence by early temporal interval condition **(D)** Grand-averaged ERP waveforms of subjects during face-targets in each valence by late temporal interval condition. The O2 sensor was selected for representing the P3 component over the right occipital hemisphere, where the P3 was maximal. Neg, Negative; Neu, Neutral; Pos, Positive; μV, microvolts; ms, milliseconds.

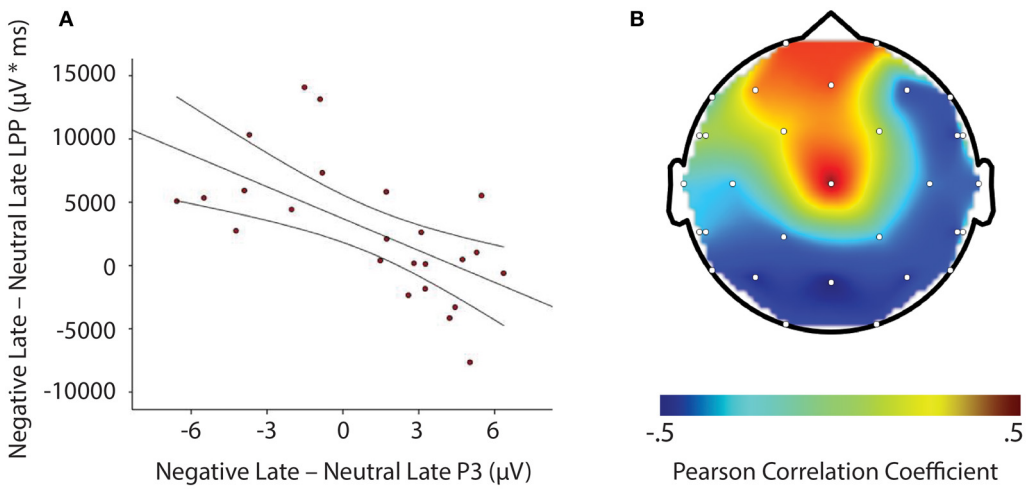

FIGURE 5 | Illustration demonstrating: (A) Correlation of difference scores from negative early minus neutral late conditions for P3 amplitude and LPP amplitude ∗ time. (B) A topographic representation of correlations between P3 amplitude and LPP difference scores from negative early minus neutral late conditions across the entire scalp. Larger LPP amplitudes to negative pictures induce smaller P3 amplitudes to following face-targets that are presented later in time, thus suggesting reactivity to predict recovery outcomes toward an emotional picture stimulus. μV, microvolts; μV ∗ ms, microvolts by milliseconds.

particularly from the negative late condition, are comparable to individual difference findings by Weinberg and Hajcak (2011), who demonstrated that individuals with larger LPPs to emotional images to have smaller parietal P300 amplitude on shape targets that were to be categorized. In contrast, however, the individual differences in this study were dependent on the temporal specificity between the emotional pictures and face-targets. The difference in findings may be due to the current study samples

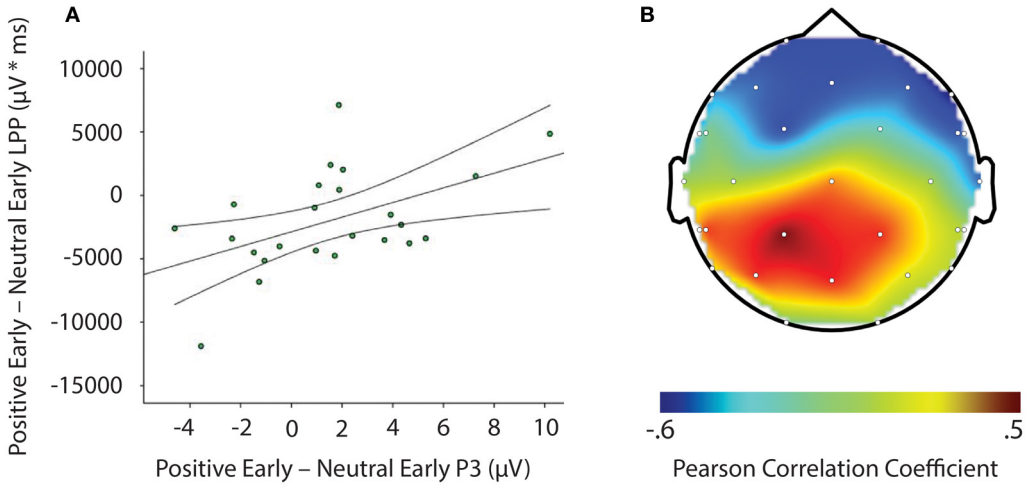

FIGURE 6 | Image signifying: (A) Correlation of difference scores from positive early minus neutral early conditions for P3 amplitude and LPP amplitude ∗ time. (B) A topographic representation of correlations between P3 amplitude and LPP difference scores from positive early minus neutral early conditions across the entire scalp. Larger LPP amplitudes to positive pictures generate enahnced P3 amplitudes to following face-targets that are presented earlier in time. These results suggest reactivity to predict recovery outcomes toward an emotional picture stimulus. μV, microvolts; μV ∗ ms, microvolts by milliseconds.

interpretation of the IAPS content (see Weinberg and Hajcak, 2010) as we found negative pictures to elicit the largest LPP and highest arousal ratings, whilst we found positive images to produce a small LPP and lower arousal ratings than negative images. Nevertheless, the results from this study are novel and highlight the importance of individual differences in temporal dynamics of attention toward emotional events. More specifically, those individuals who allocated more attention to: (1) negative, relative to neutral images showed interference from negative images upon face-targets up to 2400–3500 ms after negative image onset, and (2) positive, relative to neutral images demonstrated facilitation from positive images upon face-targets up to 400–1500 ms after positive image offset. With the current data set, it can be posited that greater sustained attention to affective stimuli may lead to continued processing after offset of the affective stimulus (Davidson, 1998; Hajcak and Olvet, 2008). But what that continued processing consists of is hitherto not clear. Tentatively, we can postulate that it may involve further processing of the emotional events' content and relevance. Understanding this continued processing of emotional stimuli may be vital for identifying maladaptive recovery in affective disorders due to e.g., extreme worry and rumination in anxiety and depression (Siegle et al., 2002; Larson et al., 2007; Nolen-Hoeksema et al., 2008; Heller et al., 2009).

We did not find RT or the N170 component to vary as a function of valence or valence by temporal interval interaction. These observations indicate that early perceptual encoding of faces may not be modulated by previous attentional engagement with valenced information. However, other reports in the literature have also demonstrated mixed results on the influence of emotional picture stimuli on perceptual bottom up processing. For instance, emotional stimuli have been shown to disrupt early ERP components on flash probe tasks but not Gabor tasks (Brown et al., 2012). The N170 results found here may also reflect the longer temporal interval manipulations. More specifically, earlier ERP components have been found to be modulated when the temporal intervals between stimuli are relatively short (Ihssen et al., 2007; Brown et al., 2012). With regards to RT data, we postulate that a combination of task factors may have masked possible attentional effects. Firstly, the demands of the current task may have not been particularly challenging (Brown et al., 2012), as demonstrated by the high accuracy scores found. Secondly, in our task there was large visual disparity between the emotional stimuli and face-targets, whilst previous studies have used the same stimuli for affective primes and task-relevant targets e.g., words (Bocanegra and Zeelenberg, 2009; but see Ihssen et al., 2007). Thirdly, the task used longer temporal distances between emotional pictures and face-targets, whilst in contrast previous studies have enlisted immediate presentation (Weinberg and Hajcak, 2011) or shorter temporal intervals (Ihssen et al., 2007; Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010) between emotional distractor and neutral target presentation. Given these points, the gender categorization task utilized may have been a less sensitive probe for emotional recovery, compared to previous studies (e.g., Ihssen et al., 2007; Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010; Weinberg and Hajcak, 2011). Future research should aim to develop more sensitive task designs, in order to elucidate emotional recovery mechanisms.

Results revealed a main effect of temporal interval, where RTs were shown to be faster and face-locked N170 amplitudes were enhanced when faces were presented in the later temporal interval (e.g., 2400–3500 ms), relative to the earlier temporal interval (e.g., 400–1500 ms). Face-locked P3 amplitudes, however, were shown to be larger in earlier time intervals, relative to later time intervals, indicating a reverse effect to that of the N170. We propose the differential modulation of temporal interval found upon the N170 and P3 to reflect a perceptual enhancement trade-off, where: (1) the N170 to early face-targets is reduced because of the competition between the previous attention demanding stimulus and

face-target, thus resulting in a larger P3 to compensate for this detriment, (2) the N170 to later face-targets is enhanced due to less competition between the previous attention demanding stimulus and face-target, which subsequently allows for re-orienting of attention and anticipation of face-target onset, and therefore this consequently reduces the size of the P3 component. Overall, these behavioral and electrophysiological findings are in line with temporal attention research (for review see Correa et al., 2006), as previous work has shown both early and late ERP components to be reliably modulated by temporal expectations in this fashion when the task at hand is perceptually demanding. These findings indicate the experimental task to be sufficiently robust in producing perceptual effects.

In conclusion, the present study demonstrates emotional events to modulate subsequent processing on face-targets, indexed by the P3 component, but not early perceptual processes on face-targets, indexed by the N170 component. Both negative and positive pictures enhanced P3 amplitude on subsequent face-targets, regardless of whether the temporal interval was early or late between picture and target e.g., 400–1500 ms and 2400–3500 ms. These results indicate emotional stimuli to accentuate attentional processing on subsequent face-targets even during longer temporal intervals (Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010). At the individual level, larger LPP magnitude to negative relative to neutral images was found to predict smaller P3 amplitudes on following face-targets uniquely in the later temporal interval, i.e., 2400–3500 ms, whereas larger LPP magnitude to positive relative to neutral images was found to predict enhanced P3 amplitudes on following face-targets exclusively in the earlier temporal interval, i.e., 400–1500 ms. That is, in the face of overall facilitation, those individuals who responded more strongly to negative stimuli produced attentional interference from the negative stimuli in the late stages of recovery, whilst those individuals who reacted more strongly to positive stimuli produced attentional facilitation from the positive stimuli in the earlier stages of recovery. Overall, these findings confirm the LPP to serve as a useful metric of emotional reactivity (Lang and Bradley, 2010), as well as a useful predictor of emotional recovery (Weinberg and Hajcak, 2011). In addition, the face-locked P3 component can be used as a marker to assess the extent of emotional recovery, similar to that of other measures which show emotion modulation after stimulus offset, such as the N1 (Ihssen et al., 2007; Brown et al., 2012), P300 (Weinberg and Hajcak, 2011) and defense startle reflex (Jackson et al., 2003; Larson et al., 2007). Further work using attentional paradigms in combination with ERP methodology is needed in order to further specify the role of individual differences in emotional reactivity upon attention and emotional recovery. Isolating those psychological processes that are relevant to adaptive emotional recovery may provide important information for researchers aiming to improve health and well-being in those populations where emotional recovery is compromised.

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The impact of anxiety upon cognition: perspectives from human threat of shock studies

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Anxiety disorders constitute a sizeable worldwide health burden with profound social and economic consequences. The symptoms are wide-ranging; from hyperarousal to difficulties with concentrating. This latter effect falls under the broad category of altered cognitive performance which is the focus of this review. Specifically, we examine the interaction between anxiety and cognition focusing on the translational threat of unpredictable shock paradigm; a method previously used to characterize emotional responses and defensive mechanisms that is now emerging as valuable tool for examining the interaction between anxiety and cognition. In particular, we compare the impact of threat of shock on cognition in humans to that of pathological anxiety disorders. We highlight that both threat of shock and anxiety disorders promote mechanisms associated with harm avoidance across multiple levels of cognition (from perception to attention to learning and executive function)—a "hot" cognitive function which can be both adaptive and maladaptive depending upon the circumstances. This mechanism comes at a cost to other functions such as working memory, but leaves some functions, such as planning, unperturbed. We also highlight a number of cognitive effects that differ across anxiety disorders and threat of shock. These discrepant effects are largely seen in "cold" cognitive functions involving control mechanisms and may reveal boundaries between adaptive (e.g., response to threat) and maladaptive (e.g., pathological) anxiety. We conclude by raising a number of unresolved questions regarding the role of anxiety in cognition that may provide fruitful avenues for future research.

Keywords: anxiety, cognition, threat of shock, anxiety disorders, perception, attention, learning and memory, executive function

INTRODUCTION

Anxiety disorders are a major worldwide health problem with sizeable psychological, social, and economic costs (Beddington et al., 2008). The impact of anxiety on cognitive function is a major contributing factor to these costs; anxiety disorders can promote a crippling focus upon negative life-events and make concentration difficult, which can lead to problems in both social and work environments. In such situations the state of anxiety can be seen as *maladaptive*. Anxiety can, however, also improve the ability to detect and avoid danger which, under the right circumstances—such as walking home alone in the dark—can be *adaptive*. The precise impact of anxiety on cognition is, however, unclear. In this narrative review we focus on an emerging, translational, within-subjects state anxiety induction method—threat of unpredictable electrical shock—which may help quantify the impact of anxiety on cognition.

DEFINING COGNITION AND ANXIETY

COGNITION

We define *cognition* as "information processing" (the term comes from the Latin *cognoscere*, which means "to conceptualize," "to know," or "to recognize"). Processing information from the outside world and determining how to use that information increases adaptive strength and reproductive success. In this review, we make broad a distinction between *hot cognition*, which involves affective (i.e., emotionally valenced) information, and *cold cognition*, which involves affectively neutral information. These categories are likely too simplistic, but they have heuristic value as a broad framework in which to dissociate effects. Across both of these cognitive categories, we also make a distinction between (1) *sensory-perceptual processes* (i.e., early processing and detection of stimuli); (2) *attention/control* (i.e., the ability to attend to some stimuli and ignore others); (3) *memory* (i.e., maintenance and retrieval of information); and (4) *executive function* (i.e., complex integrative and decision-making processes). These functions are presented in order of, broadly speaking, ascending phylogenetic "complexity"; perceptual processes occur rapidly, largely in subcortical and posterior cortical circuits, and attention, higher-order learning and executive processes require progressively more complex integration of cortically processed information. There are, of course, many exceptions, but these four broad divisions form the logical hierarchical structure for this review.

ANXIETY

Throughout this paper, we examine the effects of anxiety on the above cognitive functions. To this end, anxiety is defined as the response to prolonged, unpredictable threat, a response which encompasses physiological, affective, and cognitive changes

(Grillon et al., 1991; Grillon, 2008; Davis et al., 2010). According to this definition, anxiety is distinct from fear; a response to acute predictable threats. Fear and anxiety are dissociable at the behavioral, neural, and pharmacological level (Grillon et al., 1991; Grillon, 2008; Davis et al., 2010). Anxiety states appear to be well-conserved across numerous species, and as such (similarly to fear), they confer adaptive value. Specifically, in unfamiliar and uncertain environments, cautious avoidance while maintaining heightened vigilance and action readiness for signs of imminent danger improves survival odds (Kalin and Shelton, 1989). However, if this behavior is adopted permanently it can become maladaptive.

In this review, we focus on functional responses evoked in healthy volunteers using the translational threat of shock paradigm, an experimental model of anxiety which operationalizes anxiety in the same manner as our definition above—as responses to prolonged unpredictable threats. These threats are non-contingent upon the task and are rare and uncontrollable.

Why do we need human models of anxiety? By examining anxiety under carefully controlled conditions, we can clarify cause-effect relations and bridge the gap between the human and animal literatures on anxiety. Although human models have important limitations (e.g., no knockout models or single cell recording), they also present the key advantage of taking into account certain features of behavior and higher-order cognition that cannot be modeled in animals (e.g., subjective, conscious experiences, or language). Human models of anxiety, such as threat of shock, do not model a pathological state but an adaptive response. As such, they provide research tools to study *functional* responses, which are a prerequisite to identifying dysfunctional mechanisms. Despite the ubiquity of anxiety, and the global burden of maladaptive anxiety (Beddington et al., 2008), our understanding of the neural, systems, and psychological mechanisms underlying anxiety-cognition interactions is surprisingly lacking.

The objectives of this review are thus two-fold, (1) to describe the effect of induced-anxiety on various cognitive processes and (2) to identify commonalities and differences with these cognitive processes in pathological anxiety and, where possible, in high dispositionally (i.e., trait) anxious individuals (see **Table 1** for a thorough definition of these different types of anxiety). The guiding principle of this review is that on the one hand, where commonalities exist, the threat of shock paradigm can be used as an analog of pathological anxiety. On the other hand, when differences are identified, they may point to important boundaries between adaptive and maladaptive states.

SENSORY-PERCEPTUAL PROCESSING

Sensory-perceptual processing is the most basic level, and the foundation of all other cognitive processing. In this context, we define sensory-perceptual processes as the early (i.e., the most temporally immediate) processing and detection of environmental stimuli (e.g., auditory tones or discrete visual cues). We examine tasks assessing (1) early sensory processing and (2) gating of early sensory processing. These tasks largely utilize affectively neutral stimuli and hence fall into the broad category of "cold" cognitive functions. Following this, we also examine (3) emotional perception which falls under the category of hot cognitive processing. The effect of both anxiety disorders and threat of shock on such processes may illuminate, in particular, a profile of the adaptive effects of anxiety. Specifically, threat of shock studies point to enhanced sensory-perceptual processing across multiple stimulus modalities as a function of anxiety. There seems, moreover, to be a hierarchy of influence with threat of shock having increasing influence on stimuli that may more likely announce a potential threat (**Table 2**). These findings point to a fundamental shift whereby sensory-perceptual systems are dynamically reconfigured during anxiety states to be more sensitive to sensory perturbations. Early threat detection is adaptive because it facilitates preparation for potential danger, but it can be maladaptive when innocuous stimuli are coded as threatening and when goal-directed behavior is consistently disrupted.

COLD COGNITION

Early sensory-perceptual effects

In general, anxiety sensitizes sensory cortical systems to innocuous environmental stimuli. Supporting evidence for this claim comes predominantly from abnormalities in the mismatch negativity (MMN)-evoked response in clinically anxious and vulnerable populations. The MMN (and magnetic MMN) is elicited by passive oddball procedures in which relatively rare stimuli are embedded in an otherwise uniform sequence of stimuli (e.g., deviation in auditory tone frequency). This evoked response component, which occurs between 150 and 250 ms in the post-stimulus period, is thought to reflect preattentive change detection. Auditory MMN amplitudes have been shown to be abnormally increased in two independent samples of unmedicated patients with PTSD (Morgan III and Grillon, 1999; Ge et al., 2011) and dispositional anxiety has also been shown to positively correlate with MMN amplitudes (Hansenne et al., 2003). Consistent with these findings, an investigation of threat-induced anxiety in healthy individuals found amplified cortical responding to auditory stimulus deviance (Cornwell et al., 2007), confirming that these preattentive effects are state-related.

The evidence also suggests that anxiety-enhanced sensory-perceptual processing precedes cortical involvement. Notably, ERP studies have shown that brainstem (wave V) responses to simple auditory stimulation are increased in patients with panic disorder (Knott et al., 1994) and children with high dispositional anxiety (Woodward et al., 2001). These findings suggest that anxiety boosts auditory signaling very early (∼10 ms) in the afferent pathway at the relatively primitive level of the inferior colliculus. Using threat of shock, Baas et al. (2006) demonstrated the same result of increased wave V amplitudes in healthy subjects, extending key findings from the animal literature (Maisonnette et al., 1996) to humans.

These studies of auditory processing thus illustrate a close correspondence between findings of increased sensory-perceptual responding in patient and vulnerable populations and the effects of threat of shock in healthy subjects. There are two counterexamples to note, however. Menning et al. (2008) reported *reduced* MMN responses in a small PTSD sample, but medication status was not reported; thus, the significance of this potential exception cannot be properly evaluated. From the developmental literature, Reeb-Sutherland et al. (2009) reported no MMN

Table 1 | Definitions of anxiety.

(A) ANXIETY DISORDERS:

(1) Pathological anxiety

Pathological anxiety is associated with persistent and debilitating apprehension about negative future events, and it can have a wide range of effects on cognitive performance, including facilitative effects (e.g., threat detection) as well as detrimental effects (e.g., distractibility). Indeed, the DSM-IV definitions of anxiety disorders prominently feature "difficulty concentrating" as a key symptom. DSM-IV defines a number of different anxiety disorders including generalized anxiety disorder (GAD), phobias, panic disorder, post-traumatic stress disorder (PTSD), and obsessive–compulsive disorder [OCD; although this disorder is now thought to be more of a compulsivity disorder than an anxiety disorder (Fineberg et al., 2009)]. It should be noted that it is rare to find a patient who suffers a "pure" anxiety disorder because the rates of co-occurrence with depression are very high (Mineka et al., 1998; Kessler et al., 2012) and it is unclear how many of these symptoms can be attributed to anxiety alone.

(B) ANXIOUS STATES:

(2) The threat of shock paradigm

The threat of shock technique is a robust, translational (Davis et al., 2010), and well-validated (Schmitz and Grillon, 2012) within-subjects anxiety induction technique in which subjects are told that they are at risk of infrequent electrical shocks. Whilst anticipating the shocks subjects can be tested upon a cognitive task. This can alternate with a "safe" no shock condition to directly manipulate state anxiety *within subjects*. Such designs have a number of advantages; each subject acts as his or her own control; the psychological state of interest (i.e., anxiety) is directly manipulated; and the heterogeneities (e.g., comorbidities) of patient populations are avoided (Robinson et al., 2012b).

(3) Self-report questionnaire measures

Another popular approach to examining the impact of anxiety on cognition is through the use of non-diagnostic questionnaires to determine a disposition to anxiety [e.g., Spielberger trait anxiety scale (Spielberger et al., 1970)] or the BIS/BAS ("behavioral approach system behavioral avoidance inhibition system"; Carver and White, 1994) that seek to capture stable attributes of anxiety, including specific triggers (e.g., public speaking, mathematical problem solving, test-taking). Dispositional/trait anxiety scores are then correlated with task outcomes or, alternatively, a median split approach compares high and low anxious subjects. Dispositional anxiety is often viewed as a vulnerability factor in the development of psychopathology but there are multiple differences when comparing across induced and dispositional anxiety. It should be noted that neither pathological nor dispositional anxiety can be turned on and off (e.g., for memory tasks, effects on encoding, and retrieval cannot be studied separately) or studied in isolation. It is therefore important to note that their associated effects cannot be irrefutably attributed to anxiety versus another related aspect of the disorder [e.g., personality factors, cognitive diathesis (Abramson et al., 2002)]. Moreover, there are a number of statistical concerns regarding self-report approaches (Shackman et al., 2006). For example; correlational analyses are not directional, median split analyses, or other extreme-groups (categorical; e.g., upper/lower tercile or decile) approaches can result in arbitrary cut-offs. In the present text we refer to studies utilizing this methodology specifically as *dispositional anxiety* studies; in contrast with the *induced-anxiety* evoked by threat of shock.

(4) Other state anxiety paradigms

In addition to threat of shock, there are number of other common stress/anxiety inductions including social (speech) stressors, cold pressor tests (where the hand is submerged in cold water), and viewing anxiety-inducing movies or pictures. Although this review does not focus on these techniques, they are occasionally referenced where they illuminate differences or can help interpret results under threat of shock. One key problem with some of these manipulations (such as anxiety-inducing movies) is that they are often between-session manipulations performed once at the start of a study visit, with testing following manipulation. As such, it can be unclear whether they reveal the effects of anxiety or the recovery from a stressor (Shackman et al., 2006).

Table 2 | Effects of anxiety on sensory-perceptual processing (arrows represent direction of effect).

Domain	Task details	Threat of shock		Anxiety disorders	
			References		References
Early sensory	Presentation of sounds/pictures	↑	Baas et al., 2006; Cornwell et al., 2007; Laretzaki et al., 2010; Shackman et al., 2011a	↑	Knott et al., 1994; Morgan III and Grillon, 1999; Woodward et al., 2001; Ge et al., 2011
Sensory gating	Ocular motor response to sound	↑	Davis, 1998; Grillon, 2002#	↑	Grillon, 2002#
Sensory gating	Startle attenuated by cue (PPI)	↑	Grillon and Davis, 2007; Cornwell et al., 2008	=	Grillon et al., 1996; Ludewig et al., 2002; Hoenig et al., 2005
Emotion perception	Detection of negative information	↑	Grillon and Charney, 2011; Robinson et al., 2011, 2012a	↑	Monk et al., 2006; Blair et al., 2008; Roy et al., 2008

#, =: review paper.

differences between two adolescent groups that differed in dispositional anxiety. Surprisingly, each group contained a similar proportion of individuals with current anxiety, which seems to be the more relevant factor in modulating sensory-perceptual systems and thus potentially explains the lack of a difference in MMN response. Moreover, although there is no comparable work in patient populations, evidence from the visual system also indicates that early sensory processing of neutral stimuli (within 100 ms) is augmented under threat of shock, both in terms of higher-evoked response amplitudes (Shackman et al., 2011a) and

faster latencies (Laretzaki et al., 2010). Altogether, anxiety states appear to fundamentally alter central sensory pathways and profoundly shape bottom-up signaling to enhance the detection of even slight changes in the environment.

Sensory gating effects

Sensory gating refers to filtering mechanisms that constrain afferent signaling to allow for elaborative processing of certain stimuli. The evidence from sensory gating is mixed, but may highlight the distinction between acute and chronic effects of anxiety. Increased sensory-perceptual sensitization under anxiety may lower detection thresholds for threat stimuli, but could also overload sensory systems. One key example of sensory gating is prepulse inhibition (PPI) of the startle reflex (Grillon et al., 1991). In addition to the phylogenetically-preserved potentiation of startle responses during fear and anxiety states (Davis, 1998; Grillon, 2002), it is well-established that startle responses are diminished when a weak, non-startling stimulus (prepulse) precedes the startling stimulus by a short interval (e.g., 120 ms; Blumenthal et al., 1999). Although most clinical work has focused on schizophrenia (Braff et al., 2001), potential PPI abnormalities have been studied in clinically anxious and vulnerable populations. Reduced PPI has been documented in panic disorder (Ludewig et al., 2002), obsessive-compulsive disorder (Hoenig et al., 2005) and PTSD (Grillon et al., 1996). These patients show little or no diminution of startle reactivity when the startling stimulus is preceded shortly by a weak prepulse. Evidence from measures of dispositional anxiety is less clear, with some providing additional data of reduced PPI in high anxiety and other vulnerable populations (Corr et al., 2002; Duley et al., 2007; Franklin et al., 2009), and others reporting null results (Grillon et al., 1997; Lipschitz et al., 2005; De Pascalis et al., 2013).

Two studies investigated how PPI might be modulated during sustained threat of shock (Grillon and Davis, 2007; Cornwell et al., 2008). In stark contrast to the findings above, they reported *enhanced* PPI using various prepulse stimuli (acoustic and tactile) under threat-induced anxiety. These divergent results—that anxiety patients exhibit impaired sensory gating (decreased PPI) and healthy subjects show enhanced sensory gating (increased PPI) in a threat-induced anxiety state—deserve an explanation. We can speculate that while anxiety induced by threat of shock closely models the immediate effects of negative arousal and anticipation, it does not capture the long-term (chronic) effects of stress and worry. Threat-induced anxiety states increase PPI via facilitation of sensory-perceptual processing of weak stimuli. Sensory gating mechanisms may, however, deteriorate with persistent increased sensory-perceptual sensitization, leading to reduced PPI over the long-term.

HOT COGNITION

Emotional perception

While threat-induced anxiety can boost sensory-perceptual processing in general, it also selectively improves the processing of extrinsically and intrinsically salient stimuli. The discussion thus far has focused on studies employing simple, innocuous stimuli to study early sensory-perceptual effects. But even there we find evidence that the relative significance of some stimuli is preserved in terms of modulating sensory-perceptual responses. For instance, an infrequent oddball stimulus boosts auditory cortical processing relative to the repetitive, standard stimulus (Cornwell et al., 2007). In this case, the relative significance of the auditory stimuli is extrinsically driven by the probability of their occurrence, as though rare (i.e., unexpected) changes in the environment are especially salient in an anticipatory anxiety state (perhaps in terms of predicting imminent danger). A similar effect of threat-induced anxiety has been observed when stimuli are made relevant by task instructions (Eason et al., 1969).

More conclusive evidence that anxiety enhances sensory-perceptual processing comes from studies that include intrinsically salient stimuli. Facial displays of emotion have been heavily-used in this regard (see e.g., Haxby et al., 2000; Phillips et al., 2003). Clinical populations show comparable biases toward aversive relative to appetitive face across behavioral and neural dimensions (Monk et al., 2006; Blair et al., 2008; Roy et al., 2008), as do individuals with increased dispositional anxiety (Cools et al., 2005; Telzer et al., 2008). However, few studies have used threat of shock to determine how state anxiety may alter facial emotion processing. Behavioral measures have been used to show that compared to facial expressions of happiness, fearful expressions are correctly identified more rapidly during threat than safe conditions (Robinson et al., 2011). A follow-up fMRI study replicated this behavioral finding and provided evidence of potential neural correlates of this effect including increased prefrontal-amygdala coupling (Robinson et al., 2012a). Similarly, research has shown that while static facial displays of fear do not alone increase startle reactivity relative to neutral emotional displays, they do so if they are presented during periods of threat of shock (Grillon and Charney, 2011). These results suggest that threat-induced anxiety can boost sensory-perceptual processing of affectively-congruent stimuli, such as fearful faces that convey the more relevant signal while anticipating shock, but the methodology (e.g., sluggish fMRI response, delayed startle onset) leaves open (in contrast to the above early sensory processing findings) the possibility that other downstream cognitive processes are influencing these biases (Pessoa, 2005). Finally, a recent study examined the impact of modulating expectancy of fearful and happy faces by pairing them with neutral cues. This task revealed that threat of shock increased responses to *unexpected* fear (but not happy) faces (i.e., prediction errors) in the striatum (Robinson et al., 2013b) indicating a bias toward detecting *novel* threats under anxiety. In some respects this can be seen as adding an affective component to the MMN stimulus deviation effect outlined above (Cornwell et al., 2007).

As a contrast to studies demonstrating enhanced processing of aversive stimuli one study (Bublatzky et al., 2010) presented negative, positive, and emotionally-neutral pictorial stimuli under threat and safe conditions, but found that only the positive pictures elicited differential electrophysiological activity across contexts. In general, however, a bias toward processing negative emotional information seems to be relatively consistent across threat of shock, anxiety disorders, and dispositional anxiety.

ATTENTION/CONTROL

Anxious patients suffer from debilitating intrusive thoughts and feelings as well as dysregulated attention mechanisms [e.g., distractibility, impaired concentration (Eysenck et al., 2007)].

These symptoms have been linked to attentional bias for threat. Individuals with anxiety disorders or dispositional anxiety show a proclivity to detect and process threat-related information, which interferes with performance in various attentional tasks (Bar-Haim et al., 2007). However, it has become increasingly apparent that some of these deficits may be secondary to or occur in the context of a poor ability to use attentional resources (cognitive control) to flexibly adjust attention in the face of changing environment (Derryberry and Reed, 2002; Eysenck et al., 2007). Thus, attention problems in anxiety are complex and may result from an imbalance between bottom-up stimulus-driven processing (see previous section) and top-down attention control. This section is concerned with the literature on anxiety effects on attention control and attentional bias that may contribute to attention problems and distractibility. The first section focuses on non-emotional conflict, a "cold" cognitive function, while the last section deals with two "hot" cognitive functions, attentional bias and emotional interference.

While there is increased consensus indicating that "anxiety" promotes attentional bias for threat and has a detrimental effect on control processes, a closer look at the data reveal a more complex picture. There is convergent evidence for attentional bias in anxiety disorders, dispositional anxiety, and state anxiety. However, there is no similar convergent evidence of anxiety's negative effect on control processes. In general, deficits in attentional control have been reported in clinical and dispositional anxiety, but not for anxiety induced by threat of shock. If anything, induced-anxiety is associated with better attention control (Hu et al., 2012; Robinson et al., 2012b), possibly because of improvement in the selectivity of attention (Easterbrook, 1959) (**Table 3**).

COLD COGNITION

Non-emotional control

Increased distractibility, attentional lapses, inability to maintain attention, poor concentration, and intrusive thoughts could be secondary to amygdala-based hyper-active threat detection mechanism (Mathews and Mackintosh, 1998). However, these maladaptive behaviors also occur in the absence of external threat, raising the possibility that anxiety is associated with a general impairment in attention control (Bishop, 2009; Shin et al., 2011; Stout et al., 2013). Perhaps the most prominent model to explain deficit in cognitive performance in anxious individuals is the dual competition framework that describes the interaction between cognition and emotion (Pessoa, 2009). The model proposes that task-irrelevant threat information competes for central processing resources with cognition, potentially impairing cognitive processes (Pessoa, 2009). An extension of this model is that tasks that require attentional resources because of conflict or interference will be more affected than tasks with little conflict or interference or tasks that rely on automatic and habitual responses, which are not affected (or potentially facilitated) (Spence and Spence, 1966). An alternative is that anxiety improves the selectivity of attention because it restricts attention to peripheral cues, facilitating tasks with restricted number of cues compared to multi-cues tasks (e.g., Easterbrook, 1959). Lastly, poor attentional control could also result from sensitized perceptual processing (see above Sensory-perceptual processing). Indeed, threat of shock has dissociable effects on information processing, facilitating early perceptual processes but impairing subsequent evaluative processing (Shackman et al., 2011a,b).

So far the literature points to diverging interference effects in clinical and dispositional anxiety compared to threat of shock-induced anxiety. Clinical and dispositional levels of anxiety are both associated with enhanced interference, a finding that is consistent with the dual competition framework. In contrast, the relatively scarce studies using threat of shock tend to find *reduced* interference, suggesting that elevated anxiety states improve the selectivity of anxiety, as suggested by Easterbrook (1959). Most of the claims of poor attentional control are based on studies with individuals scoring high on measures of dispositional anxiety (Eysenck et al., 2007; Hajcak and Foti, 2008; Bishop, 2009), rather than patients with a clinical disorder. In addition, while deficits in cognitive control brain areas have been documented in clinically and dispositionally anxious populations, these deficits do not always translate into performance

Table 3 | Effects of anxiety on attentional bias and attention control tasks (arrows represent direction of effect).

Domain	Task details	Threat of shock		Anxiety disorders	
			References		References
Attention bias	Emotional Stroop bias toward threat	↑	Edwards et al., 2006, 2010	↑	Bar-Haim et al., 2007#
Attention bias	Dot-probe bias toward threat	↓	Shechner et al., 2012	↑	Bar-Haim et al., 2007#
Emotional interference	Emotional interference task	↑	Cornwell et al., 2011		N/A
Emotional conflict	Emotion conflict task	=	Robinson et al., 2011	↑	Etkin et al., 2010; Etkin and Schatzberg, 2012
Conflict adaptation	Emotion conflict task	=	Robinson et al., 2011	↓	Etkin et al., 2010; Etkin and Schatzberg, 2012
Non-emotional control	Interference on Classic Stroop	=	Tecce and Happ, 1964	↑	Litz et al., 1996; Lagarde et al., 2010
		↓	Agnew and Agnew, 1963; Tecce and Happ, 1964; Hu et al., 2012		
		↓	Choi et al., 2012		

#, =: review paper.

deficits, perhaps because anxious individuals recruit additional processing resources (Eysenck et al., 2007). Indeed, several studies have examined the performance of anxious patients in the classic color-naming Stroop (Stroop, 1935) with mixed behavioral results as both normal and impaired performance have been reported (Litz et al., 1996; Lagarde et al., 2010; Thomaes et al., 2012). Similar results have been obtained with other measures of cognitive control. For example, obsessive compulsive disorder and generalized anxiety disorders are associated with abnormal neural signs of control monitoring, as reflected in enhanced error detection mechanisms (i.e., error-related negativity; Vaidyanathan et al., 2012), without concomitant performance impairment (Stern et al., 2010; Weinberg et al., 2012).

Several studies have examined the effect of threat of shock on Stroop [or Stroop-like tasks (Choi et al., 2012), Go/NoGo (Robinson et al., 2013a), and anti-saccade tasks (Cornwell et al., 2012b)]. While all these experiments, especially Go/NoGo and anti-saccade, require some degree of control of prepotent responses, only Stroop examines interferences from task-irrelevant stimuli. Stroop findings are somewhat inconsistent with studies showing no specific influence of threat of shock on Stroop effect (Tecce and Happ, 1964) as well as impaired (Pallak et al., 1975; Choi et al., 2012) or improved (Hu et al., 2012) performance. This inconsistency could be attributed to procedural differences, especially among older non-computerized studies (Pallak et al., 1975; Choi et al., 2012). Recently, Choi et al. (2012) used a Stroop-like "response-conflict" task in which subjects had to identify whether a picture was a house or a building while ignoring task-irrelevant congruent and incongruent words (i.e., house, bldng) printed in the middle of the pictures. Shock anticipation impaired performance on the incongruent trials (Choi et al., 2012), which the authors interpreted in the context of the dual competition framework (Pessoa, 2009), i.e., shock threat monitoring competes for central resources adversely impacting conflict processing (Choi et al., 2012). However, these results were not confirmed in another study by the same group. In fact, Hu et al. (2012) found that shock threat *improved* performance on the classic Stroop. Because improved performance was accompanied by a general increase in reaction time to the congruent and control trials, it was suggested that the better ability to resolve the conflict was caused by the adoption of a more cautious approach, trading slower speed for better performance accuracy (Agnew and Agnew, 1963; Tecce and Happ, 1964; Hu et al., 2012). It seems that adopting cautious behavior would be adaptive when anxious because it would prevent any potential impulsive response that could have devastating consequence. However, it is unlikely that shock-induced anxiety generally leads to what could be considered a cautious pro-active behavior set (Braver, 2012). Most threat of shock studies do not report a slowdown of reaction time across a wide variety of tasks (Shackman et al., 2006; Cornwell et al., 2012b; Vytal et al., 2012; Robinson et al., 2013a,b). In fact, and consistent with some models (Spence and Spence, 1966), threat of shock *facilitates* habitual responses (Cornwell et al., 2012b).

Threat of shock-mediated performance improvement during Stroop tasks may be due to a narrowing of attention that restricts attention to peripheral distracting cues (Easterbrook, 1959). This possibility is supported by a number of studies using stressors other than shock such as ego threat, time pressure, or loud noises, which have been shown to reduce stress interference on conflict and Stroop tasks (O'Malley and Poplawsky, 1971; O'Malley and Gallas, 1977; Chajut and Algom, 2003; Booth and Sharma, 2009). This may be due to a general increased in non-specific arousal. Indeed, drugs that increased physiological arousal also reduce Stroop interference (Callaway, 1959; Kenemans et al., 1999).

Further evidence that threat of shock can facilitate attention to specific stimuli comes from a recent study of sustained attention (Robinson et al., 2013a). Vigilance or sustained attention is the ability to maintain attention and alertness during prolonged and monotonous tasks. The maintenance of attention is highly dependent on attentional control; failure of attentional control leads to attentional lapses and off-task thinking (Mcvay and Kane, 2010). Robinson et al. examined the impact of threat of shock in a task in which subjects responded to highly frequent "go" stimuli but withheld responses to very infrequent neutral "nogo" targets. Threat of shock significantly reduced errors of commission (i.e., accidentally pressing during nogo targets) while having no effect on go trials or overall reaction time. This indicates that threat of shock serves to improve response inhibition by focusing attention on the infrequent nogo targets.

If stress facilitates conflict processing, then why did threat of shock impair performance during Choi et al.'s (2012) conflict-response task and Pallak et al.'s (1975) Stroop task? One possibility is that these tasks may not have been sufficiently difficult to fully occupy attentional resources. When a task does not completely occupy attentional resources, available resources can be allocated to task-irrelevant distractors, interfering with the task at hand (Bishop, 2009; Vytal et al., 2012, see also below). Choi et al.'s task was clearly not as taxing as the Hu et al.'s task. Overall reaction time in the former task was faster and accuracy in in congruent trials was much higher than in the latter task (∼740 ms/3.1% errors and 960 ms/14% errors, respectively in the safe condition). Similarly, there was little time pressure in the Pallak et al.'s study. Clearly, differences in processing loads may impact the effect of anxiety on performance, a possibility that is further discussed in the memory section below.

HOT COGNITION

Attentional bias

Cognitive models of anxiety have been influential in postulating attentional bias operating at an early stage of information processing. Specifically, attentional bias for threat may play a prominent role in the etiology and maintenance of anxiety disorders (Mogg and Bradley, 2005; Bar-Haim et al., 2007; Cisler and Koster, 2010; Macleod and Mathews, 2012). There is substantial evidence showing that dispositionally and clinically anxious individuals exhibit an attentional bias toward or away from threat (Mogg and Bradley, 2005; Bar-Haim et al., 2007; Cisler and Koster, 2010; Macleod and Mathews, 2012), a finding that tends to be replicated by threat of shock. However, the nature, mechanisms, and contexts of these biases remain to be clarified.

Initial studies indicated attentional bias toward threat in clinical and dispositional anxiety (see Cisler and Koster, 2010). However, more recent studies have demonstrated qualitatively different types of threat biases, including preferential engagement, difficulty in disengagement, or attentional avoidance (Cisler and Koster, 2010; Sheppes et al., 2013). There is

now increased effort to characterize the underlying mechanisms of these components of attentional biases as well as the information processing stage at which they occur (Bar-Haim et al., 2007; Sheppes et al., 2013). Understanding the nature of anxiety mediated bias is crucial from a theoretical and a practical viewpoint. Theoretically, it is important to understand the underlying attentional mechanisms of these biases given their potential role as vulnerability markers (Bar-Haim et al., 2007). Practically, a better understanding of these mechanisms may help improve bias modification techniques aimed at changing the selective bias to threat. Such techniques show therapeutic promise as a novel treatment for anxiety (Macleod and Mathews, 2012).

There is substantial evidence that biases are not inflexible, but are, in fact, very plastic and strongly influenced by environmental stressors (Bar-Haim et al., 2010; Wald et al., 2013). These results suggest that state anxiety is a key variable in the modulation of bias (Mathews and Sebastian, 1993; Helfinstein et al., 2008). Yet, relative to the large literature on bias in clinical and dispositional anxiety, little is known about how state anxiety impacts biases. Threat of shock may be an ideal assay to investigate bias plasticity.

The two most common procedures employed to examine attentional bias are the emotional Stroop and the dot-probe tests. The emotional Stroop, which is a variation of the classic Stroop (Stroop, 1935) interference task (see below), consists of threat-related (e.g., death) and neutral (e.g., chair) words printed in varying colors (e.g., death printed in red). The subjects' task is to name the color of the word while ignoring its semantic content. Despite their high similarity, the nature of the interference in the classic Stroop and emotional Stroop are highly different. The classic color-naming Stroop examines the conflict produced by semantic incompatibility. The interference is not caused by conflict in the emotional Stroop, but by attentional capture by the emotional stimulus (Algom, 2004; Buhle et al., 2010). The emotional Stroop has been criticized because of difficulties interpreting results in term of attentional engagement and disengagement (Cisler and Koster, 2010). The dot-probe addresses some of these limitations. In the dot-probe task, word pairs, one threat-related, and one neutral are presented briefly on the screen. Subjects are required to respond as quickly as possible to a small visual stimulus that replaces one of the words following their removal. An attentional bias toward or away from threat is revealed when subjects are faster or slower, respectively, to respond to a probe that replaces a threat word relative to neutral word. Three studies examined the influence of anxiety evoked by threat of shock using the emotional Stroop in low and high dispositional anxiety individuals (Miller and Patrick, 2000; Edwards et al., 2006, 2010). Low dispositional anxious subjects displayed no attentional bias, including when they were anticipating shocks. Edwards et al. (2006, 2010) found that while high dispositional anxious subjects had no attentional bias in the control no shock condition, color-naming of threat words was delayed during shock anticipation (Edwards et al., 2006, 2010). In contrast, in another study, high dispositional anxious subjects exhibited delayed color-naming responses to threat words in the no shock control condition, an effect that was not affected by threat of shock (Miller and Patrick, 2000). The discrepancy among these studies may be explained by the different levels of dispositional anxiety of the high dispositional anxious groups. The mean dispositional anxiety score was 20% higher in the high dispositional anxious subjects in Miller and Patrick's study (54.4) compared to the Edwards et al. (2006, 2010) studies (46 and 45, respectively). Miller and Patrick's results are consistent with the literature that has documented delayed color-naming threat words in high dispositional anxiety (Bar-Haim et al., 2007), probably because high dispositional anxiety is also associated high *state* anxiety (Macleod and Mathews, 1988). Thus, threat of shock may have failed to further increase the magnitude of the effect because of a ceiling effect. These results are consistent with the proposition that in non-clinically anxious individuals, attentional bias is an interactive function of dispositional anxiety and state anxiety due to a current stressor (Macleod and Mathews, 1988).

So far, a single study has examined the effect of threat of shock on attentional bias using the dot-probe. Shechner et al. (2012) showed that under threat of shock subjects took longer to respond to a probe that followed a threat cue compared to a neutral cue, indicating vigilance away from threat (Shechner et al., 2012). These results are consistent with evidence from naturalistic studies that have demonstrated attention *away* from threat cues during combat stimulation (Wald et al., 2011) or exposure to rocket attacks (Bar-Haim et al., 2010). The apparent contradiction in the effect of threat of shock in the emotional Stroop and the dot-probe may be due to the fact that these two tests probe different aspects of bias. The emotional Stroop may engage late control processes and the dot-probe early attentional processes (Macleod et al., 1986; Bar-Haim et al., 2007). The construct of the bias within each task is also a matter of debate. It has been argued that the emotional Stroop reflects an affective reaction (i.e., a perceptual bias as outlined above) rather than an attentional process (Algom, 2004). Similarly, it is unclear whether biases associated with the dot-probe are related to disengagement difficulties or to initial orienting (Salemink et al., 2009; Clarke et al., 2013). Note, however, that it is also possible that the data from the emotional Stroop and dot-probe tests are consistent. Interference by threat cues in the emotional Stroop may reflect effortful avoidance of processing threat cues rather than attentional capture by these cues (De Ruiter and Brosschot, 1994). According to this view, threat of shock would promote threat cue avoidance, a conclusion that is consistent with a number of studies that have shown that stress can lead to a shift of attention away from danger cues (Mathews and Sebastian, 1993; Amir et al., 1996; Chen et al., 2002; Garner et al., 2006; Helfinstein et al., 2008). It may therefore be that, consistent with the emotion perception studies highlighted above (**Table 1**) (Grillon and Charney, 2011; Robinson et al., 2011, 2012a), anxiety biases the processing of threats, but the different tasks assess different adaptive responses (i.e., approach or avoidance) to these threats.

Recently, Etkin et al. (2006, 2010) introduced a novel emotion conflict Stroop-like procedure. The task requires subjects to identify the expression of a face (fearful or happy) while ignoring words "happy" or "fear" superimposed on the faces (Etkin et al., 2006). This paradigm provides a measure of two important aspects of interference, conflict detection and conflict regulation. Emotional conflict detection is the classic detection of incongruence, which results in delayed responses to incongruent

trials. Conflict regulation or adaptation is the improvement of these delayed responses to incongruent trials when they follow incongruent trials, suggesting activation of emotional regulatory mechanisms (Etkin et al., 2010). Investigations of these regulatory mechanisms are in their infancy but could provide useful in understanding implicit emotional regulation (Etkin et al., 2010). Generalized anxiety disorder and panic disorder are associated with impaired conflict adaptation (Chechko et al., 2009; Etkin et al., 2010; Etkin and Schatzberg, 2012). Individuals with vulnerability to anxiety disorders due to high trait anxiety or behavioral inhibition do not show such impairment (Jarcho et al., 2013; Krug and Carter, 2012). Similarly, in the only threat of shock study conducted so far, conflict adaptation was unaffected by the anticipation of shock (Robinson et al., 2011). These results suggest that poor emotional conflict adaptation may be associated with the disease process rather than being a vulnerability marker or an outcome of state anxiety.

One leading explanation for the attentional bias in anxiety is that threat-related stimuli have a special status, namely that they are prioritized and have privileged access to the amygdala. In other words, threat-related stimuli are processed automatically. This view is supported by studies showing amygdala activation to unattended ("unseen") threat-related stimuli (Morris et al., 1999; Vuilleumier et al., 2001). Accordingly, the amygdala plays a prominent role in the pre-attentive and *automatic detection* of threat cues. However, the automaticity of amygdala processing of such cues has been questioned by several studies arguing that amygdala activation by threat cues (e.g., fearful faces) requires attentional resources (Pessoa, 2005). These studies have demonstrated that amygdala reactivity to threat-related distractors can be abolished in perceptually demanding contexts (Pessoa et al., 2005), which is, in turn, consistent with the concept that distractors cannot be processed when perceptual capacity is exhausted (Lavie et al., 2004). Thus, while the amygdala plays an important role in threat detection it may do so in concert with other structures (Cisler and Koster, 2010).

The threat of shock could be useful to investigate the boundaries between automatic and more controlled mechanisms mediating bias. It is now clear that biases are flexible and are strongly influenced by contextual stressors (Bar-Haim et al., 2010). One possibility is that the automaticity of bias is influenced by the nature of the stressor. While there are obvious advantages in requiring control processes of mild threat distractors in an innocuous environment, this may not be adaptive when danger looms. Fast and automatic capture of potential threats may then become crucial to survival. The possibility that automaticity of threat detection depends on environmental threat was tested by Cornwell et al. (2011). These authors examined the effect of threat of shock on threat bias in a paradigm previously employed to investigate amygdala activation to task-irrelevant fearful and neutral faces under low and high perceptual load (Bishop et al., 2007). The no-threat condition replicated the basic finding of greater amygdala response to fearful compared to neutral faces under low but not high perceptual load (Cornwell et al., 2011). However, consistent with the hypothesis that anxiety sensitizes threat detection, amygdala activation to fearful faces under high perceptual load was preserved during shock anticipation (Cornwell et al., 2011). These results are therefore consistent with the hypothesis that threat detection requires processing resources in innocuous contexts but become automatic in threatening environments.

It is clear that induced-anxiety biases attention, either by changing its selectivity or it sensitivity to threat, which likely has, in turn, downstream effects on cognition that can be positive or negative depending on the nature of the task at hand.

MEMORY

Memory encompasses processes involved in the encoding, storage, and retrieval of information perceived and attended to in the prior sections. While there is clear evolutionary advantage to facilitating threat detection and rapid sensory responding in unpredictable environments, these changes observed in both induced (Robinson et al., 2011, 2012a) and pathological anxiety (Morgan III and Grillon, 1999; Ge et al., 2011) may actually come at the expense of goal-directed cognitive processes, which are central to both long- and short-term (working) memory. Anxiety induced by unpredictable threat of shock has a selective effect on memory that is dependent on modality (spatial or verbal), difficulty, and task type (working memory or long-term memory). Here we therefore divide memory into two broad categories; working (short-term) memory and long-term memory. The main focus is on cold memory processes, as we highlight a deficit of work examining the impact of threat of shock on hot memory. Broadly speaking, the current literature is mixed, but there is some agreement in findings across different anxiety manipulations and anxiety profiles (dispositional or clinical). In particular, the majority of findings demonstrate that spatial working memory is disrupted by anxiety disorders and long-term episodic memory (especially for negative emotional stimuli) is *enhanced*. Threat of shock induces decrements in short-term memory accuracy on par with those seen in patients, whereas other induction methods and dispositionally anxious subjects show only capacity deficits, suggesting that threat of shock is a better model of anxious pathology. In general, performance impairments are typically associated with high state anxiety as opposed to high dispositional anxiety (Hodges and Durham, 1972; Hockey et al., 1986), suggesting that the experience of anxiety may be the primary mechanism of impairment rather than susceptibility to stress (**Table 4**).

COLD COGNITION

Working memory

Working memory refers to a temporary storage system that can be used to encode, rehearse, and manipulate information in mind (Postle, 2006; Jonides et al., 2008). In contrast to long-term memory, working memory refers specifically to short-term storage of information, and there is evidence from patients with cortical lesions that suggests these two types of memory rely on partially separable neural systems (Baddeley and Warrington, 1970; Vallar and Shallice, 2007). One of the most commonly used working memory tasks is the n-back paradigm (where subjects respond to successive stimuli based on whether they match the stimulus 1, 2, or 3 trials back etc.), because cognitive load or task difficulty can be parametrically modulated.

Table 4 | Effects of anxiety on memory (arrows represent direction of effect).

Domain	Task details	Threat of shock		Anxiety disorders	
			References		References
Short-term memory	Performance on verbal and spatial n-back performance, Sternberg, and corsi blocks test.	↓	Lavric et al., 2003; Kalisch et al., 2006; Shackman et al., 2006; Vytal et al., 2012	↓	van der Wee et al., 2003; Boldrini et al., 2005
Short-term memory	Performance on digit span, OSPAN, or reading span; reaction time on short-term memory tasks	=	Pyke and Agnew, 1963	=	Boldrini et al., 2005
Long-term memory	Performance on recall or recognition tests of words	↑	White, 1932; Chiles, 1958; Singh et al., 1979	↑*	McNally et al., 1989; Friedman et al., 2000; Paunovic et al., 2002

* *"hot" negatively-valenced or disorder-specific material.*

Research in patients suggests that pathological anxiety may specifically impair *spatial* short-term memory performance; patients with different anxiety disorders show deficits in spatial working memory, *but not verbal* working memory performance or verbal working memory capacity (Kizilbash et al., 2002; van der Wee et al., 2003; Boldrini et al., 2005). In contrast, dispositional anxiety is frequently associated with reduced working memory capacity but not performance, as captured by digit span measures or increased reaction time on verbal and spatial short-term memory tasks (Darke, 1988; Macleod and Donnellan, 1993; Ikeda et al., 1996; Derakshan and Eysenck, 1998; Richards et al., 2000; Ashcraft and Kirk, 2001), however see Markham and Darke (1991), Eysenck et al. (2005), Hansen et al. (2009). Together these findings suggest that baseline anxiety may have in impact on short-term memory processing efficiency but not accuracy.

Consistent with the patient research, studies examining the n-back task indicate that threat of shock disrupts both verbal (Vytal et al., 2012, 2013) and spatial short-term memory (Lavric et al., 2003; Shackman et al., 2006) but the impairment is more robust in spatial working memory (Lavric et al., 2003; Shackman et al., 2006; Vytal et al., 2013) [see Kalisch et al. (2006) for evidence indicating that threat of shock does not impair verbal 2-back performance]. This may be because working memory impairment is the result of competition for cognitive and sensory-perceptual resources. In particular, induced-anxiety may have a more robust impact on spatial working memory because the extensive neural resources shared between anxiety and spatial working memory are less susceptible to top-down attentional control than the resources shared between anxiety and verbal working memory processes. Conversely, the impact of anxiety on verbal working memory is dependent upon cognitive load; low, but not high, cognitive load verbal working memory tasks are impaired by threat of shock (Lavric et al., 2003; Shackman et al., 2006; Vytal et al., 2012, 2013). High-load verbal working memory tasks have been shown to actually *reduce* anxiety, while low-load verbal working memory tasks are *disrupted* by anxiety. Thus, there may be a more complex interaction between verbal working memory and anxiety, which may depend upon top-down control, and leads to less robust overall effects of threat of shock on verbal memory. Together, these findings are consistent with theories that emphasize the role of shared resources in accuracy impairment [e.g., the two-component model (Vytal et al., 2012, 2013), and a model based on hemispheric asymmetries (Shackman et al., 2006)]. The basic premise of such models is that anxiety garners neural resources critical to working memory, resulting in decreased accuracy.

Working memory research has, however, demonstrated that shock anticipation does not alter *all* working memory functions. Working memory capacity tests (e.g., digit span) are unaffected by anxiety induced by threat of shock (Pyke and Agnew, 1963), suggesting that threat-related working memory impairments may be specific to processes that require ongoing maintenance in the face of interference (e.g., n-back tasks where rapid succession of stimuli must be attended to, responded to, and subsequently forgotten/ignored) as opposed to intrinsic resource limitations. This is in contrast with research examining the effects of other anxiety induction methods where working memory capacity is limited by anxiety (Schoofs et al., 2008). Specifically, working memory capacity, not performance accuracy (however see Oei et al., 2006), is impaired by threatening pictures (Lindström and Bohlin, 2012), the cold pressor test (Schoofs et al., 2008; Duncko et al., 2009), and incidental changes in state anxiety (Walker and Spence, 1964; Firetto and Davey, 1971; Lapointe et al., 2013). In contrast to research using threat of shock, these findings are in line with processing efficiency theory (Eysenck and Calvo, 1992), which argues that anxious worry (1) reduces working memory processing capacity and (2) increases effort necessary to perform the task, thus increasing reaction time [although Duncko et al. (2009) found decreased reaction time under stress]. However, these findings are muddled by other studies that show state anxiety is not related to a reduction in working memory capacity [e.g., threatening movies: no effect on n-back (Fales et al., 2008; Qin et al., 2009) test anxiety: no effect on auditory verbal working memory, but impaired short-term item recall, (Vedhara et al., 2000); cold pressor test: no effect on Sternberg item recognition, (Porcelli et al., 2008)]; and their incongruence with threat of shock working memory research. With effects limited to processing efficiency (i.e., reaction time) perhaps a more robust, evocative, and translational method like threat of shock is necessary to truly model working memory impairments associated with anxiety. Further, many of these studies are subject to methodological concerns (e.g., verification of sustained emotion

induction, psychometric matching of tasks to determine specificity of effects), which limit the scope of the conclusions that can be drawn from the existing body of research [see Shackman et al. (2006) for methodological considerations in the study of emotion × cognition interactions, and Vytal et al. (2012) for further articulation of these concerns]. As such, these results should be interpreted with appropriate limitations in mind.

Long-term memory

Some work has shown that in contrast with certain short-term memory tasks, patients with anxiety disorders are not impaired in long-term memory (Gladsjo et al., 1998; Kizilbash et al., 2002; Boldrini et al., 2005). However, examining the literature as whole, long-term memory findings in anxiety patients are mixed; anxiety patients have been shown to exhibit impairment in long-term episodic memory (Lucas et al., 1991; Asmundson et al., 1994; Cohen et al., 1996; Airaksinen et al., 2005).

Unlike the impairment seen in working memory studies, several studies suggest that long-term memory is *facilitated* by threat of shock. There is ample research to suggest that emotional arousal and the physiological responses that can accompany it (e.g., increase in glucocorticoids, epinephrine, and norepinephrine) facilitate encoding and memory consolidation processes by the release of hormones in the brainstem and basolateral amygdala (Ledoux, 1998; Cahill et al., 2003; Roozendaal et al., 2009). Hippocampal connections with the amygdala are thought to mediate this memory enhancement (Roozendaal, 2002; Roozendaal et al., 2006). In line with this: recognition of paired word associates (Chiles, 1958; Singh et al., 1979) and free recall of word lists (White, 1932) is greater when subjects are at risk of shock [but see Weymar et al. (2013) for a null finding]. From an evolutionary standpoint, it is fitting that threatening environments may lead to better declarative memory of such experiences, so that similar situations in the future can be recognized as such and avoided.

However, the relationship between anxiety and memory is anything but straightforward. It is important to note that a meta-analytic review of studies examining the effects of stress and stress hormones on memory found the opposite effect—that declarative long-term memory is impaired by stress and that this impairment is related to an increased cortisol response (Sauro et al., 2003). A closer look at these studies reveals that timing is a key component in determining the effects of anxiety on long-term memory. The timing of the stressor (e.g., encoding, post-encoding, retrieval etc.) can impact whether or not a memory trace is solidified or disrupted (Roozendaal, 2002). Specifically, an anxiety-provoking context during episodic memory *formation* is facilitative, but during *retrieval* it is detrimental. These effects however can only be isolated in long-term memory paradigms where encoding and retrieval periods are separate. Future work should seek to dissociate the effects of anxiety upon different stages of memory formation and retrieval.

Regarding other anxiety inductions, and in contrast to working memory, long-term memory studies indicate that both encoding and retrieval are disrupted by induced-anxiety. The cold pressor test has been shown to impair long-term memory encoding and retrieval of both verbal and spatial information (Kuhajda et al., 1998; Ishizuka et al., 2007). However, there are studies to suggest that these manipulations do not affect long-term memory (Wolf et al., 2001, 2002). Again, the inconsistencies observed suggest that these methods, while sometimes effective, may not be ideal for modeling anxiety-related memory impairments.

HOT COGNITION

Studies examining the impact of threat of shock on affective memory tasks are lacking. Psychosocial stress has been shown to impair retrieval of emotional words (Kuhlmann et al., 2005) and event-related potential research has shown that dispositional anxiety leads to a decreased ability to filter out threatening distractors in a working memory task (Stout et al., 2013), indicating that hot cognitive processes which impact attention also impact working memory storage efficiency. In long-term memory tasks, patients with anxiety disorders generally show impairment *unless the memories are affectively negative*, in which case long-term memory may be facilitated (Friedman et al., 2000; Paunovic et al., 2002). Specifically, individuals with clinical anxiety (McNally et al., 1989; Friedman et al., 2000; Paunovic et al., 2002) or high dispositional anxiety (Mathews et al., 1989; Reidy and Richards, 1997) tend to have better recall of threatening information [but see Mogg et al. (1987) for an alternate view]. However, the recall bias observed in dispositionally anxious participants is somewhat fragile [e.g., not replicable over experiments or experimental blocks (Norton et al., 1988; Nugent and Mineka, 1994)]; suggesting that episodic memory biases in dispositional anxiety may be transient and surface only when there are strong relationships among disposition/pathology, mood, and stimuli. This is somewhat inconsistent with the long-term memory facilitation for *neutral* stimuli under threat of shock. One possible explanation is the emotional state of subjects during encoding; in healthy subjects, when anxiety is induced or emotionally-arousing stimuli encountered, episodic memory encoding, and consolidation is enhanced, however in clinical populations, this enhancement is tied to anxiety-relevant stimuli. A large body of research demonstrates an attentional and perceptual bias toward threatening information in anxious individuals [except for PTSD where evidence for a threat bias is mixed (Buckley et al., 2000)] see previous sections; Bar-Haim et al. (2007). When anxiety is induced by threat of shock, all information is contextually linked to the anxious state and hence preferentially processed (maintained or encoded). By contrast, in anxiety disorders only negative stimuli are anxiety-relevant and so encoding may be restricted to these stimuli. In general, however, the lack of threat of shock studies in this area makes conclusions premature and future work is needed to dissociate the causes of this discrepancy.

EXECUTIVE FUNCTION

Broadly speaking, we define "executive" functions as those which require *combining* information processed by the mechanisms previously reviewed. Aspects of learning, perception, and attentional control, both hot and cold, are all integrated to guide complex future-oriented behaviors. In reviewing the literature on this final cognitive domain, we focus on three types of executive function: (1) decision-making behavior, (2) planning, and (3) spatial navigation. Given the integrative nature of these functions we do

not make a distinction between hot and cold processes. We show threat of shock mimics, at least in part, the effects of anxiety disorders on both planning (i.e., no effect) and decision-making (i.e., promoting harm avoidant decisions), while at the same time having the opposite effect upon spatial navigation (**Table 6**).

Decision-making

There is evidence that both translational threat of shock and anxiety disorders promote harm avoidant, loss aversion, decision-making. Decision-making behavior can become more cautious and conservative under anxiety [see Starcke and Brand (2012) for a review examine a broader range of "stress" manipulations]. On the one hand, anxiety induced by threat of shock has been shown to induce premature responding (before all options are presented) in decisions where options are revealed sequentially (Keinan, 1987), but the opposite pattern (increased response time) is seen when subjects are asked to make decisions on a trial to trial basis (e.g., matching on card sorting tasks; Murphy, 1959). Moreover, in gambling tasks where probabilities are known, threat of shock can increase risk-avoidant decision-making and lead to more conservative gambles (Clark et al., 2012). This latter effect is consistent with loss aversion [alongside indifference to rewards (Shankman et al., 2012)] which has been shown in pathological anxiety disorders (Mueller et al., 2010). The same conservative style is also seen following the cold pressor test (Mather et al., 2009) [especially in female subjects (Lighthall et al., 2009, 2012)] although it may depend upon whether decisions are being made to increase gains or minimize losses. Specifically, the "reflection effect"—the tendency of individuals to make risky decisions in the loss domain but conservative decisions in the gain domain—is increased by anxiety induced via the cold pressor test (Porcelli and Delgado, 2009).

Dispositional anxiety and speech anxiety inductions, however, demonstrate the opposite effect. *Reduced* risk avoidance has been shown following speech stressors (Starcke et al., 2008); but this effect seems to be gender-dependent, with slightly improved decision-making (i.e., increased gains on Iowa gamble task) seen in anxious females and impaired decision-making restricted to anxious males (Preston et al., 2007; van den Bos et al., 2009). Similarly, high dispositional anxiety is associated with *impaired* performance on the Iowa gambling task (Miu et al., 2008) [which is also gender-dependent (de Visser et al., 2010)], and problem gamblers with high dispositional anxiety demonstrate more severe pathological gambling problems (Ste-Marie et al., 2002) [anxiety disorders can also be comorbid with problem gambling (Petry et al., 2005)]. In general, firm conclusions are premature, but there is evidence that both translational threat of shock and anxiety disorders promote harm avoidant, loss averse, decision-making while dispositional anxiety and speech anxiety inductions promote the opposite pattern.

Spatial navigation

Spatial navigation in anxiety has been assessed via virtual reality maze tasks as well as simple pen and paper "trail-making" tasks. Note that, as a caveat, although we define this as an executive function which requires integration of multiple facets of cognition, there is an extensive literature in rodents which links aspects of spatial navigation to reflexive responding in the hippocampus (Ekstrom et al., 2003). Threat of shock in healthy individuals has been shown to enhance spatial navigation (Cornwell et al., 2012a), as has the cold pressor anxiety manipulation (Duncko et al., 2007) [with null effect of speech stressors (Starcke et al., 2008)]. In anxiety disorders, however, the opposite effect is seen; spatial navigation is impaired (Cohen et al., 1996; Mueller et al., 2009). This discrepancy could possibly be driven by the *context* of the anxiety. Anxiety may prioritize fast and easy navigation away from threats, but impair navigation which is unrelated to threats. In healthy individuals undergoing anxiety induction, the anxiety and task are contextually linked, whereas in a person with an anxiety disorder, the task is unrelated to their anxiety. As such, task-driven anxiety may improve performance while task-unrelated anxiety impairs performance. Another possibility is that there is a key difference between the "adaptive" anxious state triggered by acute anxiety inductions and the pathological, more trait-related anxiety in anxiety disorders (discussed in more detail in the Discussion section below). Acute state anxiety may improve navigation; chronic trait anxiety may impair navigation. Regardless, translational anxiety inductions and anxiety disorders seem to have opposite effects upon spatial navigation.

Planning

Finally, planning ability can be assessed by the Tower of London task (and its variants; e.g., the Tower of Hanoi or the Stockings of Cambridge) in which subjects have to work out how many moves are required to make two patterns look identical. Threat of shock has no effect upon the one touch tower of London (**Table 5**; previously unpublished data using this task, see Appendix for trial example). This is, in fact, consistent with the effects of pathological anxiety disorders, which also leave planning ability intact (van Tol et al., 2011) [in contrast with depression (Elliott et al., 1997) and sad mood induction (Robinson and Sahakian, 2009) which both impair planning on this task]. This null finding (and dissociation from sad/depressed mood) provides important context, because it demonstrates that threat of shock does not have broad indiscriminate effects on executive function; it can increase risk avoidance and improve spatial navigation while leaving planning performance intact.

DISCUSSION

While the threat of shock paradigm has been used extensively to examine emotional responses and defensive mechanisms (Davis et al., 2010), it is also emerging as a powerful tool to study the effects of anxiety on cognition. Below, we summarize the findings of this review before addressing questions for future research.

THE IMPACT OF THREAT OF SHOCK ON COGNITION

Threat of shock facilitates early sensory-perceptual processing of neutral stimuli, improves the detection of negative information, impairs performance on tasks with emotional distractors, and facilitates resolution of conflict. In addition, threat of shock impairs short-term memory but facilitates long-term memory as well as certain aspects of decision-making and executive function. In general, the changes can be seen as part of an overall adaptive mechanism of harm avoidance in which threatening stimuli are

Table 5 | Impact of threat of shock on accuracy (Acc) and planning time (RT; ms) on the one touch tower of London task.

	Safe				Threat			
	2 move	**3 move**	**4 move**	**5 move**	**2 move**	**3 move**	**4 move**	**5 move**
Mean Acc	0.72	0.66	0.49	0.28	0.73	0.70	0.55	0.32
s.e.m.	0.07	0.07	0.06	0.04	0.07	0.06	0.05	0.04
Mean RT	4784	5762	6231	7214	4696	5447	6344	6892
s.e.m.	231	250	207	224	253	230	247	291

Twenty two healthy subjects (per structured clinical interview completed by a physician; e.g., Robinson et al., 2013a) underwent a shock work-up procedure (e.g., Robinson et al., 2011) and then completed the task under alternating threat and safe conditions (order counterbalanced). The task was adapted from previously published studies (e.g., Elliott et al., 1997; Murphy et al., 1999, 2002) and involved intermixed 2, 3, 4, and 5 move problems (see ***Figure A1*** *for an example). Subjects completed a short 5 trial practice session before commencing the task. There were a total of 6 different problems within each difficulty level. During each trial subjects were provided with 4 options for the number of moves required. Response reaction time and accuracy data were analyzed in 2 × 4 threat (safe, threat) × load (2, 3, 4, 5 move) ANOVAs. Across safe and threat conditions, task performance deteriorates as load increases [*$RT = F_{(3,\ 19)} = 42$, $p < 0.001$; $Acc = F_{(3,19)} = 17$, $p < 0.001$*] but this does not interact with anxiety induced by threat of shock [*$RT = F_{(3,19)} = 0.7$, $p = 0.6$; $Acc = F_{(3,19)} = 0.2$, $p = 0.9$*].*

Table 6 | Effects of anxiety on executive functions (arrows represent direction of effect).

Domain	**Task details**	**Threat of shock**		**Anxiety disorders**	
			References		**References**
Decision-making	Risk avoidance on gamble tasks	↑	Clark et al., 2012	↑	Mueller et al., 2010
Spatial navigation	VR maze navigation performance	↑	Cornwell et al., 2012a	↓	Cohen et al., 1996; Mueller et al., 2009
Planning	Calculate moves on tower of London	=	**Table 5**	=	Elliott et al., 1997; van Tol et al., 2011

privileged at all levels of cognitive function, but at a potential cost for some functions (e.g., short-term memory).

Thus, anxiety boosts sensory-perceptual processing, which subsequently influences downstream stages of information processing. These effects may be facilitative or detrimental depending on task demands. Consistent with the dual-model process theory (Pessoa, 2009) and attentional control theory (Eysenck et al., 2007), threat of shock affects the balance between stimulus-driven and goal-directed behaviors (Shackman et al., 2011a; Cornwell et al., 2012b), such that performance is improved when emotional information is task-relevant but impaired when it is task-irrelevant.

It is generally assumed that anxiety induces an impairment in inhibitory control, (Derryberry and Reed, 2002; Eysenck et al., 2007), which comprises the ability to inhibit prepotent responses and to resist interference from distractors (Friedman and Miyake, 2004). These two types of inhibitory control have been traditionally tested with the classic Stroop, a test of inhibition of prepotent responses, and the emotional Stroop, a test of interference by an emotional distractor. Threat of shock does not have a uniformly detrimental effect on these two tests. In fact, threat of shock impairs performance on the emotional Stroop, but, inconsistent with theoretical assumption, it *improves* performance on the classic Stroop as well as on a measure of response inhibition (Robinson et al., 2013a). There is no simple explanation for these divergent effects, which may have multiple causes, including non-specific effects [e.g., tasks not psychometrically matched (Thomaes et al., 2012)]. A critical distinction between these two tests, however, is that one is a measure of conflict and the other is not. Specifically, the classic Stroop is a true test of conflict between two responses (or inhibitory control), whereas the emotional Stroop is perhaps better characterized a measure of attentional bias (Buhle et al., 2010; Etkin et al., 2011). This suggests that the threat of shock facilitates inhibitory control, a result consistent with findings using sustained attention tasks (Robinson et al., 2013a), while at the same time increasing perceptual processing of affectively negative information. These results could, nevertheless, also be explained by other mechanisms. For example, anxiety could have opposite effect on regions of the anterior cingulate or prefrontal cortex that are differently affected by affective and non-affective incongruency (Haas et al., 2006). Anxiety also improves the selectivity of attention (Easterbrook, 1959), which could facilitate a narrowing of attention to the target during the classic Stroop. The emotional Stroop would not benefit from this selectivity because emotional distractors may be processed implicitly by the amygdala.

The differential effect of threat of shock on short-term vs. long-term memory is also of note and might be attributed to (1) to the overlap in neural resources between anxiety and short-term memory and (2) the protracted role that stress hormones play in consolidation. Short-term memory (Cohen et al., 1997) and anxiety (Etkin, 2010) both engage prefrontal mechanisms, and competition for this neural circuitry may result in temporary *impairment* due to disrupted *maintenance* of information. In contrast, episodic information *encoding* may be *facilitated* by threat of shock with the release of stress hormones in the amygdala and brainstem that serve to modulate long-term storage via the hippocampus (Cahill and McGaugh, 1998).

The impact of threat of shock on more complex executive processes such as decision-making processes can also be seen as consistent with a model of anxiety promoting cautious harm avoidance including risk-avoidant decision-making (Clark et al., 2012) and improved spatial navigation (Cornwell et al., 2012a). However, this domain of cognition is also notable for the relative paucity of studies and so considerable further work is needed to specify the precise effects.

DIFFERENCES ACROSS THREAT OF SHOCK AND ANXIETY DISORDERS

Threat of shock may thus accurately model the impact of anxiety disorders on hot cognition. One critical observation is that anxiety disorders and threat of shock have discrepant effects on (1) PPI, (2) classic Stroop, (3) conflict adaptation, (4) short-term memory capacity, and (5) spatial navigation. These unique effects in anxiety disorders are largely in cold cognitive functions which require some form of cognitive control, and are consistent with models (e.g., Bishop, 2007) postulating that anxiety disorders are associated with poor attention control. The disorder-specific effects may reflect long-term changes in response to prolonged stress or dispositional anxiety. Specifically, there may be a true dysfunctional vulnerability linked to cold function (impaired attention control; Litz et al., 1996; Lagarde et al., 2010) which either (1) predisposes vulnerable people to experience sustained affective biases which lead to a vicious cycle toward anxiety disorders; or (2) makes people anxious, which then lead to affective biases. By contrast, hot cognitive functions, including those that require cognitive control seem to be consistent across threat of shock and anxiety disorders (although it should be noted that this may vary across different anxiety disorder diagnoses). A further possibility is that threat of shock accurately induces *state* effects of anxiety, but sufferers are not always in a state of elevated anxiety and so the discrepancies across threat of shock and anxiety disorders reveal a distinction between state and trait effects. One final possibility is that discrepancies are due to the traditional inverted-U relationship between anxiety and performance. However, this seems unlikely. Many subjects experience very high levels of anxiety during threat of shock, probably higher levels relative to anxious patients tested in the laboratory (without threat of shock). In fact, one of the advantages of the threat of shock is that we can compare performance across a number of tasks keeping the level of anxiety constant. Clarifying the causes of these divergent effects is a key question for future research (see below).

NEURAL MECHANISMS

A comprehensive understanding of the neural mechanisms underlying these effects is beyond the scope of this review. However, it is worth highlighting some recent advances pointing toward circuitry which may be involved. Both anxiety disorders and threat of shock are strongly implicated in activity in the (a) amygdala and (b) dorsal medial prefrontal cortex/dorsal anterior cingulate cortex (Shin et al., 2005; Etkin and Wager, 2007; Shin and Liberzon, 2009; Hartley and Phelps, 2012; Linnman et al., 2012; Maier et al., 2012; Robinson et al., 2012a). In fact, a circuit between these two regions is thought to drive a bias toward aversive information (Robinson et al., 2012a). This is consistent with the idea that the dorsal prefrontal (encompassing cingulate and dorsomedial) cortex is involved a emotional processing (Etkin et al., 2011), especially appraisal (Maier et al., 2012) negative affect and cognitive control (Shackman et al., 2011b). As such, it is possible that anxiety engages this circuit which then underlies some improvements in cognitive functions (both hot and cold) which promote the avoidance of danger. If turned on excessively, however, this circuit may lead to the pathological biases in anxiety disorders.

By contrast, functions which are down-regulated in anxiety share some of this neural real estate. Working memory and neutral cognitive control are both adversely affected by anxiety and are thought to be processed within regions overlapping this circuit (Pessoa et al., 2002; Shackman et al., 2011b). One possibility, therefore is that resource "overload" occurs when neural real estate critical for the aforementioned harm avoidance processes overlaps with circuitry involved in anxiety-*unrelated* processes. The preferential processing of threat avoidant stimuli may thus come at the expense of threat-unrelated processes (e.g. working memory). Cognitive functions, like planning, which are unperturbed by either threat of shock or anxiety disorders may, moreover, rely on entirely separate circuitry (Shackman et al., 2006). Of course this is likely an oversimplification, and it is worth noting that a large number of regions are implicated in anxiety, including some brain stem areas highlighted above. Going forward, the threat of shock paradigm may prove a promising tool to clarify some of these neural mechanisms.

FUTURE QUESTIONS

Taken together, the above findings highlight a number of broad questions that might be tackled in future research:

WHAT CAUSES THE SHIFT FROM ADAPTIVE TO MALADAPTIVE ANXIETY?

As indicated above, there were a number of discrepant effects across threat of shock and anxiety disorders, largely on cold cognitive functions. An important question, therefore, is what drives the difference between the effect of induced-anxiety and anxiety disorders on cold cognitive functions? One possibility is that this discrepancy reveals the differences between *adaptive* and *maladaptive* anxiety. Specifically, in a threat of shock experiment, the state of anxiety is entirely rational and an adaptive response to an imminent threat. Anxiety disorders are, however, characterized by anxiety at inappropriate times or to mildly aversive stimuli; so called maladaptive anxiety. It will be important to identify the mechanism(s) by which adaptive responding becomes maladaptive. One possibility is that the same processes underlie both effects, but in the case of maladaptive anxiety, the circuitry gets "stuck" in the anxious state. This causes a broader array of stimuli to constitute threats (stimulus generalization) and impairs the ability to down regulate threats (Lissek et al., 2009; Shackman et al., 2009). What causes this switch to occur? Is there a ratcheting effect whereby once the system is pushed too far it is unable to restore healthy function? And once this occurs is that what leads to the "cold" control impairments which appear to be restricted to anxiety disorders? Clarifying the causes of these differences may

reveal important mechanisms of relevance to the development of anxiety disorders.

CAN WE USE THIS UNDERSTANDING TO IMPROVE DIAGNOSIS AND TREATMENT EFFICACY IN ANXIETY?

Clarifying the impact of anxiety on cognition may allow us to more accurately assess the efficacy of treatments (Harmer et al., 2011). For instance, a potential use of threat of shock in healthy volunteers is as an analog model to identify the underlying mechanisms of these affective components in anxiety disorders. Assuming that the same mechanisms that are responsible for the effect of anxiety evoked by threat of shock on hot functions are also implicated in anxiety disorders, we can use the impacts of threat of shock on cognition in healthy individuals to screen candidate anxiolytic compounds. A serious impediment to bringing candidate anxiolytics to the marketplace is the lack of effective models to screen drugs (Rodgers, 1997; Kola and Landis, 2004; Dawson and Goodwin, 2005). This is because compounds that have anti-anxiety profile in animal models subsequently lack clinical efficacy in patients. Thus, developing a model for evaluating efficacy in humans could facilitate the screening process and bridge the gap between basic drug development and the psychopharmacological treatment of patient. Threat of shock, which appears to be a closer analog to pathological anxiety than some other anxiety inductions based upon the evidence reviewed above (e.g., Starcke et al., 2008 vs. Clark et al., 2012), could be such a model.

CAN WE USE COGNITIVE INTERVENTIONS TO TREAT ANXIETY?

On the other hand, clarifying the impact of performing cognitive tasks on anxiety, may allow us to better understand and refine cognitive treatments for anxiety. In particular, at least one threat of shock study reviewed above showed that high cognitive load serves to distract *away from* the state of anxiety (Vytal et al., 2012). Specifically, performance of a "cold" verbal n-back task reduced psychophysiological concomitants of anxiety but only under the highest (3-back) load conditions. Future work might explore whether this observation has therapeutic value. In addition, recent advances have begun to use "hot" cognitive training tasks to shift the negative biases in anxiety. In such "cognitive training" tasks, a subject's attention is implicitly shifted toward positive (at the expense of negative) emotional cues, which over time leads to reduced negative biases when assessed on cognitive tasks (Browning et al., 2010, 2012; Hakamata et al., 2010; Macleod and Mathews, 2012). This technique may eventually be used to reduce the debilitating negative biases, thus reducing anxious mood in anxiety disorders. Either way, it may be possible to adopt both hot and cold cognitive interventions to reduce the symptoms of anxiety disorders.

FUTURE CHALLENGES

A key advantage of threat of shock is that it provides a well-controlled manipulation of state anxiety in a within-subject design. It may help address many fundamental questions concerning the components and underlying mechanisms control, bias and regulation mechanisms at different processing stages, the role of context, and factors that contribute to inter-individual differences in bias. However, there is no single standardized "threat of shock" paradigm across the majority the reviewed studies and a clearer picture may be achievable if more variables (e.g., block-length, shock frequency) were held consistent across studies and key methodological considerations were taken into account [see, for instance the "4 methodological desiderata" in Shackman et al. (2006)]. Similarly, many investigators use the word "anxiety" without being specific about what they are talking about. Anxiety can refer to anxiety disorders, dispositional anxiety, or state anxiety (experimentally-induced anxiety); we recommend that investigators be more specific going forward.

A number of further caveats are also worth considering. First, given the number of cognitive processes there are very few studies utilizing threat of shock, leaving a large number of gaps in the literature to get a good picture of the effect of induced-anxiety on cognition. In addition, many tasks have yet to be comprehensively tested across anxiety disorders and threat of shock. Second, some threat of shock effects could reflect non-specific increased in arousal rather than specific effects due to negative affective states. However, many of the effects were selective, promoting the processing of threat- or potential threat-relevant stimuli as opposed to neutral stimuli (Mogg and Bradley, 2005; Bar-Haim et al., 2007) or stimulus-relevant as opposed to stimulus-irrelevant stimuli (Eason et al., 1969). Third, it is possible that subjects who participate in a threat of shock experiment are representative of a uniquely harm avoidant population; high dispositional anxiety subjects or subjects afraid of shock may not be inclined to participate in such experiments [although it should be noted that some researchers have used high dispositional anxiety subjects under threat of shock (Miller and Patrick, 2000; Edwards et al., 2006, 2010)]. Finally, although very few shocks are administered in threat of shock studies, it is possible that some of the effects observed were due to sensitization mechanisms (Richardson, 2000).

Future work should aim to rule-out and control for some of these potential confounds. As a general prescription going forward, we recommend that future studies should primarily (1) further investigate basic "cold" control mechanisms to lay a strong foundation for the study of "hot" cognition, (2) adopt recently developed procedures to isolate the various components of threat-induced bias, such as visual search, spatial cuing, eye tracking, and classical conditioning (Cisler and Koster, 2010; Sheppes et al., 2013; see also Clarke et al., 2013), (3) examine the interactions between (shock-induced) state anxiety, temperamental disposition (e.g., trait anxiety) and experiential factors (e.g., adverse life-events), (4) explore contextual-mediated shift in bias (Bar-Haim et al., 2010), e.g., caused by changes in shock predictability or shock temporal proximity, and (5) extend research on threat of shock to individuals with clinical anxiety. Indeed, one possibility is that specific cognitive deficits in anxious individuals may be latent and emerge only in stressful situations. Relatedly, one may ask to which extend attentional control deficits and bias are related to specific anxiety disorders or to proposed nosological distinction (i.e., fear disorders vs. distress/misery disorders; Vaidyanathan et al., 2012).

GENERAL CONCLUSIONS

In sum, we have presented an overview of the impacts of anxiety on cognition. Both threat of shock—a translational anxiety induction—and pathological anxiety disorders promote the detection of potentially harmful stimuli at multiple levels of cognition from perception to attention to memory and executive function. At the most basic level this tends to be associated with improved perception of environmental changes irrespective of valence, but at more complex levels of cognition, leads to promotion of cognitive processes relevant to harm avoidance at a cost to certain functions such as working memory, while leaving still further processes (such as planning) unperturbed. However, we also draw attention to a number of processes, such as spatial learning, PPI and non-emotional Stroop which are discrepant across threat of shock and anxiety disorders. We argue that this discrepancy, largely in cold cognitive functions, may reveal the differences between adaptive and maladaptive anxiety. Future work should attempt to delineate the causes of these differences, as well as explore the possible use of (1) cognitive interventions for the treatment of anxiety and (2) the use of threat of shock as an analog screen for candidate anxiolytics. The precise neural mechanisms underlying these effects are far from clear; this review, which is the first to collate the growing number of studies using the translational threat of shock paradigm, aims to highlight the value of this paradigm as a means to clarify these neural mechanisms. Given the large burden represented by anxiety disorders, such research is of pressing concern.

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APPENDIX

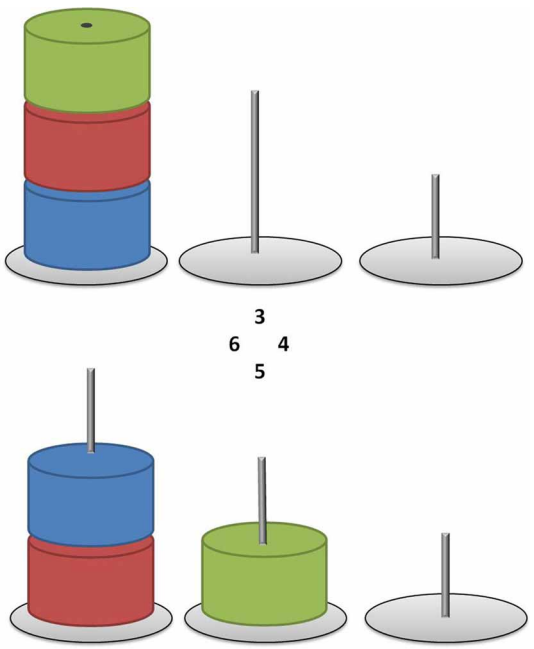

FIGURE A1 | An example stimulus from the adapted version of the tower of London—this stimulus represents a 5 move problem. Problems are presented under both safe and threat conditions.

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Affective attention under cognitive load: reduced emotional biases but emergent anxiety-related costs to inhibitory control

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Trait anxiety is associated with deficits in attentional control, particularly in the ability to inhibit prepotent responses. Here, we investigated this effect while varying the level of cognitive load in a modified antisaccade task that employed emotional facial expressions (neutral, happy, and angry) as targets. Load was manipulated using a secondary auditory task requiring recognition of tones (low load), or recognition of specific tone pitch (high load). Results showed that load increased antisaccade latencies on trials where gaze toward face stimuli should be inhibited. This effect was exacerbated for high anxious individuals. Emotional expression also modulated task performance on antisaccade trials for both high and low anxious participants under low cognitive load, but did not influence performance under high load. Collectively, results (1) suggest that individuals reporting high levels of anxiety are particularly vulnerable to the effects of cognitive load on inhibition, and (2) support recent evidence that loading cognitive processes can reduce emotional influences on attention and cognition.

Keywords: cognitive load, trait anxiety, threat processing, visual attention, antisaccade task

INTRODUCTION

Efficient goal-directed behavior depends upon top-down attentional control, allowing goal-relevant information to be attended to rather than irrelevant information. However, the efficiency with which we employ attentional control depends upon a combination of both internal factors, one's inherent attentional control abilities, and external factors, the amount a task or goal taxes our attentional control abilities in order to accomplish. One internal factor that has been shown to affect attentional control is an individual's self-reported level of trait anxiety (Eysenck and Derakshan, 2011).

It has been well-documented that trait anxious individuals show a bias in their selective attention toward irrelevant threat-laden information, with a meta-analysis finding consistent evidence of such a bias (Bar-Haim et al., 2007). For example, dot probe paradigms demonstrate that highly anxious individuals show markedly increased latency costs when ignoring threatening stimuli and responding to a target at a different spatial location (e.g., Arndt and Fujiwara, 2012). Such biases could be argued to be hardwired, even extending to individual differences in amygdala response to subliminal threat items (Etkin et al., 2004).

Based on this evidence, one potential conclusion is that anxiety does not affect attentional control in general, but selectively biases attentional control in response to the presentation of threatening stimuli. A growing body of work, however, has highlighted that anxious individuals also show impaired attentional control in situations where threat is absent. For example, trait anxious individuals show greater costs on latency performance in the antisaccade task (Derakshan et al., 2009; Ansari and Derakshan, 2011b) and increased response-competition in flanker tasks (Bishop, 2009; Pacheco-Unguetti et al., 2010). These findings can be accommodated within Attentional Control Theory (ACT; Eysenck et al., 2007), which posits that trait anxiety disrupts the three key facets of attentional control: inhibition of task-irrelevant information, flexibly shifting attention, and updating representations in working memory. Accumulating behavioral, electrophysiological, and neuroimaging evidence supports these predictions in recent years (see Eysenck and Derakshan, 2011; Berggren and Derakshan, 2013, for reviews).

According to ACT the effects of anxiety on attentional control should be greater under competing task demands. Indeed, it has been well-documented that the level of external task demands can strongly influence attentional control. This has most commonly been manipulated through varying cognitive demands on working memory during study via a secondary task such as item rehearsal. Such a manipulation is believed to tax executive resources, required for maintaining task goals and prioritizing task-relevant over irrelevant information (Baddeley, 1986). Loading working memory increases response latencies and error rates in the antisaccade task (Roberts et al., 1994; Kane et al., 2001; Berggren et al., 2011), and increases task-irrelevant interference by both response-competing and wholly irrelevant distractor items (de Fockert et al., 2001; Lavie et al., 2004; Lavie and De Fockert, 2005). Distractor interference also increases under load across modalities, impacting processing in the auditory and tactile domains (Dalton et al., 2009a,b). In particular, de Fockert et al. (2001) showed that loading working memory increased activity in the visual cortex, for face distractors in the fusiform "face" area, suggesting that attentional selection and control are strongly

influenced by the availability of working memory resources. Finally, the ability to inhibit distractor items, measured by negative priming for distractors that subsequently become targets, is eliminated when cognitive processes are taxed by load (de Fockert et al., 2010).

A number of studies have investigated whether cognitive load may particularly hamper attentional control in anxious individuals, disrupting task performance. These studies can be roughly divided into two subsets: those investigating the effect of cognitive load on distraction in the presence of task-irrelevant emotional material, and those assessing effects on distraction in the absence of emotional stimuli. For the former, evidence has been inconsistent. Studies examining fear-potentiated startle reflex have suggested that enhanced distraction in anxiety is reduced under cognitive load (Dvorak-Bertsch et al., 2007; Vytal et al., 2012), investigations examining the late positive potential (LPP; associated with emotional arousal) have implied smaller reductions under load in anxious individuals (MacNamara et al., 2011), and studies measuring distraction by emotional faces have found increased vigilance in anxiety under load (Ladouceur et al., 2009; Judah et al., 2013). However, these effects may be confounded by the influence of cognitive load on emotion processing in general. While non-emotional distraction appears to increase under cognitive load, as outlined above, emotional distraction appears to generally be reduced as indexed by emotional startle (King and Schaefer, 2011), LPP (MacNamara et al., 2011; Van Dillen and Derks, 2012) and RT distraction (Van Dillen and Koole, 2009). Thus, reductions in anxious threat biases may reflect a more general impact of cognitive load on emotion processing.

Further insight into how cognitive load affects attentional control in anxiety was obtained by Berggren et al. (2012) who employed a visual search paradigm where participants responded to a target face of a different emotional expression to a crowd (e.g., a neutral face among a crowd of happy faces). Cognitive load was induced by participants simultaneously counting back in threes from a specified number at the start of each trial. Low and high anxious participants did not differ in their performance under no-load, but while low anxious participants showed no performance cost with the introduction of counting, the high anxious participants were significantly slower. This suggested that cognitive load had a more potent effect on individuals with high anxiety, and notably this effect occurred regardless of the emotional content of distractor faces. However, this visual search paradigm contained no direct form of distraction; displays contained a target with a number of non-target items, but these additional stimuli could not be directly examined for the extent to which they impeded task performance. Thus, one could argue that group differences under cognitive load may simply be due to a general slowing of reaction time not indicative of hampered inhibitory control *per se*. In other words, anxious individuals may simply have demonstrated performance costs due to task demands rather than any effect on attentional control aspects of inhibition.

In the present study, we aimed to build upon previous work using a task containing task-irrelevant information and requiring cognitive inhibition, thus enabling a clearer test for the prediction that cognitive load should disrupt attentional control to a greater extent in high anxious individuals. We utilized the antisaccade task where participants are required to shift their overt attention toward or away from an abrupt visual onset, the latter process requiring cognitive inhibition to suppress a reflexive occulomotor response (Ettinger et al., 2008). Both anxiety and cognitive load have been previously shown to increase latencies on "look away" antisaccade trials (Derakshan et al., 2009; Berggren et al., 2011), while having no effect on "look at" prosaccade trials that require no inhibitory processing. Thus, the current study disentangled the possibility that load increases response latencies, as effects should be confined to antisaccade trials weighting on attentional control. We manipulated load using a previously demonstrated method (Berggren et al., 2011); participants heard three kinds of auditory tones while completing the antisaccade task, and responded simply with the word "tone" on low load trials or the words "high," "mid," or "low" depending on the tone's pitch in high load. We hypothesized that load should increase antisaccade eye-movement latencies, while having no effect on reflexive prosaccade latencies. In addition, based on ACT's predictions, we hypothesized that the load cost on antisaccades would be exacerbated for individuals reporting high levels of trait anxiety.

Finally, we also manipulated the emotional valence of visual onsets signaling participants to make an eye-movement saccade in the antisaccade task, using facial stimuli of different expressions (neutral, happy, and angry). We aimed to further explore whether distraction from emotional faces would be reduced under cognitive load as suggested in previous work, particularly for threatening angry/fearful stimuli (e.g., King and Schaefer, 2011). We also examined how this effect could be modulated by trait anxiety levels, in light of the wealth of literature that anxiety should enhance distraction by threat-related content as well as distraction by non-emotional information generally.

METHOD

PARTICIPANTS

Ninety-four participants (29 males; mean age = 29 years, $SD = 6$) were recruited via advertisements posted in University of London departments. All participants had normal hearing, normal or corrected-to-normal vision, and were naïve to the experimental hypotheses.

APPARATUS, MATERIALS, AND STIMULI

An SR Research Eyelink 1000 eye-tracker (SR Research, ON, Canada) was used to record eye-movements, tracking one eye. Nine-point calibration ensured that tracking accuracy was within 1° of visual angle. Stimuli were presented on a 21 inch Viewsonic CRT monitor (140 Hz), and viewing distance was held constant at 60 cm using a chinrest. The experiment was created using the SR Research Experiment Builder software. A laptop played auditory tones separately during blocks, presented in a randomized order using E-Prime software (Schneider et al., 2002). Face stimuli of neutral, angry and happy expressions were selected from the NimStim Face Stimulus Set (Tottenham et al., 2009) and the Ekman series (Ekman and Friesen, 1976). Six separate identities were used in total, with a 1:1 gender ratio. All face images were cropped and modified to only show the face and appear in black and white. For saccade recording, an amplitude of 2° each side of

fixation was used as saccade boundaries; eye-movements crossing either boundary were recorded for latency and accuracy.

PROCEDURE

The study was approved by the departmental ethics committee. The experiment was conducted within a sound-protected room. After providing consent, participants completed the State-Trait Anxiety Inventory[1] (STAI; Spielberger et al., 1983), a reliable measure of self-report trait anxiety level through the sum of scaled multiple choice responses (Spielberger et al., 1995), before being given the experimental instructions. Each trial began with a fixation cross (approximately 0.67 × 0.67° of visual angle) in the center of the screen appearing for up to 1000 ms. Participants were instructed to fixate this cross and, once they had fixated between 500 and 1000 ms after its onset, the trial moved forward immediately acting as a drift correct to tracking. Following this, face stimuli subtending approximately 3.44 × 5.25° appeared in the left or right periphery (at an eccentricity of approximately 11.23° from stimulus center to fixation) for 600 ms. At the start of each block participants were signaled how they should respond to the stimuli; in prosaccade blocks, participants were asked to move their eyes and fixate the face stimuli as quickly and as accurately as possible. In antisaccade blocks, participants were told to move their eyes away from the face stimuli to the mirror location in the other periphery as quickly and as accurately as possible. It was also emphasized that on antisaccade trials, participants should try their best to avoid looking at the face stimuli. A 1500 ms inter-trial interval was used (see **Figure 1** for details).

Auditory tones played via a laptop provided the secondary load manipulation. In high load blocks, participants heard three differently-pitched tones presented every 1900–2300 ms (at any possible increments of 100 ms). Participants verbally responded to whether the pitch of the tone was "low," "mid," or "high" while continuing to complete the anti/prosaccade task. In low load blocks, participants only ever heard the middle pitched tone, and were simply required to respond by saying the word "tone" whenever they heard one. Participants were told to respond promptly and accurately to the tones, and the experimenter monitored their performance, giving feedback at the end of blocks if errors had been made.

There were thus four different blocked conditions, prosaccade/antisaccade with low/high cognitive load. Facial expression of visual onsets in the task was presented randomly within blocks and each expression appeared on an equal number of trials. Participants were given initial practice at discriminating the auditory tones, and subsequently 16 practice trials in the antisaccade/prosaccade task. Participants then completed eight blocks of 36 trials, with block order following an ABCDDCBA format (condition to letter counterbalanced across participants). Participants were then thanked and debriefed.

[1]The STAI has high internal consistency in measuring trait anxiety. In the present study, the spread of anxiety scores is consistent with previous work, where medians tend to sit around a score of 37 (Fox et al., 2002). Furthermore, as illustrated in **Figure 2**, we had an adequate proportion of scorers below 35 and above 40, suggested to be appropriate cut-offs to reflect clear low and highly anxious individuals (Fox et al., 2002).

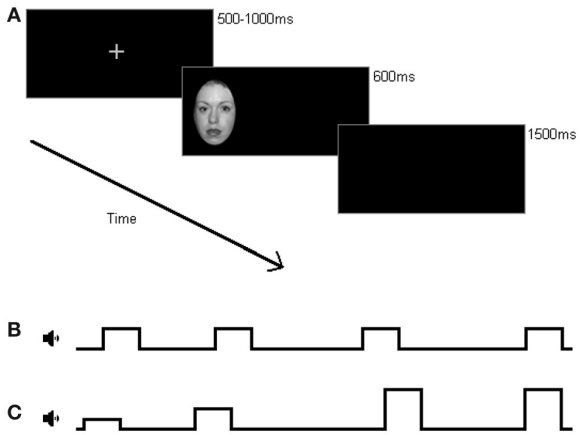

FIGURE 1 | Example trial display (not to scale). (A) Following fixation, a face image appeared either in the left or right periphery, displaying either a neutral, angry, or happy emotional expression. Depending on the block type, participants were asked to move their eyes from fixation to the image as quickly as possible, or look away from the image and move their eyes to the opposite end of the screen. **(B)** In addition to eye movements, participants simultaneously responded verbally to tones played during blocks. Under low load, participants always heard a mid-pitched tone, and responded by saying "tone" each time they heard a sound. **(C)** Under high load, tones were presented at three different pitches, and participants responded to this with "low," "mid," or "high" when a tone played. All tones played randomly every 1900–2300 ms.

RESULTS

WITHIN-SUBJECTS EFFECTS

Data from 10 participants were removed due to overall antisaccade errors of over 50%. Anticipatory saccade (eye movements quicker than 85 ms; $M = 1.74\%$ of data) and no recorded saccade trials ($M = 1.65\%$ of data) were also removed from the data prior to error rate analysis.

Saccade latencies

Correct response latencies from 84 participants were entered into a three-way ANOVA with the factors expression (neutral, angry, happy), load (low, high), and condition (antisaccade, prosaccade). Descriptive statistics are shown in **Table 1**. Analysis showed a main effect of load [$F_{(1,\ 83)} = 24.52$, $p < 0.001$], indicating slower saccade latencies under high load ($M = 251$ ms, $SD = 29$) vs. low load ($M = 243$ ms, $SD = 33$). A main effect of condition [$F_{(1,\ 83)} = 495.74$, $p < 0.001$] also demonstrated faster latencies on prosaccade ($M = 200$ ms, $SD = 30$) compared with antisaccade trials ($M = 294$ ms, $SD = 40$). Importantly, a two-way interaction of load × condition [$F_{(1,\ 83)} = 18.54$, $p < 0.001$] revealed that load increased latencies on antisaccade trials [$M = 286$–302 ms; $t_{(83)} = 6.36$, $p < 0.001$], but did not affect prosaccade speed ($M = 200$–201 ms; $t < 1$).

There was no main effect of expression, or an interaction of expression × condition (F's < 1). However, there was both a significant two-way interaction of expression × load [$F_{(2,\ 166)} = 5.25$, $p < 0.01$], and a Three-Way interaction of expression × load × condition [$F_{(2,\ 166)} = 3.68$, $p < 0.03$]. To decompose these effects, separate ANOVAs were firstly conducted within each level of the condition factor. For prosaccades, there was no main

effect of expression (F's < 1), and no two-way interaction with load [$F_{(2,\ 166)} = 1.45$, $p = 0.24$]. On antisaccade trials, there was no main effect of expression ($F < 1$), but a significant interaction with load did emerge [$F_{(2,\ 166)} = 5.74$, $p < 0.01$]. One-Way ANOVAs showed no significant effect of expression under high load [$F_{(2,\ 166)} = 1.14$, $p = 0.32$], but a significant effect under low load [$F_{(2,\ 166)} = 5.91$, $p < 0.01$]. As reflected in **Table 1**, latencies were fastest in response to happy expressions and slowest for angry, corresponding to a strong linear contrast [$F_{(1,\ 83)} = 11.6$, $p = 0.001$]. Pairwise comparisons showed a significant difference between angry and happy expressions [$t_{(83)} = 3.41$, $p = 0.001$], neutral vs. happy differences were just short of significance [$t_{(83)} = 1.98$, $p = 0.05$]. However, neutral and angry expressions did not differ [$t_{(83)} = 1.44$, $p = 0.15$].

Error rates

There was a main effect of condition [$F_{(1,\ 83)} = 150.45$, $p < 0.001$], reflecting higher errors on antisaccade trials ($M = 18\%$, $SD = 11$) compared to prosaccade ($M = 5\%$, $SD = 6$). There was also a main effect of load [$F_{(1,\ 83)} = 8.14$, $p < 0.01$] indicating modest but significantly higher errors under high load ($M = 12\%$, $SD = 8$) compared with low load ($M = 11\%$, $SD = 9$). Furthermore, a significant two-way interaction of load × condition [$F_{(1,\ 83)} = 8.56$, $p < 0.01$] mirrored latency data by showing increased errors under high compared to low load on antisaccade trials [$M =$ 16–20%; $t_{(83)} = 3.40$, $p = 0.001$], but no effect on prosaccade trials ($M =$ 5–5%; $t < 1$).

There was no main effect of expression or interaction with load (F's < 1), or condition [$F_{(2,\ 166)} = 1.13$, $p = 0.33$]. However, a Three-Way interaction of expression × load × condition was observed [$F_{(2,\ 166)} = 5.77$, $p < 0.01$]. Separate ANOVAs within each level of condition factor showed a trend under prosaccade trials for a main effect of expression [$F_{(2,\ 166)} = 2.42$, $p = 0.09$], and for an interaction of expression × load [$F_{(2,\ 166)} = 2.71$, $p = 0.07$]. On antisaccade trials, there was no main effect of expression ($F < 1$) but a significant expression × load interaction [$F_{(2,\ 166)} = 3.17$, $p < 0.05$]. While there was no effect of expression under high load ($F < 1$), an effect in low load was seen [$F_{(2,\ 166)} = 3.74$, $p < 0.03$]. Similar to response latencies, **Table 1** shows the lowest errors on happy expression trials, with the highest on angry expression trials, reflected by a strong linear contrast [$F_{(1,\ 83)} = 9.09$, $p < 0.01$]. Pairwise comparisons showed that errors on angry and happy expression trials significantly differed [$t_{(83)} = 3.02$, $p < 0.01$]. Differences between neutral and angry expression trials did not reach significance [$t_{(83)} = 1.70$, $p = 0.09$], and nor did neutral vs. happy expression trial error rates [$t_{(83)} = 1.02$, $p = 0.31$].

EFFECTS OF INDIVIDUAL DIFFERENCES IN TRAIT ANXIETY

Saccade latencies

Trait anxiety scores varied across participants (Med = 39, $SD =$ 11, range = 20–69). As occulomotor speed differs between individuals, we subtracted prosaccade latencies from antisaccade for each participant, creating a measure of cost to saccade speed on trials requiring a controlled eye-movement vs. a baseline reflexive response. Using trait anxiety score as a continuous measure, we then correlated this with inhibitory cost from the low and high load conditions. Under low load, there was no significant correlation between trait anxiety score and inhibitory costs ($r = 0.105$, $N = 84$, $p = 0.34$). However, anxiety was associated with inhibitory costs under high load ($r = 0.244$, $N = 84$, $p < 0.03$). Furthermore, when subtracting the inhibitory cost under low load from high to reveal the extent of load in disrupting inhibition, a positive correlation with anxiety again emerged ($r = 0.182$, $N = 84$, $p < 0.05$ one-tailed; see **Figure 2**). Thus, anxiety was associated with the magnitude of cost on inhibition under cognitive load.

To assess whether the effect of anxiety and inhibition was modulated by the emotional expression of the visual onset, we conducted further correlational analyses with anxiety and inhibitory costs for each expression under each level of load. Under low load, anxiety did not correlate with inhibitory costs on neutral ($r = 0.150$, $N = 84$, $p = 0.17$) or either emotional expression level (r's < 1). Under high load, evidence of a positive correlation between inhibitory costs and anxiety was observed regardless of expression being neutral ($r = 0.269$, $N = 84$, $p = 0.01$), angry ($r = 0.186$, $N = 84$, $p = 0.05$ one-tailed), or happy ($r = 0.179$, $N = 84$, $p = 0.05$ one-tailed). Modulations by anxiety therefore appeared to occur regardless of stimulus emotion.

Table 1 | Mean saccadic latencies (milliseconds) and percentage error rates within expression, load, and condition factors (standard deviation of the mean in parentheses).

Expression	Level of load and condition			
	Low load		High load	
	Antisaccade	Prosaccade	Antisaccade	Prosaccade
Neutral	286 (45)	199 (34)	302 (42)	202 (35)
	16 (14)	5 (7)	20 (14)	4 (7)
Angry	290 (49)	202 (38)	299 (46)	201 (34)
	18 (13)	5 (7)	19 (13)	6 (9)
Happy	281 (43)	200 (35)	305 (48)	200 (31)
	15 (13)	6 (8)	20 (14)	5 (8)

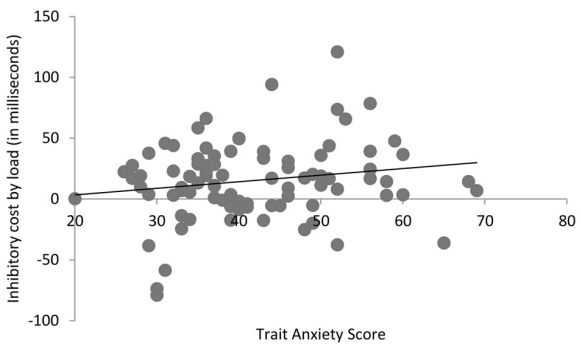

FIGURE 2 | Correlation between trait anxiety score and load-induced inhibitory costs on saccadic eye-movements.

Error rates

Anxiety score did not correlate with inhibitory cost error rates under either level of load (r's < 1), and did not correlate with the load cost ($r = -0.107$, $N = 84$, $p = 0.33$). Likewise, there was no evidence of anxiety associated with inhibitory costs for different emotional expressions at any load level (all r's < 0.148, p's > 0.18).

DISCUSSION

Results from the present study suggest that increasing cognitive load not only disrupts attentional control processes, but this effect is especially potent for individuals with high levels of trait anxiety. Furthermore, results show an effect of emotional valence by load, in that evidence of emotion modulating task performance was evident on antisaccade trials only under low load; high load eliminated all emotional expression differences.

ATTENTIONAL CONTROL IN TRAIT ANXIETY UNDER COGNITIVE LOAD

Deficits in attentional control in trait anxiety, particularly on the subcomponent of cognitive inhibition, have been suggested in a number of previous investigations examining covert (e.g., Pacheco-Unguetti et al., 2010) and overt (e.g., Derakshan et al., 2009) attention, with additional electrophysiological and neuroimaging studies suggesting individual differences in the prefrontal attentional control network (Bishop, 2009; Ansari and Derakshan, 2011a). However, ACT's prediction that the cognitive demands in a task should hamper performance to a greater extent in individuals with pre-existing deficits in attentional control has to date received far less empirical support. Previous evidence for this theory has primarily come from language-based experiments, where anxious individuals perform worse under more difficult test conditions (Calvo, 1985; Calvo et al., 1992) or when cognitive load is manipulated through digit rehearsal of increasing difficulty (MacLeod and Donnellan, 1993; Derakshan and Eysenck, 1998; Wood et al., 2001) during tasks that assess grammatical reasoning. However, as with a recent study by Berggren et al. (2012), described in our Introduction, these studies cannot clearly show that attentional control in anxiety was further disrupted by load, as increased costs could be due to general issues in performance and not attributable to attentional control *per se*. The present study rules out this possibility; anxious individuals did not perform worse on prosaccade trials under load, where no element of inhibition is required to be efficient in the task. On the other hand, performance on antisaccade trials requiring inhibitory control to suppress a reflexive eye-movement was impaired under load, and the extent of this impairment directly correlated with participants' anxiety levels.

While the present study argues that anxious individuals should exercise poorer attentional control as a task's difficulty increases, it is worthy to address claims that the opposite may be the case. For example, Bishop (2009) showed that increasing perceptual task demands eliminated task-irrelevant distraction and individual differences in anxiety modulated distraction under low perceptual load. While this effect can be attributed to perceptual load reducing basic perception of distractors (see Berggren and Derakshan, 2013, for comment), it was noted that attentional focus could play a role in the effect of anxiety on attentional control. In other words, under low attentional demands, anxious individuals may be more distracted but this effect wanes as more demanding tasks prompt focused attention. Similarly, it has been suggested that working memory capacity/span relates to attentional control abilities. While there have been many demonstrations of attentional control being disrupted by taxing working memory, it has also been documented that individuals with low working memory span are less susceptible to cognitive load manipulations (Kane and Engle, 2000).

One explanation for this finding is that anxious individuals already have impaired attentional control abilities, and using a load to tax inhibitory ability would have a reduced effect when baseline ability is already nearer floor. Importantly, in the present study, inhibitory ability between groups did not differ under low cognitive load; rather than group differences attenuating, they emerged as cognitive load was raised. Therefore, it is possible that attention focus in anxious individuals was enhanced in light of increased task demands but that high cognitive load taxed attentional control and counteracted this process. Whether or not factors such as motivation can impact attentional control deficits in low cognitively demanding tasks is a theoretically important question for future research. Indeed, according to one of the major predictions of ACT, motivation may play a key role in attentional control deficits in anxiety, with poor performance under low motivation and improved performance when encouraged (see Berggren and Derakshan, 2013).

EMOTION PROCESSING UNDER COGNITIVE LOAD

Results from the present study also showed that cognitive load affected emotion processing. Under low load, emotional expression modulated both latencies and error rates, and this effect was confined to the antisaccade condition rather than prosaccade. As prosaccade performance is mainly reflexive, it is likely that the absence of an effect of emotional expression in this condition reflects latency speed being at ceiling. In the antisaccade condition, where participants should inhibit the reflexive eye-movement, there is greater scope for differences to emerge. Notably, such valence differences only occurred under low load; high load both slowed antisaccade latencies and eliminated differences between valence conditions. This finding is unlikely to be due to converse floor effects on latencies with the imposition of load, considering that individual differences in anxiety influenced performance under high load.

Our findings with emotion and cognitive load mirror that of a number of previous studies that have primarily examined interactions of load with negative emotions. Van Dillen and Koole (2009) found that angry, compared to happy, distractors slowed reaction times under low load, but did not differ under high load. Emotional startle effects from threatening images has also been shown to be reduced under cognitive load, as has LPP amplitude reflecting emotional arousal (e.g., MacNamara et al., 2011). Even neural activity in the amygdala, seen as a clear index of the processing of negative emotion, has been suggested to show weaker response to emotion under cognitive load or distraction techniques (Van Dillen et al., 2009; McRae et al., 2010). Collectively, these results support the view that the

processing of emotional information may share resources with other cognitive processes (e.g., Pessoa, 2010).

However, the effects by emotion observed in the present study did not appear solely driven by the threat value of angry expressions. Differences between happy and angry expression trials were seen for both response latencies and error rates, but comparison with neutral expression trials acting as a baseline did not differ from the other emotional conditions significantly for latencies or error rates. Consequently, the present study supports the view that cognitive load can reduce the impact of emotional stimuli on cognitive processes such as inhibitory control, but cannot clarify whether low load effects were predominantly caused by negative emotion impairing performance or perhaps positive emotion facilitating it. While there is ample evidence that positive emotional stimuli are also prioritized for attention (e.g., Williams et al., 2005), we avoid speculation given that the locus of emotion modulations are unclear here; our hypothesis was concerned with whether cognitive load would attenuate emotional influences on inhibitory control, which was supported.

Finally, we did not observe any differential biases toward threat in anxiety under low cognitive load, despite a wealth of previous literature supporting such a bias for highly anxious groups (see Bar-Haim et al., 2007). A similar finding was also obtained in Berggren et al. (2012) where anxiety led to performance costs under cognitive load but did not adversely affect emotion processing in general. One probable explanation for this result is that threat biases overall were weak when making comparisons with neutral expression trials. In other words, effects by anxiety may not have been evident due to the threat value of angry stimuli not being sufficiently high enough in this experimental context to elicit biases for high anxious participants. Thus, it remains unanswered here how inhibitory control of irrelevant *threat* stimuli in anxiety is affected by loading cognitive processes.

FUTURE DIRECTIONS

While the present study establishes clear evidence that trait anxiety results in poor attentional control under high cognitive demands, a number of avenues for future research remain. Firstly, previous studies examining attention to threat in anxiety under cognitive load have found conflicting results, with some indication of enhanced threat processing (Ladouceur et al., 2009; Judah et al., 2013), smaller reductions in LPP arousal responses in anxiety (MacNamara et al., 2011), but also reduced emotional startle for high anxious participants under load (Dvorak-Bertsch et al., 2007; Vytal et al., 2012). It is noteworthy that these studies can be separated reasonably well in relation to their measure of anxiety; increased threat biases seem to occur when trait anxiety is examined (Ladouceur et al., 2009; Judah et al., 2013), while reduced emotional effects seem to dovetail studies where anxiety has been induced in participants (Dvorak-Bertsch et al., 2007; Vytal et al., 2012; but see MacNamara et al., 2011).

Both trait anxiety and mood induction of state anxiety, such as through threat of shock, have been shown to have similar effects on distractibility in some contexts such as the antisaccade task (Cornwell et al., 2012), but may do so through different means. For example, Pacheco-Unguetti et al. (2010) found that trait anxiety reduces executive control of attention while state anxiety modulates the alerting and orienting functions. Thus, the effect of cognitive load may differ in that it exacerbates behavioral effects for trait anxious participants while alleviating effects of state mood. Indeed, it is a possibility that cognitive load could attenuate the priming aspect of a mood induction, while having little effect on fundamental neural differences associated with a trait anxious personality. Future research should examine whether cognitive load can be a beneficial therapy intervention in reducing unwanted emotional experience, as proposed by some (e.g., Van Dillen et al., 2009), or whether it can conversely be detrimental to emotion regulation. The type of anxiety experienced, whether trait or state, could be a crucial factor in this regard. This is particularly important to clarify considering that trait anxiety is a major vulnerability factor in the development of pathological anxiety disorders.

Secondly, future research may further examine how cognitive load impairs more general attentional control in anxiety. Here, we have suggested that anxiety exacerbates cognitive load effects on attention, but it remains unclear how this influences across tasks. As we did not record accuracy for our secondary auditory task, it is possible that cognitive load may have impaired performance on both tasks, further compromising attentional control in anxiety. Furthermore, individual differences in response to emotional stimuli may have been evident on the secondary load task, with anxious participants prioritizing the saccade task in such instances and reducing accuracy and/or response times to the tones. Further work should examine how high anxious individuals coordinate their resources under dual task conditions, as well as the effect of divided attention paradigms. This would also provide more insight into the underlying neural mechanisms behind the present results; previous work has highlighted that anxiety modulates areas associated with attentional control such as dorsolateral prefrontal cortex (Bishop, 2009; Basten et al., 2011), and cognitive load has been shown to increase visual representations for distractor information (e.g., de Fockert et al., 2001). On this basis, the ability to suppress distractor representations under load may have been more strongly impaired in anxious individuals. How cognitive load effects may translate in anxiety under dual task conditions requiring more internal suppression of task goals when switching between tasks remains an open question.

CONCLUSION

The present study suggests that increasing cognitive load disrupts performance in tasks requiring attentional control, particularly for individuals reporting high levels of trait anxiety. This supports ACT's prediction that increasing task demand causes greater attentional control decrements in high anxiety, pointing to a poorer ability to maintain task goals when pre-existing deficits in attentional control are further compromised. Finally, results also suggest reduced threat biases in attention under cognitive load, supporting accounts of shared emotion-cognition resources.

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Psychosocial deprivation, executive functions, and the emergence of socio-emotional behavior problems

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Early psychosocial deprivation can negatively impact the development of executive functions (EFs). Here we explore the impact of early psychosocial deprivation on behavioral and physiological measures (i.e., event-related potentials; ERPs) of two facets of EF, inhibitory control and response monitoring, and their associations with internalizing and externalizing outcomes in the Bucharest Early Intervention Project (BEIP; Zeanah et al., 2003). This project focuses on two groups of children placed in institutions shortly after birth and then randomly assigned in infancy to either a foster care intervention or to remain in their current institutional setting. A group of community controls was recruited for comparison. The current study assesses these children at 8-years of age examining the effects of early adversity, the potential effects of the intervention on EF and the role of EF skills in socio-emotional outcomes. Results reveal exposure to early psychosocial deprivation was associated with impaired inhibitory control on a flanker task. Children in the foster care intervention exhibited better response monitoring compared to children who remained in the institution on the error-related positivity (Pe). Moreover, among children in the foster care intervention those who exhibited larger error-related negativity (ERN) responses had lower levels of socio-emotional behavior problems. Overall, these data identify specific aspects of EF that contribute to adaptive and maladaptive socio-emotional outcomes among children experiencing early psychosocial deprivation.

Keywords: event-related potential (ERP), error-related negativity, executive function, conflict monitoring, inhibitory control, institutionalization

INTRODUCTION

Psychosocial deprivation that occurs in conjunction with institutional rearing can result in perturbations in the development and reactivity of brain regions involved in cognitive processing (Chugani et al., 2001; Eluvathingal et al., 2006; Hanson et al., 2012; Sheridan et al., 2012). Significant impairments have been found amongst children experiencing early psychosocial deprivation on executive functions (EFs; Bos et al., 2009; Loman et al., 2013), skills known to contribute to regulated and goal-directed behavior. In particular, institutional rearing has been linked to perturbations in specific EF skills such as inhibitory control (Colvert et al., 2008a; Pollak et al., 2010; McDermott et al., 2012), conflict resolution (Loman et al., 2013), and working memory (Colvert et al., 2008a; Bos et al., 2009). Across various studies, longer periods of adversity and later age at adoption following psychosocial adversity have both been associated with greater impairment in EFs (Colvert et al., 2008a; Pollak et al., 2010; Merz and McCall, 2011).

In addition to deficits in EF skills, early exposure to psychosocial adversity is associated with elevated rates of neuropsychological problems. These problems are characterized by poor attention as well as dysregulated emotional and behavioral control that may interfere with social relations and academic functioning in childhood (Beckett et al., 2007; Loman et al., 2009). While removal from deprived caregiving environments generally improves developmental outcomes for children (McGoron et al., 2012), continued risk for psychopathology is apparent even after adoption (Colvert et al., 2008b) or placement into high quality foster care (Zeanah et al., 2009), with some problems persisting into adolescence (Colvert et al., 2008b). Recent efforts to identify factors involved in the etiology of these problems among children who experienced early psychosocial deprivation have identified influential biological (McLaughlin et al., 2011) as well as interpersonal factors (McGoron et al., 2012), yet, to our knowledge, no studies have investigated the degree to which deficits in specific EF skills predict maladaptive social outcomes. Given the continued importance of EF skills throughout development, this line of inquiry may be particularly useful in: (1) elucidating cognitive mechanisms that underlie specific socio-emotional problems among previously institutionalized children, and (2) identifying specific areas to target for continued intervention efforts as EF skills.

Two EF skills particularly relevant to risk for psychopathology among children experiencing early psychosocial deprivation are inhibitory control and response monitoring. Inhibitory control is the ability to withhold prepotent actions and suppress irrelevant or distracting information. Response monitoring (also referred to as error monitoring) is the evaluation of one's own actions after they have occurred. This latter skill of response monitoring works in tandem with other EF skills like inhibitory control by signaling the need to adjust behavior to meet task goals. Engagement of inhibitory control and response monitoring (Casey et al., 1997; Bunge and Wright, 2007; Perlman and Pelphrey, 2011) are both guided by areas of the prefrontal cortex (PFC) and anterior cingulate (ACC) and both skills undergo considerable development throughout childhood (e.g., Ridderinkhof et al., 1997; Davies et al., 2004; McDermott et al., 2007; Van Meel et al., 2012). However, the degree to which early experience impacts the emergence and refinement of these skills remains unknown.

Among children experiencing early psychosocial deprivation mixed patterns of inhibitory control performance have emerged. Modest or no differences have been found on basic tests of inhibitory control tracking impulsive responding such as the go/nogo paradigm (McDermott et al., 2012; Loman et al., 2013) and the Knock and Tap test (Pollak et al., 2010). However, measures requiring inhibitory control in the face of distracting stimuli reveal more pronounced deficits with previously institutionalized children exhibiting impairments on Stroop (Colvert et al., 2008a) and flanker tasks (Loman et al., 2013). These patterns suggest that early psychosocial deprivation may differentially influence various brain regions involved in inhibitory control. However, different components of inhibitory control could rely more strongly on specific regions of the PFC and may have variations in developmental patterns. For instance, the go/nogo paradigm assesses delay inhibition, or more specifically, the ability to withhold a prepotent response. This type of inhibitory control involves activation of the ventrolateral PFC (VL-PFC; Durston et al., 2002; Schultz et al., 2004; Goya-Maldonado et al., 2010). In contrast, the flanker paradigm assesses conflict inhibitory control, also referred to as resistance to interference. Conflict inhibitory control is associated with engagement of the dorsolateral prefrontal region (DL-PFC; Casey et al., 2000; Wang et al., 2010; Perlman and Pelphrey, 2011). Brain imaging work suggests that the ability to efficiently engage the DL-PFC may have a more protracted period of development compared to the VL-PFC (e.g., Bunge and Zelazo, 2006). Thus, it is possible that early psychosocial deprivation may differentially influence the development of specific inhibitory control skills or the potential for plasticity in these skills with interventions following early psychosocial deprivation.

Early psychosocial deprivation is also thought to negatively impact the development of response monitoring. The primary measures of response monitoring are two event-related potentials (ERPs): the error-related negativity (ERN; Falkenstein et al., 1991; Gehring et al., 1993) and the error-related positivity (Pe; Falkenstein et al., 1991, 2000). Both components are time locked to subject's responding, however, the ERN is a negative deflection that is maximal at frontocentral sites and generally peaks within the first 100 ms of a response whereas the Pe is a large positive peak with a central-parietal scalp distribution occurring in a later window around 200–500 ms (Falkenstein et al., 2000; Torpey et al., 2012). Functionally, these components are postulated to represent unique processes involved in response monitoring. The ERN is thought to reflect conflict detection associated with response selection or an evaluative signal for action (Coles et al., 2001; van Veen and Carter, 2002; Hermann et al., 2004; Arbel and Donchin, 2009; Roger et al., 2010; Hughes and Yeung, 2011) whereas the Pe represents conscious levels of performance evaluation (Nieuwenhuis et al., 2001). Both the ERN and Pe have been localized to the ACC; however, additional generators have been postulated for the Pe including the anterior insular cortex (Overbeek et al., 2005; Ullsperger et al., 2010; Schroder et al., 2012).

An additional behavioral measure of response monitoring involves the comparison of reaction times (RTs) after correct and incorrect trials. Longer RTs following incorrect trails represent enhanced monitoring via orienting to mistakes (Notebaert et al., 2009), and this RT slowing is postulated to represent efforts to maximize future task performance (Dudschig and Jentzsch, 2009). However, post-error slowing has not been consistently reported across studies and evidence suggests that differences in post-error slowing may be strongly influenced by motivation and personality factors (Luu et al., 2000; Pailing and Segalowitz, 2004).

Recent work examining response monitoring among children experiencing early psychosocial deprivation suggests strong influence of both early psychosocial deprivation and caregiving interventions such as foster care and adoption. McDermott et al. (2012) found that children between 8 and 9 years of age who experienced a high quality foster care intervention following early psychosocial deprivation exhibited stronger response monitoring in the form of a larger ERN compared to children who did not receive the intervention on a go/nogo paradigm. In a study of internationally adopted children, Loman et al. (2013) also found that children who had been in foster care and children who had never been adopted had significantly larger ERN amplitudes compared to children who had previously received institutionalized care on a flanker task. Given that go/nogo and flanker paradigms tap somewhat distinct cognitive skills and neural regions, it is plausible that the impact of early psychosocial deprivation on response monitoring may be more pronounced on flanker as compared to go/nogo tasks. Although these studies reveal deficits in the neural correlates of response monitoring among children experiencing institutional rearing, the potential role of this EF skill in moderating socio-emotional outcomes for these children remains unknown.

The presence of strong EF skills, like inhibitory control or response monitoring, have generally been linked to positive developmental outcomes whereas deficits in EF skills tend to be central components of negative outcomes. In particular, the EF skills of inhibitory control and response monitoring have been strongly implicated in externalizing problems (Olson et al., 2011; Bohlin et al., 2012) such as attention deficit hyperactivity disorder (ADHD; Barkley, 1997; Nigg, 2001; Shiels and Hawk, 2010). Although both externalizing issues and ADHD

symptomology are prevalent among children experiencing prolonged psychosocial adversity (Juffer and van Ijzendoorn, 2005; Gunnar et al., 2007; Zeanah et al., 2009), it remains unclear whether differences in EFs may moderation risk for adaptive and maladaptive outcomes among children experiencing early adversity.

Among typically developing children, there is evidence that EFs moderate risk for socio-emotional outcomes. For example, behaviorally inhibited children high in inhibitory control or response monitoring are at increased risk for anxiety issues (McDermott et al., 2009; White et al., 2011) whereas behaviorally inhibited children with high attention shifting skills are at lower risk (White et al., 2011). Such patterns of moderation, along with studies suggesting strong plasticity in EF skills (Rueda et al., 2005), suggest that children at risk for negative socio-emotional outcomes, as in the case of psychosocial deprivation, may benefit from interventions that promote EFs skills. However, no work to date has explored whether EFs moderate socio-emotional outcomes in children experiencing early institutionalized care.

The overarching goals of the current study were to investigate associations among inhibitory control and response monitoring components of EF and the influence of theses skills in social developmental outcomes in a sample of children who experienced early institutionalization and were enrolled in the Bucharest Early Intervention Project (BEIP; see Zeanah et al., 2003 for details). Children in the study were randomized to one of two conditions (1) to be taken out of the institution and placed into foster care (Foster Care Group; FCG) or (2) to remain in institutional care (Care as Usual Group; CAUG). In addition, a typically developing sample of children (Never Institutionalized Group; NIG) was recruited from the community. Behavioral and ERP measures were collected during a flanker task when children were 8 years of age.

Based on a growing literature demonstrating poorer EF skills in children experiencing institutionalized care compared to non-adopted children or children adopted from foster care (see Merz et al., 2013, for a review), it was predicted that children in the CAUG would perform worse than the NIG on the EF measures of inhibitory control and response monitoring whereas children in the FCG would perform at an intermediate level compared to the CAUG and NIG on these measures. Moreover, given the heterogeneity of socio-emotional outcomes exhibited in both the CAUG and FCG at earlier assessments (e.g., Ghera et al., 2009; Zeanah et al., 2009) and the potential for cognitive processes to moderate such outcomes (e.g., McDermott et al., 2009; White et al., 2011), both inhibitory control and response monitoring skills were predicted to moderate associations between early experience and socio-emotional outcomes for all groups such that better EF skills would be associated with lower rates of socio-emotional problems.

MATERIALS AND METHODS

PARTICIPANTS

The sample was comprised of 136 children, abandoned at birth and placed into institutional care in Bucharest, Romania who were part of the BEIP. At 8 years, 49 CAUG (25 female), 54 FCG (28 female), and 47 NIG (26 female) children remained in the study and completed the Flanker task that is the subject of this paper. The mean age of test was 104.79 ($SD = 8.27$) months for the CAUG, 104.65 ($SD = 12.98$) months for the FCG, and 100.83 ($SD = 9.14$) months for the NIG. **Figure 1** presents a Consort Diagram for the sample at 8 years of age. Although many of the institutionalized children at age 8 were no longer in their original randomized placement, the data to be presented in this paper uses an intent-to-treat approach such that data are analyzed using a child's initial placement.

The University Institutional Review Boards of the principal investigators (Fox, Nelson and Zeanah) and the University of Bucharest, Romania approved the study protocol. Romanian law dictated that consent be given by the local Commission on Child Protection for each child participant who lived in their sector of Bucharest. Electrophysiology assent was obtained from each caregiver who accompanied a child to the visit.

FLANKER TASK

The flanker task assesses children's ability to respond to a central target in the context of distracting stimuli. For this study the target stimuli consisted of right or left facing arrows. Children were instructed to respond as quickly and correctly as possible via button press to indicate the direction of the middle arrow (right or left). Congruent trials consisted of stimuli all in the same direction (> > > > > or < < < < <), whereas incongruent trials had the central target in a row of stimuli facing in the opposite direction as the flanking stimuli (< < > < < or > > < > >). A practice block of 20 trials was presented to familiarize children with the stimuli and button box. The test trials consisted of equal numbers of congruent and incongruent trials presented in a pseudo random order across two test blocks of 80 trials each for a total of 160 test trials.

Trials began with the presentation of a warning cue (*****) for 500 ms, followed by a blank screen and then the presentation of the target display for 1000 ms and then another a blank screen for 500 ms. Children were required to respond within 1500 ms of the presentation of the target array. Task difficulty level was controlled by varying the presentation rate of the flanker stimuli. Based upon participant accuracy across 10 trials, stimulus presentation time sped up (7 or more correct responses), slowed down (5 or less correct responses), or remained the same (6 correct responses). This manipulation resulted in an overall average error of commission rate of ∼60%. Stimulus presentation was controlled by computer software (Cognitive Activation System; CAS, James Long Company, Caroga Lake, NY, USA) run on an IBM PC on which the flanker task was programmed. Measures of response time and response accuracy per trial were directly recorded by CAS program software.

ELECTROENCEPHALOGRAM (EEG)

EEG was collected via a lycra Electro-Cap (Electro-Cap International Inc., Eaton, OH, USA) according to the 10–20 system from the following sites: F3, F4, Fz, C3, C4, P3, P4, Pz, O1, O2, T7 and T8 and the right and left mastoids. Site Cz served as reference and Afz served as ground. Impedances were kept at or below 10 kΩ. Eye movement was tracked via electrooculogram (EOG) collected from a pair of Beckman mini-electrodes with

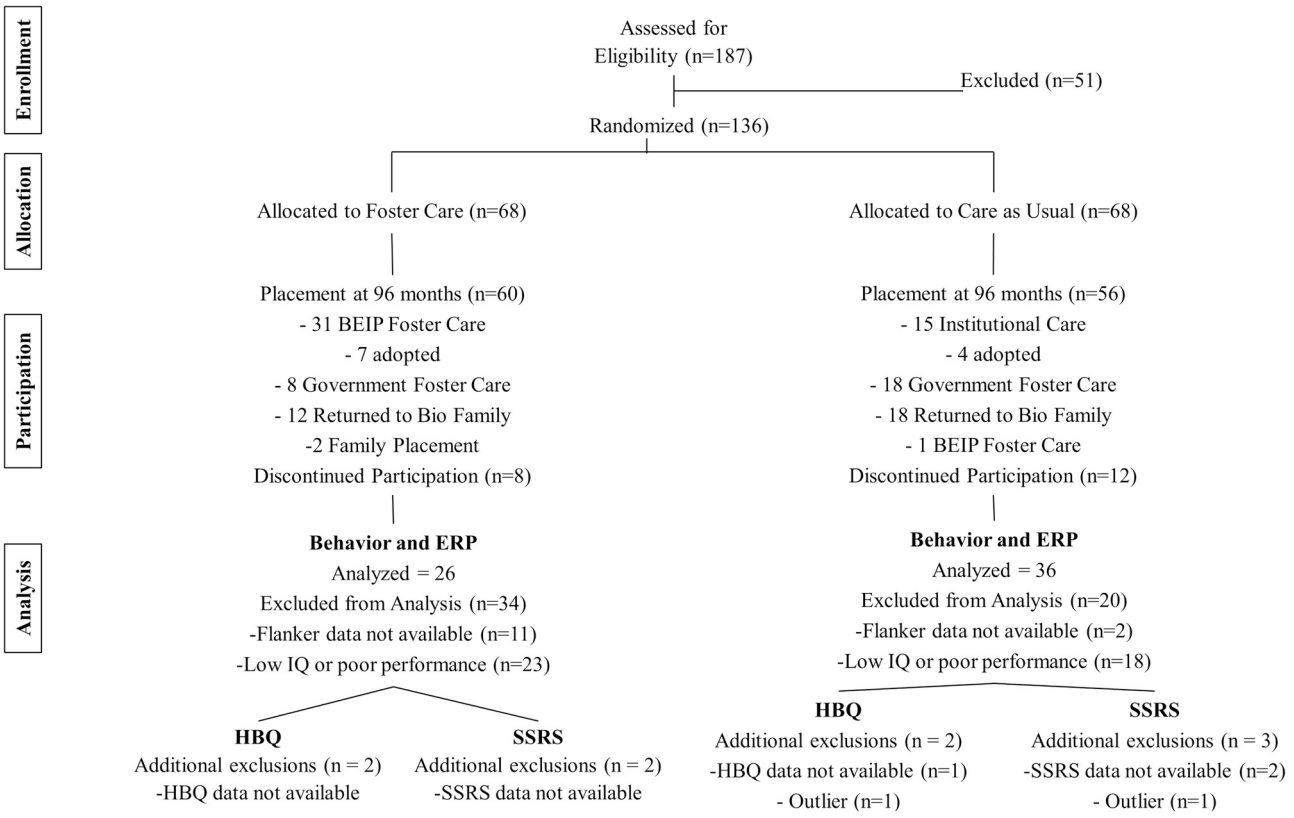

FIGURE 1 | Group assignment over time: current status at 8 years of age.

one placed above and one below the left eye. Electrophysiological signals were amplified at 5000 for EEG and 2500 for EOG. Bandpass filters of 0.1–100 Hz were applied with custom bioamplifiers from the James Long Company (Caroga Lake, NY, USA) and data were digitized at 512 Hz. For ERP analysis a 30-Hz lowpass filter was applied, epochs containing signals exceeding ±200 uV were excluded and EOG artifact was regressed. An average mastoid configuration was used to re-reference the data and baseline correction for individual averages was calculated with the 200–100 ms prior to response. Averages were calculated for correct and incorrect trials to examine patterns of the ERN and Pe. Peak amplitudes for both the ERN and Pe were assessed at the midline electrodes (Fz, Cz, Pz) and time-locked to button press. The ERN was examined in the windows of −50 to 100 ms where as the Pe was assessed in the window of 110–210 ms.

HEALTH AND BEHAVIOR QUESTIONNAIRE (HBQ, MacArthur)

For the present paper, four behavioral subscales of the HBQ were used: internalizing behaviors, externalizing behaviors, ADHD symptoms, and social withdrawal. The internalizing scale is comprised of items related to depression and overanxious behaviors. The externalizing scale consists of measures of oppositional defiance, conduct problems, overt hostility, and relational aggression. The ADHD scale measures inattention and impulsivity. Finally, the social withdrawal scale is comprised of asocial behavior with peers and social inhibition. Each participant's primary teacher completed the HBQ.

SOCIAL SKILLS RATING SYSTEM (SSRS, PEARSON ASSESSMENTS)

The SSRS assesses three broad scales: problem behaviors, social skills, and academic competence. The problem behaviors scale focuses on three types of issues that can interfere with social development: externalizing, internalizing, and hyperactivity. The social skills scale assesses aspects of positive social behavior such as cooperation, empathy, assertion, self-control, and responsibility. Academic competence reflects a child's performance on reading, mathematics, global cognitive ability, motivation, and parent support. The SSRS was completed by each participant's primary teacher.

IQ

At 8 years of age, IQ was assessed in the BEIP laboratory using the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003). The WISC-IV uses 10 subtests to assess intellectual functioning in four domains: verbal comprehension, perceptual reasoning, working memory, and processing speed. In addition, a full-scale IQ composite score is calculated based on the 10 subtest scores, scaled for age. The four subscale scores and full-scale IQ scores were used in the present analyses. The IQ data were previously reported in Fox et al. (2011). Trained and reliable Romanian psychologists administered all of the IQ scales.

PARTICIPANT INCLUSION

To verify capacity to complete the flanker task, children who scored less than 70 on the WISC or had less than 60% accuracy on congruent trials were excluded from analysis (23 CAUG, 18 FCG, 4 NIG) [$\chi^2_{(2,\ N=150)} = 17.316, p < 0.001$]. The final sample for behavioral analysis included 26 (15 female) CAUG children, 36 (19 female) FCG children, and 43 (25 female) NIG children. For ERP analysis, children with fewer than eight usable trials for the response-locked ERN (1 NIG) (Olvet and Hajcak, 2009) and five additional NIG children who only completed the task behaviorally were excluded from analysis. The final sample for ERP analysis included 26 (15 female) CAUG children, 36 (19 female) FCG, and 37 (24 female) NIG children. Finally, for the social outcome moderation analyses, four children were removed from the HBQ analyses (2 IG, 1 FCG, 1 NIG) and six children were removed from the SSRS analyses due to missing data (2 IG, 2 FCG, 2 NIG). An additional three children with extreme (more than 3 SD from the group mean) scores on the HBQ and SSRS scales were excluded (1 FCG, 2 NIG). The final moderation samples included 24 (14 female) CAUG children, 34 (17 female) FCG, and 34 (22 female) NIG children for HBQ analyses and 24 (14 female) CAUG children, 33 (16 female) FCG, and 33 (21 female) NIG children for SSRS analyses.

RESULTS

STATISTICAL PROCEDURES

To assess behavioral responses a series of repeated measures ANOVAs were used with Greenhouse-Geisser corrections applied as necessary. Participant group (CAUG, FCG, NIG) served as a between-subjects factor and flanker trial type (congruent vs. incongruent) served as a within-subjects factor.

To assess group differences in the ERN and Pe, separate ANOVAs were conducted with participant group (CAUG, FCG, NIG) as the between-subjects factor. Additionally, to assess the influence of participant group and the ERN on children's socio-emotional outcomes (HBQ and SSRS scales) a series of linear regressions were run. To address potential mulitcollinearity and clarify in analysis interpretation, interaction terms were standardized and mean centered. The three groups of children (CAUG, FCG, NIG) were effect coded into two variables in order to exhaust all possible comparisons. Group and the flanker-related variables were entered first followed by the interaction terms to look for moderation effects of accuracy or neural reactivity (ERN/Pe). Significant Group by flanker-related variable moderation effects were probed by follow-up 3 Group (IG, FCG, NIG) $\times$2 ERN Size (large, small) ANOVAs.

BEHAVIOR

Accuracy

A main effect was found for trial type [$F_{(1,\ 102)} = 361.96$, $p = 0.00$] with more accurate responding on congruent ($M = 81.94\%$, $SD = 9.05$) compared to incongruent trials ($M = 44.60\%$, $SD = 18.88$). This main effect was qualified by an interaction of trial type and group [$F_{(2,\ 102)} = 4.23$, $p = 0.02$]. Follow-up tests revealed that the groups differed in accuracy rates on incongruent trials [$F_{(2,\ 104)} = 6.28$, $p = 0.00$] such that the CAUG and FCG were significantly less accurate on incongruent trials than children in the NIG (p's $= 0.02$). The CAUG and FCG did not differ in their accuracy rates.

Reaction time

Congruency effects were analyzed by comparing RT on correct congruent and correct incongruent trials. A main effect for trial emerged [$F_{(1,\ 102)} = 112.27$, $p = 0.000$] such that children responded faster on congruent ($M = 694$ ms, $SD = 107$ ms) as compared to incongruent trials ($M = 776$ ms, $SD = 135$ ms). Both the main effect of trial along with a main effect for group [$F_{(2,\ 102)} = 3.70$, $p = 0.028$] were qualified by an interaction between trial type and group [$F_{(2,\ 102)} = 3.44$, $p = 0.036$]. Follow-up tests revealed group differences for RTs on congruent trials [$F_{(2,\ 104)} = 6.21$, $p = 0.003$]. Specifically, children in the CAUG and FCG groups had slower congruent trial RTs than children in the NIG (p's < 0.05). The CAUG and FCG groups did not differ in their overall RTs on congruent trials (see **Table 1**).

Post-error RT slowing was assessed by comparing RTs after correct trials to RTs following errors of commission. A main effect for trial emerged [$F_{(1,\ 102)} = 112.27$, $p = 0.00$] with faster responding after correct trials ($M = 731$ ms, $SD = 117$ ms) compared to errors of commission ($M = 750$ ms, $SD = 117$). Additionally, main effect of group [$F_{(2,\ 102)} = 3.70$, $p = 0.028$] revealed differences in general processing speed across the groups. The follow-up analysis revealed that collapsed across trial type the CAUG responded significantly slower than the NIG ($p = 0.018$) whereas the FCG did not significantly differ in their response speed from either the CAUG or NIG. No interactions between reaction and group emerged for post-error RT slowing.

EVENT-RELATED POTENTIALS

ERN

Main effects for trial [$F_{(1,\ 98)} = 18.138$, $p = 0.000$] and site [$F_{(2,\ 196)} = 6.027$, $p = 0.007$] as well as a trial $\times$ site interaction [$F_{(2,\ 196)} = 20.906$, $p = 0.000$] emerged on a repeated measures ANOVA that revealed larger ERN amplitudes on incorrect trials that were maximal at site Fz. In order to examine group differences in the ERN peak amplitude at Fz, a 3 Group (CAUG, FCG, NIG) One-Way ANOVA was performed. Results indicated that there were no significant group differences in ERN peak amplitude [$F_{(2,\ 96)} = 1.310$, $p = 0.275$] (**Figure 2**). Additionally, among the FCG, ERN peak amplitude was not correlated with

Table 1 | Descriptive statistics.

	NIG	CAU	FCG
Age (months)	8.31 (0.27)	8.49 (0.44)	8.68 (0.35)
BEHAVIOR			
Overall accuracy (%)	67.5 (11.10)	58.9 (8.00)	61.3 (10.13)
Congruent trials	83.0 (9.51)	78.4 (8.13)	82.3 (8.65)
Incongruent trials	52.1 (16.345)	39.5 (17.23)	39.4 (20.15)
Reaction time (ms)	702 (115)	777 (97)	739 (115)
Congruent trials	653 (100)	736 (89)	713 (113)
Incongruent trials	754 (146)	822 (121)	768 (126)

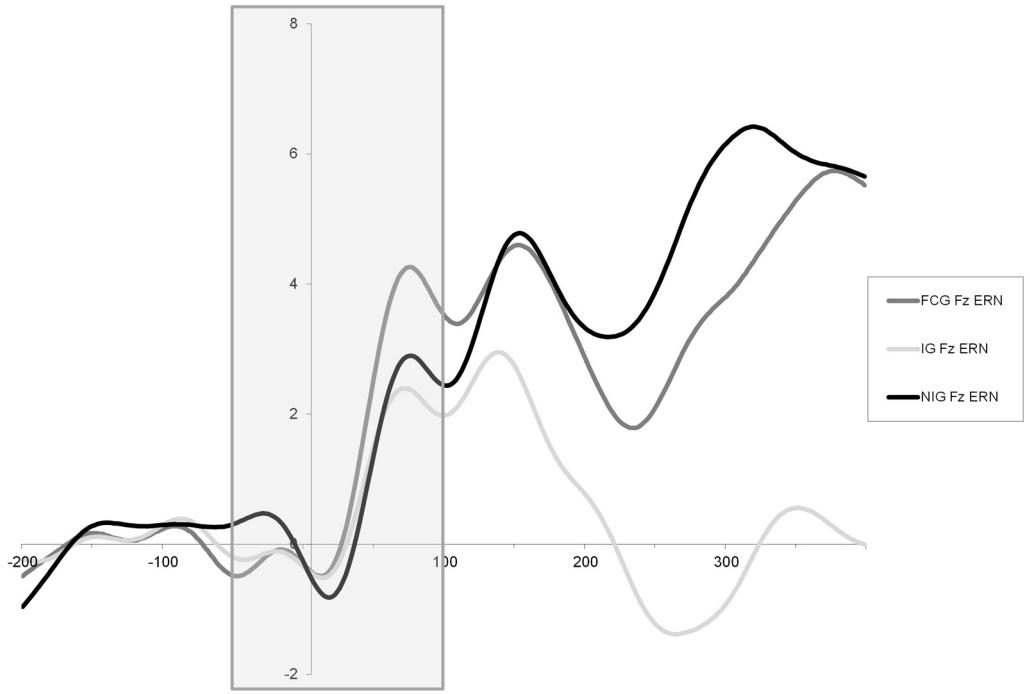

FIGURE 2 | Response-locked ERN waveform at Fz. ERN time window is outlined.

percent of life spent in institutionalized care [$r_{(34)} = 0.020$, $p = 0.906$].

Pe

A repeated-measures ANOVA revealed main effects for trial [$F_{(1, 98)} = 12.215$, $p = 0.001$], site [$F_{(2, 196)} = 53.014$, $p = 0.000$] that were qualified by a trial × site interaction trial [$F_{(2, 196)} = 37.786$, $p = 0.000$] showing that Pe amplitude was larger on incorrect trials and greatest at sites Cz and Pz. Separate One-Way ANOVAs were used to examine group differences (CAUG, FCG, NIG) in Pe peak amplitude at Cz and Pz. Main effects for group emerged at site Cz [$F_{(2, 96)} = 6.925$, $p = 0.002$] and Pz [$F_{(2, 96)} = 5.621$, $p = 0.005$] and follow-up tests reveal that at site Cz the NIG displayed larger Pe responses compared to the CAUG ($p = 0.001$) and the FCG ($p = 0.057$) with similar patterns emerging at site Pz ($p = 0.009$ and $p = 0.030$, respectfully). Pe peak amplitude was not correlated with percent of life spent in institutionalized care among the FCG at site Cz [$r_{(34)} = -0.117$, $p = 0.364$] or Pz [$r_{(34)} = -0.040$, $p = 0.759$].

EFFECTS OF EXECUTIVE FUNCTION MEASURES ON SOCIO-EMOTIONAL OUTCOMES

Separate multiple regression analyses were used to test if the EF measures of inhibitory control (i.e., accuracy, RT) or response monitoring (i.e., ERN, Pe, post-response RT) predicted socio-emotional outcomes on the HBQ (externalizing-ADHD, internalizing, and social withdrawal) and the SSRS (academic competence, social skills, and problem behaviors).

INHIBITORY CONTROL

The analyses examining potential moderating effects of inhibitory control variables (accuracy and RT) for both the HBQ and SSRS outcome variables failed to reach significance.

RESPONSE MONITORING

HBQ

A significant Group × ERN moderation predicted externalizing-ADHD behaviors [$\beta = 0.292$, $t_{(86)} = 2.781$, $p = 0.007$]. This moderation was probed by a 3 Group (CAUG, FCG, NIG) ×2 ERN median split (large, small) ANOVA. A main effect for Group [$F_{(2, 86)} = 7.997$, $p = 0.001$] emerged, but was qualified by a Group × ERN interaction [$F_{(2, 86)} = 4.699$, $p = 0.012$]. *Post-hoc* tests revealed that within the FCG, children with smaller ERNs exhibited significantly more externalizing-ADHD behaviors than children with large ERNs (see **Table 2**, **Figure 3A**). This pattern was further supported by the finding that among children with small ERN responses, FCG and CAUG exhibited significantly more externalizing-ADHD behaviors than NIG children. Children with large ERN responses showed a similar number of externalizing-ADHD problems, regardless of participant group.

The Group × ERN moderation analyses examining internalizing problems and social withdrawal failed to reach significance. Additionally, the Group × Pe moderation analyses did not reach significance for any of the HBQ outcomes variables.

SSRS

A significant Group × ERN moderation predicted academic competence [$\beta = -0.325$, $t_{(84)} = -3.914$, $p < 0.001$] and social skills

Table 2 | ANOVA moderation means.

	NIG		CAU		FCG	
	Large ERN	**Small ERN**	**Large ERN**	**Small ERN**	**Large ERN**	**Small ERN**
HBQ						
Externalizing-ADHD	0.25 (0.33)	0.15 (0.16)	0.47 (0.30)	0.65 (0.39)	0.29 (0.27)	0.67 (0.37)
SSRS						
Academic competence	36.5 (5.8)	37.1 (5.9)	25.2 (7.0)	25.5 (6.4)	35.5 (5.8)	27.5 (7.5)

scores [$\beta = -0.225$, $t_{(84)} = -2.418$, $p = 0.018$]. These moderations were probed by a 3 Group (CAUG, FCG, NIG) ×2 ERN median split (large, small) ANOVA. For academic competence, a main effect of group emerged [$F_{(2,\ 84)} = 23.972$, $p < 0.001$], but was qualified by a Group × ERN interaction [$F_{(2,\ 84)} = 4.936$, $p = 0.009$]. *Post-hoc* tests indicated in the FCG group, children with a large ERN response exhibited more academic competence than FCG children with a small ERN (see **Table 2**, **Figure 3B**). This pattern was further supported by the finding that FCG children in the large ERN group had the same level of academic competence as the NIG and significantly more academic competence than the CAUG. Furthermore, FCG children with a small ERN response showed academic competence similar to CAUG children and significantly less academic competence than NIG children. The follow-up analyses for the social skills failed to reach significance.

The Group × ERN moderation analyses for problem behaviors outcome failed to reach significance.

Pe

At site Cz a significant Group × Pe moderation predicted academic competence [$\beta = -0.252$, $t_{(86)} = -2.803$, $p = 0.006$] and social skills [$\beta = -0.227$, $t_{(86)} = -2.356$, $p = 0.021$]. These moderations were probed by separate 3 Group (CAUG, FCG, NIG) ×2 Pe median split (large, small) ANOVAs. For academic competence, a main effect for Group [$F_{(2,\ 84)} = 23.849$, $p = 0.000$] emerged that was qualified by a Group × Pe interaction [$F_{(2,\ 84)} = 6.013$, $p = 0.004$]. *Post-hoc* tests revealed that within the NIG, children with smaller Pe responses exhibited significantly less academic competence than children with large Pe responses. Among children with large Pe responses, FCG and CAUG children exhibited significantly less academic competence than NIG children (p's $= 0.000$). However, among children with low Pe responses, both the NIG ($p = 0.015$) and FCG ($p = 0.029$) exhibited higher academic competence than CAUG children.

For social skills the Group × Pe interaction failed to reach significance. The moderation analyses for the problem behaviors outcome also failed to reach significance.

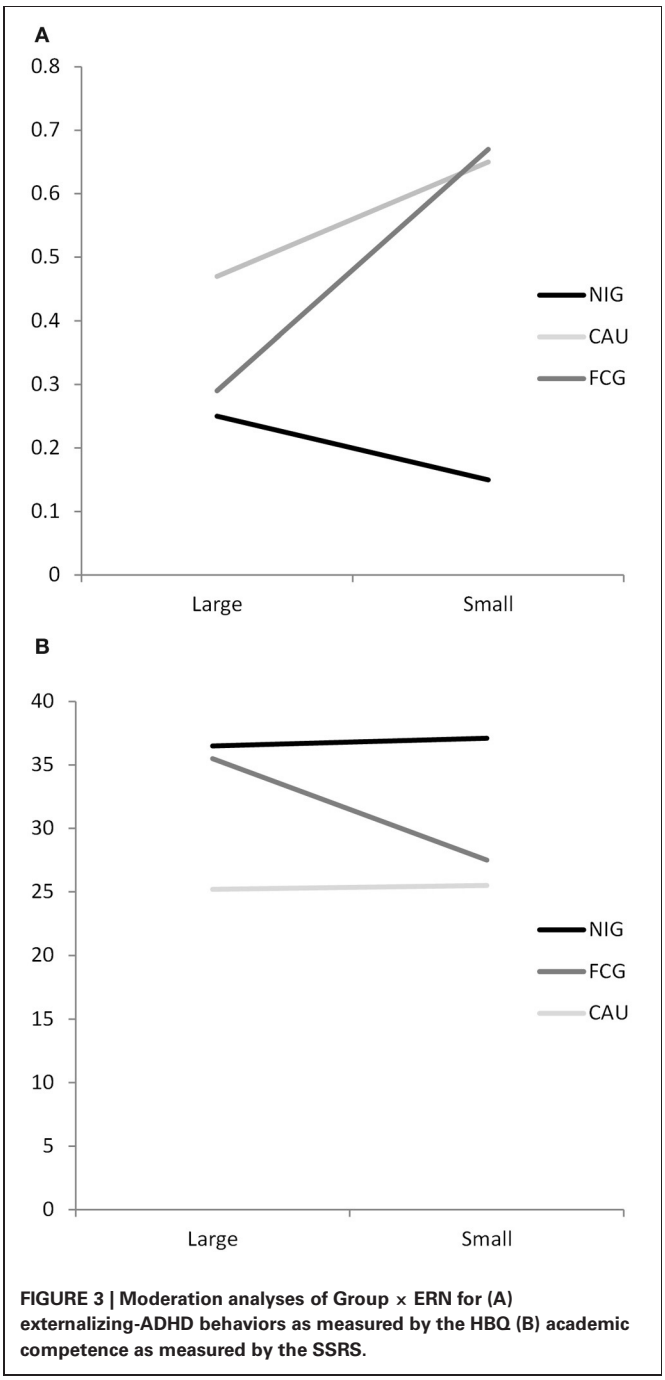

FIGURE 3 | Moderation analyses of Group × ERN for (A) externalizing-ADHD behaviors as measured by the HBQ (B) academic competence as measured by the SSRS.

DISCUSSION

The current study examined the impact of early psychosocial deprivation on the EF skills of inhibitory control and response monitoring. The potential influence of these skills on socio-emotional outcomes was also investigated. Two sets of results emerged. First, impairments in inhibitory control, but

not response monitoring, were noted among children who experienced psychosocial deprivation. Second, neural markers of response monitoring were enhanced among children in the foster care intervention and moderated associations between deprived caregiving experience and the expression of socio-emotional behavior problems in childhood. Combined, these results highlight the multi-faceted impact of early psychosocial deprivation on the development of cognitive processing skills and behavioral functioning in childhood.

Although all children performed the flanker task as expected, with standard patterns of increased accuracy and faster RTs on congruent as compared to incongruent trials, there were several notable group differences. Both the CAUG and FCG were less accurate than the NIG children on incongruent trials. Poor performance on incongruent trials suggests that the nature of inhibitory control deficits that continue into childhood among children experiencing early psychosocial deprivation might be strongly influenced by conflict inhibition rather than delay inhibition. This notion is supported by work that has shown impairments in previously institutionalized children on a Stroop task that involves similar levels of cognitive conflict as the flanker (Colvert et al., 2008a) and also by the lack of impulsivity problems exhibited by these children in go/nogo tasks (McDermott et al., 2012; Loman et al., 2013).

Whereas the current study found group differences on the cognitively demanding incongruent trials of the flanker task, Loman et al. (2013) found general deficits in behavioral accuracy on a flanker task among a group of previously institutionalized children. Both task structure and participant age, may have contributed to performance variations found between the two studies. Namely, the current study employed a version of the flanker paradigm that dynamically adjusted throughout the task and thus may have magnified participant focus and minimized potential differences in errors of omission. Additionally, the children in the current study were also slightly younger than the children in the study by Loman et al. (2013). Because the flanker task is a cognitively challenging task even among typically developing children of this age range (e.g., Ridderinkhof et al., 1997) it is plausible that improvements in incongruent trial accuracy may emerge with age among the previously institutionalized children in the BEIP sample.

Deficits in processing speed also emerged for both the CAUG and FCG children compared to never institutionalized children. Interestingly, the differences were significant only for congruent trials. This pattern may reflect general deficits in processing speed and corresponds to recent work demonstrating alterations among children experiencing early psychosocial deprivation in white matter structure postulated to underlie processing speed (Hanson et al., 2013). Alternatively, it may indicate different task strategies among the groups as the FCG RTs on incongruent trials were more in line with RTs by the NIG compared to the CAUG. Thus, the slowed response among the FCG children on the "easier" congruent trials could result from a performance strategy to maximize accuracy outcomes rather than a standard deficit in processing speed. Further longitudinal work is needed to illuminate whether processing speed differences are maintained or remediated over time and among children in the foster are intervention as processing speed capacity early in life is strongly associated with later cognitive function (Rose et al., 2012).

Although recent work has emphasized the impact of psychosocial deprivation on sustained attention in middle childhood (McDermott et al., 2012; Loman et al., 2013), the current data support the premise of multiple aspects of cognitive impairment depending upon the nature of the cognitive task and the underlying neural regions that it taps. For instance, the ability to execute delay aspects of inhibitory control that rely on VL-PFC, does not guarantee developmentally appropriate mastery of conflict inhibitory control that depend more heavily upon DL-PFC. It is likely the case that the dynamically adjusting version of the flanker task employed in the current study was challenging enough to expose continuing difficulties in the realm of conflict inhibitory control within the BEIP children who experienced early psychosocial deprivation.

A key group difference emerged on the Pe measure of response monitoring such that children experiencing early adversity exhibited diminished neural processing of errors on this component compared children who never experienced early adversity. This result is in line with findings from the study by Loman et al. (2013) in which internationally adopted children exhibited a reduced Pe response. Although this component has been reported to be prominent in children (Torpey et al., 2012), it remains unknown what factors influence the stability of the Pe across contexts or throughout childhood. This is one of the first studies to report associations between Pe amplitude and outcomes among children as children in the NIG with large Pe responses had the highest ratings of academic competence. Given its role in error awareness and orienting to errors, additional work to determine what factors contribute to stronger Pe responses in children are warranted.

Although group differences were not found on the ERN, this component also moderated socio-emotional outcomes for children in the foster care intervention. Specifically, among the FCG a larger ERN response appeared to function as a protective factor as it was linked to in lower rates of externalizing-ADHD and higher academic competence. The opposite pattern of outcomes was found among FCG children with a small ERN response. In contrast, the ERN was not influential for children in the CAUG or NIG. Namely, children in the CAUG had elevated rates of socio-emotional issues and the NIG had lower rates of socio-emotional issues regardless of the magnitude of their ERN response.

The finding of larger ERN responses being linked to more adaptive outcomes among the FCG corresponds to other work examining the ERN and socio-emotional outcomes. Specifically among young children, a larger ERN response is generally adaptive (Meyer et al., 2012) whereas a smaller ERN response has been associated with increased ADHD and externalizing rates and risk for substance use (e.g., Stieben et al., 2007; Euser et al., 2012; Geburek et al., 2012). Further work is needed to determine whether this component indexes awareness and attention toward task performance and/or increased affective relevance of performance outcomes in the FCG. It will also be imperative to determine what aspect of the foster care intervention

influences the development of the ERN response and whether strong response monitoring continues to function in an adaptive fashion among the FCG children over time.

Interestingly, the ERN did not modulate risk for internalizing issues in this sample. Emerging work suggests that the standard association between the ERN and increased risk for anxiety (Olvet and Hajcak, 2008) may not be evident across development, as young children with a large ERN response have decreased risk for anxiety problems (Meyer et al., 2012). In children experiencing early psychosocial adversity, emotion regulation issues that result in risk for internalizing problems may continue to increase with age or may be mitigated by a different set of cognitive factors not covered in the current study. Overall the group differences in the current study are a result of a conservative approach to examining the effects of early experience amongst the BEIP sample.

In sum, the current study reveals that psychosocial deprivation negatively impacts the development of conflict inhibitory control with effects lasting through early childhood. Response monitoring skills are similarly impacted by early psychosocial deprivation, however, certain facets of response monitoring are remediated by a foster care intervention. Given work in young children demonstrating links between responsive caregiving can specific aspects of EF (Bernier et al., 2010, 2012) as well as evidence from intervention work in preschool aged children linking enhanced caregiving and improved cognitive control (Bruce et al., 2009), it is plausible that caregiving impacts both neural development underlying error processing as well as performance motivation.

The current data also highlight that the degree of plasticity in certain cognitive skills such inhibitory control or response monitoring may occur over a protracted time period, there is a subset of children from the FCG exhibited a large ERN and more adaptive socio-emotional outcomes. It remains to be determined the mechanism through which some children in the FCG developed a larger ERN response than others. To our knowledge, this is the first paper to demonstrate that response monitoring moderates associations between early psychosocial deprivation, foster care intervention, and socio-emotional outcomes. Future work is needed to explore specifically which aspects of caregiving interactions impact changes in neural development underlying EF and socio-emotional outcomes.

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Emotion regulation choice: selecting between cognitive regulation strategies to control emotion

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Consider the anger that arises in a heated argument with your romantic partner, or the dreadful anxious anticipation in the dentist's waiting room prior to a root canal procedure. Our daily lives are densely populated with events that make us emotional. Luckily, however, we developed numerous ways to control or regulate our emotions in order to adapt (Gross, 2007; Koole, 2009 for reviews). A central remaining challenge to explain adaptation, involves understanding how individuals choose between the different emotion regulation strategies in order to fit with differing situational demands. Specifically, when is the aforementioned romantic partner or dental patient more likely to "put aside" or disengage from the emotional situation, and when are they more likely to "make sense" or engage with their emotional reactions?

In this opinion article we concentrate on the intersection between affective science and decision making as manifested in emotion regulation choice, defined as the act of making an autonomous choice between different regulation strategies that are available in a particular context.

HOW IMPORTANT ARE OUR EMOTION REGULATION CHOICES?

Recent advances in the field of emotion regulation suggest that regulation strategies have different consequences in different contexts. Accordingly, several emerging conceptual accounts emphasize the importance of *flexibly choosing* between emotion regulation strategies in a manner that is adaptive to differing situational demands (e.g., Bonanno, 2005; Kashdan and Rottenberg, 2010; Troy and Mauss, 2011; for reviews).

While emotion regulation choice has become an important concept in modern conceptual accounts, direct empirical support has been lacking until recently. The main reason is that previous experimental studies in the field have instructed participants to employ rather than choose between different regulation strategies (e.g., Bonanno et al., 2004; Westphal et al., 2010; Webb et al., 2012, for a recent review), leaving the determinants and underlying mechanisms of emotion regulation choice unexplored.

To address these important gaps we recently developed a conceptual framework to explain the (1) major determinants and (2) underlying mechanisms of emotion regulation choice (Sheppes et al., 2011, 2013; Sheppes, in press). The starting point of this conceptual framework was set to explain the differential consequences of employing (rather than choosing between) different regulation strategies (Sheppes and Gross, 2011, 2012). Specifically, according to this framework due to limited cognitive capacity, a constant competition emerges between emotion generation and emotion regulation processes (Gross et al., 2011a,b) for dominance over behavior. The conceptual account borrows from information processing theories (e.g., Pashler, 1998; Hubner et al., 2010) and the process model of emotion regulation (Gross and Thompson, 2007) to suggest that emotion regulation, involves recruiting *deliberate executive control mechanisms* that try to modify the nature of emotional information processing at two major cognitive stages: early attentional selection and late semantic meaning stages.

Incoming emotional information can be regulated at an early attentional selection processing stage by *disengaging* from emotional information processing before it undergoes elaborated processing in working memory (the aforementioned "put aside" option). A classic early selection strategy is distraction, which involves producing neutral thoughts that are independent from and not in conflict with emotional information (e.g., van Dillen and Koole, 2007; Thiruchselvam et al., 2011). Engagement with incoming emotional information that passes the early attentional selection stage can still be regulated at a late semantic meaning processing stage before it determines behavior (the aforementioned "make sense" option). A classic late selection regulation strategy is reappraisal, which involves changing the meaning of emotional information in a late processing stage (e.g., Gross, 2007; Thiruchselvam et al., 2011; Blechert et al., 2012). In reappraisal, the original emotional appraisal functions as the building block of the reinterpretation, and as such the two are semantically dependent and in direct conflict.

According to the conceptual framework, the underlying characteristics of disengagement distraction and engagement reappraisal result in a differential cost-benefit tradeoff (Sheppes and Gross, 2011, 2012). Specifically, *emotionally* blocking affective information early before it gathers force via distraction can modulate high intensity information more successfully, relative to reappraisal that allows emotional information to gather force prior to a late modulation (Sheppes and Meiran, 2007). *Cognitively*, the generation process in distraction that involves producing neutral thoughts that are independent from and not in conflict with the original emotional information, is simpler than generating reappraisals, where neutral reinterpretations are in direct conflict

with emotional appraisals (Sheppes and Meiran, 2008; Sheppes et al., 2009). *Motivationally*, distraction does not allow for emotional events to be attended to and provided with adequate explanation which is non-beneficial in many emotional events where long term adaptation requires facing difficulties in order to adapt (Wilson and Gilbert, 2008 for a review), relative to reappraisal which allows emotional processing (Kross and Ayduk, 2008; MacNamara et al., 2011; Thiruchselvam et al., 2011; Blechert et al., 2012).

Utilizing the original framework to explain emotion regulation choice involved hypothesizing that regulatory choices of healthy individuals would be sensitive to the costs and benefits tradeoff associated with the implementation of each regulatory option in different contexts. With regard to underlying mechanisms of emotion regulation choice we argue that healthy regulation choice requires, in some contexts, the ability to recruit deliberate executive control processes that can override contrasting associative emotional processes (cf. Muraven and Baumeister, 2000). Moreover, differences in strategies' underlying engagement with or disengagement from emotional processing dimension heavily determine regulation choice, relative to other potent factors such as differential cognitive effort.

EMOTION REGULATION CHOICE: EMOTIONAL, COGNITIVE, AND MOTIVATIONAL DETERMINANTS

The first determinant of regulation choice examined is *emotional* intensity which is a key dimension of variation across emotional contexts (Sheppes et al., 2011). To test our predictions, we manipulated emotional intensity with emotional images or unpredictable electric stimulation and had participants choose between distraction and reappraisal (Sheppes et al., 2011). Confirming the conceptual framework, we found that under low negative intensity situations, participants prefer late selection engagement reappraisal over early selection disengagement distraction, presumably because reappraisal can both successfully modulate immediate emotional responding as well as provide long term adaptation. However, under high negative intensity situations participants mostly prefer early disengagement distraction over reappraisal, because only distraction can successfully block emotional information before it gathers force. A follow up study demonstrated the robustness of this effect in showing that both regulatory preferences are maintained even when participants are offered high monetary amounts to choose the contrasting strategy (Sheppes et al., 2013).

The second determinant of regulation choice examined was the *cognitive* complexity of generating a strategy (Sheppes et al., 2013). According to the conceptual framework, the generation process in reappraisal is more complex than in distraction because the formation of a neutral reinterpretation depends on the original appraisal of emotional information. It was therefore predicted and found that when the generation process was simplified, by providing participants with concrete regulatory suggestions for distraction and reappraisal, reappraisal was more frequently chosen.

The third determinant of emotion regulation choice involved investigating the influence of *motivational* goals (Sheppes et al., 2013). According to our framework, emotional stimuli that are encountered multiple times can be better regulated for long term adaptation with strategies like reappraisal that involve engaging with emotional processing. As predicted, it was found that participants who anticipated encountering emotional stimuli more than once preferred to reappraise more than participants who expected to encounter each emotional stimulus only once.

The aforementioned emotional, cognitive, and motivational factors tended to independently influence regulatory choices between distraction and reappraisal manifested in findings main effects.

EMOTION REGULATION CHOICE: UNDERLYING MECHANISMS

According to our conceptual framework, emotion regulation choice should involve a general ability of deliberate executive control processes to override competing associative emotional processes. An alternative more parsimonious account, suggests that emotion regulation choice can be fully explained by a direct influence from simple associative emotional processes (e.g., Bradley et al., 2001). Specifically, a basic defensive system directly motivates the organism toward engagement (resulting in reappraisal) under low negative intensity situations, and toward disengagement (resulting in distraction) under high negative intensity. To determine between the two accounts we investigated a context where the two accounts would diverge—down-regulation of positive-emotional situations. Specifically, the associative-emotional process account would argue that as positive emotional intensity increases it directly activates a basic appetitive system that would lead to an increased preference to engage. By contrast, we found that the operation of deliberate control processes, whose goal is to provide down-regulation of positive emotional situations, involved overriding the associative tendency to engage, resulting in an increased preference to disengage as positive emotional intensity increased (Sheppes et al., 2013).

A further investigation of underlying mechanisms involved asking what are the dimensions that receive central weight in the choice between distraction and reappraisal? Two potential central dimensions include engagement/disengagement and cognitive effort involved in distraction and reappraisal. Specifically, when people prefer to distract in high negative emotional intensity situations, are they choosing distraction mainly because they prefer to disengage from emotional processing or mainly because they prefer to reserve cognitive resources?

To begin investigating this issue we pitted these two alternative accounts by having participants choose between two types of distractions: one regulatory option was cognitively simple and involved minor disengagement from emotional processing (performing mathematical subtract 2s) and a second regulatory option was cognitively effortful yet highly disengaging from emotional processing (subtract 7s). Findings supported the centrality of the engagement/disengagement factor with an increased preference to use the more disengaging (despite it being also more effortful) subtract 7s distraction as negative emotional intensity increased. These findings suggest that individuals are

willing to exert substantial cognitive effort in order to obtain adequate levels of disengagement. Nevertheless, future studies should parametrically manipulate varying levels of engagement/disengagement and cognitive effort in order to better understand the relationship between them. In a complementary study we showed that the engagement/disengagement dimension is central within the reappraisal category. Specifically, we found that under high negative emotional intensity participants choose to use "reality challenge" reappraisals (e.g., "this picture is fake") which involves disengaging by not considering emotional consequences of events (Sheppes et al., 2013).

We end this section with broader considerations that should be investigated in future studies. First, while our conceptual model makes a broad distinction between early and late selection regulation strategies, empirical support comes from studies that concentrate on only one early selection strategy (distraction) and one late selection strategy (reappraisal). It is clear that people typically use many other strategies and that their regulatory choice patterns may have important consequences for well-being and psychopathology. Consider avoidance which disengages from emotional processing at an early selection stage, and rumination which involves magnifying emotional information at an early attentional stage and elaborating it in a late selection phase. Our account suggests that deviations from the preference to disengage from high emotional intensity by overly engaging via rumination may be related to depression (Nolen-Hoeksema et al., 2008). At the same time, deviations from the preference to engage with tolerable emotional intensity events by disengaging via avoidance may be linked to anxiety disorders (Campbel-Sills and Barlow, 2007).

Second, we concentrated on deliberate regulatory choices among explicit regulation strategies. While the vast majority of studies in the field concentrated on explicit forms of regulation (Gross and Thompson, 2007), implicit forms of emotion regulation are central and dominant (Gyurak et al., 2011). Given that unconscious processes can perform most complex functions (Hassin, 2013), it may well be that regulatory decision making processes, including those that make use of central executive resources (see Marien et al., 2012), can be performed unconsciously. Central factors such as prior practice with choosing regulation strategies in different situations, strong motivational forces to perform one strategy over another and a general central executive ability that allows efficient information processing may all influence regulatory choices. Future studies should link explicit and implicit processes in determining emotion regulation choice (see Sheppes and Gross, under review, for such an effort).

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The emotional attentional blink: what we know so far

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The emotional attentional blink (EAB), also known as emotion-induced blindness, refers to a phenomenon in which the brief appearance of a task-irrelevant, emotionally arousing image captures attention to such an extent that individuals cannot detect target stimuli for several hundred ms after the emotional stimulus. The EAB allows for mental chronometry of stimulus-driven attention and the time needed to disengage and refocus goal-directed attention. In this review, we discuss current evidence for the mechanisms through which the EAB occurs. Although the EAB shares some similarities to both surprise-induced blindness (SiB) and other paradigms for assessing emotion-attention interactions, it possesses features that are distinct from these paradigms, and thus appears to provide a unique measure of the influence of emotion on stimulus-driven attention. The neural substrates of the EAB are not completely understood, but neuroimaging and neuropsychological data suggest some possible neural mechanisms underlying the phenomenon. The importance of understanding the EAB is highlighted by recent evidence indicating that EAB tasks can detect altered sensitivity to disorder relevant stimuli in psychiatric conditions such as post-traumatic stress disorder (PTSD).

Keywords: emotion, attentional blink, stimulus-driven attention, amygdala, anxiety

Rapid detection of emotionally salient events is critical for survival. However, given capacity limits on attention and awareness, the ability of emotional stimuli to preferentially capture attention comes with a cost. Specifically, if attentional resources are drawn to an emotional stimulus, there will be less processing capacity available for other stimuli. Although several different tasks have been used to explore the effects of emotional stimuli on spatial and selective attention, recent studies using more novel paradigms have begun to provide insights into the time course of attentional capture to emotionally salient stimuli and the impact of this capture on the ability to perceive subsequent stimuli. In this review, we discuss the emotional attentional blink (EAB) as a model paradigm for understanding stimulus-driven influences of emotion on attention. We contrast the EAB to other paradigms for studying emotion-attention interactions and review current neuroimaging and neuropsychological data for the mechanisms underlying the EAB. We conclude with a review of emerging evidence on the potential utility of the EAB as a measure of attentional biases to concern-relevant stimuli in psychopathology.

INITIAL STUDIES OF THE EAB

The attentional blink (AB) paradigm measures the temporal capacity limits of attention (Dux and Marois, 2009). In the standard AB task, identification of a first target (T1) during a rapid serial visual presentation (RSVP) stream transiently impairs the ability to detect a second target (T2) (see **Figure 1A**). The refractory period during which T2 cannot be detected is labeled the AB. The EAB involves the presentation of task-irrelevant emotional distractors during an RSVP target detection task (see **Figure 1B**). In this paradigm, emotional distractors elicit an AB, even though the distractor stimuli are not targets (Arnell et al., 2004; Most et al., 2005). This type of emotion-induced AB indexes the ability of emotional stimuli to rapidly capture attention.

Most et al. (2005) provided an early description of the EAB, and coined the term emotion-induced blindness. On each trial, they had participants search for a single rotated image depicting a landscape or building within an RSVP stream of upright landscape or architectural photos. At 200 (lag 2) or 800 (lag 8) ms prior to the target, a distractor appeared consisting of either a negative, neutral, or scrambled image. Accuracy was impaired when a target followed a negative distractor at lag 2 relative to lag 8. Critically, performance was substantially worse following the negative distractors than the neutral distractors at lag 2. The EAB could not be easily accounted for by factors such as the color of the negative distractors because the emotionally salient distractors caused a robust AB relative to scrambled distractor images that were created by rearranging and blurring the negative images. Examination of the time course of the EAB indicates that the effect can be seen as early as lag 1 (Most and Junge, 2008), but declines substantially as one moves longer than lag 2, such that it is progressively weaker at lag 4 and lag 6. The effect is typically gone by lag 8, and indeed there may be a modest enhancement of target detection at lag 8 (Ciesielski et al., 2010). Overall, the length of the emotion-induced blindness is roughly similar to the standard AB, which typically lasts for approximately 200–500 ms (Raymond et al., 1992).

The EAB is not limited to negative or aversive images. In a number of studies, we have observed that erotica induce an EAB that is often larger than that produced by aversive images

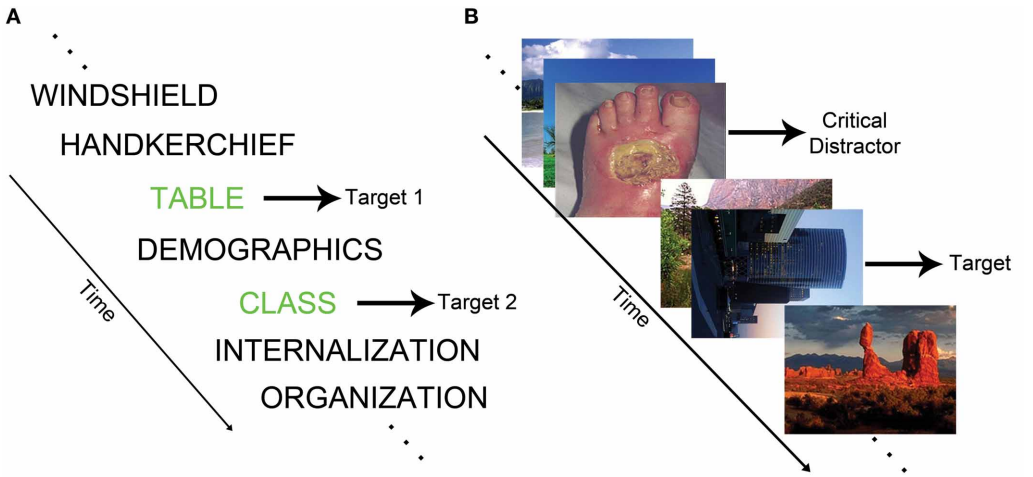

FIGURE 1 | (A) Schematic of a standard AB task in which the goal is to report the identity of two words printed in green. **(B)** Example of an EAB trial in which participants must detect a rotated image in the presence of a disgust distractor.

(Most et al., 2007; Ciesielski et al., 2010). Such findings suggest that arousal rather than valence is a critical feature in generating attentional capture. The effect also occurs with verbal stimuli. Some of the first published demonstrations of an EAB effect utilized a verbal RSVP task in which participants had to detect words printed in a specific color (Arnell et al., 2004, 2007; Mathewson et al., 2008). In this paradigm, emotionally arousing and taboo distractor words produced an AB relative to neutral words when a color target occurred soon after an emotionally arousing distractor word.

The current meaning or value of the distractor stimulus can modulate the ability of a stimulus to cause an EAB. Smith et al. (2006) demonstrated that aversively conditioned stimuli cause a blink and Piech et al. (2009) showed that current motivational state of the participant can modulate the extent of an EAB (e.g., food stimuli induced a greater EAB when subjects were fasting). These modulations of the EAB appear to be relatively modest compared to the large magnitude of attentional capture by aversive or erotic pictures, but may enable use of the EAB as a measure of dynamic changes in stimulus valuation. This sensitivity to changes in stimulus value suggests the potential utility of the EAB as an objective marker of the effects of therapeutic interventions in psychiatric conditions in which stimulus-reinforcer associations potently drive behavior.

COMPARISON WITH OTHER EMOTION-ATTENTION INTERACTIONS

The EAB provides a unique measure of attentional capture by emotional stimuli. Although several paradigms have been commonly used to study emotion-attention interactions, none of these paradigms appear to measure the same phenomenon as the EAB, or if they do, they lack the robustness of the EAB effect. Methodologically, the most similar paradigm to the EAB involves a variant of the standard AB in which a T1 target is followed by an emotional stimulus presented as the T2 target. This variant allows examination of the extent to which emotional stimuli can break through the refractory period of the AB. Critically, emotionally salient T2s emerge from the standard AB window more readily than their neutral counterparts (Keil and Ihssen, 2004; Anderson, 2005; Milders et al., 2006). For instance, in AB studies by Anderson and Phelps (Anderson and Phelps, 2001; Anderson, 2005) in which subjects had to detect words written in a specific color, the T2 was more likely to be detected if it consisted of an emotionally salient word instead of a neutral word. This effect occurred even though the meaning of the emotional and neutral words was irrelevant to the instructed task, which only required subjects to attend to each word's color. This type of enhanced detection of emotional T2 stimuli has also been observed for emotional facial expressions, with highly anxious individuals showing enhanced detection of fearful vs. happy faces presented at T2 (Fox et al., 2005).

The preferential detection of emotional T2 stimuli in the standard AB and the ability of emotional stimuli to capture attention in the EAB indicate prioritized processing of emotional stimuli. However, the two paradigms differ in terms of the processes being measured. The standard AB with emotional T2 characterizes preferential target detection under a condition of limited attentional resources, whereas the EAB focuses on the impact of attentional capture on the processing of other stimuli. In particular, these two paradigms differ in the extent to which they depend on distinct types of attention. Although attention may be carved at many joints, a commonly accepted categorization divides attention into goal-directed (top-down) and stimulus-driven (bottom-up) attention (Egeth and Yantis, 1997; Corbetta and Shulman, 2002). Goal-directed attention allows us to voluntary select stimuli from the environment whereas stimulus-driven attention reflects the ability of highly salient items to capture attention. In the standard AB the emotional T2 stimulus is task relevant, and congruent with goal-directed attention to colored words. By contrast, the EAB has the hallmarks of a stimulus-driven, bottom-up engagement of attention in that attention is captured even though the emotional stimuli are task irrelevant.

We see little evidence of a goal-directed ability to overcome the EAB effect even when people receive monetary rewards for good performance (accurately detecting targets), and regardless of subjects' evaluation of how hard they try to do the task (Most et al., 2007). Of note, prior exposure to and expectation of highly arousing emotional distractors does not eliminate their ability to capture attention (Arnell et al., 2007).

In considering other tasks that can be used to examine emotion-attention interactions, we note that most of these paradigms either reflect a preferential detection of emotional stimuli, or the ability of emotional stimuli to interfere with goal-directed attention. As such, the literature often parallels the divide between standard AB with emotional T2 and the EAB. For instance, several tasks including backward masking and continuous flash suppression provide instances in which emotional stimuli are preferentially detected. In backward masking, an emotional stimulus, typically a face, is presented very briefly and followed immediately by a masking stimulus such as a neutral face (Esteves and Ohman, 1993; Pessoa et al., 2005). Emotional expressions can be detected with even short presentation times (10–20 ms). Continuous flash suppression is a technique in which awareness for a stimulus presented to one eye is suppressed while visual noise is presented to the other eye (Tsuchiya and Koch, 2005). Suppressed fearful faces appear to reach awareness more readily than happy or neutral faces (Yang et al., 2007; Tsuchiya et al., 2009). These tasks differ from the EAB primarily in that they are not typically used to measure the effect of emotion on awareness for a subsequent stimulus.

By contrast, the emotional Stroop measures the extent to which emotional information interferes with processing of non-emotional features of stimuli. This variant of the classic Stroop effect examines the extent to which individuals are slower to name the color of emotional words than neutral words (Williams et al., 1996). There is an element of stimulus-driven attention in that the semantic meaning of the word interferes with attention to the color of the word even though word meaning is incidental to the task. To minimize this distraction, subjects must use top-down attentional control to overcome emotional interference. Because it measures the extent to which emotion interferes with task relevant processing, the emotional Stroop can be argued to have at least a superficial similarity to the EAB. However, the emotional Stroop paradigm differs from the EAB in three critical ways. First, there is never a failure to see the stimulus in the emotional Stroop paradigm because the distracting emotional information and the goal relevant stimulus are not spatially or temporally dissociable. Second, unlike the EAB, in which individual stimuli capture attention, emotional Stroop effects do not show an individual stimulus effect. That is, the emotional Stroop effect is seen when entire blocks of words are threat related, but is absent when emotional words and neutral words are presented in a mixed block (Algom et al., 2004). Algom and colleagues argue that this pattern of results reflects a generic slowing rather than a classic selective attention mechanism. Finally, at least to date, there is little evidence that the EAB can be overcome by the application of top-down control, although it may be possible to modestly alter the magnitude of the EAB based on knowledge about the target (Most et al., 2005).

The effects of emotional stimuli on attention have also been examined in the context of visual search tasks. In such tasks, an emotional target (e.g., spiders) is detected faster in an array of neutral images than a neutral image is detected in an array of emotional targets, especially at larger matrix sizes (Ohman et al., 2001). Typically, this is attributed to a pop-out effect for the emotional stimuli that leads to faster detection. However, it is also possible that a slowed detection of the neutral stimuli among a matrix of threat images is due to attentional capture caused by one or more of the threat images, which transiently disrupts the ability to perceive the neutral stimuli. Unfortunately, as typically applied by researchers (without the addition of baseline measures of performance in the absence of any emotional stimuli), it is unclear to what extent findings from the visual search task reflect speeded detection of emotional stimuli, interference in detection of neutral stimuli, or both (Lipp, 2006). In contrast, the EAB paradigm allows for independent measurement of the distinct effects of emotional and neutral distractors on target detection.

The dot probe task (Macleod et al., 1986; Mogg and Bradley, 1999) is another popular measure for assessing the effects of emotion on attention. The task measures the extent to which attention is drawn to or away from a spatial location where an emotional cue (typically a threat face) has occurred by measuring whether reaction times are faster when a target appears at a position congruent or incongruent to the cue. However, unlike in the EAB, there is no evidence that the emotional cue prevents awareness of the target. Rather the emotional cue only delays the detection of the target, and this delay is extremely brief, often at the level of 20 ms or less, and the delay is not always observed in non-clinical samples (Schmukle, 2005; Frewen et al., 2008). Thus, while the dot probe task may capture an emotional impact on attention, it appears too brief and weak to represent the same phenomenon captured by the EAB, which can last for 100 s of ms, and is seen consistently in the healthy young adult samples that we have studied thus far.

In sum, the EAB phenomenon differs conceptually from common emotion-attention task paradigms and allows measurement of attentional capture in a clear manner that is not contaminated by other aspects of responsiveness to emotional stimuli. Because the EAB is robust even within healthy (non-clinical) individuals, it is well suited for studying emotion-attention interactions and the neural substrates mediating these processes. Also of note, while emotional stimuli are task relevant in emotion-attention paradigms such as the standard AB, emotional Stroop, and visual search paradigms, they are not task-relevant in the EAB. This latter factor becomes important in determining precisely which aspects of attention are influenced by emotion.

ATTENTIONAL CAPTURE AND STIMULUS-DRIVEN ATTENTION

As noted above, emotion-attention interactions can be considered in the context of goal-directed vs. stimulus-driven attention, with the EAB showing the characteristics of stimulus-driven attention. Corbetta and Shulman (2002) have proposed a model in which goal-directed and stimulus-driven attention depend on largely separable neural networks: a goal-directed dorsal frontoparietal

attention network, including the frontal eye fields (FEF), and intraparietal sulcus (IPS) and a stimulus-driven ventral network that includes the temporoparietal junction (TPJ) and ventral frontal cortex [including the anterior insula (AI) and lateral frontal regions]. The standard AB is thought to primarily relate to capacity limits to goal-directed attention. It is critically dependent on attention being allocated to the first of two targets (T1, T2) during the RSVP stream. By contrast, when the T1 is to be ignored, the T2 is readily detected (Raymond et al., 1992). According to two-stage bottleneck models of the AB, all stimuli in the RSVP stream undergo an initial stage of perceptual and semantic processing (Chun and Potter, 1995). This stage has a high capacity to process stimulus representations in parallel. When target stimuli appear, they compete for a second stage, limited capacity process that enables awareness of the target. The first stage representations are weak and susceptible to decay: failure to detect T2 occurs if processing of the T1 in the limited capacity second stage doesn't complete before the stage 1 representation of T2 fades. Two-stage bottleneck models are supported by functional magnetic resonance imaging (FMRI) data. The correct detection of targets during the AB has been linked to activation of the dorsal frontoparietal attention network in concert with primary and higher order visual areas, whereas activation of sensory cortices alone does not appear to be sufficient for conscious report of targets (Marois et al., 2000, 2004; Gross et al., 2004; Shapiro et al., 2007; Williams et al., 2008).

Non-emotional, task-irrelevant distractors can also impair target detection during an RSVP stream, particularly if they share perceptual or conceptual features with a target (Folk et al., 2002; Barnard et al., 2004; Maki and Mebane, 2006). This "contingent attentional capture" may be viewed as a hybrid condition in which there is a goal-directed attention filter that allows certain stimuli to capture attention. Contingent attentional capture has been shown to recruit cortical areas consistent with the stimulus-driven attentional network in concert with the dorsal attention network (Serences et al., 2005), reflecting the dynamic interplay of top-down and bottom-up processing in this paradigm.

Asplund and colleagues have recently characterized attentional capture driven by irrelevant, non-contingent distractors during RSVP (Asplund et al., 2010a,b). They found that novel, unexpected distractors robustly impair target detection (termed surprise-induced blindness, or SiB), but this capture effect lasts for only one or two trials. This robust SiB effect was most apparent at a distractor-target stimulus onset asynchrony (SOA) of 390 ms, and was subject to rapid habituation across trials. Asplund et al. also identified a second variant of the SiB—at a shorter distractor-target SOA (130 ms) they detected a longer-lasting but weaker capture effect; target detection was impaired, but not to the extent it was during the first two trials with a 390 ms SOA. SiB differs from the standard AB not only in its dependence on a task-irrelevant stimulus, but it is also unaffected by placement of a blank immediately following the surprise stimulus (a condition that typically attenuates the standard AB). Neuroimaging evidence supports the notion that the robust form of the SiB is distinct from the standard AB. Activity in the TPJ, a region thought to be critical for reorienting attention in a stimulus-driven manner (Corbetta et al., 2008), is increased on trials in which surprise distractors capture attention (Asplund et al., 2010b). By contrast, this area is not commonly observed during more traditional AB tasks (Marois et al., 2004).

Mechanistically, the EAB shares more in common with SiB than either the standard AB or contingent attentional capture. SiB and the EAB occur despite the task-irrelevance of the critical stimulus. They also both appear to be relatively automatic, and largely outside of voluntary control. The persistence of EAB and the weaker form of the SiB may be similar as well: experiments using a verbal form of the EAB (Arnell et al., 2007) and the weak form of the SiB suggest a decline of the effect after ∼100 trials. Whether the EAB using aversive or erotic pictures diminishes after a similar number of repetitions remains to be seen, as studies to date have generally used fewer than 100 emotional stimuli for a given class of stimuli. The EAB and SIB also are similar in terms of a lack of lag 1 sparing (Most and Junge, 2008; Asplund et al., 2010a). Lag 1 sparing is a feature often found in studies of the AB (and contingent attentional capture) in which the blink is decreased if presentation of the T2 occurs in the serial position immediately following the T1 (Chun and Potter, 1995). The precise cause for lag 1 sparing is a source of debate, but most explanations center on either the importance of a specific temporal relationship between T1 and T2 (approximately 100 ms) or on the characteristics of the post-T1 stimulus (Dux and Marois, 2009). Lag 1 sparing is conceptually important in the AB literature, as the ability to explain this sparing has proven critical in the evaluation of different models of the AB. The absence of lag 1 sparing in the EAB and SIB thus suggests that the EAB and SIB involve mechanisms that are at least partially distinct from that of the standard AB.

Despite their similar levels of endurance across trials the weaker form of the SiB and the EAB differ dramatically in their time course within a given trial. The lag-dependent time course of the EAB more closely resembles the AB. Beginning at lag 2, emotional distractors robustly capture attention and the effect gradually returns to baseline (Ciesielski et al., 2010). Additionally, SiB is more dependent upon contextual novelty. The weak lag 1 SiB disappeared when surprise distractors were presented as frequently as the non-critical distractors (Asplund et al., 2010a). However, the EAB still occurs when emotional critical distractors are just as likely to appear as neutral critical distractors (Arnell et al., 2007).

BOTTLENECK MODEL OF THE EAB

As noted previously, AB effects have often been explained with a two-stage bottleneck model (Chun and Potter, 1995) in which a target cannot be processed if the bottleneck stage is occupied with other processing. Although such a model could explain the EAB, in which an emotional distractor (like a T1 target) could occupy a second stage bottleneck, Most, Wang and colleagues (Most and Wang, 2011; Wang et al., 2012) have proposed an alternative possibility, in which emotional distractors generate increased competition for perceptual resources during stage 1 perceptual processing rather than limiting awareness at the central bottleneck stage (**Figure 2**). In this model, a robust representation of the emotional stimulus actively inhibits spatiotemporally adjacent

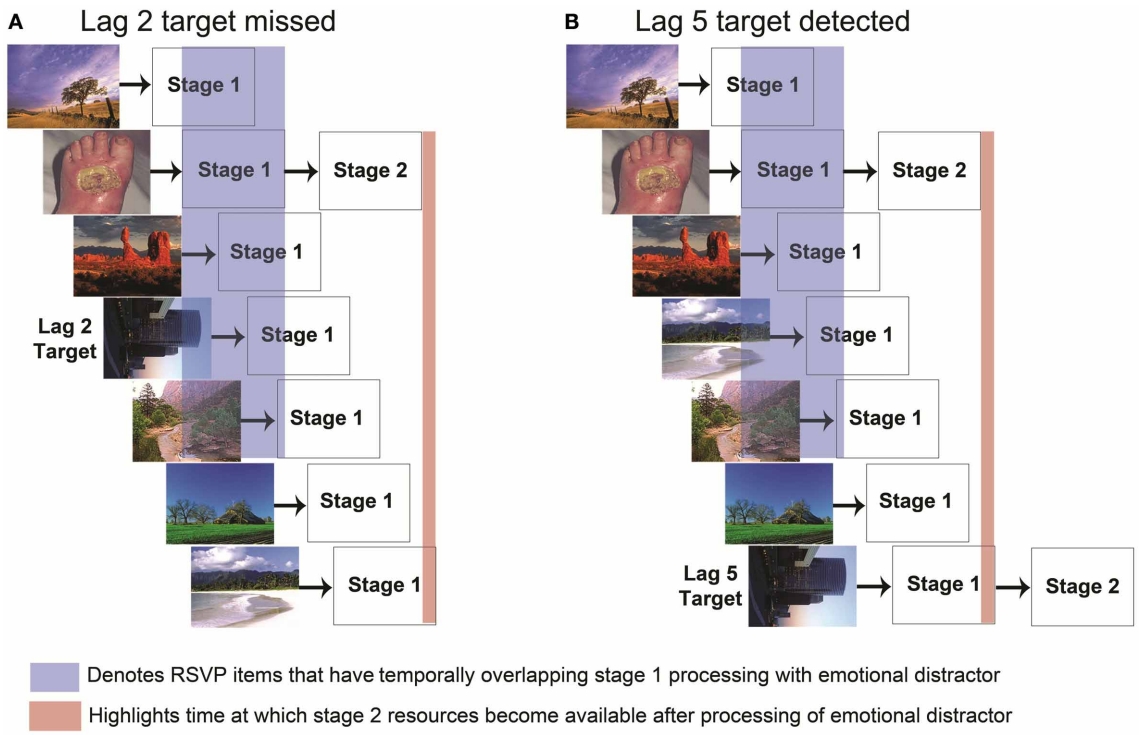

FIGURE 2 | Two stage bottleneck model of the emotional attentional blink with emphasis on stage 1 competition. Each stimulus in the RSVP stream is processed by stage 1 perceptual resources in parallel. The time at which a stimulus enters stage 1 processing is determined by its presentation order in the RSVP stream. **(A)** If stage 1 processing of a task irrelevant emotional stimulus and the target overlap (highlighted in blue), their representations compete for selection into stage 2 processing. When the emotional stimulus is sufficiently strong (arousing), the strength of its representation combined with its appearance prior to T1 during the RSVP stream enables it to out-compete the target stimulus for entry into stage 2 processing. Despite being goal relevant, the representation of the target fades before the stage 2 processing of the emotional stimulus is completed (highlighted in red). **(B)** By contrast, if the target were to occur at a later lag, such as lag 5, there will be less competition due to the reduced temporal proximity to the emotional stimulus, and the target representation can last beyond the end of the stage 2 processing of the emotional stimulus (highlighted in red). In such a case the target would be able to enter stage 2 processing.

goal relevant stimulus representations. Most and Wang (2011) hypothesized that if emotional distractors induce an EAB by creating competition for first-stage perceptual resources, the distractors should interfere with target processing primarily when the emotional distractor and target appear in the same spatial location. By contrast, if the distractor caused an EAB even when the target was at a different spatial location, it would suggest that the EAB occurred at a later, central processing bottleneck. To examine this possibility, they constructed a task in which participants searched for a single target in either of two simultaneously presented RSVP streams. Emotional and neutral distractors could appear in the stream containing the target or the other stream. Critically, the emotional distractors produced an EAB only when they were presented in the stream containing the target. These data are striking in that they suggest that the EAB does not depend on a single central bottleneck, but rather occurs at a spatially specific (and presumably) stage 1 processing level. This finding further suggests that the mechanisms underlying the EAB are at least partly dissociable from those of the standard AB: spatial selection is impaired during the AB (Jiang and Chun, 2001), whereas it appears to be largely intact during the EAB.

NEURAL SUBSTRATES OF THE EAB

Emotional stimuli elicit strong activation across the ventral visual stream (Sabatinelli et al., 2010) and this emotional modulation of visual processing is thought to be a key means by which emotionally salient items capture attention (Vuilleumier, 2005). The amygdala is robustly activated by emotional stimuli (Zald, 2003; Sergerie et al., 2008) and has been posited to enhance activation of higher order visual areas through its strong projections to visual regions (Amaral et al., 2003; Freese and Amaral, 2005). Support for the amygdala's role in such a process has been demonstrated for face processing in the fusiform gyrus (Vuilleumier et al., 2004), although it is possible that the amygdala is less critical for this modulation of other types of emotional stimuli.

If amygdala-driven persistence of the sensory representation of emotional distractors is a key factor in their ability to generate an EAB, there should be: (1) increased amygdala activity in response to emotional distractors when they capture attention, and (2) patients with amygdala lesions should exhibit a decreased EAB. At present, data directly supporting these two assertions remain lacking. Although a few studies have explored the neural correlates of the EAB with fMRI, to date, no study has specifically examined or reported amygdala activity in response

to task-irrelevant emotional distractors when they do and do not capture attention. Most et al. (2006) investigated the extent to which amygdala activity in response to emotional distractors was influenced by top-down attentional settings. As expected, negatively valenced distractors elicited increased amygdala activity when presented during an RSVP stream similar to that used to study the EAB. However, the authors only examined activation on trials in which no target was presented, leaving the impact of this amygdala activation on attentional processing unclear. Neuropsychological data suggest that the amygdala may not be required for an EAB to occur. Our group recently examined whether patients with unilateral amygdala damage exhibit an EAB (Piech et al., 2011). We found that amygdala lesion patients, regardless of the side of the lesion, displayed comparable EABs to healthy controls for both negative and positive arousing distractors. Although it remains possible that the amygdala contralateral to the lesion was able to produce an EAB, the lack of even a mild decline in the frequency of the EAB following lesions to either hemisphere is striking. To rule out the possible compensation of the contralateral amygdala in producing an EAB, it would be helpful to determine whether patients with bilateral lesions show a similar preservation of the EAB. Such a preservation would be consistent with recent suggestions that there are multiple neural circuits by which emotional stimuli can influence attention (Pessoa and Adolphs, 2011).

An alternate hypothesis for understanding the mechanisms of the EAB is that emotional distractors capture attention by interrupting top-down attentional settings through interactions with the ventral attention network (Yamasaki et al., 2002) or by direct modulation of region in the goal-directed attention network (Pourtois et al., 2006). During attention tasks, the ventral stimulus-driven attention network is deactivated, which is thought to reflect a top-down filtering mechanism that helps suppress processing of information that is likely to be irrelevant to current goals (Corbetta et al., 2008). This suppression is interrupted by stimuli that attract attention. Findings from SiB experiments support this hypothesis: surprise distractors that generated a blink were linked not only to TPJ activity but also to activity in the inferior frontal junction (IFJ), a key locus in coordinating the interplay of stimulus-driven and goal-directed attention (Dux et al., 2006; Asplund et al., 2010b).

Despite the potential role of the TPJ in the SiB, it may not be critical for directing attention to emotionally salient events. The ventral attention network generally does not respond to salient, behaviorally irrelevant stimuli in a prolonged manner (Indovina and Macaluso, 2007; Corbetta et al., 2008), yet the EAB lasts for many trials. Indeed, in their study of the SiB, Asplund et al. (2010b) found that although surprise distractors elicited greater TPJ activity when they captured attention, both the behavioral index of attentional capture and TPJ activity rapidly habituated. Of note, while the amygdala and orbitofrontal cortex (OFC) responded to surprise distractors, they did not track attentional capture as measured by behavior. Given the divergence of the SiB and EAB as described above, additional work is needed to determine whether the TPJ plays a role in the EAB, and how this and other ventral attention regions interact with the amygdala and OFC in the presence of emotional distractors during RSVP.

Given the paucity of studies examining the neural substrates of the EAB, it is worth considering how findings from emotional variants of the standard AB task might relate to the EAB. A growing body of literature indicates that a network of regions including the amygdala, rostral anterior cingulate, thalamus, middle frontal cortex, and higher order visual areas contribute to the enhanced detection of emotional T2s during the AB window (Anderson and Phelps, 2001; Keil et al., 2006; De Martino et al., 2009; Lim et al., 2009; Padmala and Pessoa, 2010). The emotional standard AB finding most closely related to the EAB comes from a study by Schwabe et al. (2010) in which both T1 and T2 could be emotional or neutral. Critically, this manipulation allows assessment of activity both in response to emotional T1 that impair processing of subsequent T2 (somewhat analogous to the EAB) and emotional T2 that "break through" the AB. The authors found no evidence of amygdala activation when emotional T1 stimuli caused participants to miss T2 (either emotional or neutral). However, the AI, lateral OFC and dorsal anterior cingulate (dACC) were more active when an emotional T1 word impaired T2 identification compared to when T2 were correctly reported. These data suggest that anterior components of the ventral attention network such as the AI may play a more important role than posterior areas in orienting attention to distracting emotional cues and driving attention effects. Although the task is not a perfect match to EAB studies in that T1 was goal relevant, the absence of amygdala activation supports the possibility that extra-amygdalar neural circuits play a role in the EAB. Future FMRI studies are necessary to better understand whether the circuits involved in emotional target detection play a role in the EAB. Finally, emotional T2 detection during the standard AB is enhanced by increasing endogenous levels of norepinephrine (De Martino et al., 2008). This finding is particularly intriguing given a hypothesis proposed by Aston-Jones and Cohen (2005) that firing of norepinephrine-producing neurons of the locus coeruleus is responsible for the AB. It would be of interest to examine whether the EAB is similarly subject to noradrenergic modulation.

DISENGAGEMENT AND DELAYED ENHANCEMENT OF ATTENTION

While the natural focus of the EAB paradigm is the disruptive effect of stimulus-driven attention, by measuring the length of time (lag number) at which individuals return to baseline performance (equivalent to neutral or no distractor trials), it is possible to obtain a metric of how long it takes an individual to disengage from an emotional stimulus and reassert top-down control of attention. Alternatively, in a study with just an early and a late lag, a disengagement efficiency index can be calculated by simply taking the difference in accuracy between an early and a late lag performance (e.g., lag 8 performance—lag 2 performance) (Olatunji et al., 2011b). In our past studies subjects show the largest disengagement efficiency for erotic images, reflecting a large blink at lag 2, but a strong ability to disengage and reassert top-down control at lag 8.

At long distractor-target delays, performance may reflect more than just disengagement. In the original studies of the EAB, lag 8 was treated as equivalent to baseline, and indeed there

was no overall difference between neutral and aversive targets at this time point. However, in some samples, we and others have observed that performance is modestly improved following emotionally salient stimuli relative to neutral stimuli at lag 8 or longer lags, with notable individual differences in the magnitude of the effect (Bocanegra and Zeelenberg, 2009; Ciesielski et al., 2010). Bocanegra and Zeelenberg (2009) have referred to this type of late enhancement as emotional hypervision. They reason based on a two-stage bottleneck model that an emotional cue could trigger an enhancement during stage 1 processing that could allow for a facilitation of processing that carries over onto targets that are temporally far enough removed from the initial target (or distractor) so as to not be in competition. In other words, if such an enhancement at the stage 1 level lasts longer than the stage 2 bottleneck's refractory period, it will produce a period of improved detection at lags slightly longer than the typical length of the EAB effect. Bocanegra and Zeelenberg (2009) suggest that a single common source of emotional modulation could produce both the EAB and emotional hypervision effects through simultaneous influences on stage 1 and stage 2 processes. The parsimony of this model has appeal, as it requires only a single stimulus-driven process. There is however an alternative possibility in which hypervision effects during RSVP paradigms are not caused by the same mechanisms as the EAB, but rather reflect a distinct, independent source of stage 1 enhancement that is slower and longer lasting than the stage 2 bottleneck's refractory period. The relative slowness of the effect could reflect a multisynaptic pathway that requires more time for stimulus evaluation before it can modulate stage 1 perceptual processing. Regardless of the specific mechanism, assessment of individual differences in performance at intermediate and longer lags may provide useful information regarding the mental chronometry of emotion-attention interactions.

EAB SENSITIVITY AND ANXIETY

Cognitive and neural models highlight the role of dysregulated attentional processes in the etiology of anxiety (Eysenck et al., 2007; Bishop, 2008) In a series of studies, we have used the EAB to measure the extent to which individuals with different anxiety disorders exhibit increased attentional capture or difficulty disengaging from concern-relevant stimuli. Recent data from patients with post-traumatic stress disorder (PTSD) is perhaps the most striking result from these studies. Attentional biases that automatically direct attention to trauma-relevant cues have been argued to play a key role in the maintenance of PTSD (Ehlers and Clark, 2000). Combined with a general hypervigilance, preferential attention to threat may lead to heightened fear responding to cues and repeated accessing of trauma-related memories. In a recent study employing the EAB paradigm, we observed that combat-exposed veterans with PTSD showed a powerful EAB for combat images relative to both healthy controls and combat exposed veterans without PTSD (Olatunji et al., 2012). Disgust and positive distractors evoked EABs in the PTSD veterans that were comparable to those observed in non-PTSD veterans and healthy controls, suggesting the absence of global hypervigilance. As discussed previously, the EAB is sensitive to current stimulus value (Smith et al., 2006). Future studies examining the extent to which the EAB is modulated following gold standard interventions for PTSD such as prolonged exposure therapy (Powers et al., 2010) would be informative.

By contrast, patients with obsessive compulsive disorder (OCD) have shown relatively normal levels of attentional capture at lag 2, but problems related to disengagement and the reestablishment of top-down attentional control at lag 8 (Olatunji et al., 2011b). This problem with disengagement emerged across emotional stimuli (reflected in a low disengagement efficiency index), but was most notable for erotic images. This may reflect a disorder specific concern (related to guilt or moral scrupulousness), or may reflect measurement sensitivity (since erotica consistently produces the most robust levels of attentional capture across samples, it provides the biggest challenge for disengagement mechanisms).

Patients with generalized anxiety disorder (GAD) displayed heightened attention to threat-related distractors at both short and long lags relative to healthy controls, consistent with elevated threat sensitivity (Olatunji et al., 2011a). However, the data from this study indicate that GAD is also associated with a reduced ability to recruit attentional control in response to neutral distractors, which may suggest the presence of a more general problem in attentional control that extends beyond the emotion domain. Indeed, in that study GAD patients reported significantly lower attentional control on a self-report measure, and the relationship between task performance for neutral stimuli and GAD diagnosis was shown to be mediated by attentional control as assessed by the Attention Control Scale (Derryberry and Reed, 2002).

CONCLUSION

In summary, the EAB paradigm provides a robust and unique behavioral measure of the ability of emotional stimuli to preferentially capture attentional resources in a stimulus-driven manner. EAB effects can be characterized in relation to a two-stage bottleneck model of attention, and provide the ability to examine the mental chronometry of emotion-attention interactions. Data on the neural mechanisms of the EAB remain scarce, but current evidence suggests that the ventral frontoparietal attention network involved in stimulus-driven attention plays a critical role. Given the sensitivity of the EAB paradigm for detecting specific alterations in attentional capture and disengagement in anxiety disorders, the further delineation of the neural basis of the EAB may prove fruitful for identifying mechanisms underlying unique aspects of anxiety pathophysiology. Such research may lead to not only a better understanding of the neural correlates of psychopathological processes in these disorders, but could provide a useful biomarker for clinical treatment studies, especially those that explicitly attempt to alter attentional biases (Schmidt et al., 2009; Bar-Haim, 2010; Hakamata et al., 2010).

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Acute stress selectively reduces reward sensitivity

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Stress may promote the onset of psychopathology by disrupting reward processing. However, the extent to which stress impairs reward processing, rather than incentive processing more generally, is unclear. To evaluate the specificity of stress-induced reward processing disruption, 100 psychiatrically healthy females were administered a probabilistic stimulus selection task (PSST) that enabled comparison of sensitivity to reward-driven (Go) and punishment-driven (NoGo) learning under either "no stress" or "stress" (threat-of-shock) conditions. Cortisol samples and self-report measures were collected. Contrary to hypotheses, the groups did not differ significantly in task performance or cortisol reactivity. However, further analyses focusing only on individuals under "stress" who were high responders with regard to both cortisol reactivity and self-reported negative affect revealed reduced reward sensitivity relative to individuals tested in the "no stress" condition; importantly, these deficits were reward-specific. Overall, findings provide preliminary evidence that stress-reactive individuals show diminished sensitivity to reward, but not punishment, under stress. While such results highlight the possibility that stress-induced anhedonia might be an important mechanism linking stress to affective disorders, future studies are necessary to confirm this conjecture.

Keywords: affect-cognition interactions, stress, anhedonia, reward, punishment, cortisol, depression, emotion

INTRODUCTION

Unraveling the connection between life stress and the onset of affective disorders continues to be a critical but complex endeavor. The reward system is often dysfunctional in affective disorders (American Psychiatric Association, 2000) and may play a central role in bridging these phenomena. Specifically, mounting evidence suggests that stress attenuates reward responsiveness through its influence on underlying neurobiological processes (Anisman and Matheson, 2005). However, a central point of ambiguity in this domain concerns the specificity of the impact of stress on reward processing. In order to gain a more comprehensive understanding of the mechanisms at play, it is necessary to clarify whether such effects might be generalizable to other valence-laden stimuli (e.g., punishment) and thus reflective of incentive processing more broadly.

A large body of preclinical work suggests that uncontrollable negative stressors blunt sensitivity to reward via disruption of mesocorticolimbic pathways. The majority of research investigating relationships between stressors and reward processing has been performed in non-human animal studies. In rodents, uncontrollable stress leads to "anhedonic" behavior and dysfunction within mesocorticolimbic dopaminergic pathways critically implicated in incentive motivation and hedonic coding (Anisman and Matheson, 2005; Henn and Vollmayr, 2005). Surprisingly, relatively few researchers have empirically examined putative relationships between stress and the reward system in humans. In an early human study, Berenbaum and Connelly (1993) found that real-life acute stressors, including military training and final examinations, reduced self-reported pleasure and positive affect in two separate samples. Moreover, this stress-induced reduction in hedonic capacity was strongest in participants with family histories of depression. In a controlled laboratory setting, Bogdan and Pizzagalli (2006) reported that an acute stressor (threat-of-shock) blunted reward responsiveness—specifically, participants' ability to modulate behavior as a function of rewards (see Bogdan et al., 2011 and Liu et al., 2011 for independent replications). Using the same probabilistic reward task, participants with high levels of perceived life stress were characterized by decreased reward responsiveness (Pizzagalli et al., 2007). Recently, Cavanagh and colleagues (2010) employed a social evaluative stress manipulation while participants completed a probabilistic stimulus selection task (PSST). They found that stress led to relatively decreased reward learning in individuals with high trait-level punishment sensitivity [as assessed using the Behavioral Inhibition System (BIS) scale] as compared to an enhanced reward learning bias in individuals with lower trait-level punishment sensitivity. Complementing these behavioral findings, two recent neuroimaging studies reported that stress inductions (e.g., cold pressor task, aversive movie clips) superimposed on reward processing paradigms reduced activity in brain areas involved in reward processing, including the medial prefrontal cortex, orbitofrontal cortex, and dorsal striatum (Ossewaarde et al., 2011; Porcelli et al., 2012).

In spite of these findings, it remains unclear whether such stress-induced effects are specific to rewards or extend to negatively-valenced stimuli, such as punishment. In Cavanagh's aforementioned study (2010), social evaluative stress led to heightened sensitivity to punishment in individuals with high trait-level punishment sensitivity, but lower sensitivity to punishment in individuals with low trait-level punishment sensitivity. In related research, various prior studies have examined aversive processing changes using threat of shock manipulations and report stress-induced increases in aversive processing during affective Stroop tasks (e.g., Edwards et al., 2006, 2010; Robinson et al., 2011). In a recent fMRI study investigating the neural circuitry underlying such findings, Robinson and colleagues (2012) reported that enhanced dorsomedial prefrontal cortex amygdala connectivity during the processing of aversive stimuli under stress (threat of unpredictable foot shock in the scanner) might underlie stress-induced threat biases. Collectively, these studies raise the possibility that, unlike reward sensitivity, punishment sensitivity might be potentiated under stress.

The current study was designed to assess the specificity of the deleterious effect of stress on reward processing by comparing the impact of stress on reward-related (e.g., positive feedback) vs. punishment-related (e.g., negative feedback) learning. To achieve this aim, a PSST (modified from Frank et al., 2004) was implemented in conjunction with an acute stressor (threat-of-shock) using a between-subjects design (e.g., "stress" vs. "no-stress"). The current study design differed from previous studies in this area (e.g., Bogdan and Pizzagalli, 2006; Bogdan et al., 2011) because it allowed evaluation of responsiveness to both positive and negative feedback. This enabled us to ascertain whether purported stress-induced reward processing deficits reflected specific reductions in sensitivity to reward feedback vs. broad reductions in sensitivity to feedback in general (regardless of valence). In addition, our experiment was initially designed to test whether the impact of stress on reward processing was conditional upon the stressor being perceived as uncontrollable. This was attempted by implementing both a "controllable" and "uncontrollable" stress condition, along with a "no stress" condition. However, this aspect of our stress manipulation was unsuccessful (see Appendix for detailed analyses) and thus the present report focuses on the comparison between "stress" (collapsed across the two controllability subgroups) and "no-stress" conditions. Based on prior findings, we hypothesized that individuals under acute stress would exhibit reduced reward sensitivity (e.g., lower reward-related accuracy and a reduced reward-related RT bias, as detailed in the Materials and Methods section) relative to individuals in the no-stress condition. Moreover, we hypothesized that reward sensitivity would be selectively more reduced relative to punishment sensitivity in those individuals completing the task under stress.

MATERIALS AND METHODS

PARTICIPANTS

All study procedures were approved by Harvard University's Committee on the Use of Human Subjects in Research. One hundred ($n = 100$) female participants, 18–25 years old, were recruited through community advertisements and the Harvard University Department of Psychology Study Pool. Only females were recruited due to sex differences in psychological and hormonal responses to stress, and because women tend to demonstrate a more pronounced stress response than men (Nolen-Hoeksema and Hilt, 2009). All subjects were right-handed, non-smokers, with normal or corrected-to-normal vision, no color-blindness, and no known current or past neurological, psychiatric or medical illnesses. Prior to participation, all individuals were screened over the phone to determine study eligibility. The evaluation included diagnostic screening questions from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1995), more detailed questions from the depression and substance abuse modules, and a handedness questionnaire (Chapman and Chapman, 1987). Subjects were excluded if they could speak or read Japanese because one of the tasks (PSST) included Hiragana symbols. Individuals who met eligibility requirements were invited for an experimental session. Prior to the session, participants were randomized to one of three experimental conditions: "no stress" ($n = 29$), "controllable stress" ($n = 35$), or "uncontrollable stress" ($n = 36$). Data from five participants (two from the "no stress" group, one from the "controllable stress" group and two from the "uncontrollable stress" group) were excluded because they never met performance criteria [see Modified Probabilistic Stimulus Selection Task (PSST) section] in the training phase of the PSST. Thus, 95 participants were included in the analyses: "no stress" group ($n = 27$), "controllable stress" group ($n = 34$), and "uncontrollable stress" group ($n = 34$). However, given the lack of success of the controllability aspect of our stress manipulation (see Appendix for detailed analyses), data from the two stress groups were combined into a single "stress" group in subsequent analyses.

PROCEDURES

Figure 1 presents a summary of the session timeline. After arriving to the laboratory, the first written informed consent was obtained using a general consent form with no mention of the stress manipulation. This procedure allowed us to obtain unbiased baseline self-report ratings and physiological indices. Participants were then asked to complete a battery of self-report questionnaires, including a demographics form, the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), the Mood and Anxiety Symptom Questionnaire (MASQ-short; Watson et al., 1995), the Perceived Stress Scale (PSS; Cohen et al., 1983), the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006), and the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS; Carver and White, 1994).

Twenty minutes after arrival, the first of three saliva samples was collected to measure baseline cortisol levels. Next, participants completed the first set of "in-the-moment" state self-report questionnaires to obtain baseline ratings of their current mood (="baseline" timepoint for analyses). These included the state versions of the State Trait Anxiety Inventory (STAI-S; Spielberger et al., 1983) and the Positive and Negative Affect Schedule (PANAS-S; Watson et al., 1988).

Next, the second written informed consent was obtained using either a "no stress" condition or a "stress" condition consent

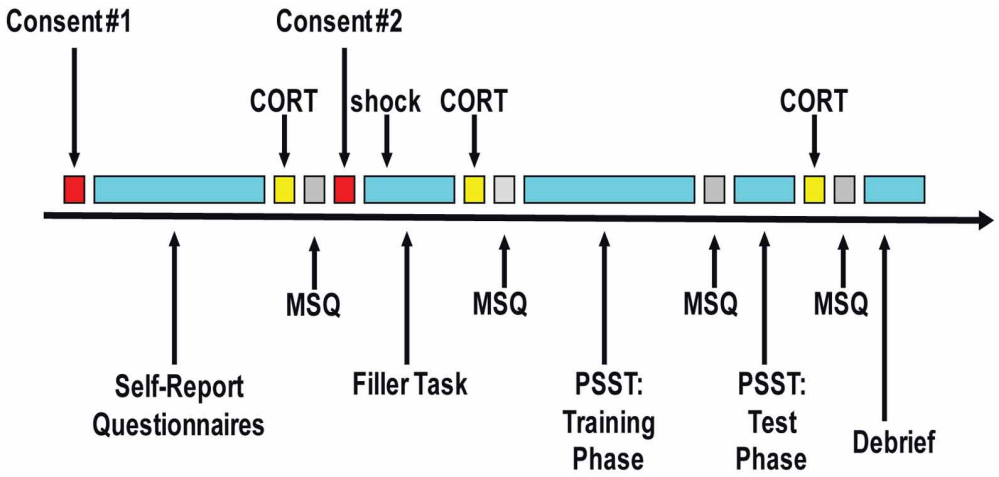

FIGURE 1 | Schematic representation of the session timeline. CORT, collection of saliva sample to measure cortisol level; MSQ, mood state questionnaires ("in-the-moment" state self-report questionnaires); PSST, Probabilistic Stimulus Selection Task.

form. The "stress" consent form stated that participants might receive electrical shocks (via two electrodes attached to their right hand) during two ensuing computer games: "up to two" shocks during the first task (a "filler" task) and "up to three" shocks during the second task (the PSST). Participants then completed a computerized basic attention task that acted as a "filler" task, during which all participants in the "stress" condition received one electrical shock (performance in this task was extraneous to study hypotheses). This task served the purpose of making the potential for shock a credible threat given that we did not actually administer any shock during the main task of interest (PSST). Following the "filler" task, participants completed a second identical set of "in-the-moment" state self-report questionnaires (="post-filler-task/pre-PSST" timepoint); additionally, participants were asked to provide a second saliva sample for cortisol level analyses (approximately 13 min after the shock).

Thereafter, participants who completed the "filler" task in the "stress" condition were further subdivided into "controllable stress" and "uncontrollable stress" conditions, and participants received the appropriate set of instructions for the PSST. Between the training and test phases of the PSST, participants completed a third set of "in-the-moment" state self-report questionnaires (="PSST" timepoint) probing affect experienced during the training phase of the task (i.e., the phase of the task involving the stress manipulation). Following the test phase of the PSST, participants were asked to provide a third saliva sample for cortisol analyses (time-locked to 10 min from the end of the training phase of the PSST in order to capture cortisol levels when participants in the stress conditions were under perceived "threat of shock"). Then, they completed a final set of "in-the-moment" state self-report questionnaires (="post-task" timepoint). Participants also completed a post-task questionnaire to probe their experiences during the session. At the end of the experiment, all participants were debriefed and either paid ($10/h) or awarded study credit for their time. The overall session took approximately 1.5–2 h, and subjects received $15–20 or 1.5–2 study credits. Please see Appendix for detailed descriptions of trait and state measures.

Stress manipulation

Two electrodes were placed on the right hand of each participant assigned to either of the stress conditions, and the electrode wires were attached to a shock box placed on the table in front of the participant. The shock level was adjusted to what each participant felt was "aversive, but not painful." This was done by beginning at the lowest level of shock intensity and having the participant experience a brief shock at each level to have the participant identify a level that she felt was "aversive, but not painful." The maximum current intensity (4 mA; Coulbourn E13–22) was approved by the local IRB. Prior to the "filler" task, these participants were told that they could receive up to two electrical shocks, but the task was actually programmed to administer only one shock. In the PSST, all participants were told they would see a multicolored bar on either side of the computer screen with a tick mark that would periodically move up and down. In the "no stress" condition, they were told that the bars had no meaning. They were also told that occasionally the border of the computer screen would flash red and they should press down on a foot pedal when they saw this visual cue in order to indicate that they were attending to the task. The task was programmed for the cue to appear 1–2 times during each practice block, but participants were not given information about the frequency of this occurrence. For participants in both the "controllable stress" and "uncontrollable stress" conditions, the border flashing red indicated that a shock might occur in the next 15–30 s and they were told that the location of the tick mark within the multicolored bars would indicate the likelihood they would receive a shock. For these participants, the multicolored bars were labeled with "danger" at the top and "safe" at the bottom, and the closer the tick mark was to the top of the bar, the higher the likelihood of receiving a shock. Moreover, participants in the stress conditions were told that the movement of the tick mark was determined

by the computer and was unrelated to their performance on the task. However, participants in the "controllable stress" condition were told that pressing the foot pedal when they saw the red border visual cue would override the computer and lower the location of the tick mark in the bars, thus reducing (albeit not fully eliminating) the likelihood they would receive a shock. When these participants pressed down on the foot pedal, the tick mark did shift down closer to the "safe" zone at the bottom of the bar, providing some visual feedback. In contrast, participants in the "uncontrollable stress" condition were instructed to press down on the foot pedal to indicate they were attending to the task (i.e., they received the same instructions about the foot pedal as those in the "no stress" condition) and this had no effect on the location of the tick mark. Participants in both stress conditions were told they could receive up to three electrical shocks during the PSST; in reality, no shock was administered during this task. Of note, the threat-of-shock stress manipulation was only in effect during the training phase of the PSST. This was the target of our stress manipulation because reward and punishment feedback were only provided during that phase of the task.

"Filler" task

Participants completed a brief version (~8 min) of a Continuous Performance Task (CPT; Conners, 1995) as a "filler" task. They were presented with a series of letters ("O," "T," "H," "Z," or "X") on a computer screen, one at a time, and were instructed to press the space bar immediately following any letter except for "X." Participants completed two blocks of 125 trials, with each letter appearing in 25 trials; on each trial, the letter stimulus was presented for 500 ms, followed by an interstimulus interval that varied between 1250–1550 ms.

Modified probabilistic stimulus selection task (PSST)

The PSST included a training phase and a test phase (**Figure 2**). During the training phase, participants were presented with three different stimuli pairs (AB, CD, EF) in random order, and were instructed to choose one of the two stimuli by pressing one of two response buttons. Following a subject's response, feedback was given to indicate whether the choice was "correct" or "incorrect." Importantly, this feedback was probabilistic, such that for AB trials, a choice of stimulus A led to correct (positive) feedback in 80% of the trials, while a choice of stimulus B led to incorrect (negative) feedback in these trials (with the relations reversed for the other 20% of AB trials). The stimulus pair CD was less reliable, with stimulus C correct in 70% of CD trials, and the stimulus pair EF was the least reliable, with stimulus E correct in 60% of the EF trials. During this training phase, subjects learned to choose stimuli A, C, and E more frequently than B, D, or F. Of note, selection of A over B could be achieved either by learning that choosing A usually leads to positive feedback or learning that choosing B usually leads to negative feedback, or both. Participants completed the training phase either under a "no stress," "controllable stress," or "uncontrollable stress" condition. The training phase was terminated after participants reached performance criteria (65% A in AB, 60% C in CD, and 50% E in EF) or after the completion of six blocks. The performance criteria were set so that all participants would be at approximately the same performance level before proceeding to the test phase (i.e., there was no "overtraining" for subjects who had already learned the contingencies because they would advance to the test phase earlier).

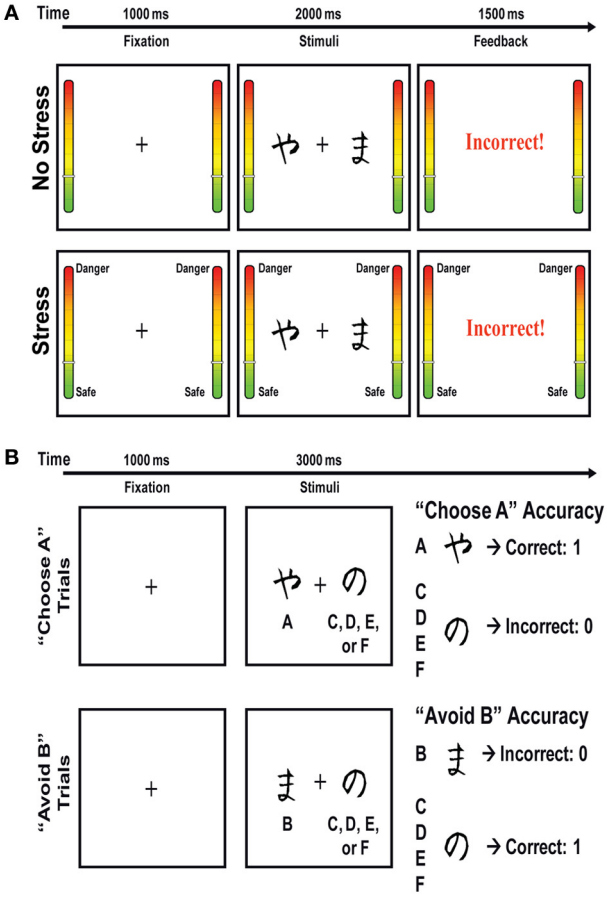

FIGURE 2 | (A) Schematic representation of the *training* phase of the Probabilistic Stimulus Selection Task, which was performed under stress or no stress conditions. In the no-stress condition, every time a red border flashed, participants were instructed to press a foot pedal to indicate they were attending to the task. In the two stress conditions, participants were told that the border flashing red indicated a shock might occur in the ensuing 15–30 s. In the controllable stress condition, participants were further instructed that they could reduce (though not fully eliminate) the likelihood of the shock if they pressed the foot pedal when they saw the red border cue. In contrast, participants in the "uncontrollable stress" condition were instructed to press the foot pedal to indicate they were attending to the task. **(B)** Schematic representation of the *test* phase of the Probabilistic Stimulus Selection Task. No stress was presented during this phase.

In the test phase, subjects were presented with the same three stimuli pairs, as well as all novel combinations of stimuli pairs, and feedback was not provided (**Figure 2**). In order to examine whether subjects learned more about the positive or negative outcomes of their decisions in the training phase, the stimuli pairs of primary interest in the test phase were those involving an A or B stimulus paired with a novel stimulus (e.g., AC, AD, AE, and AF; BC, BD, BE, and BF), referred to as "transfer pairs." These transfer pairs enabled assessment of the degree

to which participants learned from prior positive feedback to choose the most reinforced stimulus ("Choose A") and/or learned from prior negative feedback to avoid the most punished stimulus ("Avoid B"). Prior studies have shown that these conditions are differentially sensitive to dopaminergic manipulation and that performance in the "Choose A" condition is correlated with neural responses to positive outcomes, whereas performance in the "Avoid B" condition is correlated with neural responses to negative outcomes.

The stimuli presented in the PSST were black-and-white Hiragana characters. In the training phase, each trial began with a fixation cross in the middle of the screen for 1000 ms, followed by a stimuli pair for 2000 ms or until the participant made a response. Thereafter, visual feedback was provided for 1500 ms as either "Correct" in blue letters, "Incorrect" in red letters, or "No response detected" in red letters (if the subject did not respond within 2000 ms). Each block of the training phase had 60 trials with 20 trials per stimuli pair. In the test phase, each trial began with a fixation cross for 1000 ms, followed by a stimuli pair for 3000 ms or until the participant made a response. The test phase consisted of one block of 90 trials, with six trials of each of the 15 possible stimuli pairs.

Saliva samples

For saliva collection, participants were instructed to put a small cotton roll (Salivette) in their mouth for approximately 90 s, and then place the saliva-soaked cotton into a small plastic tube. Saliva samples were subsequently stored in a freezer (≤ -20 degrees Celsius) until assayed. The timing of the collection of cortisol samples (specified in the Procedures section above) was based on prior research indicating that cortisol typically peaks about 10–20 min after stressor onset (e.g., Kudielka et al., 2004). To control for diurnal rhythms in cortisol levels, all participants were run between the hours of 1 and 6 pm (Dickerson and Kemeny, 2004). To further control for fluctuations in hormone levels, participants were asked to adhere to the following instructions: no eating or brushing their teeth for at least an hour before the session; no consumption of yogurt for at least 2 h before the session; no consumption of any caffeine-containing products or alcohol the day of the session; no strenuous exercise the day of the session. Information was also collected regarding the time of day participants woke up and the time of the session.

DATA ANALYSES

Trait and dispositional self-report measures

Total and subscale scores were computed for the BDI, MASQ, PSS, TEPS, and BIS/BAS, and *t*-tests were run to compare participants who completed the task under "stress" vs. "no-stress" conditions.

"In-the-moment" state self-report measures

To assess the effectiveness of the stress manipulation, separate mixed ANOVAs were conducted on STAI-S, PANAS-PA (positive affect), and PANAS-NA (negative affect) scores, with *Time* (Baseline, PSST) as a repeated measure and *Group* (Stress, No-Stress) as a between-subjects factor. Significant findings were followed up with *t*-tests.

PSST training phase

To evaluate potential group differences in training, *t*-tests were conducted to compare groups on the number of blocks required to reach performance criteria; separate mixed ANOVAs were run for accuracy and RT on the final training block with *Trial Type* (AB, CD, EF) and *Group* as factors. Significant differences were followed up with *t*-tests.

PSST test phase

Prior to the main analyses of interest, a *t*-test was run to compare accuracy on AB trials (the "easiest" trial type) in the test phase to confirm that there were no significant differences between "stress" and "no stress" groups with regard to participants learning the basic task. Although the performance criteria in the training phase was intended to address this issue, it is possible that participants could have become confused by the lack of feedback and the addition of novel stimuli pairs in the test phase, so this served to verify that learning carried over to the test phase.

Thereafter, to assess whether participants learned more from the positive or negative feedback they received during training, data from the test phase were analyzed with respect to performance on the test trials involving novel combinations of stimuli pairs that included either an A or a B stimulus, respectively. For trials involving an A stimulus paired with a novel stimulus ("Choose A" trials), accuracy was calculated as the proportion of trials on which the participant chose A (the most frequently reinforced stimulus) over the novel stimulus. For trials involving a B stimulus paired with a novel stimulus ("Avoid B" trials), accuracy was calculated as the proportion of trials on which the participant avoided B (the most frequently punished stimulus) and chose the novel stimulus instead. Next, ANOVAs were performed with *Trial Type* ("Choose A," "Avoid B") and *Group* as factors to examine accuracy and RT separately. Significant differences were followed up with the appropriate *t*-tests.

Saliva samples (cortisol)

In order to obtain cortisol levels, saliva samples were sent to the Laboratory for Biological Health Psychology (Brandeis University, MA, USA) and analyzed in a single batch to avoid assay variability (intra-assay CV = 6.48%; inter-assay CV = 6.06%). These values were then entered into an ANOVA using *Time* (T1 = baseline, T2 = post-"filler"-task/pre-PSST, T3 = post-PSST) and *Group* as factors. Given the diurnal drop in cortisol levels throughout the day (Schmidt-Reinwald et al., 1999), and the inevitable variability in wake-up time across participants, we also calculated the difference between waking time and time of the first saliva collection; this value was used as a covariate in the aforementioned ANOVA. Next, in line with previous studies (e.g., Townsend et al., 2011), we calculated cortisol reactivity scores (i.e., difference scores from T1 to T2, or T1 to T3) for all participants. Finally, an ANOVA was run to compare cortisol reactivity scores with *Group*.

Follow-up analyses: using changes in cortisol levels and self-reported state anxiety to identify a stress-reactive subgroup

Given that "threat of shock" might only have been stressful for a sub-group of participants, we identified individuals who

were relatively high stress responders based on changes in cortisol levels and self-reported state anxiety from T1 (baseline) to T2 (∼13 min after subjects received the shock administered in the "filler" task). Initially, we examined descriptive statistics on the distribution of cortisol reactivity scores from T2-T1 within "no-stress" and "stress" groups to examine if there was indeed considerable variability in reactivity scores within each group. In order to obtain a new "stress reactive" group with only stress-reactive participants, we first standardized the T2-T1 cortisol reactivity scores across all participants. Next, using these standardized values, participants were divided into three tiers: high responders (>0.24), medium responders ($-0.27 \geq$ and ≤ 0.24), and low responders (< -0.27). These cut-off scores were selected so that approximately 1/3 of participants were in each tier. Similarly, we standardized the T2-T1 change scores in self-reported state anxiety levels (using STAI scores), and again divided participants into three tiers: high responders (>0.44), medium responders ($-0.66 \geq$ and ≤ 0.44), and low responders (< -0.66). Thereafter, a new "stress reactive" group was created that included only participants who completed the task under stress *and* were relatively high stress responders, defined as being in the "high responder" tier with regard to both changes in cortisol levels and self-reported state anxiety. Using this new "stress reactive" group, all of the aforementioned analyses were re-run to compare the "stress reactive" and "no-stress" groups on demographics, trait and state self-report measures, and performance on the PSST task.

RESULTS

TRAIT AND DISPOSITIONAL SELF-REPORT MEASURES (NO-STRESS vs. STRESS GROUPS)

As evident in **Table 1**, there were no significant differences between the "no-stress" and "stress" groups on the trait or dispositional self-report measures collected at baseline (all $ts \leq 1.67$, $ps \geq 0.10$). Accordingly, putative differences in behavioral performance or stress reactivity were not confounded by group differences in trait or dispositional affect, or ongoing stress levels.

"IN-THE-MOMENT" STATE SELF-REPORT MEASURES (NO-STRESS vs. STRESS GROUPS)

Analyses of both state anxiety (STAI-S scores) and negative affect (PANAS-NA scores) revealed similar effects: significant *Time* × *Group* interactions [$Fs_{(1,\ 93)} > 5.06$, $ps < 0.03$], along with significant main effects of *Time* [$Fs_{(1,\ 93)} > 8.80$, $ps < 0.01$] and *Group* [$Fs_{(1,\ 93)} > 4.87$, $ps \leq 0.03$]. Importantly, at baseline, groups did not differ in their levels of state anxiety or negative affect [$ts_{(93)} < 0.46$, $ps > 0.64$]. During the PSST, participants in the "stress" group reported significantly higher levels of state anxiety and negative affect than participants in the "no-stress" group [$ts_{(93)} > 3.00$, $p < 0.01$]. Within-group paired *t*-tests indicated

Table 1 | Demographics, trait and dispositional self-report measures by groups.

	No stress (NS) group ($n = 27$)	Stress (S) group ($n = 68$)	Stress reactive (SR) group ($n = 18$)	NS vs. S statistic	*p*	NS vs. SR statistic	*P*
Gender (% female)	100%	100%	100%	N/A	N/A	N/A	N/A
Age (years)	21.43 (±1.79)	21.32 (±2.20)	22.05 (±1.92)	$t_{(93)} = 0.22$	0.83	$t_{(43)} = 1.11$	0.28
Education (years)	14.81 (±1.39)	14.35 (±1.61)	14.94 (±1.35)	$t_{(93)} = 1.31$	0.19	$t_{(43)} = 0.31$	0.76
Marital status (% single)	100%	93%	89%	$\chi^2(2) = 2.10$	0.35	$\chi^2(1) = 3.14$	0.08
Income* (% < $50,000)	90%	74%	69%	$\chi^2(1) = 2.29$	0.13	$\chi^2(1) = 2.29$	0.13
Compensation form (% monetary)	85%	90%	78%	$\chi^2(1) = 0.39$	0.54	$\chi^2(1) = 0.41$	0.52
Ethnicity (% Caucasian)	85%	59%	61%	$\chi^2(2) = 10.07$	**0.01**	$\chi^2(1) = 3.39$	0.07
BDI-II	1.85 (±2.38)	2.21 (±2.34)	1.67 (±2.03)	$t_{(93)} = -0.66$	0.51	$t_{(43)} = 0.27$	0.79
MASQ: GDA	15.52 (±4.74)	15.66 (±3.90)	16.22 (±3.21)	$t_{(93)} = -0.15$	0.88	$t_{(43)} = -0.55$	0.59
MASQ: GDD	16.85 (±5.25)	18.10 (±5.12)	17.72 (±5.79)	$t_{(93)} = -1.07$	0.29	$t_{(43)} = -0.52$	0.60
MASQ: AA	20.52 (±4.82)	19.59 (±3.62)	19.28 (±3.05)	$t_{(93)} = 1.03$	0.31	$t_{(43)} = 0.97$	0.34
MASQ: AD	49.56 (±10.90)	49.71 (±10.68)	45.83 (±8.99)	$t_{(93)} = -0.06$	0.95	$t_{(43)} = 1.20$	0.24
Perceived stress scale	19.67 (±6.33)	20.68 (±5.86)	20.83 (±4.62)	$t_{(93)} = -0.74$	0.46	$t_{(43)} = -0.67$	0.51
TEPS: anticipatory	64.67 (±6.68)	64.65 (±9.78)	66.11 (±7.80)	$t_{(93)} = 0.01$	0.99	$t_{(43)} = -0.67$	0.51
TEPS: consummatory	48.41 (±5.56)	50.66 (±6.06)	52.22 (±5.70)	$t_{(93)} = -1.67$	0.10	$t_{(43)} = -2.23$	**0.03**
BIS/BAS: reward responsiveness	7.48 (±1.67)	7.51 (±2.18)	7.56 (±2.09)	$t_{(93)} = -0.07$	0.94	$t_{(43)} = -0.13$	0.90
BIS/BAS: drive	9.19 (±1.96)	9.06 (±2.13)	9.06 (±1.73)	$t_{(93)} = 0.27$	0.79	$t_{(43)} = 0.23$	0.82
BIS/BAS: fun seeking	8.04 (±2.16)	7.78 (±2.23)	8.00 (±2.47)	$t_{(93)} = 0.51$	0.61	$t_{(43)} = 0.05$	0.96
BIS/BAS: inhibition	16.00 (±2.82)	15.40 (±2.83)	15.33 (±2.74)	$t_{(93)} = 0.94$	0.35	$t_{(43)} = 0.79$	0.44

BDI-II, Beck Depression Inventory-II; MASQ, Mood and Anxiety Symptom Questionnaire; GDA, General Distress Anxious; GDD, General Distress Depressive; AA, Anxious Arousal; AD, Anhedonic Depression; TEPS, Temporal Experience of Pleasure Scale; BIS/BAS, Behavioral Inhibition and Behavioral Activation Scales.

**Participants who chose not to report income are not included in the Income statistics; 7 out of 27 (26%) "no stress" participants and 15 out of 68 (22%) "stress" participants chose not to report income. The bold values serve to highlight statistically significant values.*

that anxiety increased from baseline to PSST in the "no stress" group [$t_{(26)} = 2.17$, $p = 0.04$] and, to a much greater degree, in the "stress" group [$t_{(67)} = 8.54$, $p < 0.01$]. Meanwhile, negative affect increased significantly from baseline to PSST in the "stress" group [$t_{(67)} = 4.45$, $p < 0.01$] but not in the "no stress" group [$t_{(26)} = 0.62, p = 0.54$]. The mixed ANOVA on PANAS-PA scores revealed only a significant main effect of *Time* [$F_{(1, 93)} = 11.33$, $p < 0.01$; all other Fs < 2.58, ps > 0.11], with levels of positive affect decreasing from baseline to PSST in both groups.

PSST TRAINING PHASE (NO-STRESS vs. STRESS GROUPS)

Groups did not differ in the number of completed training blocks [$t_{(93)} = 0.27$, $p = 0.79$]; all groups took approximately three blocks to advance to the test phase (No-Stress: 3.15 ± 1.75; Stress: 3.25 ± 1.62). A *Trial Type* (AB, CD, EF) × *Group* ("no stress," "stress") mixed ANOVA on accuracy scores in the final training block indicated only a significant main effect of *Trial Type* [$F_{(1, 93)} = 24.71$, $p < 0.01$; all other Fs < 2.41, ps > 0.12]; as expected, participants were most accurate on the AB trial type and least accurate on the EF trial type. No significant differences emerged from the mixed ANOVA for RT in the final training block (all Fs < 1.06, ps > 0.30). Altogether, these findings indicate that (1) the probabilistic contingencies elicited the intended behavioral effects, and (2) groups did not differ in performance during the training phase.

PSST TEST PHASE (NO-STRESS vs. STRESS GROUPS)

The groups did not differ significantly in their accuracy on AB trials in the test phase [No-Stress Group = 90% (±12%); Stress Group = 86% (±23%); [$t_{(93)} = 0.94, p = 0.35$]], confirming that learning carried over to the test phase similarly for the two groups. Contrary to hypotheses, the *Trial Type* ("Choose A," "Avoid B") × *Group* ANOVA on accuracy scores revealed no significant effects (all Fs < 1.82, ps > 0.17).

For RT scores, the analogous *Trial Type* × *Group* ANOVA yielded a significant main effect of *Trial Type* [$F_{(1, 93)} = 29.52$, $p < 0.01$] and a trend for a *Trial Type* × *Group* interaction [$F_{(1, 93)} = 3.29$, $p = 0.07$]. These results reflected both groups being faster on "Choose A" trials than "Avoid B" trials, with the "no-stress" group demonstrating this pattern to a greater extent.

STRESS-REACTIVE SUBGROUP (DEFINED BY CHANGES IN CORTISOL LEVELS AND SELF-REPORTED STATE ANXIETY)

An examination of descriptive statistics on the distribution of cortisol reactivity scores at T2-T1 within "no-stress" and "stress" groups revealed considerable variability in reactivity scores within each group: scores in the "no stress" group ranged from −5.51 to 1.71 (mean: -1.56 ± 1.57); scores in the "stress" group ranged from −7.82 to 11.78 (mean: -0.95 ± 2.40). Per design, cortisol reactivity scores at T2-T1 were significantly higher in the new "stress reactive" group than the "no-stress" group [$t_{(42)} = 4.01$, $p < 0.01$; degrees of freedom reduced by 1 because cortisol data was missing for one subject at T2]. Importantly, cortisol reactivity scores at T3-T1 continued to be significantly higher in the "stress reactive" group than the "no-stress" group [$t_{(41)} = 3.75$, $p < 0.01$; degrees of freedom reduced by 2 because cortisol data missing for two subjects at T3], suggesting that subjects in the "stress reactive" group continued to be more physiologically stressed during the PSST than subjects in the "no stress" group. The new groups did not differ significantly from each other on any of the following demographic variables: gender, age, years of education, marital status, income level, form of compensation, or ethnicity (see **Table 1**).

TRAIT AND DISPOSITIONAL SELF-REPORT MEASURES (NO-STRESS vs. STRESS-REACTIVE GROUPS)

As compared to the "no-stress" group, the "stress reactive" group reported significantly higher scores on the consummatory subscale of the Temporal Experiences of Pleasure Scale (TEPS), which assesses individual trait dispositions in consummatory experiences of pleasure [$t_{(43)} = 2.23$, $p = 0.03$; all other ts$_{(43)} \leq 1.36$, ps ≥ 0.18]. Due to this finding, the TEPS consummatory subscore was used as a covariate.

"IN-THE-MOMENT" STATE SELF-REPORT MEASURES (NO-STRESS vs. STRESS-REACTIVE GROUPS)

State anxiety

As shown in **Figure 3**, and in line with the new group design, the ANCOVA on STAI-S scores revealed only a significant *Time* × *Group* interaction [$F_{(1, 42)} = 13.33$, $p < 0.01$], whereas the *Time* [$F_{(1, 42)} = 0.29$, $p = 0.59$] and *Group* [$F_{(1, 42)} = 3.52$, $p = 0.07$] effects were not significant. At baseline, groups did not differ in their state anxiety levels [$t_{(43)} = -0.48$, $p = 0.63$]. During the PSST, participants in the "stress reactive" group reported significantly higher levels of state anxiety than participants in the "no-stress" group [$t_{(43)} = 3.57$, $p < 0.01$]. Within-group paired t-tests indicated that anxiety increased from baseline to PSST in both the "stress reactive" group [$t_{(17)} = 6.31$, $p < 0.01$] and "no stress" group [$t_{(26)} = 2.17, p = 0.04$].

State negative affect

The ANCOVA on PANAS-NA scores indicated only a significant *Time* × *Group* interaction [$F_{(1, 42)} = 6.00$, $p = 0.02$]; *Time* [$F_{(1, 42)} = 0.95, p = 0.33$] and *Group* [$F_{(1, 42)} = 3.57, p = 0.07$]; see **Figure 3**. At baseline, groups did not differ in their levels of negative affect [$t_{(43)} = -0.12$, $p = 0.90$]; during the PSST, the "stress reactive" group reported significantly more negative affect than the "no stress" group [$t_{(43)} = 2.90$, $p < 0.01$]. Paired t-tests indicated that negative affect increased significantly from baseline to PSST in the "stress reactive" group [$t_{(17)} = 3.03, p < 0.01$], but not in the "no stress" group [$t_{(26)} = 0.62, p = 0.54$].

State positive affect

The ANCOVA revealed no significant effects (all Fs < 1.95, ps > 0.17).

PSST TRAINING PHASE (NO-STRESS vs. STRESS-REACTIVE GROUPS)

Groups did not differ in the number of completed training blocks [$t_{(43)} = 0.57$, $p = 0.58$]; all groups took approximately three blocks to advance to the test phase (No-Stress: 3.15 ± 1.75; Stress-Reactive: 3.44 ± 1.69). Separate *Trial Type* (AB, CD, EF) × *Group* ("no stress," "stress reactive") ANCOVAs on accuracy scores and RT scores revealed no significant effects (all Fs < 3.13, all ps > 0.08).

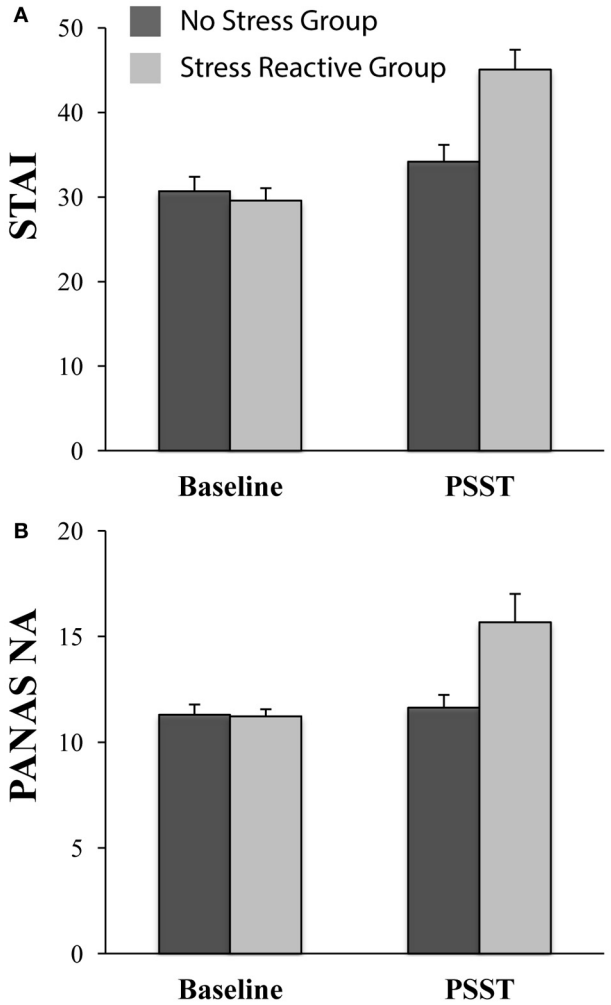

FIGURE 3 | Affective ratings in the no-stress ($n = 27$) and stress-reactive ($n = 18$) groups at baseline and during the PSST. (A) State Trait Anxiety Inventory (STAI) scores; and **(B)** Negative Affect score on the Positive and Negative Affect Schedule (PANAS). For both scales, the state version was used.

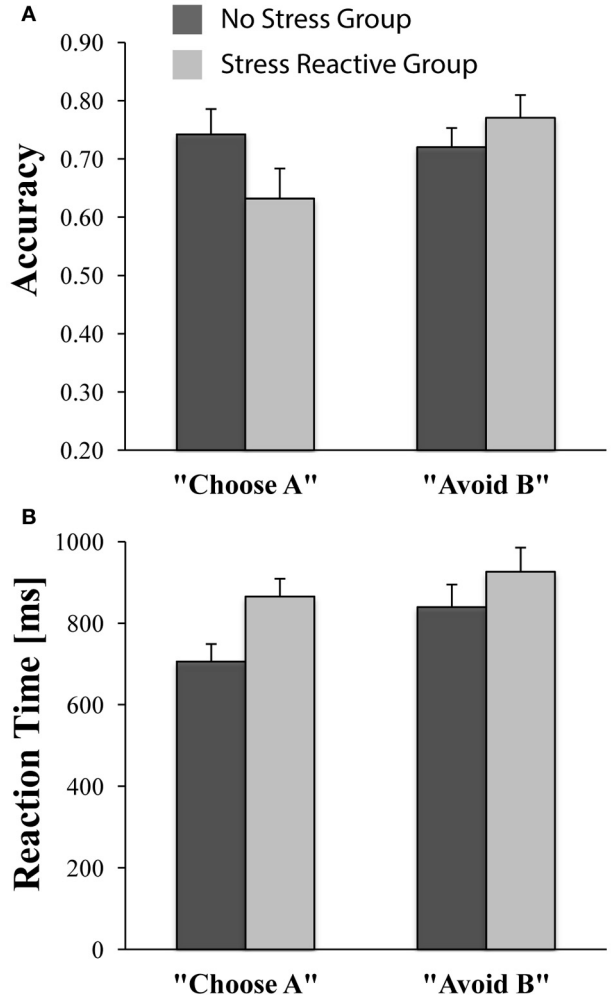

FIGURE 4 | Performance on "Choose A" and "Avoid B" trials during the PSST test phase in the no-stress ($n = 27$) and stress-reactive ($n = 18$) groups. (A) Accuracy; **(B)** Reaction Time (in ms).

PSST TEST PHASE (NO-STRESS vs. STRESS-REACTIVE GROUPS)

The ANCOVA comparing accuracy on AB trials in the test phase with *Group* ("no stress," "stress reactive") revealed no significant group differences [No-Stress Group = 90% (±12%); Stress-Reactive Group = 92% (±16%); $[F_{(1, 42)} = 0.63, p = 0.43]$, confirming that learning carried over to the test phase similarly for the two groups. Critically, the *Trial Type* ("Choose A," "Avoid B") × *Group* ("no stress," "stress reactive") ANCOVA on accuracy scores revealed a main effect of *Trial Type* $[F_{(1, 42)} = 5.72, p = 0.02]$, which was qualified by a significant *Group* × *Trial Type* interaction $[F_{(1, 42)} = 6.45, p = 0.015]$, whereas the *Group* main effect was not significant $[F_{(1, 42)} = 0.14, p = 0.71]$. As shown in **Figure 4**, these findings indicate that the "stress reactive" group displayed relatively lower accuracy on reward-related trials than punishment-related trials compared to the "no stress" group, which exhibited the opposite pattern.

For RT, an analogous *Group* × *Trial Type* ANCOVA yielded only a significant main effect of *Group* $[F_{(1, 42)} = 7.59, p < 0.01$; all other $ps > 0.18]$, due to faster RTs in the "no-stress" group than the "stress reactive" group (**Figure 4**). Follow-up analyses indicated that, compared to the "no stress" group, participants in the "stress reactive" group demonstrated significantly slower RTs on the "Choose A" trials $[F_{(1, 42)} = 13.67, p < 0.01]$, but not the "Avoid B" trials $[F_{(1, 42)} = 3.13, p = 0.08]$. Moreover, participants within the "no stress" group were faster on their "Choose A" trials than their "Avoid B" trials $[t_{(26)} = -4.47, p < 0.01]$, suggestive of a reward-related RT bias, whereas those in the "stress reactive" group had similar RTs on both trial types $[t_{(17)} = -1.41, p = 0.18]$ and did not show this effect.

DISCUSSION

This study was designed to extend our understanding of stress-related anhedonic behavior by examining whether stress specifically reduces reward processing (i.e., learning from positive

feedback) or more generally influences incentive processing (i.e., learning from both positive and negative feedback). The stress manipulation induced significantly higher levels of negative affect and anxiety in those individuals who completed the PSST under stress vs. no-stress conditions. Yet, contrary to our hypotheses, the stress manipulation did not have a significant differential impact on cortisol reactivity or task performance at the group level, likely due to large individual differences. Importantly, however, individuals with heightened cortisol reactivity and increased negative affect following acute stress did demonstrate deficits specific to reward processing. These latter findings suggest that, in highly stress-reactive individuals, stress may selectively result in reward processing deficits with no reduction in punishment processing.

Given that the "threat-of-shock" stressor did evoke significantly higher levels of self-reported negative affect and anxiety in the "stress" group than the "no-stress" group, which was in line with prior independent studies (Bogdan and Pizzagalli, 2006; Bogdan et al., 2011), we were surprised to find that the "stress" group did not demonstrate significantly higher levels of cortisol reactivity. In light of these patterns, it is possible that our stress manipulation may not have elicited as strong of a physiological stress response as intended because only a single shock was administered during the "filler" task and none were administered during the PSST. In addition, the stress manipulation did not include any social evaluative component, which has been shown to reliably produce physiological stress responses (Kirschbaum et al., 1993). Moreover, for participants in the "stress" group, the border of the computer screen flashing red during the PSST indicated that a shock could occur in the next 15–30 seconds; it is possible that this cue may have reduced the stressfulness of the "threat-of-shock" by increasing the perceived predictability of the stressor. In fact, predictable stressors typically elicit smaller physiological stress responses and are experienced as less aversive than unpredictable stressors (Anisman and Matheson, 2005). In light of these null cortisol findings, it was not entirely surprising that initial analyses of task performance across groups yielded no significant between-group differences during the training or test phases of the PSST.

One potential explanation for the lack of significant findings in this initial set of analyses may be that there was a broad range of individual differences within the group of individuals who completed the task under stress in terms of how physiologically "stressed out" participants became in response to the "threat-of-shock." An examination of cortisol reactivity scores within each group indeed confirmed that there was substantial intra-group variability. Accordingly, we conducted follow-up analyses by identifying a stress-reactive subgroup based on cortisol reactivity as well as self-reported anxiety levels; the new "stress reactive" group included only those participants who completed the task under stress and were "high responders" from both a physiological (cortisol levels) and self-reported experiential (STAI scores) perspective. In line with these demarcations, the new "stress reactive" group also demonstrated a significant increase in negative affect (PANAS-NA scores) that was not apparent in the "no stress" group, reinforcing coalescence between biological measures and self-report measures of stress response.

STRESS-SENSITIVE INDIVIDUALS DEMONSTRATE REWARD-SPECIFIC IMPAIRMENTS

Consistent with previous studies (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2007; Bogdan et al., 2010), and our main hypotheses, participants in the new "stress reactive" group demonstrated reduced reward sensitivity relative to participants in the "no-stress" group. This was supported in the following ways: first, there was a significant *Group* ("no stress," "stress reactive") × *Trial Type* ("Choose A," "Avoid B") interaction for accuracy during the test phase of the PSST, which was due to relatively lower accuracy on reward-related ("Choose A") trials than punishment-related ("Avoid B") trials in the "stress reactive" group, compared with the opposite pattern exhibited by the "no-stress" group (i.e., relatively higher accuracy on reward-related than punishment-related trials). This finding suggests that stress-sensitive participants did not experience a global decrease in accuracy on the task under stress, but rather a more specific reduction in accuracy on reward-related trials only. This reward-processing deficit may reflect reduced sensitivity to positive feedback (during the training phase of the PSST), evident in an impaired ability to use this reward information to guide decision making in novel contexts (during the test phase of the PSST). Secondly, participants in the "no-stress" group demonstrated a reward-related RT bias that was absent in the "stress reactive" group. Specifically, the "no stress" group demonstrated faster RTs on reward-related trials than punishment-related trials, while the RTs of the "stress reactive" group were not significantly different between trial types. Moreover, participants in the "no-stress" group were significantly faster than participants in the "stress reactive" group on the reward-related trials but not the punishment-related trials. Importantly, these findings suggest that speed-accuracy tradeoffs did not play a significant role in the present results. For example, the fact that the "stress reactive" group, as compared to the "no stress" group, had poorer accuracy *and* slower RTs on reward-related trials runs counter to the notion that poorer accuracy could have been due to a speed-accuracy tradeoff of faster RTs. Overall, our results expand prior lines of research on stress-induced reductions in reward responsiveness by suggesting that stress may selectively reduce sensitivity to reward feedback and does not more broadly reduce sensitivity to feedback in general.

During the test phase, there were no group differences in accuracy on the most salient trials from the training phase (e.g., AB trials), which (1) suggests that all participants learned the basic task and this learning carried over to the test phase, and (2) provides further evidence that stress did not induce a global performance deficit across the task (e.g., differences only emerged for novel trial types in the test phase). These findings, in combination with the fact that participants across groups needed a comparable number of training blocks to reach performance criteria during the training phase, also suggest that results were not likely the byproduct of psychometric artifacts. More specifically, as highlighted in experiments assessing the effects of threat on working memory performance (Shackman et al., 2006), it is important to address whether results could be merely the artifact of an additional load on attentional resources in the stress condition, rather than stress *per se*. If this were the case, however, we would expect to see global deficits in task

performance for individuals who completed the task under stress. In addition, a predominant lack of group differences on trait and dispositional self-report measures (the one exception being the consummatory subscale of the TEPS, which was controlled for in the analyses), and no group differences at baseline on any affective state self-report measures, suggests that putative differences in behavioral performance or stress reactivity were not confounded by group differences in affect, mood, or ongoing life stress.

In related research that warrants acknowledgement, Lighthall and colleagues (2013) recently reported that participants who completed a PSST *after* exposure to a cold pressor stress manipulation had relatively reduced punishment learning and increased reward learning. However, the stressor was terminated well before the beginning of the PSST (and an unrelated memory task was administered between the stressor and the PSST); this sequence of events raises the possibility that their observed results may have stemmed from "relief" experienced by participants after the stressor. In line with the conceptualization of "stress relief" as rewarding, "relief" from stressors has been recently associated with activation of reward-related neural regions (Leknes et al., 2011) and increased dopamine levels (Navratilova et al., 2012). Clearly, more research is needed to examine the putative relationship between negative stressors and decreased reward sensitivity, with particular focus on the temporal unfolding of such processes.

LIMITATIONS

There are several limitations to the current study that should be acknowledged. First, the study included only female participants due to sex differences in psychological and hormonal responses to stress (e.g., women demonstrate a more pronounced stress response than men; Nolen-Hoeksema and Hilt, 2009). Thus, future studies will be required to determine if the current stress-induced reward-specific deficits generalize to males. Second, the strength of findings is limited by the fact that significant between-group results only emerged after re-running the main analyses of interest using a "stress reactive" subgroup defined based on physiological and self-reported experiential indices of stress responsiveness. This new "stress reactive" group had a relatively small sample size and contained participants who had received two different sets of instructions regarding controllability of the stressor. However, the lack of significant differences between these participants (with regard to both self-report and physiological measures; see Appendix Analyses) mitigates the potential effect of this latter limitation. Third, it is important to acknowledge the inherently limited ecological validity of an acute "threat-of-shock" laboratory stressor and the potentially diminished strength of laboratory stressors that do not include a social evaluative component. Fourth, given that findings from this study pertain to learning from positive vs. negative feedback, it remains to be seen whether the patterns found will generalize to other types of rewards and punishments. Finally, in order to further evaluate whether stress-induced reward deficits are a potential mechanism underlying the link between stress and depression, it will be imperative to run parallel experiments in MDD individuals. In spite of these limitations, the current study has substantial translational value and significant strengths, including the use of a well-controlled experimental procedure (threat-of-shock) to superimpose an acute stress manipulation on a primary task (the PSST).

CONCLUSIONS

In sum, results from the current biologically informed analyses support *a priori* hypotheses and previous research findings (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2007; Bogdan et al., 2010) by demonstrating that stress-reactive individuals under stress exhibit reduced reward processing (i.e., reduced sensitivity to positive feedback, evident in an impaired ability to use this reward information to guide decision making in novel contexts) relative to individuals not under stress. These results are also in line with recent neuroimaging studies that have shown reduced activation in reward-related neural areas in response to stress inductions implemented immediately prior to reward processing tasks (Ossewaarde et al., 2011; Porcelli et al., 2012). Critically, findings from the current study extend this area of research by providing initial evidence that these stress-induced deficits appear to be reward-specific and not generalizable to punishment processing. Given that negative life stress often precedes depression onset (Kendler et al., 1999) and predicts clinical severity (Tennant, 2002), the current results also provide support for the possibility that stress-induced hedonic deficits may be a potential mechanism underlying the connection between negative stress and depressive episodes. In this way, such results are in line with conceptualizations of stress-induced anhedonia as a potential vulnerability factor for depression (Berghorst and Pizzagalli, 2010, for review). Although promising, it is important to emphasize that (1) these findings emerged in the context of an only partially successful stress manipulation (see Appendix); (2) findings emerged only after a subgroup of stress-reactive participants was identified; and (3) the ecological validity of the stress manipulation was limited. Accordingly, these findings await replications and conclusions should be tempered. Future studies also need to examine whether the stress-induced rapid activation of the mesocortical DA system and inhibition of the mesolimbic DA system in animal models (Cabib and Puglisi-Allegra, 1996; Cabib et al., 2002) represent biological mechanisms fundamental to the current study findings.

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DISCLOSURES

Dr. Pizzagalli has received consulting fees from ANT North America Inc. (Advanced Neuro Technology), AstraZeneca, Shire, Servier, and Ono Pharma USA, as well as honoraria from AstraZeneca for projects unrelated to the current research. All other authors report no competing interests.

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APPENDIX

DESCRIPTION OF MEASURES

Trait and dispositional self-report measures

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) is a 21-item questionnaire used to measure depressive symptoms over the past 2 weeks. It has strong internal reliability (0.86–0.92), high test-retest reliability over 1-week (0.93), and good convergent and discriminant validity (Beck et al., 1996; Steer et al., 2000; Segal et al., 2008).

The Mood and Anxiety Symptom Questionnaire (MASQ-short) is a 62-item questionnaire used to assess symptoms of anxiety and depression over the past week with good convergent and discriminant validity in clinical and community samples (Watson et al., 1995); it yields four subscales—general distress anxious, anxious arousal, general distress depressive, and anhedonic depressive.

The Perceived Stress Scale (PSS; Cohen et al., 1983) is a 14-item measure used to assess the degree to which an individual appraises the situations in his or her life as stressful over the past month. Internal reliability coefficients for the PSS range from 0.84 to 0.86 with a test-retest reliability of 0.85 (over 2 days); the measure has been demonstrated to have strong convergent validity (Cohen et al., 1983).

The Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) is a 14-item measure used to assess individual trait dispositions in anticipatory and consummatory experiences of pleasure. The scale has good internal consistency (0.71–0.79), high test-retest reliability over 5–7 weeks (0.75–0.81), and strong convergent and discriminant validity (Gard et al., 2006).

The Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS; Carver and White, 1994) are used to measure individual differences in sensitivity to two motivational systems purported to underlie behavior: a behavioral activation system and a behavioral inhibition system. It has good convergent and discriminant validity in community and clinical samples (Carver and White, 1994; Campbell-Sills et al., 2004).

"In-the-moment" state self-report measures

The state form of the State Trait Anxiety Inventory (STAI-S) includes 20 items used to quantify state anxiety levels. Internal consistency coefficients range from 0.86 to 0.95, while test-retest reliability coefficients (over 2 months) range from 0.65 to 0.75 (Spielberger et al., 1983).

The state version of the Positive and Negative Affect Schedule (PANAS) is used to measure current levels of positive and negative affect. Internal consistency coefficients range from 0.86–0.90 for the positive affect scale and 0.84–0.87 for the negative affect scale; test-retest reliability coefficients (over 2 months) range from 0.47–0.68 for the positive affect scale and 0.39–0.71 for the negative affect scale (Watson et al., 1988).

The Challenge-Threat Questionnaire (Mendes et al., 2001) was designed to assess individuals' threat appraisals (perceived resources/demands) of a task, with pre-task and post-task versions. Unfortunately, only 23 "controllable stress" participants and 21 "uncontrollable stress" participants completed this measure since it was added midway through data collection. The pre-task version typically includes 11 statements (e.g., "The upcoming task will take a lot of effort to complete," "I have the abilities to perform the upcoming task successfully") that participants rate on a scale from 1 ("strongly disagree") to 7 ("strongly agree") to indicate how they are feeling about the task they are about to complete. The pre-task version used in this study included two additional items to assess participants' perceived control over general task performance, and perceived control over whether shocks would occur in the upcoming task. Participants completed the pre-task form after receiving PSST instructions but prior to beginning the PSST. The post-task version typically includes nine statements (e.g., "The task was very demanding," "I felt that I had the abilities to perform well in the task"), which participants again rate on a scale from 1 ("strongly disagree") to 7 ("strongly agree") to indicate how they feel about the task they just completed. The post-task version used in this study also included two additional items to assess participants' perceived control over general task performance, and perceived control over whether shocks occurred in the task. Participants completed the post-task form after finishing the PSST.

ANALYSES

All analyses parallel those reported in the main manuscript (*Trait and dispositional self-report measures; "In-the-moment" state self-report measures; PSST training phase; PSST test phase*) except they were computed using *Group* with three levels ("no stress," "controllable stress," "uncontrollable stress") in mixed ANOVAs.

RESULTS

Trait and dispositional self-report measures

There were no significant differences between groups on trait and dispositional self-report measures collected at baseline (all $Fs < 2.09$, $ps > 0.13$); see **Table A1**.

"In-the-moment" state self-report measures

State anxiety. The mixed ANOVA on STAI-S scores revealed a significant main effect of *Time* [$F_{(1, 92)} = 65.68$, $p < 0.01$] and, more critically, a *Time* × *Group* interaction [$F_{(2, 92)} = 4.72$, $p = 0.01$]; *Group* was not significant [$F_{(2, 92)} = 2.71$, $p = 0.07$]. Paired t-tests indicated that anxiety increased from baseline to PSST in the "controllable stress" group [$t_{(33)} = 5.72$, $p < 0.01$], the "uncontrollable stress" group [$t_{(33)} = 6.29$, $p < 0.01$], and the "no stress" group [$t_{(26)} = 2.17$, $p = 0.04$]. At baseline, there were no group differences [$F_{(2, 94)} = 0.22$, $p = 0.81$]. In line with hypotheses, anxiety levels during the PSST were significantly different between groups [$F_{(2, 94)} = 5.04$, $p < 0.01$]. Follow-up t-tests revealed that participants in both the "controllable stress" [$t_{(59)} = 2.67$, $p = 0.01$] and uncontrollable stress groups [$t_{(59)} = 3.00$, $p < 0.01$] reported significantly higher anxiety than participants in the "no-stress" group. However, contrary to hypotheses, participants in the "controllable stress" group did not differ from those in the "uncontrollable stress" group [$t_{(66)} = -0.24$, $p = 0.81$].

State negative affect. The mixed ANOVA on PANAS-NA scores also revealed a significant main effect of *Time* [$F_{(1, 92)} = 16.87$, $p < 0.01$] and a *Time* × *Group* interaction [$F_{(2, 92)} = 3.29$, $p = 0.04$]; *Group* was not significant [$F_{(2, 92)} = 2.55$, $p = 0.08$].

Table A1 | Demographics, trait and dispositional self-report measures of the original three groups.

	No stress group ($n = 27$)	Controllable stress group ($n = 34$)	Uncontrollable stress group ($n = 34$)	Statistics	p
Gender (% female)	100%	100%	100%	N/A	N/A
Age (years)	21.43 (±1.79)	21.33 (±2.24)	21.32 (±2.20)	$F_{(2, 94)} = 0.02$	0.98
Education (years)	14.81 (±1.39)	14.44 (±1.69)	14.26 (±1.54)	$F_{(2, 94)} = 0.96$	0.39
Marital status (%single)	100%	91%	94%	$\chi^2(1) = 5.37$	0.25
Income (% <$50,000)	90%	73%	74%	$\chi^2(1) = 2.29$	0.32
Compensation form (% monetary)	85%	91%	88%	$\chi^2(1) = 0.53$	0.77
Ethnicity (% Hispanic)	7%	9%	6%	$\chi^2(1) = 0.22$	0.90
Ethnicity (% Caucasian)	85%	44%	74%	$\chi^2(1) = 12.60$	<0.01
BDI-II Score	1.85 (±2.38)	2.41 (±2.52)	2.00 (±2.16)	$F_{(2, 94)} = 0.48$	0.62
MASQ: GDA	15.52 (±4.74)	15.50 (±3.78)	15.82 (±4.06)	$F_{(2, 94)} = 0.06$	0.94
MASQ: GDD	16.85 (±5.25)	18.79 (±5.59)	17.41 (±4.59)	$F_{(2, 94)} = 1.18$	0.31
MASQ: AA	20.52 (±4.82)	19.94 (±4.32)	19.24 (±2.76)	$F_{(2, 94)} = 0.79$	0.46
MASQ: AD	49.56 (±10.90)	50.15 (±10.15)	49.26 (±11.32)	$F_{(2, 94)} = 0.06$	0.94
Perceived stress scale	19.67 (±6.33)	21.65 (±5.12)	19.71 (±6.45)	$F_{(2, 94)} = 1.18$	0.31
TEPS: anticipatory	64.67 (±6.68)	65.12 (±10.20)	64.18 (±9.46)	$F_{(2, 94)} = 0.09$	0.91
TEPS: consummatory	48.41 (±5.56)	50.82 (±6.04)	50.50 (±6.17)	$F_{(2, 94)} = 1.41$	0.25
BIS/BAS: reward responsiveness	7.48 (±1.67)	7.65 (±2.71)	7.38 (±1.50)	$F_{(2, 94)} = 0.14$	0.87
BIS/BAS: drive	9.19 (±1.96)	8.91 (±2.14)	9.21 (±2.14)	$F_{(2, 94)} = 0.20$	0.82
BIS/BAS: fun seeking	8.04 (±2.16)	7.82 (±2.36)	7.74 (±2.12)	$F_{(2, 94)} = 0.14$	0.87
BIS/BAS: inhibition	16.00 (±2.82)	15.15 (±2.81)	15.65 (±2.87)	$F_{(2, 94)} = 0.70$	0.50

BDI-II, Beck Depression Inventory-II; MASQ, Mood and Anxiety Symptom Questionnaire; GDA, General Distress Anxious; GDD, General Distress Depressive; AA, Anxious Arousal; AD, Anhedonic Depression; TEPS, Temporal Experience of Pleasure Scale; BIS/BAS, Behavioral Inhibition and Behavioral Activation Scales.

Paired *t*-tests indicated that negative affect increased significantly from baseline to PSST in the "controllable stress" group [$t_{(33)} = 2.76$, $p < 0.01$] and the "uncontrollable stress" group [$t_{(33)} = 3.50$, $p < 0.01$], but not in the "no stress" group [$t_{(26)} = 0.62$, $p = 0.54$]. At baseline, there were no group differences in negative affect [$F_{(2, 94)} = 0.25$, $p = 0.78$]. However, negative affect during the PSST was significantly different between groups [$F_{(2, 94)} = 3.52$, $p = 0.03$]. Follow-up *t*-tests revealed that participants in both the "controllable stress" [$t_{(59)} = 2.02$, $p < 0.05$] and "uncontrollable stress" [$t_{(59)} = 2.61$, $p = 0.01$] groups reported significantly higher negative affect than participants in the "no-stress" group. However, again contrary to hypotheses, the two stress groups did not differ in their levels of negative affect during the PSST [$t_{(66)} = -0.85$, $p = 0.40$].

State positive affect. The mixed ANOVA on PANAS-PA scores revealed a main effect of *Time* [$F_{(1, 92)} = 18.37$, $p < 0.01$]; the *Time* × *Group* interaction [$F_{(2, 92)} = 1.50$, $p = 0.23$] and the *Group* main effect [$F_{(2, 92)} = 1.05$, $p = 0.36$] were not significant. All participants reported a reduction in positive affect from baseline to PSST.

Challenge-threat questionnaire. Contrary to hypotheses, the "controllable stress" and "uncontrollable stress" groups were not significantly different in their pre-task [$t_{(42)} = 0.37$, $p = 0.71$] or post-task [$t_{(42)} = 0.28$, $p = 0.78$] threat appraisals. Moreover, the two stress groups did not differ in their ratings of control over performance in the task prior to task onset [$t_{(42)} = -0.03$, $p = 0.98$] or after completing the task [$t_{(42)} = 0.33$, $p = 0.74$]. In both groups and at both assessments, these ratings were close to "neutral" but fell on the "disagree" side of the scale (<4) with regard to having control over their performance.

A mixed ANOVA on ratings of perceived control over shock with *Group* (Uncontrollable Stress, Controllable Stress) as a between-subjects variable and *Time* (Pre-PSST, Post-PSST) as a within-subjects variable revealed a trend for a *Time* × *Group* interaction [$F_{(1, 42)} = 3.42$, $p = 0.07$], with significant main effects of *Time* [$F_{(1, 42)} = 29.60$, $p < 0.01$] and *Group* [$F_{(1, 42)} = 45.64$, $p < 0.01$]. On pre-task ratings of control over shock, the "controllable stress" group was significantly higher than the "uncontrollable stress" group [$t_{(42)} = 5.66$, $p < 0.01$], as predicted; however, importantly and contrary to expectations, both groups again fell in the "disagree" zone of the rating scale (<4). A paired *t*-test within the "controllable stress" group indicated that they reported significantly more control over the shock at their post-task than pre-task rating [mean increased to 5.39 ± 1.62; $t_{(22)} = 5.51$, $p < 0.01$]; interestingly, the "uncontrollable stress" group also had a significant increase in level of perceived control over shock from pre-task to post-task [2.43 ± 1.75; $t_{(20)} = 2.38$, $p = 0.03$].

Overall, findings from the state measures indicated that the "threat-of-shock" stress manipulation induced significantly higher levels of negative affect and anxiety in both stress conditions than the no-stress condition, but no significant differences

between the two stress groups. Further indications that the stress manipulation was only partially successful include the following: no significant differences between the two stress groups on pre-task threat appraisals or perceived control over general task performance, and pre-task ratings of control over shock were in the "disagree" zone of the scale for both groups.

Cortisol levels

The *Time* (T1 = baseline, T2 = post-"filler"-task/pre-PSST, T3 = post-PSST) × *Group* ANCOVA on cortisol levels, with "time since waking" as a covariate, revealed only a significant main effect of *Time* [$F_{(2,176)} = 11.37$, $p < 0.01$]. Consistent with cortisol's diurnal pattern, cortisol levels dropped throughout the experiment [linear effect: $F_{(1,\ 88)} = 15.14$, $p < 0.01$]. Similarly, an ANOVA comparing groups on cortisol reactivity scores at T2-T1, and a separate ANOVA comparing groups on cortisol reactivity scores at T3-T1, yielded insignificant findings (all $F < 1.78$, $p > 0.17$). The unpaired *t*-test comparing the "controllable stress" group with the "uncontrollable stress" group on cortisol reactivity scores at T3-T1 was not significant [$t_{(64)} = 0.36$, $p = 0.72$], suggesting that both stress conditions yielded physiologically similar responses.

PSST training phase

Groups did not differ in the number of completed training blocks [$F_{(2,\ 94)} = 0.49$, $p = 0.61$]; all groups took approximately three blocks to advance to the test phase (no-stress group: 3.15 ± 1.75; controllable stress group: 3.06 ± 1.50; uncontrollable stress group: 3.44 ± 1.73). In the ANOVA for accuracy on the final training block with *Trial Type* (AB, CD, EF) and *Group* as factors, there was only a main effect of *Trial Type* [$F_{(2,\ 184)} = 14.86$, $p < 0.01$; all other Fs < 1.30, ps > 0.30]; as expected, participants were most accurate on the AB trial type and least accurate on the EF trial type. No significant differences emerged from the ANOVA for RT on the final training block (all Fs < 1.91, ps > 0.15). Altogether, these findings indicate that (1) the probabilistic contingencies elicited the intended behavioral effects, and (2) groups did not differ in performance during the training phase.

PSST test phase

The ANOVA comparing accuracy on AB trials (the "easiest" trial type) in the test phase with *Group* confirmed that there were no significant group differences in terms of participants learning the basic task [$F_{(2,\ 94)} = 0.62$, $p = 0.54$]. For accuracy, contrary to hypotheses, the *Trial Type* ("Choose A," "Avoid B") × *Group* ANOVA revealed no significant effects (all Fs < 1.59, ps > 0.21).

For RT scores, the analogous *Trial Type* × *Group* ANOVA yielded a significant main effect of *Trial Type* [$F_{(1,\ 92)} = 29.73$, $p < 0.01$] and a *Trial Type* × *Group* interaction [$F_{(1,\ 92)} = 4.56$, $p = 0.01$]. Follow-up analyses indicated no significant group differences on "Choose-A" trials or "Avoid B" trials (all ps > 0.058). Paired *t*-tests revealed that participants in the "no stress" and "uncontrollable stress" groups were slower on their "Avoid B" trials than their "Choose A" trials [no-stress group: $t_{(26)} = 4.47$, $p < 0.01$; uncontrollable stress group: $t_{(33)} = 4.49$, $p < 0.01$]. Participants in the "controllable stress" condition, however, exhibited RTs that were not significantly different across trial types [$t_{(33)} = 0.72$, $p = 0.48$].

DISCUSSION

Inspired by non-human animal research documenting that uncontrollable stressors may be potent triggers of anhedonic-like behavior, we attempted to examine whether stressor controllability moderates the relationship between stress and reward processing dysfunction. Although the stress manipulation did induce significantly higher levels of negative affect and anxiety than the no-stress condition, the uncontrollable and controllable stress manipulations elicited similar affective and cortisol responses, which was contrary to hypotheses. Notably, these results echoed patterns with self-report measures indicating that the "controllable stress" group did not actually believe they had control over the stressor. Accordingly, due to an only partially successful stress manipulation, conclusions could not be drawn concerning the impact of perceived control over stress.

Contrary to expectations, the two stress groups ("controllable" and "uncontrollable") did not differ significantly from each other in their levels of anxiety or negative affect. Cortisol reactivity analyses similarly did not reveal differences between the "controllable stress" and "uncontrollable stress" groups. Moreover, there were no significant differences between the two stress groups on pre-task threat appraisals (perceived demands/personal resources) or perceived control over general task performance. Although pre-task ratings of control over shock were higher in the "controllable stress" group than the "uncontrollable stress" group, both groups' ratings fell in the "disagree" zone of the scale, indicating that prior to task onset, subjects in the "controllable stress" group did not actually believe that they would have control over the stressor. This lack of believability may stem from the fact that participants in the "controllable stress" group were told they would be able to "significantly reduce" the likelihood of receiving shock by pressing down on the foot pedal, but could not completely eliminate the possibility of being shocked (i.e., they were not given "complete" control). Task instructions were outlined this way because of concerns that the latter set of instructions would not induce significantly more stress than the no-stress condition. Collectively, these data suggest that the stress manipulation was only partially successful: significantly more negative affect and anxiety was reported by participants in both stress groups relative to the "no-stress" group, but the controllability manipulation was not successful.

Results from this aspect of the experiment serve to highlight key variables to consider in the design of future experiments. For example, the importance of administering an assessment of perceived control over stress *prior* to task onset and collecting data on a physiological index of stress (e.g., cortisol levels) to confirm the effects of any stress manipulation on participants. Moreover, given that participants in our "controllable" stress condition (who were told they had "partial" control over the stressor) did not report truly believing they had control over the stressor, future designs warrant including a "controllable stress" condition in which participants are given perceived *full* control over the stressor.

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Stress-induced cognitive dysfunction: hormone-neurotransmitter interactions in the prefrontal cortex

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The mechanisms and neural circuits that drive emotion and cognition are inextricably linked. Activation of the hypothalamic-pituitary-adrenal (HPA) axis as a result of stress or other causes of arousal initiates a flood of hormone and neurotransmitter release throughout the brain, affecting the way we think, decide, and behave. This review will focus on factors that influence the function of the prefrontal cortex (PFC), a brain region that governs higher-level cognitive processes and executive function. The PFC becomes markedly impaired by stress, producing measurable deficits in working memory. These deficits arise from the interaction of multiple neuromodulators, including glucocorticoids, catecholamines, and gonadal hormones; here we will discuss the non-human primate and rodent literature that has furthered our understanding of the circuitry, receptors, and signaling cascades responsible for stress-induced prefrontal dysfunction.

Keywords: working memory, stress, catecholamines, glucocorticoids, sex differences, estrogen

INTRODUCTION

Our ability to manage, update, and act on information in the absence of external cues—executive functions collectively known as working memory—is critical to daily functioning (Arnsten and Castellanos, 2002). These processes depend on the structural and functional integrity of the prefrontal cortex (PFC) (Goldman-Rakic, 1996), a highly evolved brain region that guides emotion and behavior through projections to subcortical regions like the hypothalamus, amygdala, and brainstem nuclei (Price et al., 1996). Under optimal, stress-free conditions, microcircuits within the PFC work together to inhibit inappropriate responses and allow nuanced decision-making (Goldman-Rakic, 1995). Exposure to stress, however, can disrupt PFC function, markedly impairing working memory (Arnsten, 2009; Arnsten et al., 2012). From an ethological standpoint, this loss of complex processing may have once allowed more primitive behaviors to take precedence in order to aid survival. But today, non-life-threatening stressors can activate these same circuits, eliciting scattered thought, loss of focus, and judgment errors that can be detrimental to daily life, and—in extreme cases—lead to mental illness. Over the last few decades, animal research has helped elucidate the mechanisms that underlie these impairments, revealing a complex interaction between neurotransmitter signaling and hormone actions.

Working memory in animals is assessed using delay-based tasks, which require an animal to keep a piece of information in mind over the course of a delay period, in order to make an accurate choice when the delay ends. Monkeys performing the Delayed Response task must remember the location of a briefly presented stimulus on a screen, and then move their eyes to focus on that location. In rodents, the Delayed Alternation task requires the animal to remember which arm of a T-shaped maze it previously visited, and then visit the opposite arm on the subsequent trial. Both tasks involve dozens, or even hundreds of trials, and thus during the delay the animal must not only keep the "signal" (i.e., correct choice) in mind, but also suppress the "noise"—information from previous trials. Subsets of prefrontal neurons fire exclusively during the delay (Funahashi et al., 1989), suggesting a unique role for the PFC in this aspect of the task. Moreover, lesions of the PFC disrupt accuracy only when the task involves a delay (Funahashi et al., 1993), demonstrating that the PFC is not involved in the motor or motivational aspects of these tasks. Accurate performance on working memory tasks relies on the maintenance of a balanced neurochemical milieu in the PFC—one that is easily disrupted with exposure to stress.

Many kinds of mild stressors can impair working memory in animals. The most common stressor for monkeys is a loud white noise, which also disrupts working memory in humans (Arnsten and Goldman-Rakic, 1998). Stressors in rodents include brief restraint stress (Shansky et al., 2006), and administration of the anxiogenic drug FG-7142, a benzodiazepine inverse agonist (Shansky et al., 2004). Each of these manipulations activates the hypothalamic-pituitary-adrenal (HPA) axis, eliciting a cascade of hormone and neurotransmitter release that alters cognitive and emotional processes throughout the brain (Cordero et al., 2003; Mikkelsen et al., 2005). In this review, we will focus on the contributions of the catecholamines dopamine (DA) and norepinephrine (NE), and their interactions with glucocorticoids and estrogen.

DOPAMINE AND NOREPINEPHRINE

The primary sources of DA and NE input to the PFC are the ventral tegmental area (VTA) and locus coeruleus (LC), respectively (Thierry et al., 1992). Selective lesions of these afferents

impair working memory in monkeys, suggesting that baseline catecholamine signaling is required for optimal PFC function (Brozoski et al., 1979). Investigations into the downstream mechanisms by which these neurotransmitters mediate working memory—in both stress and non-stress conditions—indicate critical roles for the DA D1 receptor, and noradrenergic alpha-1 and alpha-2 receptors (Arnsten, 1998a).

The D1 receptor is coupled to the Gs protein, whose stimulation triggers a signaling cascade that involves increases in cyclic-AMP (cAMP) and protein kinase A (PKA), the effects of which are discussed below (Arnsten, 2011a,b). Pharmacological blockade of D1 receptors in both monkeys and rodents impairs performance on working memory tasks (Sawaguchi and Goldman-Rakic, 1991; Izquierdo et al., 1998), indicating a key role for D1 signaling in normal PFC function. Electron micrographs show that D1 receptors co-localize with glutamate receptors on dendritic spines (Pickel et al., 2006, and see **Figure 1**), making them strategically positioned to modulate incoming excitatory information. Single unit physiological studies in monkeys performing a delayed response task have revealed that D1 activity plays an integral role in filtering out "noise"—suppressing firing in PFC neurons that code for information irrelevant to the immediate task, thus increasing the likelihood of a correct response (Vijayraghavan et al., 2007). Without D1 stimulation, PFC neurons become generally overactive, rendering the animal vulnerable to distractions (Vijayraghavan et al., 2007).

While a lack of D1 activity can impair working memory performance, high levels of D1 stimulation also produce cognitive deficits—the classic "inverted-U" relationship. During stress, HPA axis activation leads to stimulation of the VTA, causing excess DA release into the PFC (Murphy et al., 1996). When this DA binds to the D1 receptor, its downstream signaling cascades lead to working memory impairment (Taylor et al., 1999). Accordingly, these impairments can be reversed by intra-PFC infusions of a D1 antagonist (Zahrt et al., 1997), as well as by infusions of cAMP and PKA inhibitors (Taylor et al., 1999). Physiologically, elevated D1 signaling leads to a suppression of not only "noise"-related neurons, but of "signal" neurons as well (Vijayraghavan et al., 2007)—the information is lost, and the PFC is unable to accurately guide behavior. Moreover, this general silencing of neuronal activity loosens the PFC's regulatory influence over subcortical structures, allowing amplified and protracted emotional responses (Arnsten, 1998b).

How does this switch take place on a cellular level? Recent work has revealed a critical role for hyperpolarization-activated/cyclic nucleotide-gated (HCN) ion channels, which co-localize on dendritic spines with D1 receptors (Paspalas et al., 2012). Traditionally, HCN channels serve to normalize neuronal membrane potential, opening to allow positive ions into the cell to combat post-firing hyperpolarization (Wahl-Schott and Biel, 2009). But as their name implies, HCN channels are also sensitive to changes in cAMP levels, and when cAMP increases (as happens when D1 receptors are over-activated), HCN channels open, letting Na^+ and K^+ flow *out* of the cell (Chen et al., 2007). The net effect of this efflux is a lessening of the likelihood that an incoming stimulus will be sufficiently excitatory to propagate an action potential, thus forming the physiological basis of D1-driven information loss. Pharmacological blockade of HCN channels restores working memory performance and PFC network tuning during stress or after administration of a D1 agonist, demonstrating a functional link between these channels and upstream changes in DA signaling (Arnsten, 2011b).

HCN channel activity is also modulated by the noradrenergic alpha-2 receptor. This receptor is coupled to Gi, the activation of which results in a decrease in cAMP. This causes a slowing of HCN channel conductance, thus preserving incoming excitatory input. In this way, the alpha-2 receptor acts to strengthen PFC network activity, enhancing the "signal" for relevant information, while as noted above, the D1 receptor suppresses "noise" (Wang et al., 2007). Thus, under optimal conditions, the D1 and alpha-2 receptors work together to fine-tune PFC neuronal firing. Pharmacological stimulation of the alpha-2 receptor can increase firing in PFC neurons that code for relevant information, enhancing working memory in monkeys and rodents (Wang et al., 2007). Additionally, alpha-2 agonists reverse working memory impairments that occur during stress (Birnbaum et al., 2000).

Alpha-2 receptors have a high affinity for NE, and are primarily bound and active during non-stress conditions (O'Rourke et al., 1994). Under stress, however, the LC releases NE throughout the brain and excess NE in the PFC binds instead to the lower-affinity alpha-1 receptor (Mohell et al., 1983). Stimulation of this receptor—either pharmacologically or because of stress-induced NE release—leads to working memory impairment and a silencing of PFC network activity (Arnsten et al., 1999). Conversely, administration of an alpha-1 antagonist can restore PFC function and neuronal firing during stress (Birnbaum et al., 1999). The impairing effects of alpha-1 stimulation are due in part to downstream activation of protein kinase C (PKC), the inhibition of which also reverses stress-related impairments on working memory tasks in monkeys and rodents (Birnbaum et al., 2004). The PKC pathway inhibits neuronal firing through the cleavage of membrane phoshoplipase C (PLC), which initiates phosphatidylinositol signaling (Birnbaum et al., 2004). Downstream, intracellular stores of Ca^{2+} travel to the soma and inhibit neuronal firing through opening of local K^+ channels (Hagenston et al., 2008).

In summary, stress disrupts working memory by eliciting catecholamine release into the PFC, moving both DA and NE levels to the far end of their respective inverted U curves. Through DA D1 and NE alpha-1 receptor signaling, delay-related neuronal activity in the PFC is suppressed, and information critical to accurate task performance is lost (**Figure 1**). Because the PFC also helps to shut down the stress response, this loss of PFC function can lead to prolonged glucocorticoid release, which can exacerbate working memory impairments.

GLUCOCORTICOIDS

During emotional and stressful situations, activation of the HPA axis causes the adrenal cortex to release glucocorticoids, which travel through the bloodstream and cross the blood-brain barrier to activate glucocorticoid receptors (GRs) throughout the brain (De Kloet et al., 2005). While this release is critical to the enhancement of long term memories associated with the event

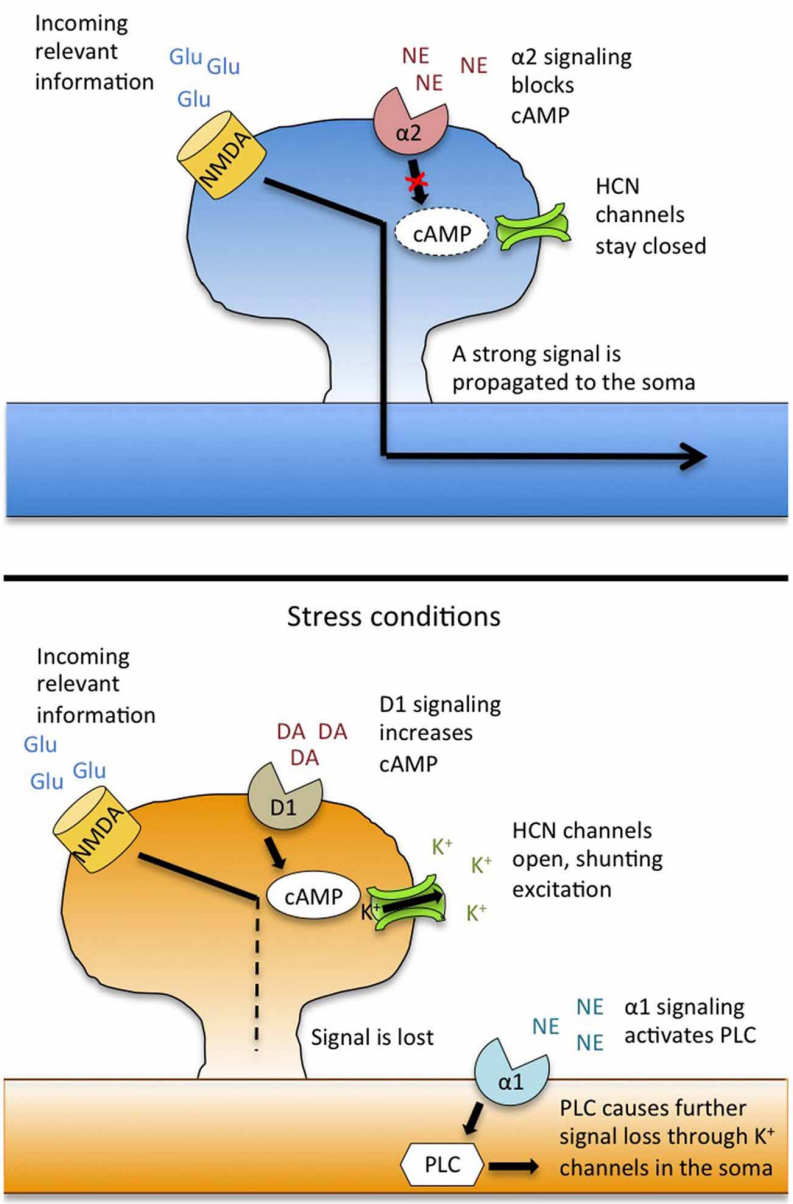

FIGURE 1 | Model for catecholamine modulation and stress-induced impairment of working memory. Under stress-free conditions (**top**), the noradrenergic alpha-2 receptor drives activity in the prefrontal cortex by suppressing cAMP levels and strengthening the signal from incoming information. Under stress (**bottom**), overstimulation of the dopamine D1 receptor activates cAMP, causing HCN channels to open, resulting in a shunting of incoming excitation. Additionally, stimulation of NE alpha-1 receptors activates a PLC signaling cascade that causes further loss of excitation through K^+ channels in the soma. This leads to a loss of information, and working memory failure. Adapted from Arnsten (2009) and Arnsten et al. (2012). Abbreviations: Glu, glutamate; NMDA, N-methyl D-aspartic acid receptors; NE, norepinephrine; DA, dopamine; HCN, hyperpolarization nucleotide-gated channels; PLC, phospholipase C.

(Rodrigues et al., 2009), glucocorticoid actions in the PFC impair working memory. Systemic injection of corticosterone in rats significantly reduces Delayed Alternation accuracy, and infusion of the GR agonist RU 28362 into the PFC similarly impairs working memory (Roozendaal et al., 2004). Finally, intra-PFC infusion of the GR antagonist RU 38486 reverses stress-induced impairments on the delayed spatial win-shift (DSWS) task, another test of prefrontal-dependent executive function (Butts et al., 2011). These findings suggest that glucocorticoids can impair PFC function through direct actions at GRs, but glucocorticoids may

also indirectly exacerbate working memory impairments through interactions with the catecholamine systems described above.

One mechanism of interaction between glucocorticoids and catecholamines is the extraneuronal catecholamine transport system. These transporters are located on glia, and remove excess DA and NE from the synapse, helping to keep balanced and optimal stimulation of dopaminergic and noradrenergic receptors. Corticosterone blocks catecholamine transporters in the PFC (Gründemann et al., 1998), resulting in increased extracellular catecholamine levels. In this way, stress-induced glucocorticoid release in the PFC could lead to overstimulation of the both dopamine D1 and α1 noradrenergic receptors, thus producing PFC dysfunction.

Glucocorticoids also modulate dopaminergic transmission in the PFC. Dopaminergic cells in the VTA and PFC express GRs that become saturated during stress (Ahima and Harlan, 1990), altering the firing of dopaminergic projections. Interestingly, glucocorticoid effects on DA release in the PFC appear to be locally driven, rather than a result of actions in the VTA itself. *In vivo* microdialysis experiments show that an infusion of GR antagonist RU-38486 into the PFC suppresses stress-induced DA release, but infusions into the VTA have no effect (Butts et al., 2011). Therefore, GRs play a role specific to the PFC in modulating the magnitude of stress-induced DA efflux.

Finally, glucocorticoids may further exacerbate catecholamine effects by activating some of the same intracellular signaling pathways. As described above, α_1 noradrenergic receptor stimulation during stress impairs PFC working memory through PKC intracellular signaling pathways (Birnbaum et al., 1999). Glucocorticoid release can also activate PKC signaling (ffrench-Mullen, 1995), thus potentially amplifying the effects of alpha-1 stimulation.

SEX DIFFERENCES AND ESTROGEN EFFECTS

The vast majority of behavioral neuroscience research is conducted in male animals, and thus our general understanding of stress effects in the PFC is within the context of the male brain. From a translational standpoint, this is problematic; stress-related mental illnesses like post-traumatic stress disorder (PTSD) and major depressive disorder are twice as prevalent in women (Becker et al., 2007), suggesting a distinct neurobiology may underlie the stress response in female brains. Though the exact mechanisms have not yet been fully identified, a growing body of literature points to an important role for estrogen in modulating the neurotransmitter and glucocorticoid effects described above.

One of the first studies to investigate sex differences in stress-induced working memory impairments used the anxiogenic drug FG7142 to generate dose-response curves in male and female rats (Shansky et al., 2004). While T-maze performance declined with increasing doses in both sexes, females became impaired after lower doses of FG7142 than those required to impair males. When the authors divided the females based on estrus cycle phase, they found that this stress sensitivity was driven by females in proestrus, when estrogen levels are highest. Similar results were found after using increasing durations of restraint stress instead of FG7142 (Shansky et al., 2006), demonstrating generalizability of the effect, and providing evidence against a simple hormone-drug interaction.

Further support for the idea that high estrogen levels confer sensitivity to stress comes from studies in ovariectomized (OVX) female rats. OVX surgery removes circulating estrogen and progesterone, hormones that can be re-introduced via a subcutaneous time-release silastic capsule. After administration of low doses of FG7142, OVX rats with long-term estrogen replacement (OVX + E) demonstrate working memory impairments that are similar to those of females in proestrus, while OVX females with a blank capsule perform more like males—impaired only at higher doses (Shansky et al., 2009). In all of the above studies, high- and low-estrogen groups did not differ in baseline working memory performance, suggesting that estrogen does not directly mediate PFC function, but instead modulates the factors that contribute to stress-induced impairments. The mechanisms by which estrogen does this are not known, but several intriguing possibilities exist.

First, estrogen may exacerbate the effects of stress-induced glucocorticoid release. Female rats in proestrus have higher baseline serum corticosterone levels than males or females in diestrus, and females have a more robust corticosterone response to acute stress than males do (Mitsushima et al., 2003). Thus, females with high estrogen levels may be primed for an amplified corticosterone surge after exposure to lower levels of stress, eliciting working memory impairments through the mechanisms described above—either through direct actions at GRs, or through blockade of extraneuronal catecholamine transporters. To date, however, estrogen-glucocorticoid interactions have not been investigated in the context of stress-induced working memory impairments.

Another means by which estrogen may sensitize the PFC to the detrimental effects of stress is through the dopaminergic system. Estrogen increases the physical number of dopaminergic projections from the VTA to the PFC (Kritzer and Creutz, 2008) and enhances extracellular DA concentrations (Xiao and Becker, 1994), putting it in a powerful position to modulate working memory. While these elevated DA levels may not have measurable behavioral outcomes on their own, they could indicate that high-estrogen females are "ahead of the curve" with respect to the D1-PFC function inverted U. In this scenario, mild stress merely pushes low-estrogen females just over the top of the U, while bumping high-estrogen females into impairment ranges. This hypothesis is illustrated in **Figure 2**.

The effects of elevated D1 signaling in high-estrogen females may be further exacerbated through estrogen's interactions with noradrenergic alpha-2a receptors. As described in the first section of this review, alpha-2a activity leads to decreased cAMP production and a closing of HCN channels, resulting in enhanced "signal" in PFC neurons coding for relevant information. This could serve to combat excess D1 activity, which leads to an opening of HCN channels, and a loss of information. Estrogen uncouples the alpha-2a receptor from its G-protein (Ansonoff and Etgen, 2001), thus potentially disrupting the delicate balance of D1 and alpha-2a activity that is required for optimal PFC function. In support of this idea, a dose of guanfacine (an alpha-2a agonist) that rescues stress-induced working memory

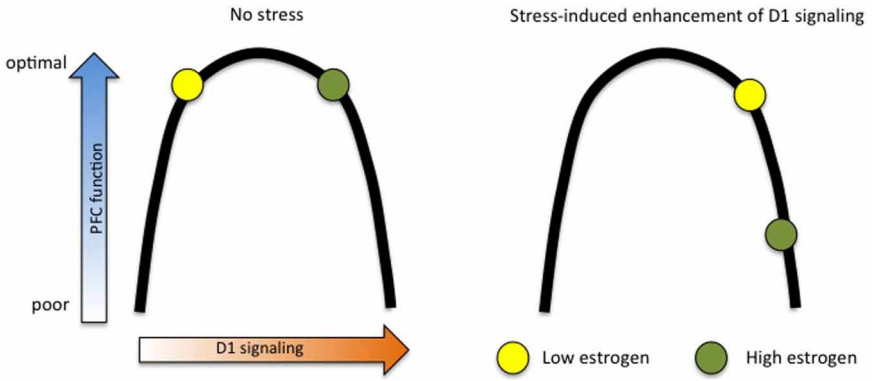

FIGURE 2 | Estrogen "ahead of the curve" hypothesis. Estrogen may amplify the stress response in females by raising baseline dopamine D1 signaling, thus making small shifts more apparent in behavioral measures. In this model, high- and low-estrogen females perform equally well at working memory tasks under no-stress conditions, but mild stress shifts high-estrogen animals down into the far end of the D1 inverted U, while only pushing low-estrogen animals slightly across the middle.

impairments in males and OVX female rats has no effect in OVX rats with estrogen replacement (Shansky et al., 2009).

CONCLUSIONS

Stressful events can lead to immediate and marked impairments in working memory, an executive function that depends on a balanced neurochemical state in the PFC. Research in non-human primates and rodents has shown that this impairment is driven by increased catecholamine signaling, which may be further modulated or exacerbated by changes in steroid hormone levels. Beyond stress, this work has provided critical insight into the mechanisms that underlie PFC function in general, and the potential for clinical application is substantial. Numerous mental illnesses—including Major Depressive Disorder, PTSD, Schizophrenia, and Attention Deficit/Hyperactivity Disorder [ADHD (Arnsten, 2007)]—are characterized by PFC dysfunction, and the pathways elucidated by the animal research described here are currently being targeted in pharmacological therapies. For example, the NE alpha-1 antagonist prazosin has been reported to be an effective treatment for PTSD (Berger et al., 2009), and the alpha-2 agonist guanfacine is used as an alternative to psychostimulant treatment for ADHD (Bidwell et al., 2011). Continued investigation into the neuromodulators that influence working memory—particularly in female populations—could lead to more nuanced and effective treatments for disorders that compromise prefrontal function.

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Anatomy and computational modeling of networks underlying cognitive-emotional interaction

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The classical dichotomy between cognition and emotion equated the first with rationality or logic and the second with irrational behaviors. The idea that cognition and emotion are separable, antagonistic forces competing for dominance of mind has been hard to displace despite abundant evidence to the contrary. For instance, it is now known that a pathological absence of emotion leads to profound impairment of decision making. Behavioral observations of this kind are corroborated at the mechanistic level: neuroanatomical studies reveal that brain areas typically described as underlying either cognitive or emotional processes are linked in ways that imply complex interactions that do not resemble a simple mutual antagonism. Instead, physiological studies and network simulations suggest that top–down signals from prefrontal cortex realize "cognitive control" in part by either suppressing or *promoting* emotional responses controlled by the amygdala, in a way that facilitates adaptation to changing task demands. Behavioral, anatomical, and physiological data suggest that emotion and cognition are equal partners in enabling a continuum or matrix of flexible behaviors that are subserved by multiple brain regions acting in concert. Here we focus on neuroanatomical data that highlight circuitry that structures cognitive-emotional interactions by directly or indirectly linking prefrontal areas with the amygdala. We also present an initial computational circuit model, based on anatomical, physiological, and behavioral data to explicitly frame the learning and performance mechanisms by which cognition and emotion interact to achieve flexible behavior.

Keywords: amygdala, orbitofrontal cortex (OFC), thalamic reticular nucleus, computational neuroscience, neural network, emotions, cognition, neuroanatomy

1. INTRODUCTION: INTEGRATING EMOTION AND COGNITION INTO ADAPTIVE PERCEPTION-ACTION LOOPS

The debate on the nature of cognition and emotion is a modern scientific manifestation of an age-old dichotomy. "Cognition" has come to refer to an assortment of useful behaviors—such as attention, memory, and symbolic reasoning, while "emotion" carries with it the connotation of behavior that is irrational, evolutionarily ancient, and antithetical to efficient rationality. In this paper we outline findings that demonstrate both functional and anatomical overlap between cognitive and emotional processes, and use computational modeling to illustrate how learning processes may make cognitive-emotional interactions adaptive. We focus on a computational neural network model of the amygdalar local circuit, a key hub embedded in a larger system that integrates cognitive and emotional processes.

We begin by describing a plausible functional perspective to frame cognition and emotion as subcomponents of a unified system devoted to categorize bodily and environmental "inputs," and link the categorized inputs with appropriate behavioral "outputs." A typical episode of mental life involves three distinctive, but interacting cognitive steps, and each one can vary in complexity: "identifying X, evaluating it as Y, and preparing for behavior that is suitable for X as Y" (cf. Pessoa, 2010). Although the third step, preparation for behavior, is quite diverse, it usually involves at least heightened attention, intentional indifference, or active ignoring. The first and third steps are often labeled with a cognitively-loaded term, e.g., "object categorization" or "stimulus recognition" for step one, and "strategy" or "plan" for step three. The second step, which involves evaluating the present-time significance of X for the agent, is more often labeled with a less cognitively-loaded term such as "affective evaluation," "emotion,"

Abbreviations: AA, anterior amygdaloid area; ACC, anterior cingulate cortex; Amy, amygdala; aOFC, anterior orbitofrontal cortex (primates); BA, basal nucleus of amygdala; BLA, basolateral amygdala; BMA, basomedial amygdala; Ce, central nucleus of amygdala; CeL, lateral subdivision of Ce; CeM, medial subdivision of Ce; CS, conditioned stimulus; CTX, cortex (model); IL, infralimbic cortex (rodents); ILd, projection from IL to ITCd (rodents); ILv, projection from IL to ITCv (rodents); IM, intercalated masses (primates); ITC, intercalated cells (rodents); ITCd, dorsal intercalated cell group (rodents); ITCv, ventral intercalated cell group (rodents); LA, lateral nucleus of amygdala; MD, mediodorsal nucleus of thalamus; Me, medial nucleus of amygdala; NBM, nucleus basalis of Meynert; PL, prelimbic cortex (rodents); pOFC, posterior orbitofrontal cortex (primates); SI, substantia innominata; SNc, substantia nigra pars compacta; Thal, thalamus; TRN, thalamic reticular nucleus; US, unconditioned stimulus; VCo, ventral cortical nucleus of amygdala; VTA, ventral tegmental area.

or "visceral reaction," depending on the intensity of the positive or negative evaluation. Nevertheless, all three steps can be regarded as cognitive, because all are facets of the agent's "coming to know" (the meaning of the root of "cognition") and all steps are capable of being corrected, if in error, by further experience. Thus, an object may be briefly misidentified as X until further experience leads to a re-categorization; a stimulus X may be initially construed as an omen of future outcome Y, but re-construed as irrelevant when Y repeatedly fails to follow X; and a plan of action suitable for responding to X as Y in one setting may need to be revised to become effective in another setting.

Though reason and emotion have been viewed as opposed processes in popular culture since ancient times, emotions have been treated as adaptive behavioral phenotypes by scientists since the time of Darwin (1872). Treating emotion as an adaptive phenotype fundamentally subverts any reason-emotion antithesis, because it places emotion as another, if distinctive, enabler of "biological rationality" (Damasio, 1994). Animals have a complex array of cognitive operations to draw upon, and an animal is rational if it knows or can learn how to draw upon those operations to maximize its well-being and minimize threats. In recent years, neuroscientists have shown that the parts of the brain that are recruited during episodes with emotion-arousing stimuli are also de-recruited when no emotion arousing stimuli are present, or when an animal learns that formerly emotion-arousing cues can be safely ignored (e.g., LaBar et al., 1998; Sehlmeyer et al., 2009; Bach et al., 2011; Hartley et al., 2011; van Well et al., 2012). Emotion is indeed a highly adaptive behavioral phenotype.

To better understand cognitive-emotional interactions, we have begun to develop "full-cycle" learning models that explicate how an animal uses its experiences to "come to know" when to engage, disengage, and re-engage its emotional evaluations, to maximize its well-being, and minimize threats, in a highly context-dependent way. Studies of repeated full cycles of acquisition and extinction of Pavlovian associations, as well as studies of repeated learning of experimenter-reversed instrumental (act-outcome) associations, generally show that very little of the associative memory formed during initial acquisition is lost during extinction or reversal phases (e.g., Schoenbaum et al., 2007; Stalnaker et al., 2007). Instead, the neural control system is thought to recruit further pathways that are capable of selectively preventing the expression of prior learning, thus leaving the underlying memory intact.

Otherwise well-regarded formal learning models (e.g., Rescorla and Wagner, 1972) have been incapable of explaining full-cycle learning, because they incorrectly treat extinction as a process that erases most or all of the specific associative memories formed during acquisition (Pearce and Bouton, 2001). For example, neural variants of such models have usually assumed that memories are coded in experience-sensitive synaptic weight values, and that these values greatly increment during acquisition, but severely decrement during extinction training. Although bi-directional synaptic adjustments have been observed during learning protocols at many central synapses (e.g., Diamond et al., 2005; López de Armentia and Sah, 2007; Müller et al., 2009; Dalton et al., 2012), a model using only the decrementing of learned weights for extinction cannot readily explain data on memory preservation. Notably, reacquisition following even very protracted extinction is much faster than initial acquisition (Napier et al., 1992; Ricker and Bouton, 1996), a phenomenon referred to as "savings" because much of the prior learning is saved from erasure by the extinction process. However, there may be exceptions to this avoidance of erasure. For example, studies in humans suggest that there may be a window of opportunity during which the efficiency of extinction can be enhanced, reducing or preventing such savings (Schiller et al., 2008, 2009).

Our treatment of emotions as part of the rational apparatus of the brain does not preclude also treating emotions as potential sources of irrationality. Emotions as such can lead to maladaptive decisions and behavior if either the learning processes for engaging and disengaging emotions, or the auto-regulatory circuits for controlling the intensity and duration of emotions, are or become dysfunctional. Here the study of full-cycle learning models, suitably rooted in the real circuitry of the brain, should be able to make pivotal contributions. For example, certain learned attractions and fears become obsessive, and extremely resistant to spontaneous reduction. If we understand the full set of processes that enable the normative (i.e., highly flexible and experience-responsive) use of emotional evaluations, then we will also understand which parametric variations of such processes lead to dysfunctions; and we will be able to classify the distinct types of dysfunction. The latter is key for designing minimal-side-effect interventions (whether behavioral, pharmacological, or a mix) that are tailored to the problem. The model introduced here is already illuminating in this regard. Below we present the computational learning model after an overview of forebrain circuits implicated in flexible emotional evaluations, including key structures used in the model. Thus, we constrain and complement the high-level functional approach with an examination of the underlying neuronal circuitry. Using the structural model for connections (Barbas and Rempel-Clower, 1997), we can infer the flow of information relating to sensation, cognition, and emotion along neural pathways. We also describe how frontal cortical regions interact directly and indirectly with the amygdala, the largely subcortical structure most often implicated in emotional processes. Thus, we connect cognition and emotion in two ways—(1) functionally, as equal partners in enabling a continuum or matrix of processes required for adaptive, flexible behavior, and (2) neurally, via diverse cortical and subcortical pathways.

These functional and anatomical perspectives are then integrated via computational modeling. We demonstrate how a neural network model sheds light on the possible mechanisms by which frontal cortical areas influence emotional processing in the amygdala, using classical fear conditioning in the amygdala as an example. Physiological studies from humans and primates are incomplete for the amygdalar circuit, so we also refer to the rodent literature to guide our specification of the model. The amygdalar circuit has rarely been modeled computationally, and therefore we began the computational component of our study here. In recent years this circuit has been delineated in increasing detail, and its complex dynamics are beginning to be understood. Our modeling approach

is designed to address some basic questions about emotional learning and behavior. What are some of the implications of the connectivity of the amygdalar local circuit? How does the connectivity allow the system to learn fear associations, and also learn to suppress them when appropriate? Is the amygdalar circuit simply a generator of responses and a repository of emotional memories, or can it participate in information-processing? How might top–down modulatory signals from prefrontal cortex affect the system? In addition to shedding light on these questions, model simulations capture past experimental findings, despite being a schematized approximation of the real amygdalar circuit.

2. ROLES OF THE AMYGDALA IN EMOTIONAL PROCESSING AND LEARNING

Pioneering work on the effects of lesions on the behavior of animals led to the gradual uncovering of emotion-related brain regions (reviewed in Maren, 2001). This work was stimulated in part by Darwin (1872), who was among the first to place emotion in a biological setting, arguing that emotional states in both humans and animals correspond with neurological phenomena related to movement. The Greek word for emotion (συγκίνηση) also refers to movement. The temporal lobe was the first brain region to be associated with emotional processing (Brown and Schäfer, 1888; Klüver and Bucy, 1937). Removal of the temporal lobe produced marked changes in behavior. Papez (1937) integrated earlier work to propose that an ensemble of linked structures including the hypothalamus, the cingulate gyrus, the hippocampus, and the anterior thalamus form the anatomical basis of emotions (Cannon and Britton, 1925; Cannon, 1927; Bard, 1928). Subsequent work established that the amygdala is also a key element in what came to be known as the Papez–MacLean limbic model (Papez, 1937; Spiegel et al., 1940; Bard and Mountcastle, 1948; MacLean, 1949; Weiskrantz, 1956).

Studies in humans and other animals employing a variety of experimental methods, have provided further evidence on the role of the amygdala in emotion (LeDoux, 1992; Kalin et al., 2004; McGaugh, 2004; Vuilleumier, 2005). The amygdala appears to be necessary for Pavlovian fear conditioning, playing a role in acquisition and expression of fear responses (Maren, 2001), and in the maintenance and retrieval of fear-related memories (e.g., Erlich et al., 2012). But the amygdala is no longer seen as dedicated solely to negative emotions—it also appears to play a role in appetitive conditioning tasks (Everitt et al., 2003), consistent with findings from functional imaging suggesting a role in positive emotions (reviewed in Fossati, 2012).

The amygdala serves as an important recipient of converging projections from much of the cortical mantle, the hypothalamus, the hippocampus, the brain stem, and the neuromodulatory systems (reviewed in Sah et al., 2003; Pessoa, 2008). Thus, the connectivity suggests that the amygdala is in a position to contribute to the categorization of the overall state of the organism by integrating information from the body and the external environment. Such categorical representations can then affect sensory, motor, executive, and memory-related processes via the amygdala's diverging outputs (McGaugh, 2002; Sah et al., 2003; Vuilleumier et al., 2004; Hadj-Bouziane et al., 2008). The amygdala can mediate widespread effects via projections to cortical areas (especially prefrontal cortex and the medial temporal lobe), as well as the striatum, nucleus accumbens, thalamus, hypothalamus, and the neurotransmitter systems (Cardinal et al., 2002; Whalen and Phelps, 2009), i.e., the cholinergic, dopaminergic, noradrenergic, and serotonergic structures. Within the forebrain, these projections are strongly implicated in attention, learning, and memory (e.g., Kilgard and Merzenich, 1998; Bao et al., 2001; McGaugh, 2004; Hasselmo, 2006; Parikh and Sarter, 2008; Miasnikov et al., 2009; Ramanathan et al., 2009; Froemke and Martins, 2011; Chau and Galvez, 2012; Medalla and Barbas, 2012).

In summary, a coarse-grained survey of amygdala connectivity suggests that it is in a position to influence, and be influenced by, a variety of neural processes necessary for flexible behavior (see Barbas et al., 2011). The amygdala has a "panoramic view" of internal and external context, and appears to be instrumental in the adaptive control of behavioral states, some of which correspond with emotions (**Figure 1**). The posterior orbitofrontal cortex (pOFC) has a similarly wide-angled view of body and environment (Barbas, 1995). Perhaps unsurprisingly given this connectional similarity, the pOFC is also implicated in emotional processing, and was incorporated into the Papez–Maclean circuit by Yakovlev (1948) and Nauta (1979). Imaging studies in human patients suffering from post-traumatic stress disorder (PTSD), phobias and social anxiety disorder suggest amygdalar involvement in emotion, particularly negative emotions (e.g., Etkin and Wager, 2007; Nitschke et al., 2009). To demonstrate how the amygdalar circuit is situated within a larger cognition-emotion continuum or matrix, below we review the interactions among prefrontal cortical regions, particularly the pOFC, and the amygdala.

3. NEURAL SUBSTRATES FOR COGNITIVE-EMOTIONAL INTERACTIONS: PATHWAYS THROUGH ORBITOFRONTAL CORTEX AND THE AMYGDALA

The following overview of pathways linking structures associated with cognitive and emotional processes in the mammalian brain has two objectives. First, to outline the essential neural structures used for the model that follows. Second, to demonstrate the need for a model in view of the complexity of the connections. This overview focuses on the intricate connections between the orbitofrontal cortex and the amygdala, regions classically associated with emotion, and lateral prefrontal cortices, which are thought to be key mediators of cognition. The cingulate gyrus and the pOFC were the first prefrontal cortical regions to be associated with emotions (Papez, 1937; Yakovlev, 1948; Nauta, 1979). Both orbitofrontal and anterior cingulate cortices (ACC) are connected with lateral prefrontal cortices. The circuits suggest that these neural structures have a profound influence on each other, inextricably linking emotion and cognition (Barbas, 1995, 2000b; Rolls and Grabenhorst, 2008; Fox et al., 2010; Shackman et al., 2011). This linkage is necessary for normal function and its disruption is at the root of a wide variety of psychiatric disorders.

The circuitry that links pOFC with the amygdala suggests a role in forming emotional associations needed to navigate in a

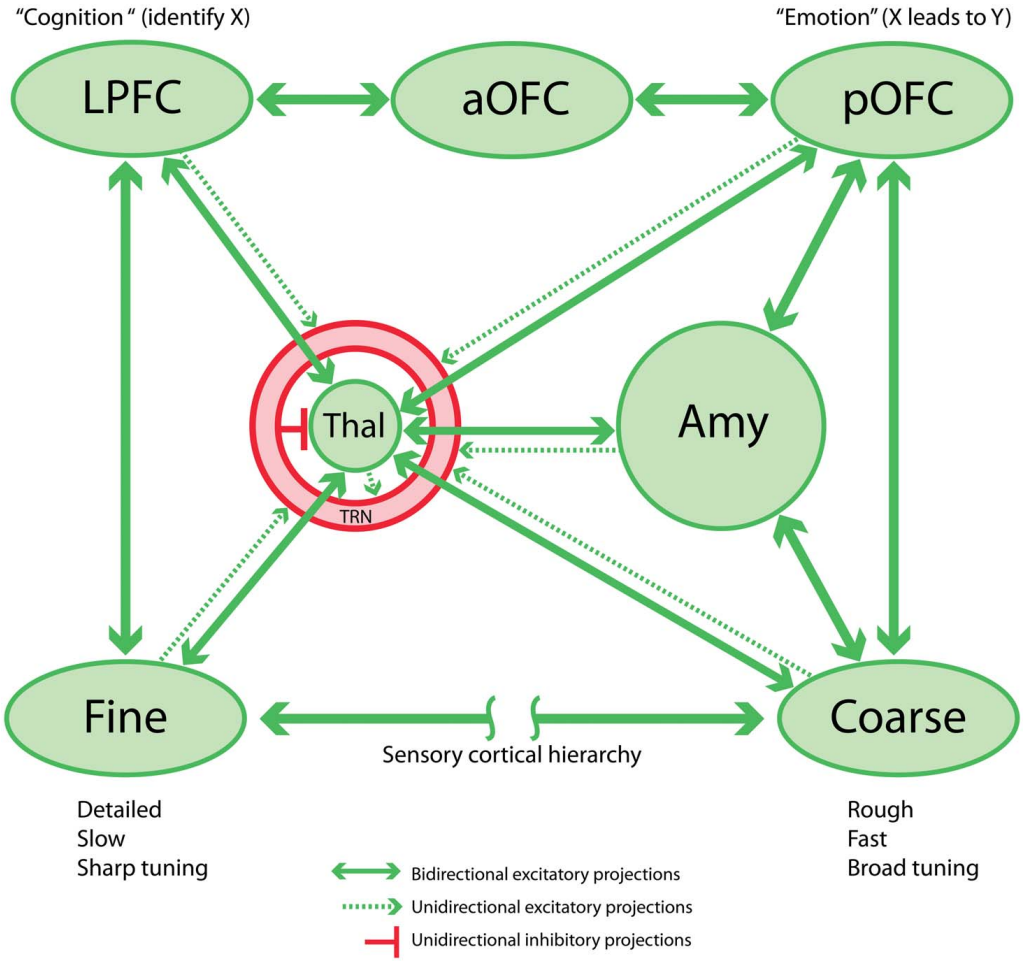

FIGURE 1 | Schematic circuit linking sensory cortex, prefrontal cortex, thalamus, and amygdala. This network is the proposed basis for the sensory aspect of the cognition-emotion continuum or matrix that facilitates flexible, adaptive behaviors. Note that the TRN is shown as a shell around the thalamus.

complex and potentially dangerous environment, and in overriding these associations when they are no longer relevant in behavior. Which specific pathways support the flexible formation of emotional associations and their disengagement, as needed? The connectivity alone points to the potential of these circuits to set the system on alert or return it to a quiescent state (Barbas et al., 2003). But the intricacies of these pathways suggest that connectivity alone is not sufficient to infer all their dynamic properties. Computational modeling may assist us in this goal, and also serves as a natural conceptual bridge to link anatomy with physiology. Here we describe the key experimentally determined pathways, providing the framework of a model to address the issue of forming flexible associations.

The posterior strip of the orbitofrontal cortex (pOFC) in macaque monkeys is of special interest for several reasons. The pOFC is by far the most multimodal among prefrontal cortices, and likely the entire cortex (Barbas and Zikopoulos, 2006), and may therefore be the chief sensor of the environment, a cortical counterpart of the older and mostly subcortical amygdala. The pOFC receives information from every sensory system through monosynaptic projections from high-order sensory association cortices including visual, auditory, somatosensory and gustatory cortices, and uniquely from primary olfactory cortices. Further, the pOFC receives robust projections from limbic cortices: the cingulate cortex, the temporal pole, medial (rhinal) temporal cortices and the anterior insula (Barbas, 1993; Carmichael and Price, 1995). We can view the limbic cortices as sensors of the internal, or emotional environment. Based on these connections, the pOFC may be the main cortical sensor of the external and internal environment (**Figure 1**).

The same sensory association and limbic cortices that project to pOFC also project to the amygdala (**Figure 1**), which in turn has robust bidirectional connections with the pOFC. This circuitry suggests that pathways from cortices that process environmental signals reach pOFC through a direct route as well as via an indirect route through the amygdala (Porrino et al., 1981; Barbas and De Olmos, 1990; reviewed in, Barbas, 1995, 2000b).

The primate orbitofrontal cortex is connected mainly with the basal amygdalar complex (BLA), composed of the basolateral (BL), basomedial (BM; also known as accessory basal), and the

lateral (LA) nuclei (Ghashghaei and Barbas, 2002). Sparser connections are also found with the cortical nuclei of the amygdala. Projection neurons from the basal amygdala innervate most robustly the pOFC as well as the ACC, which forms a crescent at the anterior tip of the corpus callosum. The term ACC here refers to the anterior part of areas 24, 32, and 25 in macaque monkeys. The connections of the pOFC and ACC with the amygdala are bidirectional but not equivalent in each direction (Ghashghaei et al., 2007). The projections from the amygdala to pOFC are stronger than the reciprocal projections, while the opposite is true for the ACC. The ACC sends the most robust return projections to the amygdala.

3.1. FLOW OF INFORMATION FOR EMOTIONS THROUGH SENSORY CORTICES, PREFRONTAL CORTICES, AND AMYGDALA

How is information about the external environment evaluated for salience to guide behavior? Information about the entire external environment reaches both the amygdala and pOFC. Sequential pathways from sensory cortices to the amygdala and then to pOFC may supply additional information required to assess the affective meaning of environmental signals. The anatomical reasoning that leads to this proposal begins with the study of the laminar origin of projections from sensory association cortices to the amygdala (Barbas, 2007; Hoistad and Barbas, 2008).

These findings show that sensory association cortices can engage in feedforward signaling to the amygdala, which may in turn categorize the arriving signals based on their affective salience (e.g., Lim et al., 2009; Pourtois et al., 2010a) and convey the results of this categorization to pOFC, where further integration can occur. From the panoramic vantage point of the pOFC, this integrated information is transmitted to the rest of the prefrontal cortex along pathways we examine below. Interestingly, the connections of pOFC and sensory cortices greatly overlap within the basal nuclei in the posterior half of the amygdala, suggesting an efficient passage of salient sensory stimuli from the amygdala to pOFC (Ghashghaei and Barbas, 2002).

Information from the amygdala can thus be followed to pOFC, which is associated with processing the value of stimuli, and from there to lateral prefrontal cortices associated with cognitive processes. This sequence of information processing follows laminar patterns of connections predicted by the structural model for cortico-cortical connections (Barbas and Rempel-Clower, 1997), and tested empirically. In this scheme "feedforward" projections originate from a cortical area that has more layers (or higher neuronal density) than the site of termination. Projection neurons in such a pathway originate in the upper layers and their axons terminate in the middle layers of the receiving cortex. The term "feedback" was originally applied to projections from a later to an earlier processing sensory area (reviewed in Felleman and Van Essen, 1991). In "feedback" pathways projection neurons are found in the deep layers (5 and 6) and their axons terminate mostly in layer 1. According to the structural model, feedback pathways always originate from areas with fewer layers (or lower neuronal density) and terminate in areas with more layers (or higher neuronal density) than the origin. The terms "feedforward" and "feedback" can be imported to describe connections between non-sensory cortices, via analogy with sensory systems such as the visual system (Barbas, 1986; Barbas and Rempel-Clower, 1997).

The relational rules of the structural model allow prediction of the possible flow of information from pOFC, which receives information about the affective status of the environment, to lateral prefrontal cortices, which are associated with cognitive processes. To begin with, the amygdala innervates all layers of pOFC, including the middle layers (Ghashghaei et al., 2007), which receive feedforward signals. The pOFC projects to lateral prefrontal cortices through sequential steps involving areas with increasingly better defined laminar structure, through anterior orbitofrontal areas and then lateral prefrontal areas, culminating in posterior lateral prefrontal areas 46 and 8, in that order (Barbas and Pandya, 1989). Posterior lateral areas have the best laminar definition within the prefrontal cortex. Functionally they are associated with cognitive processes. The sequential connections follow the rules of the structural model, each stage from pOFC onwards providing sequentially feedback projections to more differentiated (eulaminate) cortices. These pathways suggest that information from the pOFC reaches areas associated with cognitive processes, via successive feedback projections. Physiological data also support this pattern of information flow (e.g., Wallis and Miller, 2003; Bar et al., 2006). Interestingly, feedback projections, which reach layer 1 in all areas, also reach layer 2 and the upper part of layer 3 in most cortices, which collectively make up the upper layers. Layer 2 in several prefrontal cortices is a major target of projections from the amygdala as well (Ghashghaei et al., 2007).

The above linkages suggest an efficient flow of information along sequential feedback pathways from areas with a key role in emotions to areas associated with cognition, decision, and action. The sensory information to the pOFC originates from high-order sensory association areas. The projections from visual and auditory cortices, for example, originate mostly in anterior temporal cortices, which have large receptive fields and likely provide an overview—but not high-accuracy categorizations (Freedman et al., 2003; Freedman and Miller, 2008)—and only modest detail of the external sensory environment (**Figure 1**, **"Coarse"**). Such a system is suited to quick detection and transmission of coarse-grained or "low-resolution" information, just detailed enough to trigger actions that are imperative to the animal's survival. But what about situations where fine detail about the sensory environment is necessary? Lateral prefrontal cortices are implicated in detail-dependent categorizations (Freedman and Miller, 2008), and these cortices receive "high-resolution" projections, originating from areas representing the external environment, especially visual and auditory association cortices (reviewed in Barbas, 2000a; Barbas et al., 2002). In contrast to pOFC, lateral prefrontal areas 8 and 46 receive projections from a wide variety of visual cortices, including robust projections from early processing sensory areas adjacent to the primary areas (Barbas and Mesulam, 1981; Barbas, 1988; Schall et al., 1995; **Figure 1**, "**Fine**"). Early processing visual areas may provide detailed information about the sensory environment. Lateral prefrontal areas also project via two or three steps to orbitofrontal cortices, innervating mostly the middle layers in a feedforward manner. The middle layers in most cortices include the lower part of layer 3, layer 4, and

the upper part of layer 5. Projections from pOFC to the amygdala originate overwhelmingly from the upper part of layer 5, which receives feedforward projections from lateral prefrontal cortices.

The laminar pattern of connections thus suggests an efficient way to provide not only a quick overview of the environment to pOFC, but potentially also detailed information through projections from lateral prefrontal cortices. The communication between pOFC and lateral prefrontal cortices is important. The posterior lateral prefrontal cortices are strategically situated in front of the cortical premotor/motor system, poised to guide action using information gathered about the state of the external environment and internal environment through connections with the orbitofrontal cortex and the amygdala (reviewed in Barbas and Zikopoulos, 2007; Barbas et al., 2011). The pOFC has no direct access to cortical motor control systems.

3.2. THE pOFC INNERVATES ROBUSTLY THE INHIBITORY AMYGDALAR INTERCALATED NUCLEI IN MACAQUE MONKEYS

The discussion above shows how information from the sensory areas is distilled for valence in the amygdala and passes on to the prefrontal cortex (Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007; Hoistad and Barbas, 2008). We now turn to the reciprocal pathways through which prefrontal cortices may influence the amygdala. In this regard, it is the phylogenetically old (limbic) prefrontal cortices that reciprocate with the most robust return projections to the amygdala (Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007). The pOFC, in particular, has a unique relationship with the amygdala, not shared with any other cortical area: it innervates heavily the intercalated masses (IM) of the amygdala (Ghashghaei and Barbas, 2002), which are composed entirely of inhibitory neurons (Paré and Smith, 1993). In rhesus monkeys the IM nuclei are interposed between the various basal and central nuclei of the amygdala (**Figure 2**). The significance of the special pOFC pathway is based on the key role of IM within the amygdala, through its projections to the central nucleus (Ce), which is the chief output of the amygdala to autonomic centers (reviewed in Barbas and Zikopoulos, 2006). The medial part of the central nucleus (CeM), in particular, projects to hypothalamic autonomic structures, as well as to brainstem and spinal autonomic centers and the cholinergic and monoaminergic systems (reviewed in Sah et al., 2003). The output of the amygdala is in a position to either increase autonomic drive, as seen in emotional arousal, or facilitate return to autonomic homeostasis. The IM nuclei, therefore, appear to be a focal point for the formation of flexible associations in a behavioral setting. Activation of IM may heighten autonomic drive in emotional arousal (Barbas et al., 2003; Pape and Paré, 2010). Alternatively, IM activation may facilitate return to autonomic homeostasis by a mechanism that is not yet clear. In rodents it is the infralimbic (IL) cortex that innervates the inhibitory intercalated nuclei (ITCs). In rats the orbitofrontal cortex does not show the extent of specialization seen in primates. The equivalent region in rats to the primate pOFC is the IL cortex (reviewed in Vertes, 2006), especially for its projection to the inhibitory intercalated neurons. In rodents, the ITC clusters (ITCs) are thought to have a role in forming emotional associations based on behavioral fear conditioning experiments and physiological studies (Ehrlich et al., 2009; Busti et al., 2011). In macaque monkeys there have been fewer physiological studies on the relevant strip of pOFC and its relationship with the amygdala, but lesion studies suggest that their interactions are similarly important for emotional behavior (e.g., Kalin et al., 2007; Fox et al., 2010). The parallels between the rat and primate circuitry provide the basis for further comparison (**Figure 2**). The behavioral and physiological findings from rodents and wealth of anatomical data in primates can be linked via a computational model based on their circuit commonalities. Ongoing research may also point out differences between the circuits, and what these differences imply about generalizing the conclusions of emotional learning studies in rodents to primates and humans.

3.3. THE ROLE OF THE ANTERIOR CINGULATE

In the above discussion of cortico-cortical connections we have not considered in any detail the role of the ACC in the process of linking areas associated with emotional and cognitive processes. Like the pOFC, the ACC is part of the prefrontal limbic system (Vogt et al., 2005), and has strong connections with the amygdala as well (Ghashghaei et al., 2007). However, it differs from the pOFC in several ways. The ACC does not have the exquisite focal projection to the inhibitory IM nuclei in primates, and it lacks multimodal connections (Barbas et al., 1999) that are characteristic of the pOFC. In fact, with the exception of connections with auditory association cortices, the rest of the unimodal sensory association cortices do not have significant projections to the ACC. But the ACC has its own specializations (e.g., Buckley et al., 2009; Pourtois et al., 2010b). Among prefrontal cortices it has the strongest connections with the rest of the prefrontal cortex, and is well suited to allocate attentional resources, as is widely reported (see Medalla and Barbas, 2009, 2010; reviewed in, Burgess et al., 2000; Paus, 2001; Rushworth et al., 2007). In addition, the ACC receives strong monosynaptic projections from the hippocampus, and has bidirectional connections with medial temporal cortices (Bunce and Barbas, 2011), in pathways that are thought to convey contextual information (reviewed in Barbas et al., 2013). The ACC has robust connections with the pOFC, perhaps providing the contextual information necessary to interpret signals in the environment and contribute to emotional arousal. Interestingly, the ACC is the primary effector to brainstem autonomic structures through projections to hypothalamic and spinal autonomic centers (Ongur et al., 1998; Rempel-Clower and Barbas, 1998; Barbas et al., 2003). These features suggest that pOFC is the primary cortical sensor of emotional information, whereas the ACC is the primary effector of emotional expression, linking motor control, cognition and drive (Barbas, 2000a,b; Paus, 2001; Shackman et al., 2011).

4. EMOTIONAL LEARNING AND EXPRESSION VIA THE AMYGDALA

Below we examine a local circuit in the amygdala implicated in the learning and execution of a widely studied emotional behavior: acquisition and extinction of the fear-potentiated freezing response via Pavlovian conditioning (Pavlov, 1927; Maren, 2001), in which an initially neutral sensory cue (the conditioned

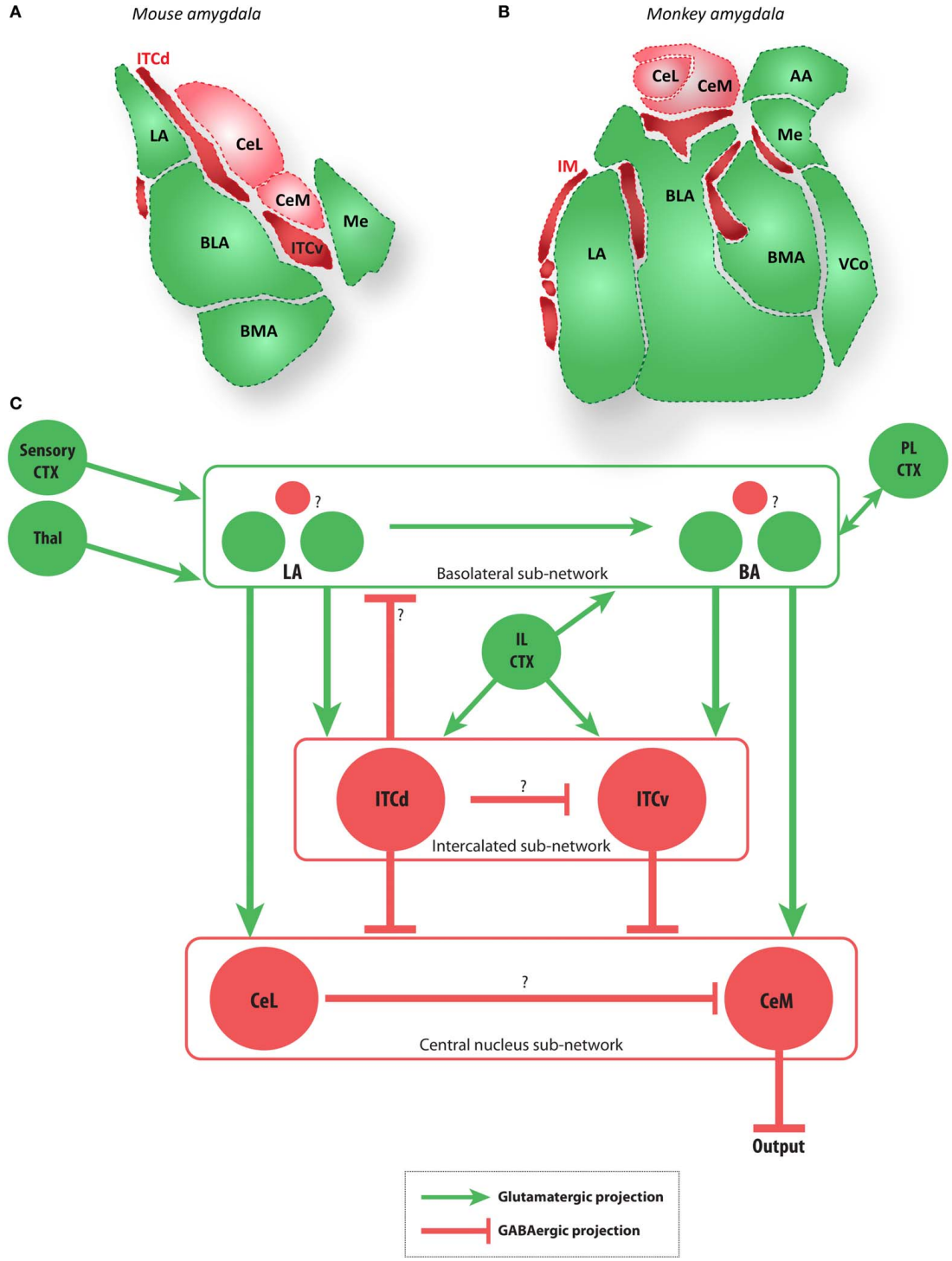

FIGURE 2 | The amygdala and main extrinsic and intrinsic circuits (A,B). Diagrams of coronal sections show key amygdalar nuclei in the mouse **(A)** and macaque monkey **(B)**. Dark red regions are the GABAergic intercalated cells modeled here (ITCd and ITCv in mouse, and IM in macaque), light red regions are the GABAergic CeL and CeM, and green regions are glutamatergic nuclei. **(C)** Schematic depiction of the amygdalar local circuit. The system consists of three components: (1) the cortex-like glutamatergic basolateral sub-network (LA and BA), (2) the striatum-like GABAergic central nucleus sub-network (CeL and CeM), and (3) the GABAergic intercalated sub-network (ITCd and ITCv). The basolateral sub-network receives information about CS and US via projections from sensory cortices (CTX) and thalamus (Thal). In rodents, cortical regions IL and PL project to the intercalated and basolateral sub-networks, respectively. The CeM is a key output node of the network. Question marks indicate local microcircuit details that remain to be fully characterized experimentally. Red circles and lines represent inhibitory cell groups and connections, and green circles and lines represent excitatory cell groups and connections.

stimulus, CS) such as an auditory stimulus is regularly followed by an emotion-evoking stimulus (the unconditioned stimulus, US). These pairings are separated by a much larger inter-trial interval. The functioning of this circuit can be viewed as a form of emotional categorization or salience-assignment. In rats this circuit receives top–down projections from medial prefrontal cortex (IL), which modulate the behavior of the inhibitory ITCs. It is important to note that much of the behavioral and physiological data on fear conditioning come from rodent studies. The degree to which the rodent circuit resembles the primate circuit is presently unclear, but many major connections appear to be similar across species. Diagrams of coronal brain sections in **Figure 2** show the amygdala local circuit in the mouse (**Figure 2A**) and the rhesus macaque (**Figure 2B**), depicted in schematized form in **Figure 2C**. After reviewing the transmission of signals through the amygdalar circuit, we demonstrate how computational modeling of this circuit can illuminate the possible mechanisms for top–down control of emotion. This modeling effort suggests possible functional roles for the ITCs that have not yet been explored experimentally.

The following general principles of amygdalar organization have been widely observed in rodents (e.g., Sah et al., 2003; Ehrlich et al., 2009; Pape and Paré, 2010): (1) The BLA nuclei consist of a majority of glutamatergic projection neurons and a minority of local GABAergic interneurons, as in the cortex; (2) the medial structures (Ce) are striatum-like, with the vast majority of neurons being GABAergic, with spiny-type morphology; (3) the internuclear projections generally follow a dorso–ventral and latero–medial direction; (4) the ITCs add an additional layer of complexity as recipients of projections from medial prefrontal areas, and specifically the IL cortex in rats. In rhesus monkeys IM neurons (the primate equivalent of ITCs; see **Figure 2**) receive projections from pOFC (Ghashghaei and Barbas, 2002). While the layout of the amygdalar circuit elements in primates is broadly similar to that of rodents (**Figure 2**), the relationship among IM neurons is not yet clear in primates.

Several recent studies of fear conditioning in rats have suggested a flow of information within the amygdala as shown in **Figure 2C** (reviewed in Debiac and LeDoux, 2009). Thus, LA is seen as the input station, receiving sensory signals from thalamus and cortex, and the central nucleus (primarily CeM) is seen as the output station, with BA and the ITC clusters serving as intermediate processing stages. Below we examine in more detail the ITCs, which may serve as important loci for cognitive control of emotions.

4.1. THE ROLE OF INTERCALATED NEURONS AND THEIR CORTICAL INPUTS

The rodent ITCs have emerged as key elements in emotional learning and expression (Ehrlich et al., 2009; Pape and Paré, 2010; Li et al., 2011; Manko et al., 2011; Palomares-Castillo et al., 2012). At least three anatomically distinct groups of ITCs have been identified in rodents. Two of these groups (**Figure 2**) appear particularly important for fear conditioning and extinction: (1) the dorsal group (ITCd), also called the medial paracapsular group; and (2) the ventral group (ITCv), also called the main intercalated nucleus. For example, Busti et al. (2011) showed that during fear conditioning in mice, the selective activation of ITCd by LA following repeated CS-US pairings triggers feedforward inhibition in ITCv, which disinhibits CeM output neurons and releases a fear response (freezing). Conversely, extinction training, in which the CS is repeatedly presented without a following US, leads to CS activation of ITCv, and suppression of fear responses.

The firing properties of ITCs also suggest possible functional roles exemplified by groups of neurons that fire at much higher rates than commonly observed in neighboring amygdalar sites in unanesthetized cats (Collins and Paré, 1999). Their high spontaneous firing rates suggest that the ITC clusters provide tonic inhibition to their targets. The firing probabilities of ITC neurons are modulated by ecologically salient stimuli, such as cat growling, dog barking, and birdsong. These findings suggest that emotionally or environmentally salient stimuli can alter the firing rates of some ITCs.

Anatomical and physiological studies implicate prefrontal projections in modulation of the inhibitory effects of ITCs. The pOFC in primates (Ghashghaei and Barbas, 2002), and IL in rodents (Berretta et al., 2005; Pinto and Sesack, 2008; Sierra-Mercado et al., 2010; Sotres-Bayon and Quirk, 2010; Pinard et al., 2012) send robust excitatory projections to the inhibitory ITCs. Some evidence suggests that prelimbic cortex (PL) in rats and cats may also project to ITCs. There are also well-established projections from PL (or primate ACC) to BLA and Ce. (reviewed in Vertes, 2004). Consistent with the inhibitory role of ITCs on amygdalar output, it has been observed that stimulation of medial prefrontal areas in cat and rat decreases the responsiveness of neurons in Ce to inputs from BLA (Quirk et al., 2003).

The projections from cortex to the ITCs also appear to have behaviorally relevant effects on learned engagement and disengagement of fear. For example, Sierra-Mercado et al. (2010) found that in rats, inactivation of IL neurons with muscimol impaired acquisition and retention of fear extinction, but left fear expression unchanged. Muscimol inactivation of PL had the opposite effect: it impaired fear expression but did not disrupt extinction. The IL (analogous to primate pOFC) was more important for learning to engage and disengage fear, whereas PL (analogous to primate ACC) was more important for expressing fear.

In summary, data suggest that ITC neurons play an important role in acquisition and extinction of fear responses. Further, this role appears to be subject to top–down modulation or control from IL cortex in rodents and pOFC in primates. These projections can thus serve as conduits for cognitive modulation of fear expression and suppression.

4.2. "TEACHING SIGNALS" WITHIN THE AMYGDALA

In order to model flexible learning in the local circuit outlined above it is necessary to have plausible neural "teaching signals" that can modify network connections in response to aversive events. Teaching signals, as defined in theories of reinforcement learning (reviewed in Sutton and Barto, 1998), are signals that co-occur with salient events or prediction errors, and therefore facilitate learning from experience. Neural signals that co-occur with appetitive or aversive events and also facilitate synaptic plasticity, such as phasic changes in firing rate or neurotransmitter

release, are typically employed as teaching signals in neural models of reinforcement learning. The amygdala receives convergent pathways that carry information about the CS and about the US to the same zones, wherein associative learning processes assess whether a particular CS is predictive of a particular US. If so, synapses transmitting CS information gain control of emotional responses that are typically evoked by the US. In short, information about the US that arrives in the amygdala constitutes a specific teaching signal for intra-amygdala learning. In the case of learned fear, for example, important US pathways include ascending somatosensory-nociceptive pathways to amygdala (Bourgeais et al., 2001; Lanuza et al., 2004; Johansen et al., 2010; McNally et al., 2011). The co-occurrence of such signals with CS signals can trigger associative learning in the amygdala, which can enable CSs to elicit anticipatory freezing in order to avoid pain. Studies in humans have also demonstrated expectation-related activity in the amygdala (e.g., Sarinopoulos et al., 2006; Pourtois et al., 2010b).

5. COMPUTATIONAL MODELING OF THE AMYGDALA CIRCUIT

We employ computational modeling techniques to understand how the amygdalar circuitry reviewed above can serve as the mechanistic basis for some emotional processes, and how top–down modulatory signals from cortex can influence these processes. In this section we show that a computational model of the amygdalar local circuit described above can exhibit flexible acquisition and suppression of stimulus-triggered emotion-related responses, using classical fear conditioning as a test case. Learning in the model can be interpreted as the categorization or labeling of stimuli based on their affective consequences. Stimuli that have been thus categorized can then drive fear-related behavior such as the freezing response in rodents. Cortical modulation in the model adds some flexibility, so fear-related responding is not an inevitable consequence of presenting categorized stimuli. Our modeling approach provides a simplified coarse-grained perspective on the amygdala local circuit: we implement rate-coding rather than spiking in order to investigate properties of the network that arise from connectivity as opposed to the physiological parameters of particular neuronal types.

The circuit diagrams proposed in prior studies can be combined into a single schematic diagram (**Figure 2C**) that captures the general flow of information common to many of the anatomical and physiological studies. At least three sub-networks can be distinguished in many of the relevant rodent studies: (1) the BLA sub-network, an input stage consisting of excitatory projection neurons and inhibitory interneurons in LA, BL, and BM; (2) the ITC sub-network, an intermediary stage consisting of at least two sub-populations of inhibitory cells; and (3) the central sub-network, an output stage consisting of inhibitory projection neurons and interneurons in CeL and CeM. Fear-related responses appear to be expressed via excitation of CeM either directly, or via disinhibition. The key external sources of inhibition to the CeM are neurons in the ITCs and in CeL. As reviewed above, extinction and suppression of learned fear responses seem to involve enhancing inhibition from these sources.

5.1. MODEL DESCRIPTION

We simulate a neural network based on the simplified amygdala connectivity depicted in **Figure 3**. Rate-coded cell activities representing incoming stimuli such as auditory or visual cues project topographically to LA from the cortex (CTX). We leave out projections from thalamus to LA, but the model would work in similar fashion if equivalent sensory information is also conveyed through the thalamic projections. Cells in LA then project topographically to a similar array in BA. Thus, for every stimulus encoded in CTX there is a corresponding cell in LA and in BA. Cells in LA converge onto a single ITCd cell. Similarly, the array of cells in BA converges onto a single ITCv cell. The ITCd cell inhibits ITCv and CeL. The ITCv cell inhibits CeM, the main output station of the amygdala. This circuit is based on evidence from rodent studies reviewed above.

Each cue (CS) can come to be associated with a negative consequence such as footshock, via classical conditioning. A signal (R^+) that corresponds to the foot shock (an unconditioned stimulus; US) arrives at three network locations, as shown (**Figure 3**). A signal (R^-) corresponding to the non-occurrence of an expected US arrives only at the ITCv. These two signals gate Hebbian synaptic change, and therefore serve as teaching signals. We will now briefly describe the model's performance, before demonstrating the simulation results.

The learning process causes the potentiation of synapses on LA cells whenever the corresponding CS co-occurs with the US (Erlich et al., 2012). BA cells in turn are potentiated whenever LA activities co-occur with the US. Synapses onto the ITCd cell are potentiated whenever LA activity overlaps with the US. Similarly, synapses onto the ITCv cell are potentiated whenever BA activity overlaps with the absence of an expected US. Depression of synaptic weights onto the ITC cells occurs whenever the conditions for their potentiation are not met. Weights onto the ITCd cell decrease when the CS-US pairing is extinguished, whereas weights onto the ITCv cell follow the opposite pattern: when CS-US pairing is extinguished, the weights of synapses from BA onto ITCv increase, allowing ITCv to suppress previously learned fear responding. Over time, the activities of LA and BA cells co-occur with those CSs that have been paired with the US. Learning is modeled phenomenologically—this captures empirically established rules regarding the experience-dependence of long-term potentiation (LTP) and long-term depression (LTD) at selected amygdalar synapses. (See Methods section for a brief description of our phenomenological modeling approach).

Synaptic depression is assumed to be much faster in the ITC clusters than in LA and BA. Direct evidence for this assumption is not yet available, but physiological findings on ITCs are consistent with it (Pape and Paré, 2010; Busti et al., 2011; Manko et al., 2011). Weights onto cells in LA and BA, once potentiated, are assumed to decay only negligibly over the time scales simulated. The difference in decay rate allows for flexibility in the face of changing contingencies without erasure of previously learned CS-US associations. In the model, weights of synapses onto ITCd and ITCv cells change rapidly, allowing the system to switch from a response mode to a response-suppression mode, without necessitating unlearning at the level of LA or BA. Thus,

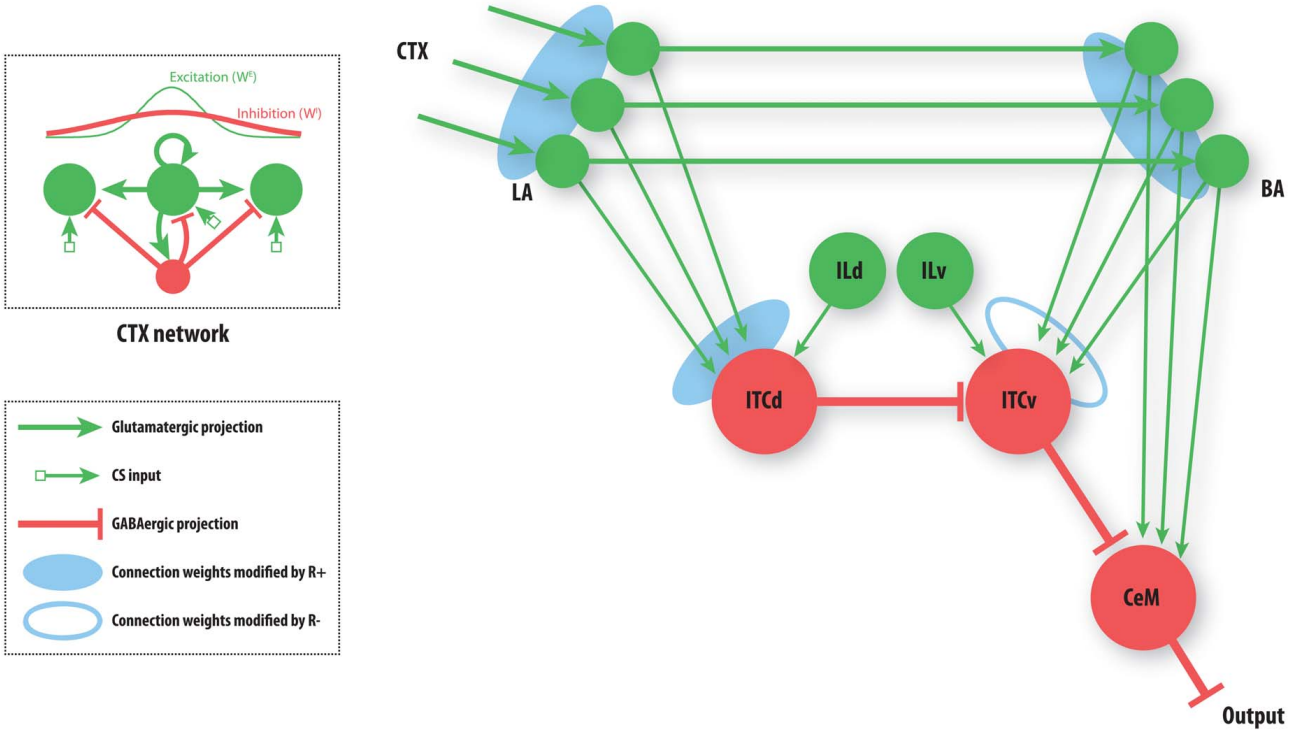

FIGURE 3 | A simplified amygdala circuit for emotional responding. An array of stimulus-related excitatory outputs from a cortical network (CTX) projects in a topographic manner to the lateral nucleus of the amygdala (LA). The cortical network (top inset) is constructed as a distance-dependent on-center off-surround network. Amygdalar input station LA sends excitatory projections topographically to the basal nucleus of the amygdala (BA). Thus, for every cortical cell there is a corresponding cell in LA and in BA, and a corresponding weight from LA onto the inhibitory dorsal intercalated cell (ITCd) and from BA onto the inhibitory ventral intercalated cell (ITCv). The whole array of excitatory LA cells converges onto one ITCd cell. Similarly the array of excitatory BA cells converges onto one ITCv cell, and one cell of the central nucleus of the amygdala (CeM). The ITCd cell inhibits the ITCv cell. The ITCv cell inhibits the CeM cell. The ITCd and ITCv cells each receive projections from infralimbic cortex (IL). Green arrows represent excitatory glutamatergic projections. Red flat arrows represent inhibitory GABAergic projections. Blue ovals represent modifiable synaptic weights. The filled blue ovals represent weights that are potentiated by the arrival of the US (R^+). The empty blue oval represents weights that are potentiated by the arrival of a US prediction-error signal (R^-).

the synapses onto LA and BA allow for post-extinction savings, whereas synapses onto the ITCs allow for sensitivity to changes in contingency.

The basic performance of the model is as follows (**Figure 4**): after fear acquisition, weights on LA, BA, and ITCd are potentiated, leading to inhibition of ITCv, and excitation of CeM, the output cell of the network that triggers the fear response. After fear extinction, weights on LA and BA are almost unchanged, but the weights on ITCd have decreased, and weights on ITCv have increased, causing CeM to be inhibited and the fear response to be suppressed. Simulation results also show some degree of redundancy in the ITCd and ITCv synapses. In some situations this apparent redundancy may be unmasked, so the two areas can serve distinct functions. Simulations also reveal a possible information-processing role for the ITCs.

Cortical modulation from IL onto ITCd and ITCv can be used to bias the circuit's behavior toward or away from extinction. IL can be used to enhance the activity of ITCd, thereby increasing inhibition of ITCv and leading to greater disinhibition of CeM. Alternatively, IL can be used to enhance the activity of ITCv, increasing inhibition onto CeM. The IL (pOFC in primates) is thus well placed to bias the information-processing role of the ITCs.

The cortical network (CTX) is structured as a distance-dependent on-center- off-surround shunting network. Networks of this type offer a simple, neurally plausible means of implementing contrast-enhancement, as well as a host of other processes (Grossberg, 1973). The strength of the off-surround inhibition can be varied to determine how sharply the cell activities represent a set of incoming stimuli. In other words, controlling inhibition modulates the tuning curve of each cell. Strong inhibition allows for sharp contrast, whereas weak inhibition leads to spreading activity and lower contrast. This can serve as a simple model of top–down attention. High attention corresponds to sharp tuning or high contrast, whereas low attention can lead to broader tuning or lower contrast. Low contrast can be used to make "fuzzy" representations that can be used as a basis for generalization of stimuli. In the case of fear conditioning, the amygdala circuit can be interpreted as categorizing stimuli as either predictive or non-predictive of an aversive US. High contrast in the CTX will allow the system to accurately respond only to the CSs paired with the US. But the system will not generalize to CSs that have not

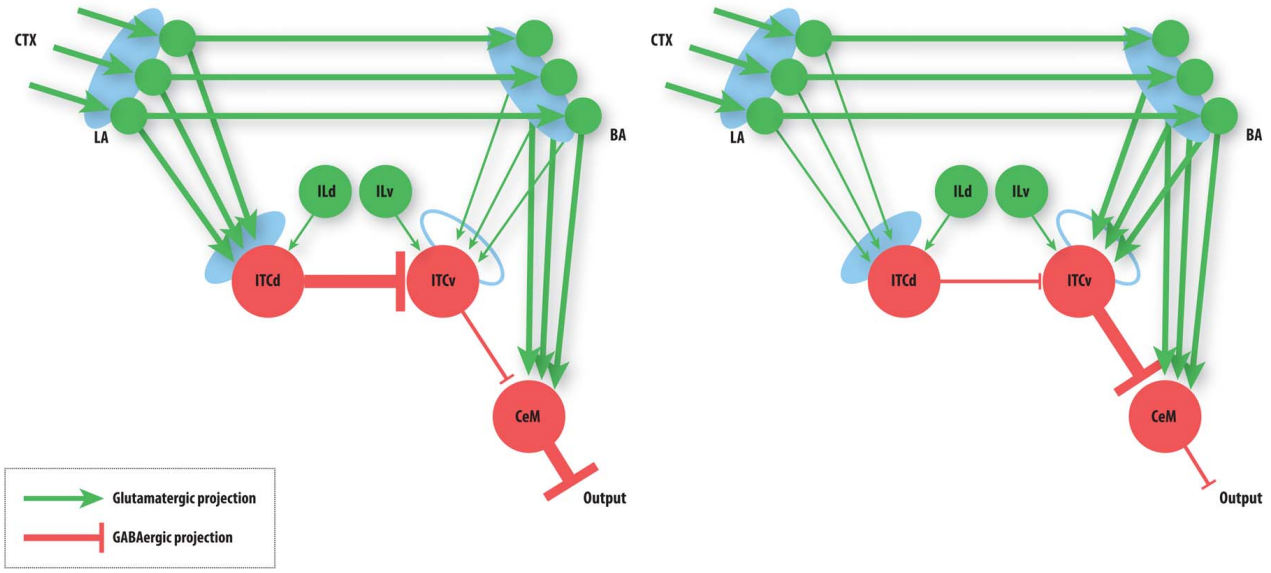

FIGURE 4 | Summary of basic model behavior. Line thickness denotes strength of activity. **Left:** The state of the network after fear acquisition. ITCd inhibits the ITCv, thereby disinhibiting CeM, allowing BA to excite it. CeM excitation leads to fear responding. **Right:** The state of the network after extinction. ITCv inhibits CeM, so CeM becomes insensitive to BA excitation. Note that the learning at LA and BA synapses is not lost. CeM inhibition suppresses fear responding. See caption of **Figure 3** for key to symbols and a description of the circuit.

been presented. For instance, if a sound of a particular frequency is paired with footshock, then a range of similar frequencies will also elicit a fear response. In situations of generalization, the range that is determined to be similar is widened, so more frequencies come to elicit the fear response. Thus, modulating inhibition in the CTX provides a way to investigate the effects of attention or stimulus tuning on fear learning. Some studies of generalization during fear conditioning implicate hippocampal dysfunction (reviewed in Kheirbek et al., 2012). It may be that an analogous mechanism to the cortical one posited here may be applied to hippocampus-dependent changes in generalization.

5.2. SIMULATION RESULTS

The circuit in **Figure 3** has many degrees of freedom. Here we focus on the possible roles of the ITC masses ITCd and ITCv in emotional learning. The only weights that are subject to synaptic change are the weights from the cortex to LA, from LA to BA, from LA to ITCd, and from BA to ITCv. All other weights are held constant.

In these results, we ignore the projection from CeL to CeM in order to focus on the inhibitory action of ITCv on CeM. As the network diagram suggests (**Figure 2**), there is redundancy in the inhibitory pathways to CeM. Simulations (not shown) confirm the idea that CeL and ITCv have very similar roles in the simplified circuit shown in **Figure 3**. For simplicity we omit the activity of CeL in the results that follow. A more detailed model incorporating additional connections will be necessary to investigate asymmetrical roles for each source of inhibition to CeM.

5.2.1. Fear-related learning

The basic behavior of the model is illustrated schematically in **Figure 4**. The model is taken through four consecutive learning epochs: (1) fear acquisition, (2) fear extinction, (3) fear retrieval (the post-extinction re-engagement of fear responding), and (4) extinction retrieval (the re-engagement of fear extinction). The CTX network receives two CSs with overlapping representations, i.e., the two CSs activate a common subset of cells in the CTX array. For instance, two auditory signals with overlapping frequencies, represented in a tonotopic manner, can be used as the CSs. The two CSs are presented in alternation, and while on, each co-occurs with the US (R^+) during epochs 1 and 3. The prediction-error signal (R^-) takes non-zero values in epochs 2 and 4. The time course of model cell activities is shown in **Figure 5**. The red plots in **E–G** indicate R^+ (the US), and the green lines in **E–G** indicate absence of R^+, or extinction trials. When the CS is shut off ($E_i = 0$), a trial ends, and the activities are reset to zero. Only the connection weights persist through the intertrial intervals. The corresponding time course of changes to connection weights is shown in **Figure 6**.

The key development during acquisition is the learning of the CS-US association by the weights onto LA and BA. Once these associations have been formed, they are not significantly weakened during extinction epochs, as is apparent in **Figures 6A** and **6B**, though the modeled synapses can undergo both LTP and LTD at a slow rate.

5.2.2. Using frontal cortex to bias the system

Tonic excitation from cortex (ILd and ILv) to ITCd and ITCv can be used to bias the output of the circuit, i.e., the activity of CeM. For example, if the net excitatory input to ITCd is above a certain threshold, the system is no longer able to extinguish previously learned fear responding (**Figure 7-I**). The system has effectively been placed in a "cautious" mode, so during an

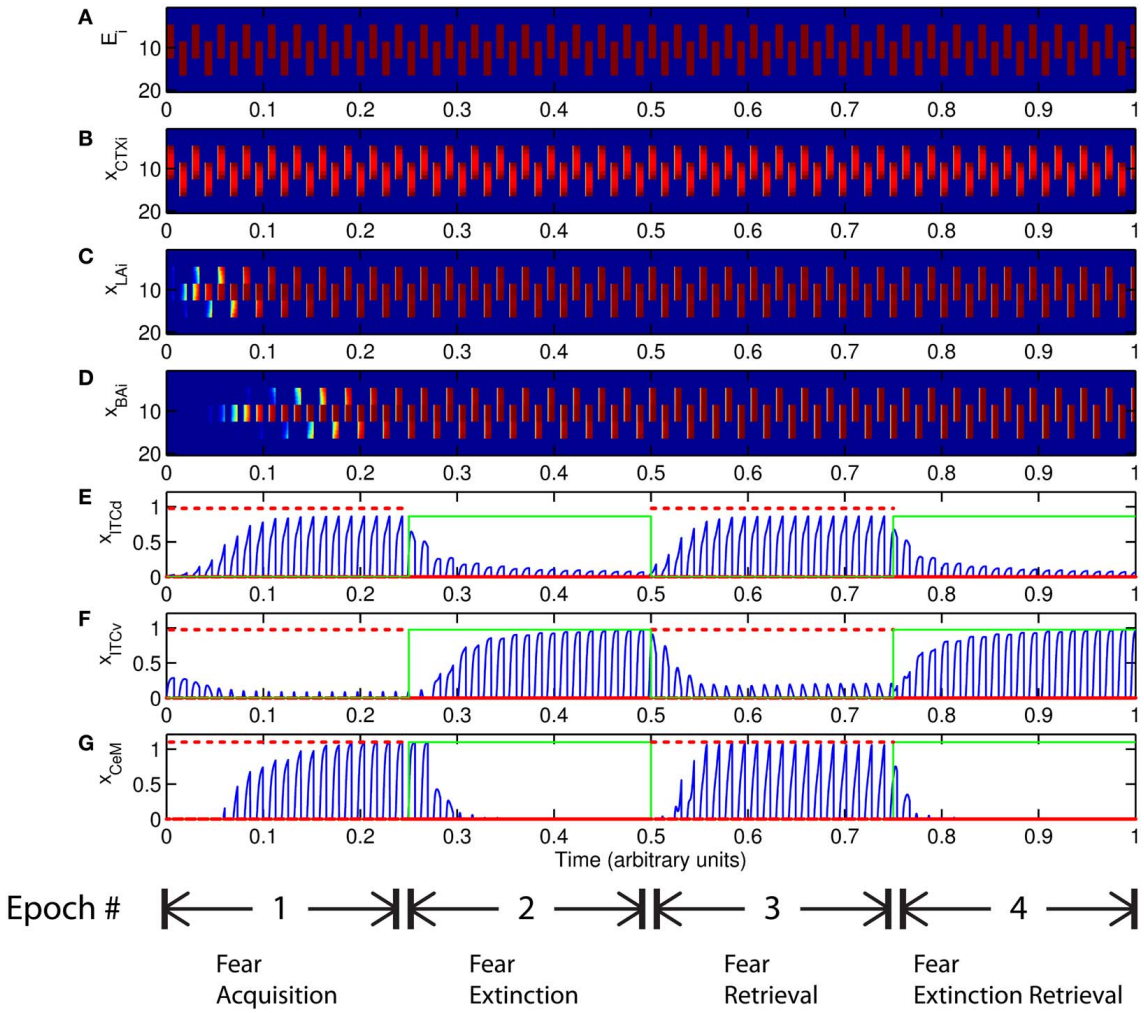

FIGURE 5 | Time course of model cell activities during "normal" mode. The system exhibits fear acquisition, extinction, fear retrieval, and extinction retrieval. Plots show the time evolution of model cell activities during four consecutive epochs. Each plot **(A–D)** shows the temporal evolution of an array of 20 cells, with the y-axis representing the cell index, and the color representing strength of activation (Blue is low, red is high). At any given time there is either a CS1-US pairing, a CS2-US pairing, a presentation of CS1 alone, a presentation of CS2 alone, or an intertrial interval. Because the features of CS1 and CS2 overlap, the indices of activation bars for corresponding representations in **(A–D)** also overlap. Each plot **(E–G)** shows the temporal evolution of a single cell, with the y-axis representing strength of activation of that cell. In the first and third epochs, the CS signals, shown in **(A)**, co-occur with R^+, the US. In the second and fourth epochs, the CS signals are presented without R^+. The red dotted lines in **(E–G)** indicate presence of R^+. The green lines indicate extinction epochs in which $R^+ = 0$. (Parameters: strength of inhibition $f_I = 3.0$; input from IL to ITCd $E_{\mathrm{ILd}} = 0$; input from IL to ITCv $E_{\mathrm{ILv}} = 2$).

extinction epoch the system does not suppress the fear-related responses to associations that were formed during the preceding acquisition epoch. Similar results are obtained when the input to ITCv sinks below a threshold. These effects occur due to the inhibitory effect of ITCd on ITCv. If ITCv cannot be driven by cells in BA, it cannot suppress previously learned fear responding. In other words, in configurations of this type, the system is insensitive to weakening of the link between CSs and the aversive US. In a "cautious" mode, the system does not let down its guard, and continues to generate fear-related responses to CSs long after they cease to co-occur with the US.

Conversely, if excitatory signal E_{ILv} from ILv to ITCv is high and signal E_{ILd} from ILd to ITCd is low, the system rapidly switches from fear responding to no response after fewer extinction trials (**Figure 7-II**). The system has effectively been placed in a "rapid switch" mode, so during an extinction epoch it can more quickly learn to suppress fear-related responses. These simulations agree with experimental results showing the importance of the ITCs in fear learning and expression. The cortical control of the ITCs may be an important route for top–down cognitive control of emotional learning and behavior, adding additional flexibility to responses that are often considered automatic. Further, because the inputs from ILd and ILv can take continuous values, the system's rate of extinction of fear-related responses—or, conversely, its degree of "caution"—can be smoothly varied between the two extreme states.

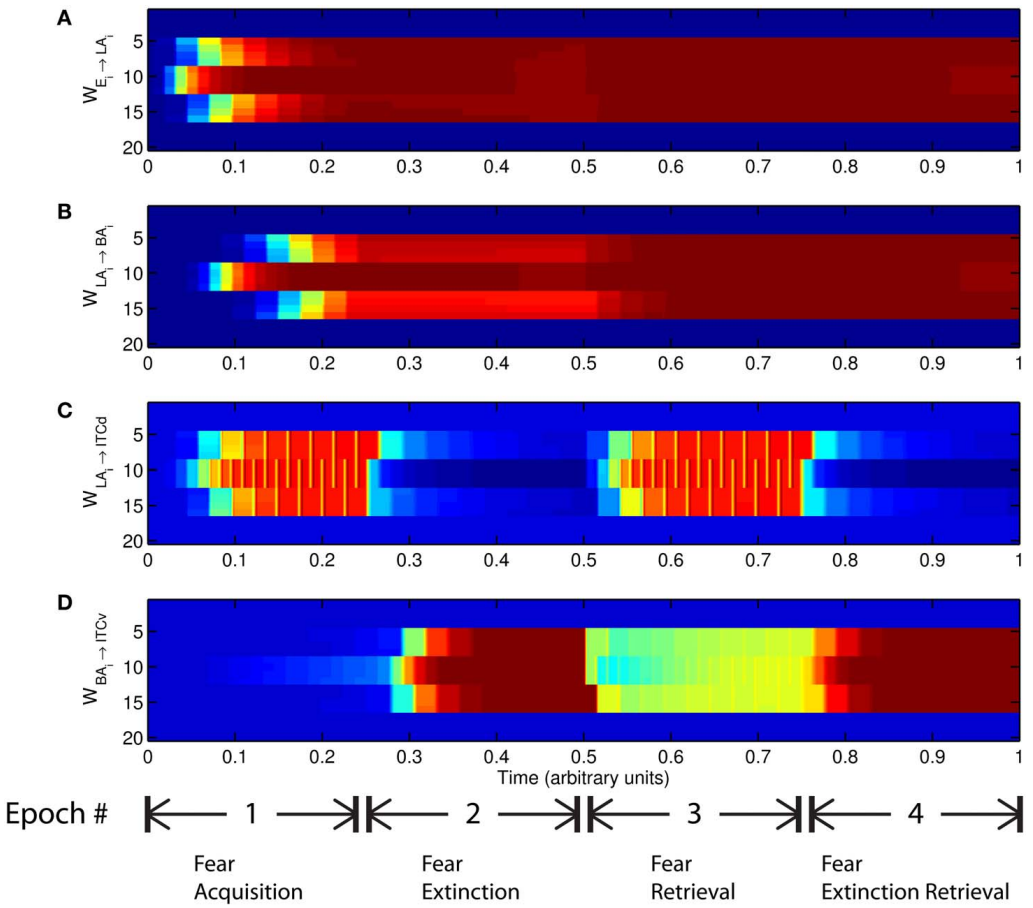

FIGURE 6 | Time evolution of model synaptic weights during "normal" mode. The system exhibits fear acquisition, extinction, fear retrieval, and extinction retrieval. Plots show the time evolution of model connection weights during four consecutive epochs. Each plot **(A–D)** shows the temporal evolution of an array of 20 connection weights, with the y-axis representing the index of the corresponding cell, and the color representing connection strength (Blue is low, red is high). In the first and third epochs, the CS signals co-occur with R^+, the US. In the second and fourth epochs, the CS signals are presented without R^+. (Parameters: strength of inhibition $f_I = 3.0$; input from IL to ITCd $E_{\mathrm{ILd}} = 0$; input from IL to ITCv $E_{\mathrm{ILv}} = 2$).

5.2.3. Redundant learning

An important question that arises when modeling a given circuit is whether all the network's dynamic processes are required to produce the same qualitative output, or if a subset will suffice. In some circumstances the weights onto ITCv appear to encode redundant information. The apparent redundancy can be demonstrated by turning off learning in the ITCv and ITCd weights one by one. In **Figure 8-I** there is no learning in the LA-ITCd weights, so the amplitude of the CeM response is weakened, resulting in failure to acquire an appreciable fear response to CS presentation. In **Figure 8-II** there is no learning in the BA-ITCv weights, and the CeM response is normal during acquisition trials. During extinction epochs there is some reduction in the CeM reponse, but it is partial. Thus, the learning at BA-ITCv synapses may appear redundant, as a reduction in CeM response amplitude can be achieved without it.

However, the apparent redundancy of learning at the weights onto ITCv is unmasked in other circumstances. To demonstrate this, we modify the fear extinction paradigm. In the next set of simulations, only one of the two overlapping CS signals is extinguished. A subset of cells in CTX, LA and BA are therefore activated during both CS presentations, due to the aforementioned overlap. For example, let CS1 be an auditory signal containing frequencies from 500 to 1500 Hz, and let CS2 be a signal containing frequencies from 1000 to 2000 Hz. The two CSs overlap in the range from 1000 to 1500 Hz. During the extinction epochs, the cells in LA and BA that are activated during both CS presentations are subject to conflicting affective outcomes—they co-occur with both the US (R^+) and its unexpected absense (R^-). The cells in the amygdala circuit representing the range of overlap convey ambiguous information to the CeM cell. We therefore describe the situation as one of "confusing outcomes." Thus, during extinction epochs the weights from LA onto ITCd and from BA onto ITCv that correspond to these overlapping cells in LA and BA take on fluctuating, intermediate values. These weights are alternately increased and decreased by the US and its absense, respectively. Because of these intermediate weight values, during extinction epochs the activities of ITCd and ITCv do not clearly distinguish the extinguished CS from the non-extinguished CS. This can be seen in the simulation results. In **Figures 9-II-A** and

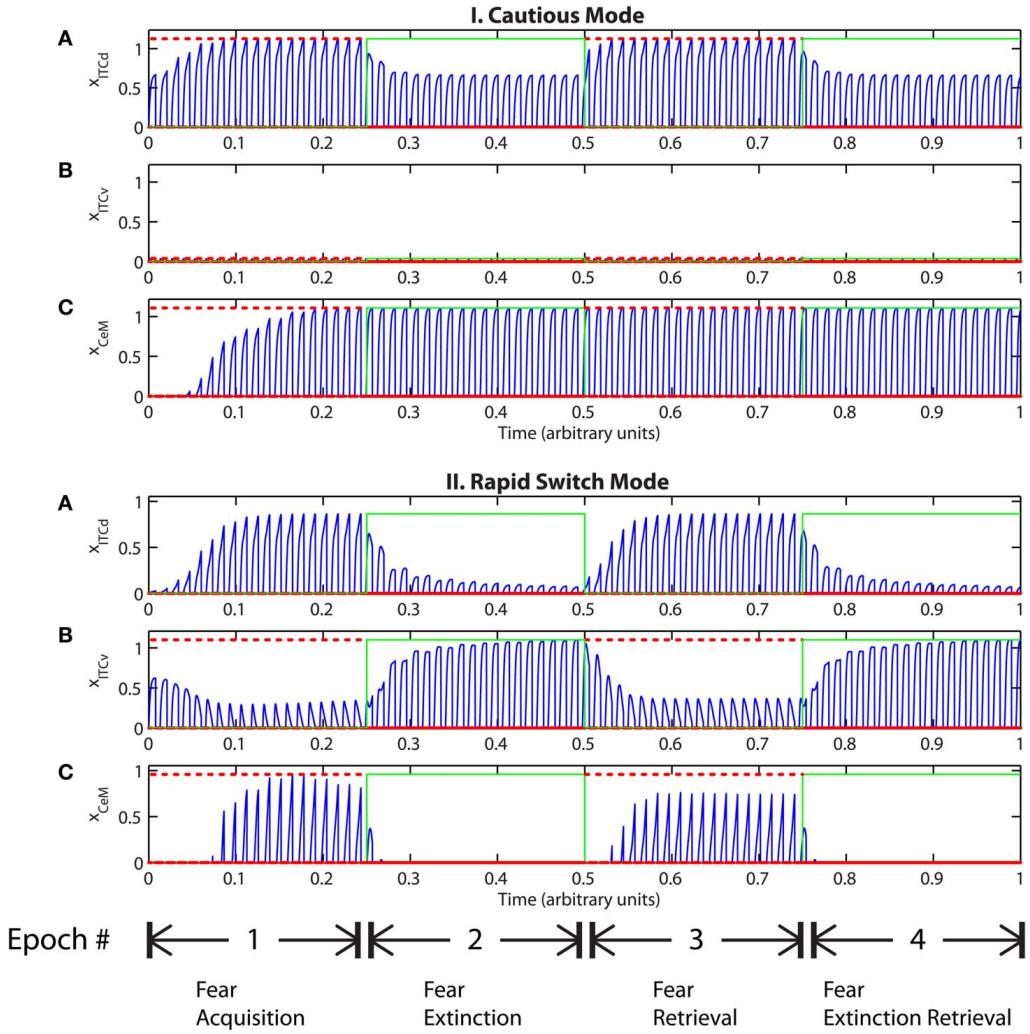

FIGURE 7 | (I) Time evolution of model cell activities during "cautious" mode (when ITCd activation is much higher than ITCv activation): the system is biased to prevent extinction. (Parameters: strength of inhibition $f_I = 3.0$; input from IL to ITCd $E_{\mathrm{ILd}} = 5$; input from IL to ITCv $E_{\mathrm{ILv}} = 2$). **(II)** Time evolution of model cell activities during "rapid switch" mode (when ITCv activation is much higher than ITCd activation): the system is biased to enhance extinction. (Parameters: strength of inhibition $f_I = 3.0$; input from IL to ITCd $E_{\mathrm{ILd}} = 0$; input from IL to ITCv $E_{\mathrm{ILv}} = 5$). Each plot shows the temporal evolution of a single cell over four consecutive epochs, with the y-axis representing strength of activation. In the first and third epochs, the CS signals, co-occur with R^+, the US. In the second and fourth epochs, the CS signals are presented without R^+. The red dotted lines indicate presence of R^+. The green lines indicate extinction epochs in which $R^+ = 0$.

III-A, the ITCd activity takes non-zero values during presentation of both the extinguished CS and the non-extinguished CS. In **Figures 9-I-B** and **III-B**, the ITCv activity takes non-zero values during presentation of both the extinguished CS and the non-extinguished CS.

In **Figure 9-I** there is no learning in the LA-ITCd weights. Once again we see weaker magnitude CeM responses. In **Figure 9-II** there is no learning in the BA-ITCv weights, but here we see that fear responding to the second CS signal has not been extinguished at all. In **Figure 9-III** learning occurs in both sets of weights, and we see correct extinction learning, along with higher magnitude CeM activity. The activities of ITCv and ITCd—which are each ambiguous on their own—act synergistically to improve the performance of the system.

These results suggest the possibility that ITCd and ITCv—and by extension, their cortical inputs—play roles in contrast-enhancement, or in modifying the system's effective signal-to-noise ratio. In other words, the fear enhancing or suppressing roles of ITCd and ITCv might not function purely as on-off switches, but may also supplement the signal processing and filtering steps that occur at prior stages in the circuit.

5.2.4. Attention and generalization

As described above, in certain configurations the CTX network may be unable to form a sharp representation of the CS. There may be contexts in which top–down attentional resources are overtaxed or spread too thinly. We model this low attention as weakened inhibition in the competitive-cooperative CTX

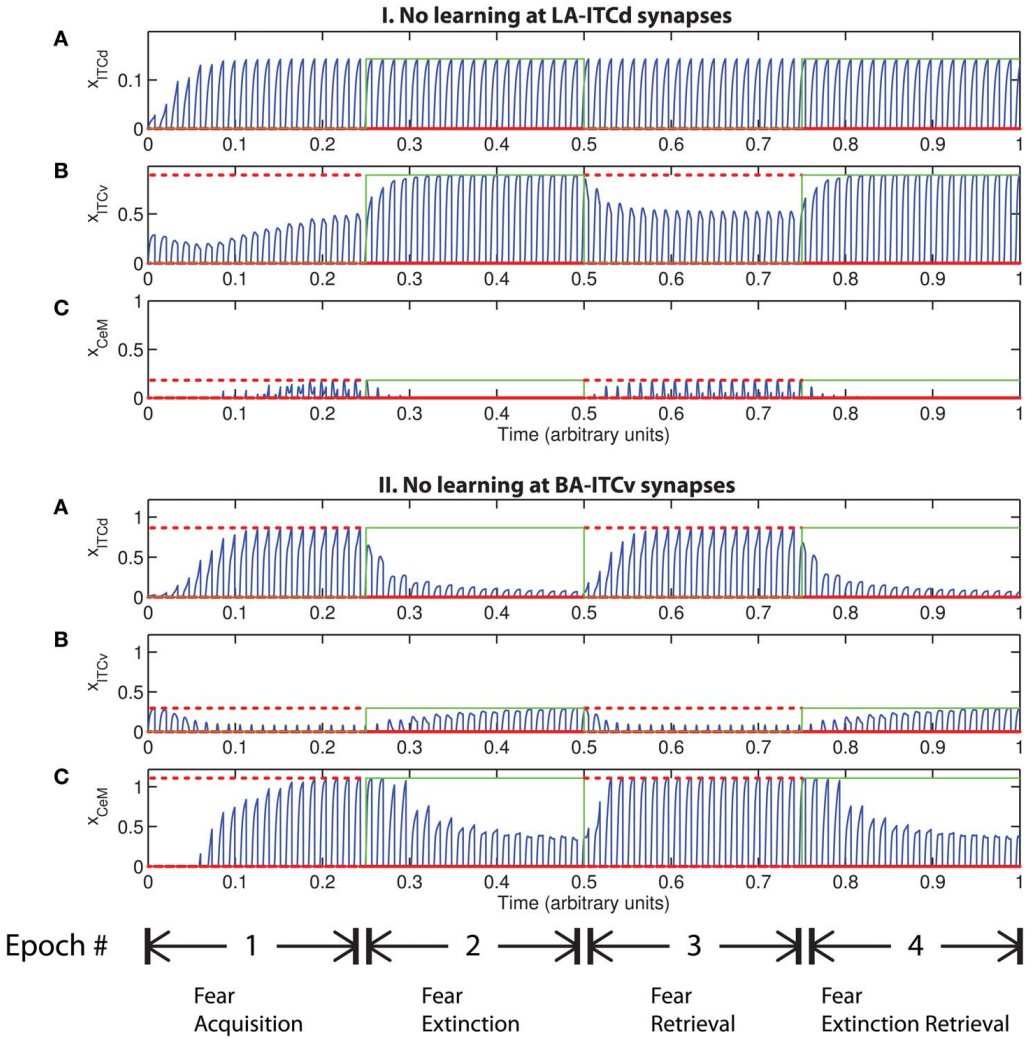

FIGURE 8 | Time evolution of model cell activities. (I) No learning occurs at the LA-ITCd synapses. **(II)** No learning occurs at the BA-ITCv synapses. Each plot shows the temporal evolution of a single cell over four consecutive epochs, with the y-axis representing strength of activation. In the first and third epochs, the CS signals, shown in (A), co-occur with R^+, the US. In the second and fourth epochs, one of the CS signals is presented without R^+. The red dotted lines indicate presence of R^+. The green lines indicate extinction epochs in which $R^+ = 0$. (Parameters: strength of inhibition $f_I = 3.0$; input from IL to ITCd $E_{ILd} = 0$; input from IL to ITCv $E_{ILv} = 2$).

network, leading to a spreading of activity, which in turn leads to spurious associations of the US with CSs that were not presented. If the outcomes are not "confusing," learning can appear normal (**Figures 10**, **11**). But if the outcomes are "confusing," the system cannot extinguish learning, even if ILd is used to drive ITCd and put the network in "cautious" mode (**Figure 12**). Low attention prevents the system from discriminating between threatening and non-threatening stimuli, because the two have been categorized as the same via a process analogous to generalization.

6. DISCUSSION

6.1. IMPLICATIONS OF THE SIMPLIFIED MODEL

The simplified circuit model demonstrates some of the key emotional processes the rodent amygdala subserves—fear learning, extinction, and extinction retrieval. The model simulations demonstrate that if learning in the intercalated masses (ITCd and ITCv) is faster than in the BL complex (LA and BA), the system can rapidly switch between fear responding and extinction without discarding the CS-US associations in LA and BA. Cortical modulation from IL can be used to bias the system toward either a "rapid switch" mode or a "cautious" mode. Also, learning in ITCd and ITCv sometimes seems redundant, but in situations involving conflicting outcomes, these two regions may cooperate to disambiguate the incoming signal, prior to the final output stage of the amygdala. This synergy between ITCd and ITCv enhances the performance of the system in "confusing" situations, serving effectively as a form of information-processing. Cognitive control over the intercalated cells (ITCs in rodents, IM in primates) via IL/pOFC projections may serve as a mechanism to flexibly modify

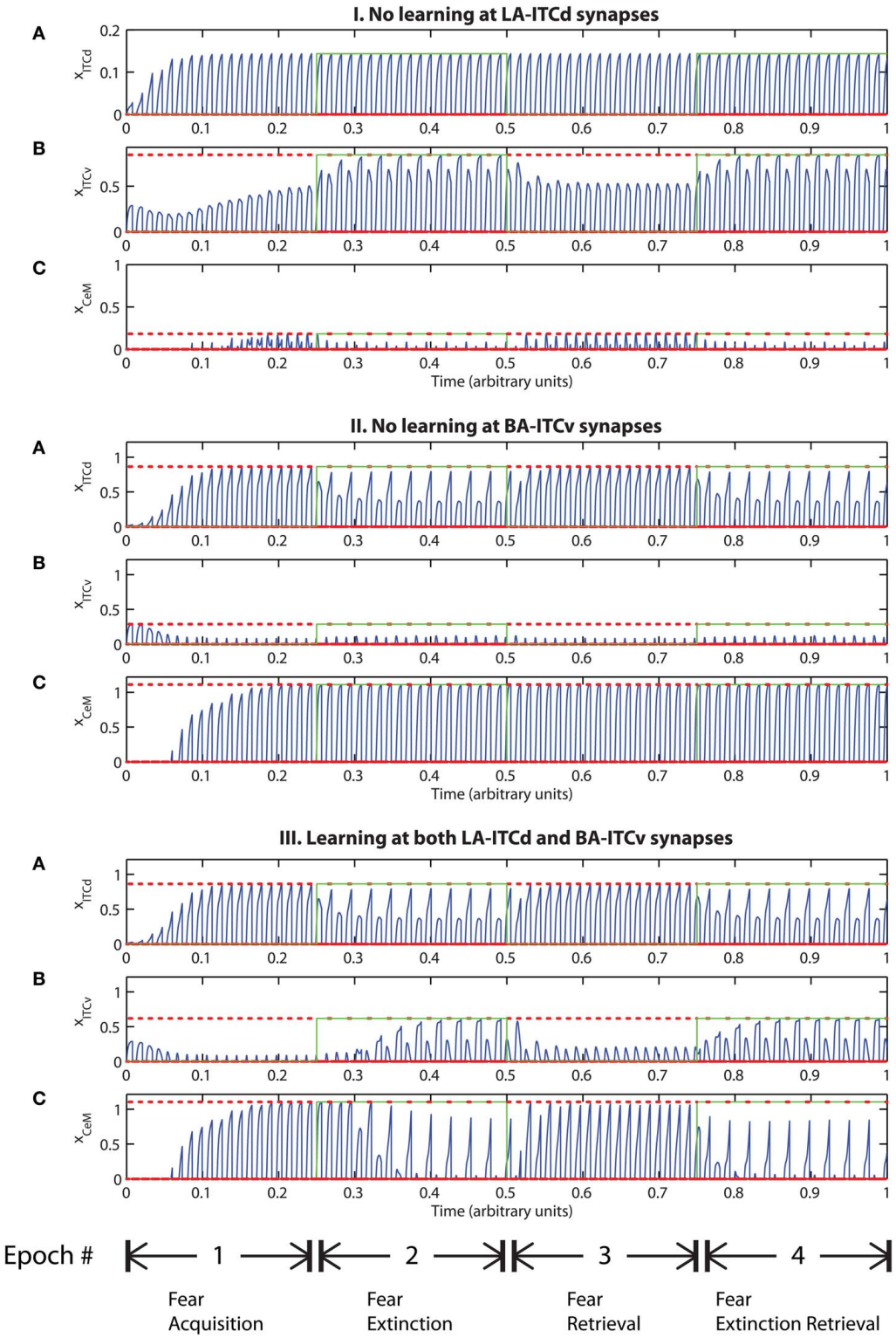

FIGURE 9 | Time evolution of model cell activities during "confusing" outcomes. Only one of the two overlapping CS signals is extinguished. **(I)** No learning occurs at the LA-ITCd synapses. **(II)** No learning occurs at the BA-ITCv synapses. **(III)** Learning occurs in both LA-ITCd and BA-ITCd weights. Each plot shows the temporal evolution of a single cell over four consecutive epochs, with the y-axis representing strength of activation. In the first and third epochs, the CS signals, shown in **(A)**, co-occur with R^+, the US. In the second and fourth epochs, one of the CS signals is presented without R^+. The red dotted lines indicate presence of R^+. The green lines indicate extinction epochs in which $R^+ = 0$. (Parameters: strength of inhibition $f_I = 3.0$; input from IL to ITCd $E_{ILd} = 0$; input from IL to ITCv $E_{ILv} = 2$).

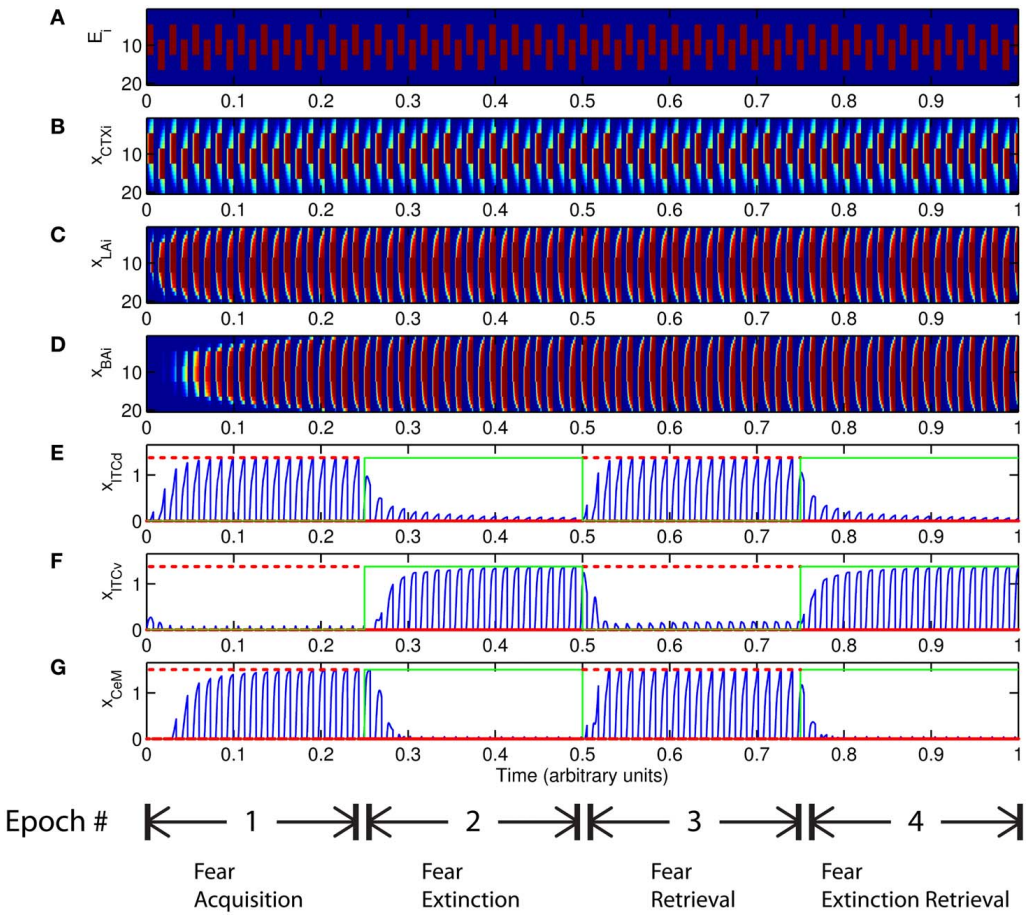

FIGURE 10 | Time evolution of model cell activities during "generalization" mode. Both CS signals are extinguished. Plots show the time evolution of model cell activities during four consecutive epochs. Each plot **(A–D)** shows the temporal evolution of an array of 20 cells, with the y-axis representing the cell index, and the color representing strength of activation (Blue is low, red is high). Each plot **(E–G)** shows the temporal evolution of a single cell, with the y-axis representing strength of activation of that cell. In the first and third epochs, the CS signals co-occur with R^+, the US. In the second and fourth epochs, the CS signals are presented without R^+. (Parameters: strength of inhibition $f_I = 0.3$; input from IL to ITCd $E_{\mathrm{ILd}} = 0$; input from IL to ITCv $E_{\mathrm{ILv}} = 2$).

behavioral strategies in response to environmental contingencies. For instance, environments containing a mixture of appetitive and aversive stimuli may necessitate the "rapid switch" mode, so that the organism is brave enough to discover useful resources without being so foolhardy as to ignore threats. Extremely dangerous environments, on the other hand, may require the "cautious" mode, and an attenuation of exploratory behavior. Environments that are "confusing," containing stimuli that are hard to distinguish, or whose affective consequences change over time, may require cortical or hippocampal (e.g., Frankland et al., 1998) enhancement of the information-processing abilities of the intercalated cells. The model demonstrates in simplified form how the amygdala and IL/pOFC can flexibly readjust fear responses as contingencies change—such roles have also been inferred from human fMRI research (Schiller et al., 2008).

The model also allows us to demonstrate that weakened top–down attention can prevent the system from discriminating between threatening and non-threatening stimuli. This occurs via a process of over-generalization, in which two stimuli cannot be separated on the basis of their affective consequences. Though we posit that this over-generalization occurs as a result of cortical mechanisms, the basic process may also be applied to model the pathological over-generalizations that have been attributed to hippocampal dysfunction (reviewed in Kheirbek et al., 2012). Pathological over-generalization may also have a basis within the amygdalar circuit (Mahan and Ressler, 2012). Patients diagnosed with PTSD display over-generalization (e.g., Lissek and Grillon, 2010), and this could result from the kind of attentional dysfunction employed in the model. But it is premature to extrapolate from our simplified model to complex human psychological phenomena. Nevertheless, the modeling results can be used to guide hypotheses to be explored further in experimental animals and humans. For instance, medical interventions that enhance attention may allow patients with PTSD to better discriminate between threatening and non-threatening stimuli.

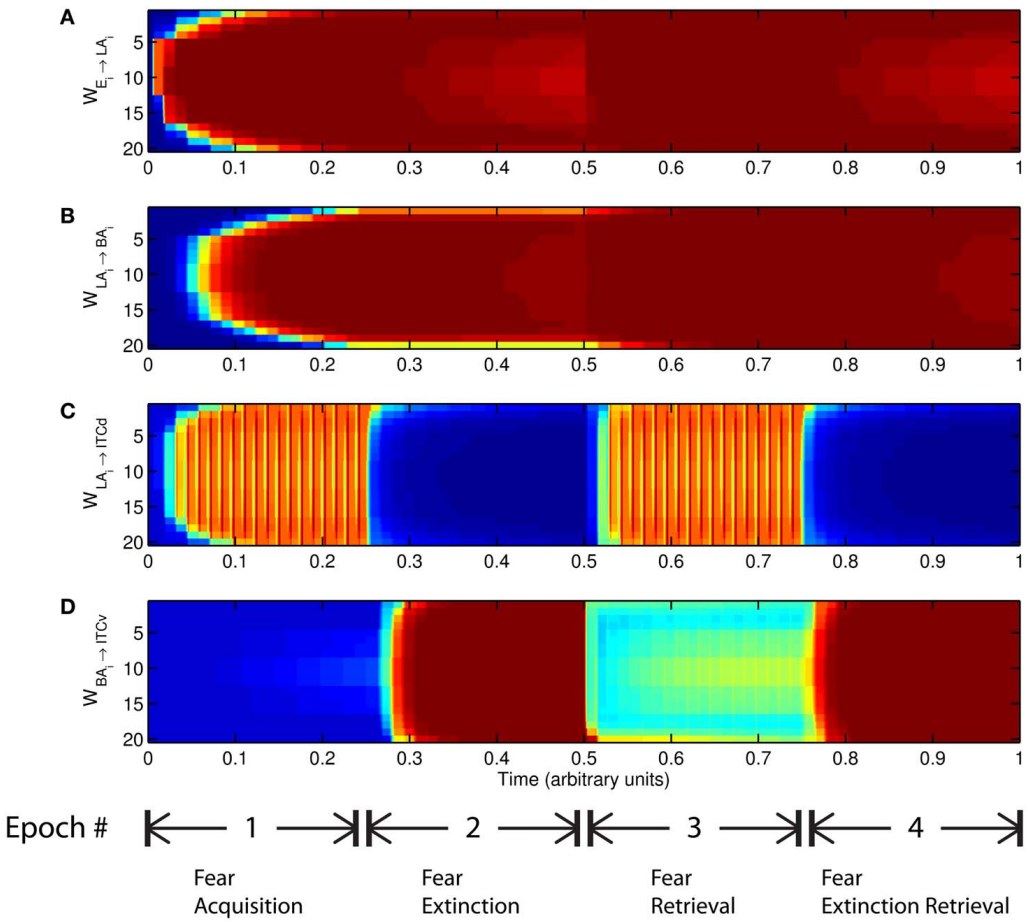

FIGURE 11 | Time evolution of model synaptic weights during "generalization" mode. Both CS signals are extinguished, but weights corresponding to stimuli that were never presented are also increased. Each plot **(A–D)** shows the temporal evolution of an array of 20 connection weights, with the y-axis representing the index of the corresponding cell, and the color representing connection strength (Blue is low, red is high). In the first and third epochs, the CS signals co-occur with R^+, the US. In the second and fourth epochs, one of the CS signals is presented without R^+. (Parameters: strength of inhibition $f_I = 0.3$; input from IL to ITCd $E_{\mathrm{ILd}} = 0$; input from IL to ITCv $E_{\mathrm{ILv}} = 2$).

The modeling results show that learning in a simplified subset of the possible amygdalar network connections is sufficient to exhibit flexible emotional learning. More complex tasks will be necessary to resolve the roles of seemingly redundant connections or representations in the network. Future anatomical and physiological studies will allow us to make more specific claims about the nature and location of synaptic changes, and also about the neurochemical signals that are necessary for these changes to occur.

More generally, the approach here shows that simple simulations of a neural circuit constructed from the bottom up not only agree with experimental findings, but also suggest and predict novel roles for network elements that go beyond straightforward extrapolations from experiment. For instance, the model simulations point to possible information-processing roles for the ITCs. The model suggests that these cells are not simply on-off switches for the fear response, but can act synergistically to enhance the model's ability to discriminate between stimuli in situations that are confusing. Further, since the ITCs receive projections from prefrontal cortex, they may be part of a circuit for top–down effects on emotional expression and suppression. These results are consistent with an earlier biophysical modeling study by Li et al. (2011), which shows that IL can overcome inter-ITC inhibition to control CeM output. That study is the only other computational model that explicitly incorporates the ITCs. As we have done here, Li et al. (2011) also omitted the effects of CeL due to paucity of data.

Another comparable computational model is that of Krasne et al. (2011). Their amygdalar model is also rate-coded and incorporates learning, but has a complementary focus—one of their central modeling targets is an extensive exploration of hippocampus-dependent contextual fear conditioning. Our model does not incorporate hippocampal connections, but uniquely highlights the possible effects of IL projections to ITCs. The model of Krasne et al. (2011) posits that extinction takes place via interneurons in BLA, whereas we propose that extinction occurs due to learning at the ITCs. Their computational approach also differs: their implementation can be described as

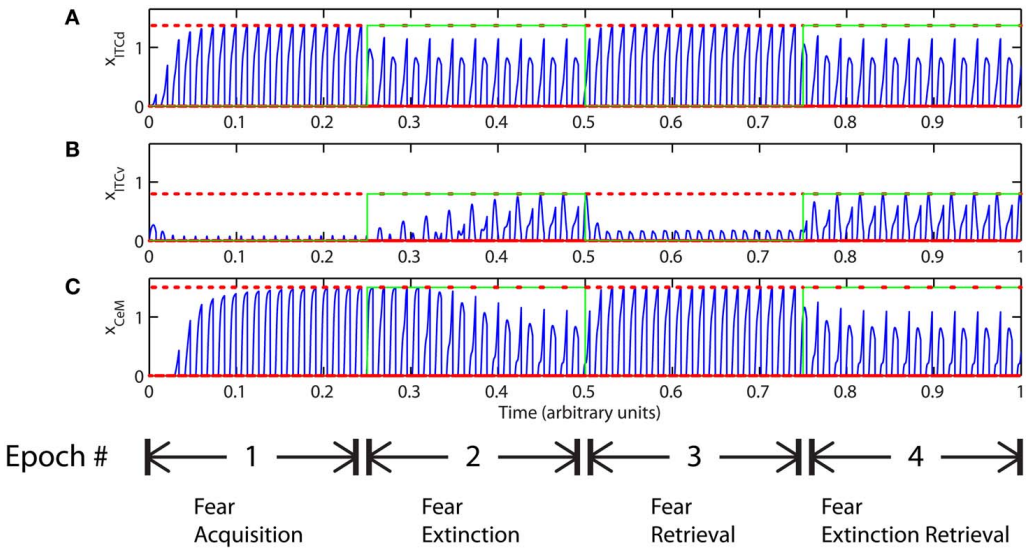

FIGURE 12 | Time evolution of model cell activities during "phobic" mode. Only one of the two overlapping CS signals is extinguished. Each plot **(A–C)** shows the temporal evolution of a single cell over four consecutive epochs, with the y-axis representing strength of activation. In the first and third epochs, the CS signals, shown in **(A)**, co-occur with R^+, the US. In the second and fourth epochs, one of the CS signals is presented without R^+. The red dotted lines indicate presence of R^+. The green lines indicate extinction epochs in which $R^+ = 0$. (Parameters: strength of inhibition $f_I = 0.3$; input from IL to ITCd $E_{ILd} = 0$; input from IL to ITCv $E_{ILv} = 2$).

algorithmic and algebraic, whereas ours is based on dynamical systems.

Thus, we show that a rate-coded model can corroborate and extend insights gained from more fine-grained biophysical spiking models such as that of Li et al. (2011), and can also complement other higher-level approaches such as that of Krasne et al. (2011). Simplified models such as ours also have the benefit of greater computational tractability than biophysical models, allowing for rapid investigation of qualitative circuit-level phenomena. Further, our model is the only one we are aware of to incorporate synaptic learning at the ITCs. The information-processing role predicted by our model may be linked with the integrative roles for ITCs proposed by Palomares-Castillo et al. (2012).

Our model shows how the amygdalar local circuit depicted in **Figure 3** can assign emotional significance to stimuli and use these categorized stimuli to drive emotional behavior such as the freezing response. The model is based on circuits described in rodents, in which behavioral and physiological data are available. As discussed above, in rhesus monkeys the principal pathway from the cortex to IM (the primate equivalent to rodent ITCs) originates in pOFC (Ghashghaei and Barbas, 2002). In rhesus monkeys IM neurons are not segregated into dorsal and ventral clusters, but belong to at least three neurochemical classes of inhibitory neurons which are intermingled within IM (Zikopoulos and Barbas, 2011). The distinct classes of inhibitory neurons may have critical, and perhaps specific, roles in emotional arousal and return to autonomic homeostasis.

6.2. FUTURE DIRECTIONS: EXTENDING THE MODEL

Ongoing work will incorporate more of the local amygdalar circuit connections, and embed the amygdala more fully into the cognitive-emotional continuum we described earlier. We aim to progressively expand the computational model, so that it can tie together more of the experimental data, display more diverse, flexible behaviors, and suggest neural accounts of psychiatric disorders that can inform translational research.

In order to form a more nuanced picture of the relationship between emotion and attention, it is necessary to address the fact that attention-related neural mechanisms can both affect the amygdalar circuit and be affected by amygdalar outputs. In keeping with this goal we hope to include in future iterations of the model the recently discovered projections from amygdala to the thalamic reticular nucleus (TRN) (Zikopoulos and Barbas, 2012). Thalamic processing for the suppression of irrelevant stimuli is crucial for selective attention, and may be accomplished early in neural processing through the inhibitory TRN. The TRN lies between the thalamus and cortex and plays a key role in processes that direct attention to relevant/significant stimuli (**Figure 1**). The TRN receives projections from all cerebral cortices and their associated thalamic nuclei, but sends inhibitory output only to the thalamus, effectively gating thalamo-cortical communication (Crick, 1984; Montero, 1997; Weese et al., 1999; Pinault, 2004; McAlonan et al., 2008; Petrof and Brown, 2010). Projections from sensory and motor cortices and their thalamic nuclei map topographically on TRN (reviewed in Guillery and Harting, 2003; Pinault, 2004; Zikopoulos and Barbas, 2007). In primates, prefrontal cortices innervate the anterior sector of TRN (Zikopoulos and Barbas, 2006). However, lateral prefrontal cortex (areas 46 and 9) and pOFC, which are major sensory-recipient prefrontal regions, and their associated thalamic nucleus, the mediodorsal (MD), have widespread projections that extend beyond the frontal sector of TRN to sites innervated by sensory and motor cortices (Zikopoulos and Barbas, 2006).

Through this unique type of projection, lateral prefrontal and posterior orbitofrontal cortices may control the passage of signals through the thalamus to shift attention to relevant stimuli and suppress distracters (Barbas and Zikopoulos, 2007). The amygdala may be in a position to modulate this attentional mechanism via a novel and robust excitatory pathway from the basal amygdala that also innervates widely the inhibitory TRN in rhesus monkeys (Zikopoulos and Barbas, 2012). This pathway innervates the entire antero–posterior axis of TRN, and converges at sites that receive widespread projections from MD, pOFC and lateral prefrontal cortices. An additional distinguishing feature of this amygdalar pathway is the presence of large and efficient synapses that target TRN neurons proximally. This unique and widespread pattern of connectivity suggests that this system is suited for an overseeing role in events that require heightened attention to stimuli that are essential for survival, or simply for rapid attention to salient stimuli to make a judgment for a course of action.

Attentional and emotional processes are also linked via the widely projecting neurotransmitter systems (relevant human studies are reviewed in Davis and Whalen, 2001). For instance, the cholinergic projection system in the basal forebrain, which includes the nucleus basalis of Meynert (NBM) and the substantia innominata (SI), may play an important role in the interactions between the amygdala and the prefrontal cortex. The amygdalar central nucleus (Ce) and the IM (ITCs in rodents) project to the basal forebrain (Paré and Smith, 1994; Bourgeais et al., 2001). These cholinergic pathways from the basal forebrain may have widespread effects on the entire cortex, and may affect general vigilance through tonic signals, or enhance attention through phasic activity (Davis and Whalen, 2001; Sarter and Parikh, 2005; Parikh and Sarter, 2008). Among prefrontal cortices the ACC and the pOFC receive the strongest cholinergic projections from the basal forebrain (Mesulam et al., 1992; Ghashghaei and Barbas, 2001).

It has long been established that both emotional salience and direct stimulation in the amygdala promote memory formation (McGaugh, 2004; Chau and Galvez, 2012), a process which may involve the substantial projections from midbrain dopaminergic areas to amygdalar nuclei (Björklund and Dunnett, 2007; Cho and Fudge, 2010). Dopaminergic signals can serve as teaching signals that affect synaptic plasticity and memory, often in conjunction with other neurotransmitters (Nader and LeDoux, 1999; LaLumiere et al., 2004). More recent studies have established that DA is necessary for normal learning of cued fear responses, and that an absence of normal DA signaling during fear conditioning instead leads to the development of generalized anxiety (Zweifel et al., 2011).

In summary, incorporating the TRN and the neurotransmitter systems may allow us to expand our simplified attentional mechanism, and also investigate teaching signals and synaptic plasticity, both within the amygdala and in regions affected directly and indirectly by amygdalar output. These pathways to and from the amygdala may be well suited to serve as the basis of a more general phenomenon of emotional "perception" (Vuilleumier et al., 2004; Hadj-Bouziane et al., 2008; Lim et al., 2009; reviewed in, Barrett and Bar, 2009).

7. CONCLUSION

We have argued that rather than being opposing forces, cognition, and emotion can be seen as points on a continuum or gradient of flexible processes required for adaptive categorization of, and response to, changes in the external and internal environment of an organism. While this conceptualization may not capture all the psychological nuances of the terms, it highlights the experimentally tractable facets of "cognition" and "emotion."

The functional continuum is based on the robust connections between areas associated with cognition and those associated with emotion. The amygdala and the pOFC receive coarse-grained information from a variety of brain regions, and are both in a position to integrate internal and external environmental signals into broad emotion-related representations of stimuli and overall context. The pOFC sends "feedback" projections to lateral prefrontal cortices, which are associated with cognition, and receive fine-grained sensory information. Compared with pOFC, lateral prefrontal cortices may thus form more precise representations of the environment. Such representations can then be sent via "feedforward" projections to areas associated with emotions and goal-directed behavior (pOFC), from which they can influence internal states and behavior through specialized projections to the amygdala.

Our simplified computational model illustrates one way that the amygdala can carry out emotional categorization and response-generation. The model also shows how the prefrontal cortex, acting via the intercalated cell groups, can modulate learned fear responding, and facilitate flexible switching between fear expression and suppression without loss of prior learning. The prefrontal cortical projections can put the system in a "cautious" mode in which fear cannot be suppressed, or in a "rapid-switch" mode in which extinction is sped up. "Reducing" the level of attention in the model provides a mechanism by which the system can generalize the consequences of a stimulus, or enter into a "phobic" mode that is resistant to extinction. In future studies attentional modulations may be incorporated into the model by adding the known projections of amygdala to TRN and the neuromodulatory systems. Thus, emotional categorization of stimuli that arrive at the amygdalar circuit not only drives responses, but can also lead to widespread changes in high-level cortical processing.

In conclusion, the model demonstrates how a computational approach can suggest non-trivial functional roles of network components. Among these, the model simulations reveal an information-processing role for intercalated neurons in learning emotional associations and flexibly altering expectations when stimuli no longer signal a threat (or lack of reward) in the environment. The computational model based on key nodes in the amygdalar circuit also provides a plausible mechanism for the generalization of stimuli, which may underlie the pattern of activation in the amygdalar-prefrontal circuit in a variety of anxiety disorders including phobias and PTSD.

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AUTHOR CONTRIBUTIONS

Yohan J. John, Daniel Bullock, Basilis Zikopoulos, and Helen Barbas designed the circuit model. Yohan J. John performed and analyzed the simulations. Yohan J. John, Daniel Bullock, Basilis Zikopoulos, and Helen Barbas prepared the manuscript.

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APPENDIX

METHODS

Our modeling approach can be described as "phenomenological"—the equations governing neural activity and synaptic weight change are not intended to accurately reflect fine-grained biophysical detail or fit quantitative experimental data. Instead, our simplified model provides qualitative results that agree with several experimental studies, and also allow us to suggest possible functional roles for components of the network. As described in the Introduction, this approach can address several questions related to how the components of the amygdalar local circuit work together as a substrate for flexible fear-related learning and responding.

We implement the model as a rate-coded system to investigate those properties of the amygdalar network that depend on connectivity, rather than fine-grained biophysical details. We assume as a first approximation that all the model neurons obey the same set of differential equations. We assign an activity x_s to each neuron s:

$$\tau_{x_s}\frac{dx_s}{dt} = -A_s x_s + (B_s - x_s)E_s - (x_s + C_s)I_s \qquad \text{(A1)}$$

where subscript s is an index for the particular neuron in the network, and E_s and I_s correspond to the excitatory and inhibitory inputs, respectively. The term A specifies the passive decay rate, B is the maximum activity ($B > 0$), and $-C$ is the minimum activity ($C \geq 0$). The time constant of integration is τ_{x_s}.

Synaptic weight changes occur via the following learning rule:

$$\tau_c\frac{dW_c}{dt} = \{-A_c W_c + R(W_m - W_c)\}\left[x_{\text{pre}}\right]^+\left[x_{\text{post}}\right]^+ \qquad \text{(A2)}$$

where W_c is a connection weight between two neurons, R is a reinforcing signal, x_{pre} is the presynaptic neural activity, and x_{post} is the postsynaptic neural activity. The constant W_m is the maximum attainable weight. The square brackets indicate positive rectification (if $q \geq 0$, $[q]^+ = q$, else $[q]^+ = 0$). The weight change is presynaptically and postsynaptically gated. Weight W_c increases if x_{pre} and x_{post} take non-zero values and the teaching signal R is simultaneously greater than zero. Weight W_c decreases if x_{pre} and x_{post} take non-zero values, but there is no accompanying teaching signal, i.e., $R = 0$. Parameter A_c represents a rate of gated decay or "active forgetting." Subscript c is an index that specifies the connection (see **Table A1** for a complete list). For example, in **Table A1**, $W_{\text{CTX}_i \to \text{LA}_i}$ corresponds to the connection weight from the ith cortical cell to the corresponding LA neuron.

Let there be N cells each in CTX, LA, and BA. Each CTX neuron receives one input E_i (where i is an index that runs from 1 to N). Each E_i is a neutral stimulus that can, after learning, come to modulate an emotional response. Each E_i can represent a point in a feature space, such as a particular auditory frequency. Each CTX cell sends excitatory projections to nearby CTX cells, as well as inhibitory projections, which can be interpreted as taking place via intermediary inhibitory interneurons, as depicted in the top inset of **Figure 3**. Parameters are chosen so that the CTX cells work together as a distance-dependent on-center off-surround network. Excitatory connections between CTX cells are determined by a Gaussian, such that

$$W^E_{\text{CTX}_k \to \text{CTX}_i} = e^{-[(k-i)/\sigma_E]^2} \qquad \text{(A3)}$$

Table A1 | Excitatory and inhibitory inputs to each network component.

Cell index	Excitation term E_s	Inhibition term I_s
CTX_i	$E_i + \sum_{k=1}^{N} W^E_{\text{CTX}_k \to \text{CTX}_i} E_k$	$\sum_{k=1}^{N} W^I_{\text{CTX}_k \to \text{CTX}_i} E_k$
LA_i	$f_{\text{LA}} W_{\text{CTX}_i \to \text{LA}_i} [\text{CTX}_i]^+$	0
BA_i	$W_{\text{LA}_i \to \text{BA}_i} [x_{\text{LA}_i}]^+$	0
ITCd	$\sum_{i=1}^{N} W_{\text{LA}_i \to \text{ITCd}} [x_{\text{LA}_i}]^+ + E_{\text{ILd}}$	0
ITCv	$\sum_{i=1}^{N} W_{\text{BA}_i \to \text{ITCv}} [x_{\text{BA}_i}]^+ + E_{\text{ILv}}$	$W_{\text{ITCd} \to \text{ITCv}} [x_{\text{ITCd}}]^+$
CeM	$\sum_{i=1}^{N} [x_{\text{BA}_i}]^+$	$W_{\text{ITCv} \to \text{CeM}} [x_{\text{ITCv}}]^+$

Table A2 | Parameter values common to all simulations.

Parameter	Value
N	20
E_i	10 (peak value)
τ_x	0.001
$A_{\text{CTX}i}$	0.1
$B_{\text{CTX}i}$	2
$C_{\text{CTX}i}$	2
$A_{\text{LA}_i, \text{BA}_i, \text{ITCd, ITCv, CeM}}$	10
$B_{\text{LA}_i, \text{BA}_i, \text{ITCd, ITCv, CeM}}$	2
$C_{\text{LA}_i, \text{BA}_i, \text{ITCd, ITCv, CeM}}$	0
f_{LA}	10
$\tau_{\text{CTX}_i \to \text{LA}_i}$	0.0016
$A_{\text{CTX}_i \to \text{LA}_i}$	0.001
$\tau_{\text{LA}_i \to \text{BA}_i}$	0.0066
$A_{\text{LA}_i \to \text{BA}_i}$	0.001
$\tau_{\text{LA}_i \to \text{ITCd}}$	0.133
$A_{\text{LA}_i \to \text{ITCd}}$	50
$\tau_{\text{BA}_i \to \text{ITCv}}$	0.133
$A_{\text{BA}_i \to \text{ITCv}}$	50
W_m	20
$W_{\text{ITCd} \to \text{ITCv}}$	10
$W_{\text{ITCv} \to \text{CeM}}$	25
$W_s(t = 0)$	0.05

Terms with "(t = 0)" specify initial values.

Similarly, inhibitory connections between CTX cells are given by

$$W^{I}_{\mathrm{CTX}_k \to \mathrm{CTX}_i} = f_I e^{-[(k-i)/\sigma_I]^2} \tag{A4}$$

where f_I governs the strength of inhibition.

Each CTX cell projects to a corresponding LA cell, resulting in a one-to-one topographic mapping. Similarly, each LA output in turn serves as an input to a corresponding BA neuron. All subsequent processing stages involve a convergence or fan-in of activity from LA and BA. There is a single activity corresponding to each of the following regions: ITCd, ITCv, and CeM. The excitatory input to ITCd consists of a weighted sum of inputs from LA. The excitatory input to ITCv consists of a weighted sum of inputs from BA. ITCd inhibits ITCv. The excitatory input to CeM consists of a sum of inputs from BA. The inputs to CeM are not weighted, and are not subject to synaptic change.

The activities of the artificial neurons in **Figure 3** are each governed by equation A1, with the excitation term E_s and inhibition term I_s specified in **Table A1**. Weight change occurs via equation A2 in the following sets of weights: W_{CTX_i}, $W_{\mathrm{LA}_i \to \mathrm{BA}_i}$, $W_{\mathrm{LA}_i \to \mathrm{ITCd}}$, and $W_{\mathrm{BA}_i \to \mathrm{ITCv}}$. The teaching signal R for the first three of these sets is given by R^+, which takes a value of 1 when the US is present, and is zero otherwise. The teaching signal R^- for $W_{\mathrm{BA}_i \to \mathrm{ITCv}}$ is assumed to carry complementary information to R^+, and is given by:

$$R^- = (1 - R^+)\mathrm{sgn}\left\{\sum_{i=1}^{N}[x_{\mathrm{BA}_i}]^+\right\} \tag{A5}$$

This term can also be described as a binary expectation-violation signal. If the sign of the sum of BA activities is interpreted as a long-term expectation of the US co-occurring with the CS, then R^- takes non-zero values when there is a discrepancy between the outcome and the expectation encoded by the BA activities, i.e., when $[x_{\mathrm{BA}_i}]^+$ take non-zero values, but there is no US signal, so $R^+ = 0$.

SIMULATION DETAILS

In all the simulations shown here, parameters take the values specified in **Table A2**. The equations are integrated using the simple Euler method, with a step size of 0.00001. The simulations are run for 40,000 time steps, so each epoch lasts for 10,000 time steps. The CSs (CS1 and CS2) and US are rectangular pulses. The onset of US occurs at the half-way point of the CS. The CS and US are reset to zero simultaneously. Activities x_s begin at zero, and are reset whenever the CS signal returns to zero. The values of the strengths of inhibition f_I, excitatory input E_{ILd} from IL to ITCd and excitatory input E_{ILv} from IL to ITCv vary across different simulations, as specified in the corresponding figure captions.

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Top-down modulation of attention by emotion

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Due to their evolutionary salience, threat-related stimuli, such as snakes, spiders, and angry faces constitute a special class of stimuli believed to capture attention in an involuntary, bottom-up manner. Most research in affective neuroscience has focused on unraveling neural pathways that support this "automatic" capture of attention by emotional stimuli (Vuilleumier and Driver, 2007). However, it is well known that in addition to stimulus-driven bottom-up factors (Itti and Koch, 2001), attention is guided by goal-driven, top-down factors (Hopfinger et al., 2000) such as anticipated locations and features of upcoming targets (Moran and Desimone, 1985; Treue and Martinez Trujillo, 1999). In real life, we often utilize emotional information endogenously to guide our attention, for example, when looking for cars while crossing a street or for a restaurant when hungry. These anticipatory search behaviors, aimed at detecting sources of potential threat or reward are deployed in a wide range of habitats from the savannah to social gatherings. Below, we review behavioral and neural data that highlight the importance of emotional factors in top-down voluntary guidance of attention. Based on these findings, we espouse a shift in emphasis from examining emotional factors as primarily impacting attention in a bottom-up manner to examining them in an endogenous, voluntary role wherein emotional information is strategically utilized to guide perception and attention. Cognitive behavioral formulations of anxiety have proposed an important role for threat-related schemata in the development and maintenance of anxiety (Beck, 1976; Mogg et al., 1989). In light of this, research examining the role of expectation and anticipatory attention toward threat will contribute not only to a more comprehensive understanding of normal emotion-attention interactions but also to our understanding of the development and maintenance of anxiety.

BOTTOM-UP CAPTURE OF ATTENTION BY EMOTIONAL STIMULI

To deal with the overwhelming excess of incoming information, the visual system utilizes mechanisms that bias the competition between stimuli toward preferential representation of the most relevant subset of stimuli (Desimone and Duncan, 1995). This biasing process consists of two attentional mechanisms: a bottom-up sensory driven mechanism that biases selection of stimuli based on their physical saliency, and a top-down mechanism, which directs attention endogenously under volitional control. In contrast to the top-down mechanisms, bottom-up attention mechanisms are thought to operate by involuntarily or exogenously shifting attention to salient visual stimuli. For example, stimuli that create a local discontinuity in the visual environment, such as abrupt occurrence of a new object (Jonides and Yantis, 1988), sudden motion (Abrams and Christ, 2003; Franconeri and Simons, 2003), looming, and luminance contrast changes (Enns et al., 2001) are given more attentional priority. Emotional stimuli are another class of stimuli believed capture attention involuntarily (Ohman et al., 2000; Ohman and Mineka, 2001). For example, in visual search arrays, angry faces are detected faster and more efficiently than neutral and happy faces (Eastwood et al., 2001; Tipples et al., 2002) and attentional probes appearing in the same location as threatening faces are detected faster than probes appearing in the opposite location (Mogg and Bradley, 1999; Armony and Dolan, 2002; Pourtois et al., 2004). It remains unclear if the bottom-up capture of attention by an emotional stimulus such a threatening face is driven by specific physical features of the stimulus such as a downward pointing "V," which is similar to the geometric configuration of the face in angry expressions (Larson et al., 2008) or by complex interactions between facial feature configurations and elicited emotion (Lundqvist and Ohman, 2005).

The literature on the impact of emotion on attention has been biased toward examining emotion in a bottom-up role, for example, when attention is captured by an emotional stimulus that "pops out" in a crowd of non-emotional stimuli (Fox et al., 2000; Ohman et al., 2001) or is presented peripherally in a covert attention task (Mogg and Bradley, 1999; Armony and Dolan, 2002), or creates emotion-induced blindness to a preceding or succeeding target in a stream of images (Most et al., 2005), or is the irrelevant to the task (Williams et al., 1996; Algom et al., 2004). This involuntary capture of attention by emotion-related information is hypothesized to involve amygdala and orbitofrontal cortex mediated modulation of visual processing (Anderson and Phelps, 2001; Bar et al., 2006; Vuilleumier and Driver, 2007; Lim et al., 2009) and is considered independent of attention-related frontoparietal modulation of visual processing (Vuilleumier and Driver, 2007), although there is evidence that activity in this network is modulated by attentional demands (Lim et al., 2009).

TOP-DOWN MODULATION OF BOTTOM-UP ATTENTIONAL CAPTURE BY EMOTIONAL STIMULI

Considerable research has shown that bottom-up capture of attention by emotional stimuli and related neural mechanisms, including amygdala and its influence on the visual cortex, is susceptible to top-down factors like task-context and attentional control (Pessoa, 2008; Pessoa and Adolphs, 2010). In addition to these cognitive top-down factors, emotional/motivational top-down factors (e.g., searching for threat or anticipating reward) can modulate bottom-up capture of attention. For example, happy and threatening facial expressions capture attention when they are the target of search (Williams et al., 2005; Hahn and Gronlund, 2007) but not when they are in opposition to task goals, indicating that in addition to stimulus characteristics, emotion-related top-down goals guide the efficiency of facial expression search. Reward contingencies associated with different targets influence priming of pop-out, measured as improved search performance for pop-out targets (e.g., red among green) that are repeated vs. non-repeated on successive trials, indicating a motivational top-down influence of goals on a phenomenon considered sensitive only to bottom-up manipulations (Kristjansson et al., 2010). Reward, promise of reward and punishment are associated with greater perceptual sensitivity on an exogenous spatial attention task (Engelmann and Pessoa, 2007) and greater distractor inhibition (Della Libera and Chelazzic, 2006). In a spatial attention task, words associated with temporary goals hold attention longer than semantically related words, suggesting that these goals influence the allocation of attention (Vogt et al., 2010). Following disgust induction, participants orient toward pictures representing disgust and cleanliness indicating that, in addition to being stimulus-driven, deployment of attention is guided by the goal to alleviate the aversive state (Vogt et al., 2011).

This competition between bottom-up and top-down factors is explicated by the arousal-biased competition (ABC) model of attention which proposes that emotional arousal related to a top-down goal or state can increase attention toward high priority information, while diminishing attention toward low priority information, regardless of whether the information has priority because of its bottom-up attention grabbing nature or top-down goals, expectations, or contexts (Mather and Sutherland, 2011).

TOP-DOWN GUIDANCE OF ATTENTION BY EMOTIONAL CUES

Increasingly, research is showing that emotional information can be employed endogenously to guide attention. Studies are beginning to elucidate the psychological and neural mechanisms involved in anticipatory biasing of attention by threat or reward-related cues. These studies utilize functional neuroimaging and covert attention paradigms wherein attention is engaged voluntarily ("endogenously") via a central cue directing attention toward expected peripheral locations of salient attentional targets (Small et al., 2005; Mohanty et al., 2008, 2009). It is well-established that that the network of brain regions involved in sensory-motor aspects of top-down spatial biasing of attention include posterior parietal cortex (PPC), including intraparietal sulcus (IPS) and extending to inferior and superior parietal lobule (IPL/SPL), lateral frontal cortex, including the frontal eye fields (FEF), and cingulate gyrus, including its anterior (AC) and posterior (PC) segments (Mesulam, 1981, 1999; Corbetta and Shulman, 2002). Recent research on the top-down guidance of attention by emotional cues has focused on understanding how limbic and dopaminergic regions that encode motivational salience of attentional cues interact with the frontoparietal spatial attention network that guides attention toward salient attentional targets.

While it is clear that limbic and frontoparietal regions are involved in motivational guidance of attention, how exactly is prior motivational information integrated with sensory-motor components of spatial attention? One possibility is that emotional and spatial information is integrated in the amygdala, as has been shown in a recent primate study (Peck et al., 2013). An alternative possibility is that the spatial and emotion-related information is integrated by combining anatomically segregated frontoparietal and limbic inputs in the visual cortex. A third possibility is that prior access to spatial and emotional information regarding the attentional target allows the integration of these two sources of information in frontoparietal regions that provide the top-down biasing of visual cortical areas (**Figure 1**). The spatial attention network forms an integrated search template (a "top-down salience map") that combines the spatial coordinates of an event with its task relevance and biases visual neurons in preparation for the search process in both humans and monkeys (Thompson et al., 2005; Gottlieb, 2007; Egner, 2008). IPL and IPS (area LIP) neurons are sensitive to the motivational value of stimuli in monkeys (Mountcastle et al., 1975; Bushnell et al., 1981; Sugrue et al., 2004) and limbic regions such as amygdala are important in assessing the motivational salience of stimuli in humans (Pessoa et al., 2002; Vuilleumier and Driver, 2007), but whether and how these regions communicate is unclear. The rostro-caudal parts of the cingulate gyrus send monosynaptic projections to frontoparietal regions and PC neurons signal reward outcomes associated with shifts of gaze (McCoy et al., 2003) and subjective preferences that guide visual orienting (McCoy and Platt, 2005) in monkeys, raising the possibility that the cingulate gyrus is the conduit for information on motivational salience used by the spatial attention network (Mesulam et al., 1977; Shackman et al., 2011).

Neural hypotheses regarding the integration of emotional and spatial information in frontoparietal brain regions (**Figure 1**) were tested in a study in which centrally-located cues predicted locations of peripherally presented food or tool-related attentional target images (Mohanty et al., 2008). The motivational value of the food targets was experimentally manipulated via hunger and satiety. Hemodynamic responses were measured to the central cues preceding the food targets, as opposed to the target stimuli that are typically imaged in bottom-up attention studies. Results showed increased amygdala, PC, locus coeruleus (LC), and substantia nigra (SN) activity for food-related cues when hungry but not when satiated. Since the spatial resolution of the fMRI does not allow for precise localization of small structures such as the LC and SN, caution must be used when

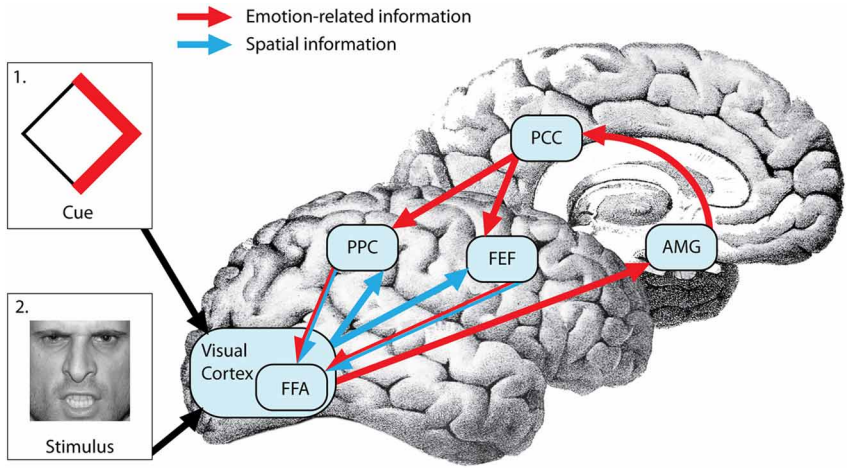

FIGURE 1 | Neural mechanisms of top-down emotional modulation of attention. Prior information regarding upcoming attentional targets (via cue depicted in box 1) is processed in the visual cortex (VC). Emotion-related information from the VC is evaluated in the amygdala (AMG) and projected to the posterior parietal cortex (PPC) and frontal eye fields (FEF) through the post cingulate cortex (PCC). On the other hand, spatial information encoded in the cue is projected from the VC to the FEF and PPC. The FEF and PPC form an integrated search template (a "top-down salience map") that combines the spatial coordinates of the an event with its emotional salience and bias the visual cortex (more specifically fusiform face area or FFA in this case because the attentional target is a face) in preparation for the search process resulting in faster detection of the target (depicted in box 2).

identifying these regions. However, the activation locations found were compatible with locations reported in previous studies (O'Doherty et al., 2002; Wittmann et al., 2005). Furthermore, activation in components of the spatial attention network such as PPC, banks of the IPS, and PC was more positively correlated with the speed of attentional shifts to food targets when hungry than full. These findings indicate that anticipatory allocation of attention via spatial attention regions is sensitive not only to motivational state but also to the motivational value of the upcoming targets. Furthermore, in this study PC neurons were sensitive to the motivational valence of an upcoming stimulus, positively correlated with the speed of attentional shifts to food targets when hungry than full, and showed stronger functional coupling with IPS during spatial biasing of attention toward motivationally relevant stimuli providing support for the possibility that the PC serves as a neural interface between limbic system that encodes motivational value of upcoming targets and the frontoparietal regions that direct attention to these targets.

In another study, *endogenous* guidance of attention was manipulated by predictive cues that offered probabilistic information related to the location and emotional salience of an upcoming stimulus (Mohanty et al., 2009). This study utilized a visual cued search task in which centrally located cues provided spatial information (valid cues indicated the location of upcoming targets while uninformative cues provided no information) and emotional information (valid cues indicated the valence of upcoming targets and uninformative cues provided no information) regarding upcoming peripherally presented targets. While spatially valid cues enhanced the detection of targets, cues validly predicting threatening face targets (endogenously driven attention) resulted in faster reaction times than uninformative cues followed by threatening faces (bottom-up capture of attention), indicating that the emotional cue-related acceleration of spatial attention can be endogenously mediated and is not solely dependent on bottom-up target features. Functional imaging showed, even before the appearance of the target, spatially informative cues activated the spatial attention network including IPS and FEF, as well as fusiform gyrus (FG), whereas cues predicting angry faces also activated limbic areas, including the amygdala. Anatomically overlapping, additive effects of spatial and emotional cueing were identified in IPS, FEF, and FG. The FG also displayed augmented connectivity with the amygdala following angry face cues. These data suggest that anticipatory search for a threatening stimulus elicits amygdala input to the spatial attention network and inferotemporal visual areas, facilitating the rapid detection of upcoming motivationally significant events.

From these studies it is clear that attention can be driven endogenously by both appetitive and aversive factors. Although brain regions involved in the evaluation of motivational value of stimuli (appetitive or aversive) may be different; for example, aversive information may be evaluated in regions such as amygdala (Dolan and Vuilleumier, 2003) while appetitive information is processed in areas including the dopaminergic mid-brain and striatum (O'Doherty et al., 2002), motivational and spatial information regarding attentional targets is integrated in the frontoparietal attention network regardless of stimuli valence. Separate from the effects of attention, expectations regarding upcoming targets can enhance their perception (Summerfield and Egner, 2009). According to the "predictive coding" theory, rather than passively absorbing sensory input, the brain actively predicts what is upcoming, generating a pre-stimulus template against which observed sensory information is matched (Summerfield et al., 2006; Zelano et al., 2011). Knowledge and past experience set expectations for the likely sensory input, facilitating the speed and accuracy of subsequent perceptual judgments. Hence, the expectation of, rather than actual encounter with emotional stimuli may be a key factor in accounting for enhanced perception of these stimuli. Put another way, predictive representations of emotional stimuli might confer a distinct processing advantage compared to neutral stimuli.

In summary, it is clear that the role of emotional factors in anticipatory allocation of spatial attention has been relatively neglected. To understand how emotional factors guide spatial attention, it is necessary to consider not only how they influence involuntary shifts in attention, but also how they voluntarily shift attention

toward visual targets. Furthermore, it is necessary not only to consider emotional and spatial attention effects on spatial orienting, but to assess how these effects are integrated, as well as how emotional features (Lundqvist and Ohman, 2005) may be utilized to guide attention. The examination of voluntary recruitment of attention for threat-related information may yield important clues into both the development and maintenance of anxiety. For example, this research would help clarify how top-down aspects of anxiety, such as worry, rumination, threat-based schemas, and poor attentional control contribute to the development of attentional biases to threat and ultimately contribute to development and maintenance of anxiety.

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The complex interaction between anxiety and cognition: insight from spatial and verbal working memory

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Anxiety can be distracting, disruptive, and incapacitating. Despite problems with empirical replication of this phenomenon, one fruitful avenue of study has emerged from working memory (WM) experiments where a translational method of anxiety induction (risk of shock) has been shown to disrupt spatial and verbal WM performance. Performance declines when resources (e.g., spatial attention, executive function) devoted to goal-directed behaviors are consumed by anxiety. Importantly, it has been shown that anxiety-related impairments in verbal WM depend on task difficulty, suggesting that cognitive load may be an important consideration in the interaction between anxiety and cognition. Here we use both spatial and verbal WM paradigms to probe the effect of cognitive load on anxiety-induced WM impairment across task modality. Subjects performed a series of spatial and verbal *n*-back tasks of increasing difficulty (1, 2, and 3-back) while they were safe or at risk for shock. Startle reflex was used to probe anxiety. Results demonstrate that induced-anxiety differentially impacts verbal and spatial WM, such that low and medium-load verbal WM is more susceptible to anxiety-related disruption relative to high-load, and spatial WM is disrupted regardless of task difficulty. Anxiety impacts both verbal and spatial processes, as described by correlations between anxiety and performance impairment, albeit the effect on spatial WM is consistent across load. Demanding WM tasks may exert top-down control over higher-order cortical resources engaged by anxious apprehension, however high-load spatial WM may continue to experience additional competition from anxiety-related changes in spatial attention, resulting in impaired performance. By describing this disruption across task modalities, these findings inform current theories of emotion–cognition interactions and may facilitate development of clinical interventions that seek to target cognitive impairments associated with anxiety.

Keywords: anxiety, working memory, cognition, startle, electromyography, performance

INTRODUCTION

Anxiety disorders are more prevalent than any other mental health disorder, composing the majority of lifetime mental health disorders worldwide (Kessler et al., 2009). Given this, the study of anxiety is a critical public health issue because it places a considerable emotional, social, and financial burden on both the individual and society as a whole. Along with the emotional facets of the disorder, anxiety patients have difficulty concentrating and report feeling distracted, which in turn can negatively impact their job performance and interpersonal relationships. One popular hypothesis is that working memory (WM) plays a key role in the cognitive problems experienced by anxious people by limiting resources necessary to perform goal-directed tasks (Eysenck and Calvo, 1992; Eysenck, 1998; Shackman et al., 2006; Vytal et al., 2012). Despite difficulties with replicating anxiety-related impairment in the lab (Fales et al., 2008; Porcelli et al., 2008; Qin et al., 2009) WM capacity and performance is shown to be significantly reduced in patient populations (Lucas et al., 1991; Boldrini et al., 2005) and individuals with trait anxiety (Darke, 1988; Eysenck, 1998). WM is central to healthy functioning because it supports online maintenance and manipulation of information (e.g., carrying on a conversation, or tallying the cost of a grocery bill while shopping). Cognitive disruption in anxiety is thought, in part, to reflect the presence of an attentional bias (Robinson et al., under review), where anxiety takes the reins of certain sensory, perceptual, and attentional processes, and threatening information is preferentially processed over other potentially important information (for a meta-analytic review of attentional bias in anxiety see Bar-Haim et al., 2007).

Anxiety's influence on behavior encompasses changes in early perceptual processes as well as changes in higher-order cognitive processes later downstream. Anxiety alters early sensory-perceptual processes in the auditory (Cornwell et al., 2007) and visual system (Lim et al., 2009; Shackman et al., 2011) that may serve to promote threat detection (e.g., detection of auditory tones or visual cues), and this garnering of resources extends

into cognitive-affective biases that are manifested in behavior. Examples of this are found in studies where negatively valenced stimuli are processed more rapidly under anxious conditions (Robinson et al., 2011, 2012). However, this bias may be detrimental to other goal-directed behaviors that are not threat-relevant. As such, performance on tasks that involve attention, maintenance of information, and rapid sensory perception may be impaired.

Further impairment may result from additional competition for resources, this time at the level of executive processes. There are several theories [e.g., processing efficiency (Eysenck and Calvo, 1992), two-component model (Vytal et al., 2012), and hemispheric asymmetry hypothesis (Shackman et al., 2006)] that have built upon this basic premise, and although they are not necessarily mutually exclusive, they make different predictions about the influence of anxiety on cognition. One important distinction that underlies each of these theories is that anxiety can be described by both anxious arousal (e.g., physiological changes in heart-rate variability and eccrine responses, increased vigilance, and priming of other sensory-dependent defensive mechanisms) and anxious apprehension (e.g., awareness of physiological changes, worry, and rumination) (Heller et al., 1997). These two components rely on separable neural systems (Nitschke et al., 1999). In a similar vein, although verbal and spatial WM share many neural resources, they also engage separable neural systems, some of which overlap with the systems above [e.g., anxious apprehension and verbal WM engage dorsal, medial, and ventral prefrontal cortex (PFC) (D'Esposito et al., 1998; Kalisch et al., 2006; Engels et al., 2007; Paulesu et al., 2010), anxious arousal and spatial WM engage unique regions in middle and ventral PFC (Clark et al., 2003; Dalton et al., 2005; Silk et al., 2010), for a meta-analysis of spatial and verbal WM neuroimaging studies see Owen et al., 2005]. As such, although both components of anxiety (anxious apprehension and anxious arousal) are likely to affect any type of WM, they may differentially disrupt verbal and spatial WM. Specifically, anxious apprehension and anxious arousal may preferentially disrupt verbal and spatial WM, respectively. This is because verbal WM processes may share more neural circuitry with anxious apprehension (e.g., mechanisms involved in verbal information encoding and verbal-based worry) and spatial WM may share more neural circuitry with anxious arousal (e.g., mechanisms involved in spatial attention).

Based exclusively on the anxious apprehension component, processing efficiency theory proposes that anxious worry reduces WM capacity in general by competing for executive resources; the greater the worry and the more difficult the task, the greater the disruption (Eysenck and Calvo, 1992). This claim is based on the proposal that worry reduces decreases processing efficiency and increases the amount of effort necessary to perform a task. Increased effort is reflected in *increased RT*, not performance impairment. Alternatively, the two-component model claims that anxious apprehension disrupts WM performance *accuracy*, and that this disruption is greatest when WM tasks are *easy* because there are free resources for anxious apprehension to engage. Further, the two-component model proposes a differential effect of anxiety on verbal versus spatial WM based on competition for a separate combination of resources. The assertion is that high-load verbal WM impairment abolishes the impact of anxiety by engaging top-down emotional control mechanisms (similar to those involved in explicit emotion regulation). In contrast, high-load spatial WM impairment persists, in part because of resource competition with the priming of defensive mechanisms (e.g., perceptual sensitivity, autonomic arousal), which unlike anxious apprehension is sustained regardless of WM load. Finally, others (Shackman et al., 2006) have proposed that anxiety uniquely disrupts spatial WM performance accuracy, because task-irrelevant anxious arousal components and spatial WM processes compete for resources in the right PFC and other more posterior regions (e.g., intraparietal sulcus, posterior parietal cortex). Support for all three theories has been found (see Eysenck and Calvo, 1992) for a review of support for processing efficiency, Vytal et al., 2012 for support of the two component model, and Lavric et al., 2003; Shackman et al., 2006 for findings in line with the hemispheric asymmetry proposal, however, no single study has ever directly compared support for all three theories by combining both task modality (i.e., spatial and verbal) and cognitive load (i.e., task difficulty). Previous research has come close (Shackman et al., 2006), but psychometric differences in low-load tasks prevented explicit evaluation of these two factors.

Recently, a pivotal study on the impact of anxiety on verbal WM processes has provided findings that implicate a central role for cognitive load in the interplay between anxiety and cognition (Vytal et al., 2012). Using *n*-back tasks of varying difficulty during periods of threat (shock) and safety (no shock), the authors found that performance was impaired by anxiety, but only when the task was easy or moderately challenging. When the task was difficult, anxiety was reduced, and performance did not differ between threat and safe conditions. As the first study to show that verbal WM is impaired by anxiety under low cognitive load, and that high-load verbal WM reduces anxiety, it highlights the importance of considering cognitive load in the study of emotion–cognition interactions. Together with key findings that suggest high-load spatial WM is susceptible to anxiety-related impairment (Shackman et al., 2006), these results indicate that although anxiety disrupts both verbal and spatial WM, the presence or degree of disruption is a function of both task modality and cognitive load. Studies that use a translational method of anxiety induction (threat of electric shock, used in conjunction with a no-shock safety condition) find robust anxiety-related performance deficits (Robinson et al., under review). Such studies have found that verbal (Vytal et al., 2012) and spatial WM (Lavric et al., 2003; Shackman et al., 2006) are impaired by anxiety, yet only low-load verbal WM is susceptible to disruption, whereas spatial WM is disrupted under high cognitive load. Thus, at 3-back, there is equitable performance under threat and safety when the task involves verbal stimuli, and impaired performance under threat, when the task involves spatial stimuli. However, it is unknown whether or not low-load spatial WM tasks are susceptible to disruption, and whether there is a differential impact of anxiety on verbal and spatial WM across a varying of cognitive load. In this study we sought to tease apart the impact of anxiety on both verbal and spatial WM, and determine whether or not task difficulty plays a role in this disruption. By determining the precise profile of WM impairment in anxiety, we will

have a more comprehensive understanding of anxiety's impact on cognition. This knowledge can then be used to target the aberrant mechanisms that disrupt cognitive processes in pathological anxiety.

In the current experiment, threat of shock was used to induce sustained anxiety, and anticipatory anxiety was measured using acoustic startle reflex (eye blink) and subjective ratings. The startle reflex is an effective index of anxiety because it is robustly potentiated under anxious conditions, and this potentiation is thought to reflect priming of defense mechanisms in both humans and non-human animals (Davis, 1998; Grillon, 2002). On two separate sessions, participants performed a series of verbal and spatial *n*-back tasks of varying difficulty (1-back, 2-back, and 3-back) under threat and safe (no shock) conditions. Based on evidence that suggests low and medium-load verbal WM (Vytal et al., 2012) and other low-load tasks are disrupted by anxiety (Lavie, 2005) (but in opposition to the processing efficiency theory and the hemispheric asymmetry hypothesis), we predicted that both verbal and spatial low-load and medium-load WM (i.e., 1-back and 2-back) would be impaired under threat versus safe conditions. Here, we define impairment as a decrease in performance accuracy. However, we predicted that high-load spatial WM but not verbal WM would be affected by anticipatory anxiety (i.e., performance would be impaired during threat compared to safe conditions). These hypotheses are based on previous findings and predictions from both the two-component model and hemispheric asymmetry hypothesis that suggest high-load verbal and spatial WM are differentially impacted by anxiety. Finally, we predicted that individual differences in state anxiety (as indexed by anxiety potentiated startle and state anxiety ratings) would be negatively correlated with individual differences in performance, indicating that greater anxiety is associated with greater anxiety-related cognitive impairment. Along these same lines, we predicted that anxiety-potentiated startle would be positively correlated with anxiety (consistent with the claim that startle potentiation indexes anxiety). These predictions were all based on previous research suggesting that individual differences in anxiety predict impairment and startle potentiation is a robust index of anxiety (Shackman et al., 2006; Vytal et al., 2012). In summary, we expected that anxiety would differentially impact verbal versus spatial WM across increasing levels of cognitive load, such that (1) anxiety induction would impair lower-load (1-back and 2-back) but not higher-load (3-back) verbal WM, and (2) anxiety induction would impair both low and high-load spatial WM.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-seven healthy individuals (13 males) received monetary compensation for their participation in the study. Participants were recruited for the study via online resources, paper flyers, and advertisements placed in local newspapers. Upon arrival, participants completed an intake evaluation consisting of a brief physical exam, urine screen, and a Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). Exclusion was based on the following criteria: (1) past or current psychiatric disorder(s), (2) contraindicated medical condition, and (3) use of psychoactive medications or illicit drugs. Three participants were excluded because of equipment failure. The final group of participants consisted of 24 adults (11 males; mean age 29.5 years; age range: 18–46 years). Subjects provided written informed consent that was approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health.

STIMULI AND APPARATUS

All visual stimuli were presented on a PC using Presentation® software (Version 0.70, www.neurobs.com). Presentation® software was also used to control all electric shocks and startle probes via a commercial system (Contact Precision Instruments, London, United Kingdom). Shocks (up to 5 mA and 200 ms duration) were produced by a constant current stimulator and administered to the median nerve of the left wrist using two 6 mm Ag/AgCl electrodes. Shock level was determined independently for each participant using a shock workup procedure where the shock level began at 3.5 mA and was increased by increments of 0.2 mA until the subject rated the shock as highly uncomfortable, but still tolerable ($M = 5.9$; $SD = 2$) based on a 1–9 scale (1, not at all painful, to 9, extremely painful). Acoustic startle probes [40 ms, 103 dB(A), near instantaneous rise/fall times] were presented binaurally through over-the-ear headphones. The eye blink reflex was measured using two 6 mm Ag/AgCl electrodes (impedances below 15 kΩ) placed over the orbicularis oculi muscle under the left eye. Electromyographic (EMG) data were recorded by Psylab 7 software (Contact Precision Instruments, London, UK).

PROCEDURE

Procedures and task-design were identical to the those described in (Vytal et al., 2012), with the exception that in the current study, there were two sessions (counterbalanced order), one for the verbal *n*-back and the other for the spatial *n*-back (similar in design except that the location of a red star in one of four corners of a diamond was the target, as opposed to a letter). The basic layout was the same across sessions. To assess stable trait anxiety and experiment-induced state anxiety, all participants completed the Spielberger state-trait anxiety inventory (STAI; Spielberger et al., 1983) when they first arrived. Prior to the experiment, participants practiced all four levels (view, 1-back, 2-back, and 3-back) of each task (spatial and verbal) to reduce changes in performance as a result of learning. Participants indicated "same" or "different" with a keyboard button press based on the stimulus (verbal: letter, spatial: location) 1-back, 2-back, or 3-back from the current stimulus, or simply attended to the stimuli ("view" task) without making a response (see **Figure 1B** for a sample verbal block and **Figure 1C** for a sample spatial block). Following practice, participants were presented with nine startle probes every 17–20 s during a rest period in order to habituate initial startle reactivity.

Each session included four experimental runs, consisting of eight alternating threat and safe blocks (see **Figure 1A** for a sample run). Participants were reminded of the condition they were in [threat (at risk to receive shock) or safe (no shocks were delivered)] by colored borders (verbal: the word THREAT or SAFE was written inside, spatial: a red or blue border, represented threat and safe, respectively). Each run began with three habituation probes,

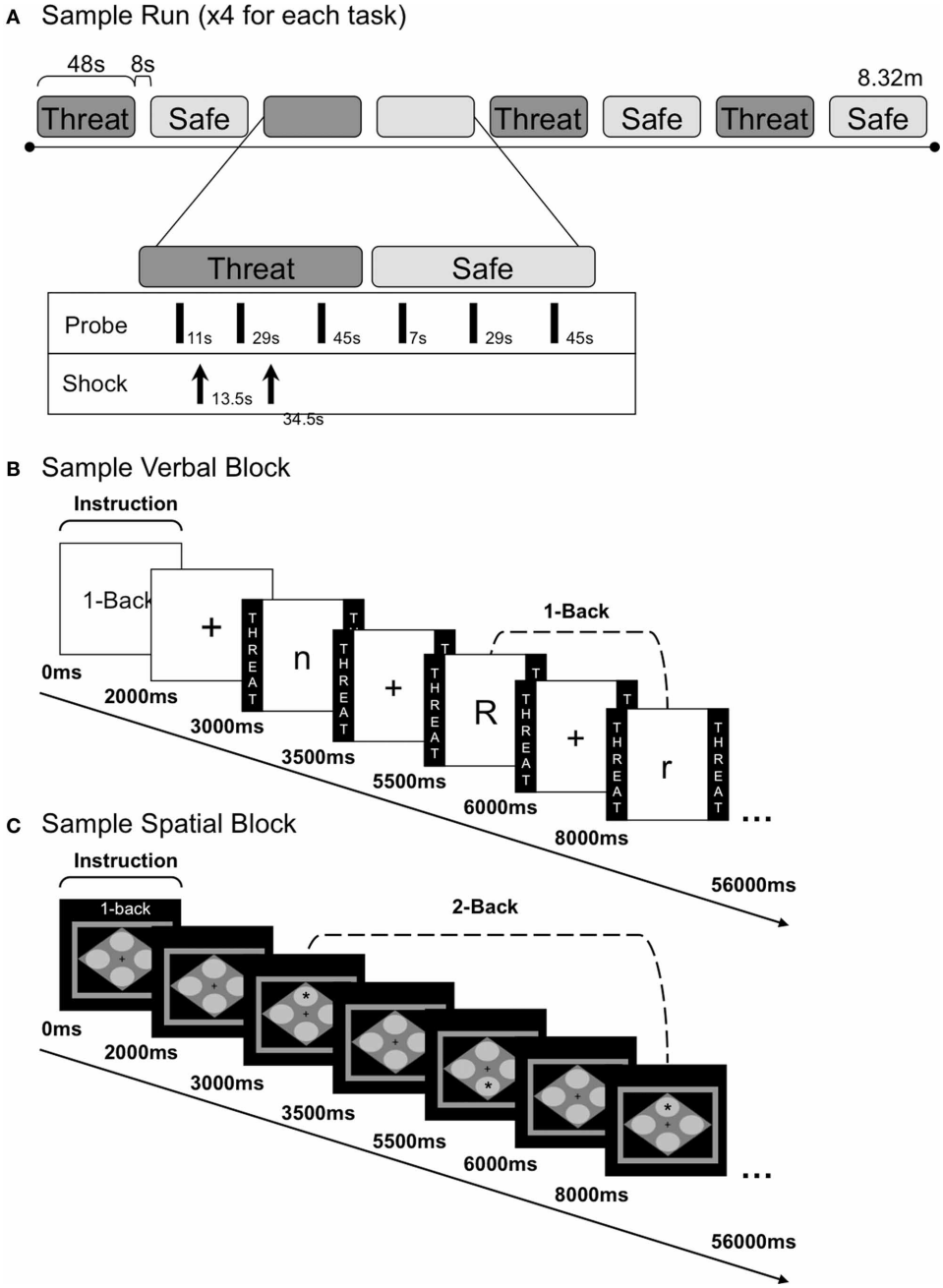

FIGURE 1 | Task run and block structure. (A) Schematic diagram of a sample run with alternating threat and safe *n*-back blocks. During each *n*-back block, three acoustic probes were delivered. Shocks were delivered three times during each run (with 0–2 shocks each threat block). **(B)** Sample verbal 1-back block and internal trial structure. Each block began with an instruction screen, followed by a fixation cross. Eighteen letters were presented in succession during each block, separated by a 2 s ITI (fixation). Participants made a keyboard button press response for every letter presented; one button indicated a target letter (e.g., "r") and another button indicated a distractor letter (e.g., "n" and "R"). During the view condition subjects attended to the letters without making a button press. **(C)** Sample spatial 2-back block and internal trial structure. Block structure was identical to the verbal *n*-back except that spatial stimuli were used. Participants made a keyboard button press response every time a star appeared in one of four locations; one button indicated a target location (e.g., "top") and another button indicated a distractor location (e.g., "bottom").

followed by a 2-s instruction screen (e.g., "1-back") and a 1000 ms fixation cross. Stimuli (18 in each block; 144 per *n*-back task; 288 threat, 288 safe) were presented for 500 ms each, separated by 2000 ms (±250 ms) fixation inter-trial intervals (ITIs). All verbal stimuli were presented in Arial, 48-point font in the center of the screen. Verbal *n*-back targets consisted of eight letters (B, F, K, H, M, Q, X, R), in both upper and lowercase to reduce reliance on perceptual similarity (as such, "b" and "B" were treated as

identical targets). The spatial *n*-back target was a single asterisk, Arial 64-point font, successively presented in one of the four corners of a gray diamond (height: 7.5 cm, width: 10.8 cm), centered in the middle of the screen. During the ITI, twelve shocks (0–2 per threat block; 3 per run) and nine startle probes (every 17–20 s) were administered. To reduce sensitization effects of the shocks on startle, shocks preceded probes by at least 16 s, and followed probes with a mean latency of approximately 2 s. Shocks were only delivered during half of the threat blocks to prevent shock desensitization and to reduce potential effects of the shock itself (versus anticipation of the shock) on performance and startle. Blocks were separated by an 8 s inter-block interval.

DATA REDUCTION AND ANALYSIS

EMG data were sampled at 1000 Hz, filtered (30–500 Hz), rectified, and smoothed with a 20-ms time constant. Startle responses were defined as the peak magnitude of the eye blink reflex (20–100 ms after stimulus onset) relative to a 50-ms average baseline that immediately preceded the probe onset. Less than one percent of trials was excluded based on large baseline artifacts. T-score transformation was used to attenuate large inter-individual differences in raw reflex magnitude. Peak eye blink magnitudes were T-scored (across all conditions) and averaged within each condition for each subject. For correlation analyses, differential accuracy scores (threat–safe) and differential startle scores (threat–safe) were averaged across 1-back, 2-back, and 3-back blocks, resulting in an aggregate impairment score and aggregate startle potentiation score for each subject. To confirm that accuracy did not differ as a result of shock or probe administration, trials that preceded or followed shocks, and those that preceded or followed probes were analyzed separately. No differences were found and all trials were included in the final analysis. Trials where participants failed to respond before the next stimulus appeared on the screen (i.e., 2500 ms post-stimulus onset) were omitted. However, such omissions were uncommon and unsystematic. A series of binomial tests at the individual level confirmed that all participants included in the final analysis performed above chance. Alpha was set at 0.05 for all statistical tests. Repeated-measures ANOVAs, paired *t*-tests, and Pearson product moment correlation coefficients were all used to assess statistical significance. Greenhouse–Geisser corrections (GG-ε) were used for repeated-measures ANOVAs that involved factors with three or more levels.

PSYCHOMETRICS

We sought to examine the impact of anxiety on different modalities of WM (verbal and spatial) as well as different levels of cognitive load. As such, it was important to investigate psychometric equivalence so that discrete inferences about the differential effect of anxiety could be made in the absence of a double dissociation (where two or more experimental manipulations have opposing effects on two or more dependent variables) (Shackman et al., 2006). To determine psychometric equivalence we calculated discriminating power (Chapman and Chapman, 2001), which quantifies the sensitivity of a test to detect an experimental manipulation (or a group difference) between tasks where differences were found (see the results section for a full description of these findings). Discriminating power was computed by multiplying the accuracy variance across baseline (safe) runs by the reliability in accuracy (Cronbach's coefficient alpha) across those same runs. Comparison of verbal and spatial *n*-back discriminating power at high load (3-back) demonstrated that sensitivity did not differ between the two tests [$t_{(23)} = 1.92$, $p > 0.05$; $M = 33.36$ (verbal 3-back), $M = 49.25$ (spatial 3-back)]. This is critical because the differential impact of anxiety on cognitive load between verbal and spatial stimuli was present only in the high-load data. Further, we confirmed that task difficulty was equivalent between 3-back verbal and spatial WM tasks, [performance: $t_{(23)} = -1.25$, $p = 0.226$], suggesting that the tasks were similarly challenging and that impact of threat on 3-back spatial performance cannot be attributed to the fact that it was less challenging than verbal 3-back. In addition, comparison of verbal low-load to high-load discriminating power demonstrated that sensitivity was greater in the high-load task than in the low-load task [$t_{(23)} = 5.39$, $p < 0.001$; $M = 33.36$ (high-load), $M = 12.72$ (low-load)]. Given that low-load verbal WM tasks were found to be *less* sensitive than high-load verbal WM tasks, anxiety-related performance differences in low-load tasks cannot be attributed to greater discriminating power.

RESULTS

MANIPULATION CHECK

Anxiety

Without verification that our anxiety manipulation was successful, it would be difficult to clearly interpret any performance differences observed. Anxiety ratings in both studies indicated that subjects experienced more anxiety when they were at risk for shock [verbal: threat $M = 5.5$, safe $M = 2.2$, $t_{(23)} = 7.6$, $p < 0.001$; spatial: threat $M = 5.3$, safe $M = 2.1$, $t_{(23)} = 10.1$, $p < 0.001$]. In addition to self-report, we used startle magnitude to verify that threat of shock successfully induced anxiety. Startle was consistently potentiated by threat of shock, $F_{(1, 23)} = 67.1$, $p < 0.0001$, $\eta^2 = 0.75$, confirming the manipulation. Moreover, anxiety-potentiated startle (threat–safe) was reduced by load [$F_{(3, 69)} = 12.7$, $p < 0.001$, $\eta^2 = 0.36$], indicating that load decreased anxiety [confirmed by a linear trend: $F_{(1, 23)} = 34.9$, $p < 0.0001$, $\eta^2 = 0.60$]. Startle did not differ as function of WM modality [Modality × Anxiety × Load = $F_{(3, 69)} = 1.4$, $p = 0.252$, $\eta^2 = 0.06$].

Load

To verify that the *n*-back tasks of varying difficulty resulted in differing levels of cognitive load (reflected by performance), a repeated measures ANOVA was conducted across WM task modalities. The main effect of Load on performance was significant, $F_{(2, 46)} = 113.0$, $p < 0.0001$, $\eta^2 = 0.83$, indicating that regardless of task modality and condition, overall WM performance differed across levels of cognitive load. A linear trend demonstrated that as load increased, performance decreased [$F_{(1, 23)} = 200.3$, $p < 0.0001$, $\eta^2 = 0.90$], indicating that the more demanding tasks were in fact more challenging. To investigate this effect further, the results were considered separately for verbal and spatial tasks. Both verbal and spatial WM performance was impacted by Load, [$F_{(2, 46)} = 50.8$, $p < 0.0001$,

$\eta^2 = 0.69$ and $F_{(2, 46)} = 50.1$, $p < 0.0001$, $\eta^2 = 0.69$, respectively], and planned comparisons indicate that as task difficulty increased, performance was progressively worse [verbal: 2-back performance was lower than 1-back, $t_{(23)} = -3.9$, $p < 0.002$; and 3-back performance was lower than 2-back, $t_{(23)} = -5.8$, $p < 0.001$, spatial: 2-back performance was lower than 1-back, $t_{(23)} = -4.1$, $p < 0.001$; and 3-back performance was lower than 2-back, $t_{(23)} = -8.1$, $p < 0.001$].

PERFORMANCE

Consistent with our predictions, the critical three-way interaction between Modality, Anxiety, and Load, was significant, $F_{(2, 46)} = 3.5$, $p < 0.04$, $\eta^2 = 0.13$, indicating that anxiety had a differential impact on overall WM performance across load. To decompose this interaction, performance data were analyzed separately for verbal and spatial WM tasks. For verbal WM, the interaction of Anxiety and Load was significant, $F_{(2, 46)} = 6.9$, $p < 0.003$, $\eta^2 = 0.23$, reflecting the finding that 1-back and 2-back performance was impaired during threat as compared to safe [$t_{(23)} = -2.5$, $p < 0.03$, and $t_{(23)} = -3.1$, $p < 0.006$, respectively], but 3-back performance did not differ between conditions [$t_{(23)} = 1.7$, $p = 0.101$] (see **Figure 2**). Further, performance differences between threat and safe (i.e., threat–safe) were greater for 1-back and 2-back tasks as compared to 3-back [$t_{(23)} = 2.2$, $p < 0.05$, and $t_{(23)} = 2.3$, $p < 0.04$, respectively]. We confirmed that these findings were not driven by speed and accuracy tradeoffs, with RT analyses demonstrating that RT did not differ between threat and safe across Load, $F_{(2, 46)} = 0.170$, $p = 0.845$, and more specifically, RT differences (threat–safe) were not significantly different between low (1 and 2-back) and high load (3-back) [$t_{(23)} = 0.2$, $p = 0.857$, and $t_{(23)} = 0.3$, $p = 0.741$, respectively] (see **Table 1** for RT means and standard errors of the mean). These findings suggest that in the case of verbal WM, lower-demand tasks are susceptible to disruption by induced-anxiety, whereas higher-demand tasks are not. In contrast to the verbal WM results, there was not a significant Anxiety × Load interaction for spatial WM, $F_{(2, 46)} = 0.31$, $p < 0.738$, $\eta^2 = 0.01$. However, there was a significant main effect of Anxiety on performance, $F_{(1, 23)} = 18.8$, $p < 0.001$, $\eta^2 = 0.449$, indicating that spatial WM performance was impaired overall during threat as compared to safe, regardless of task difficulty (see **Figure 2**). This finding indicates that under both low and high cognitive load, an anxiogenic context impaired spatial WM. As with verbal WM, we confirmed that RT did not differ between threat and safe across Load for spatial WM, $F_{(2, 46)} = 2.6$, $p = 0.085$.

Table 1 | Mean reaction time for verbal and spatial working memory as a function of experimental condition and cognitive load.

	1-back	2-back	3-back
VERBAL			
Threat	703 (32)	787 (41)	793 (44)
Safe	712 (35)	778 (40)	792 (40)
SPATIAL			
Threat	721 (31)	834 (48)	846 (42)
Safe	756 (42)	816 (47)	870 (48)

Note: Standard errors of the mean appear in parentheses to the right of each mean.

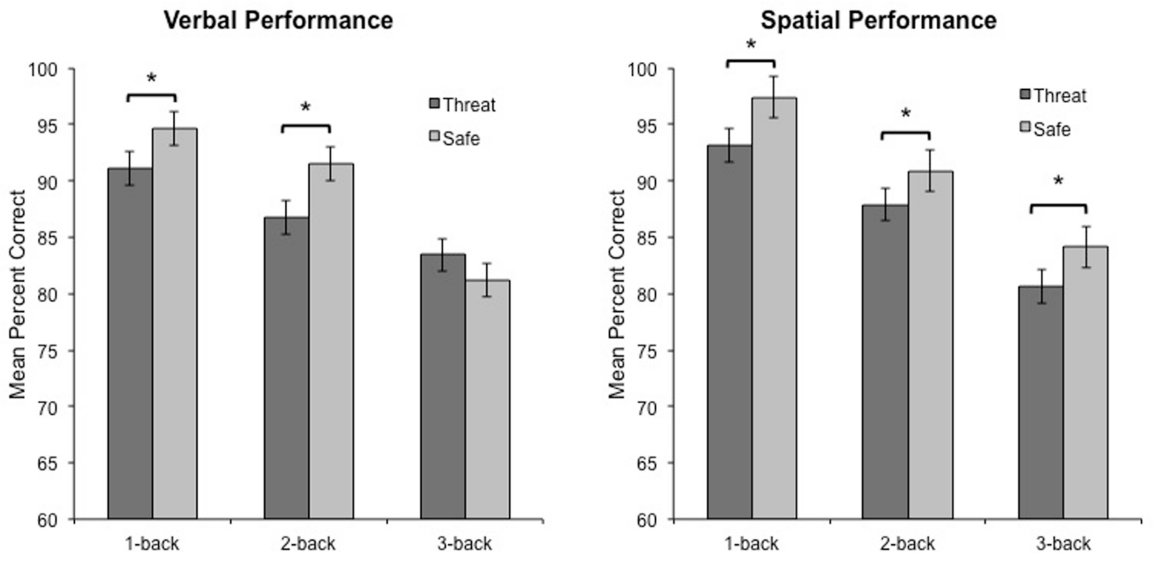

FIGURE 2 | Verbal and spatial *n*-back performance during threat and safe. Verbal performance was impaired during threat compared to safe when participants were engaged in low-load tasks (1-back and 2-back), but not high-load tasks (3-back). In contrast, spatial performance was impaired during threat compared to safe when participants were engaged in any task, irrespective of difficulty. Error bars represent the within-subjects standard error for the repeated-measures general linear model (GLM) comparing different levels of Load under threat (dark gray bars) and safe (light gray bars) conditions separately. Within-subject standard error was calculated by dividing the square root of the mean standard error for the GLM divided by the square root of n (Masson, 2003). $*p < 0.01$.

CORRELATIONS

There was a negative correlation between anxiety-potentiated startle and differential performance under threat (threat–safe) for both verbal, $r = -0.44$, $p < 0.04$, and spatial WM, $r = -0.41$, $p < 0.05$, demonstrating that increased startle potentiation was associated with increased WM impairment (see **Figure 3** for scatterplots). In line with this, there was also a negative correlation between state anxiety and differential performance under threat in verbal, $r = -0.41$, $p < 0.05$, and spatial WM, $r = -0.61$, $p < 0.01$, reinforcing the idea that high levels of anxiety were associated with greater verbal WM impairment. Additionally, we confirmed that anxiety-potentiated startle was a good index of anxiety (as assessed by state anxiety scores) in both tasks (verbal: $r = 0.66$, $p < 0.01$; spatial: $r = 0.47$, $p < 0.03$). Together, these findings suggest that anxiety is a strong predictor of threat-related verbal WM impairment.

To further unpack the interaction of Modality and Load on anxiety-related WM impairments, and to address the prediction that verbal WM will be more sensitive to parametric modulation of task difficulty, we subtracted the difference between threat and safe during high load (performance and startle), from the difference between threat and safe during low load (performance and startle) and conducted a correlation analysis. As predicted, we found that the differential anxiety-potentiated startle scores were negatively correlated with the differential performance scores (1-back minus 3-back) for verbal WM ($r = -0.58, p < 0.02$), but not spatial WM ($r = -0.17$, $p = 0.44$). Moreover, Fisher's z-test confirmed that these two correlations were significantly different, $z = 1.7$, $p > 0.05$. This negative correlation indicates that the more anxiety-potentiated startle was reduced from 1-back to 3-back (i.e., indicating reduction in anxiety), the better the performance improvement was from 1-back to 3-back in threat

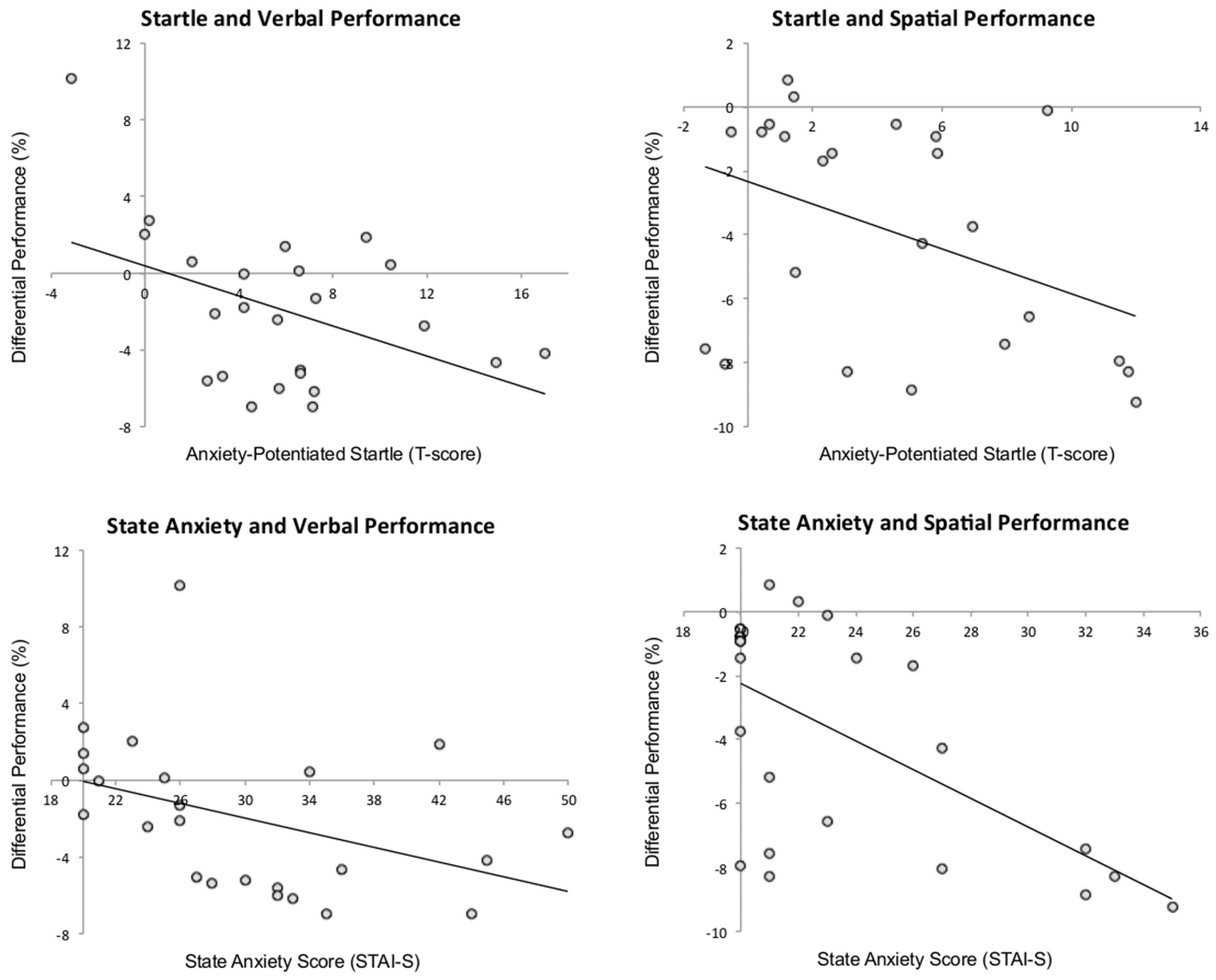

FIGURE 3 | The relationship among anxiety-potentiated startle, performance (threat–safe), and state anxiety. Startle potentiation was negatively correlated with verbal and spatial working memory performance, and state anxiety was negatively correlated with verbal and spatial working memory performance. $p < 0.05$ for all correlations.

versus safe. This suggests that load is an important manipulation in characterizing the impact of anxiety on verbal WM performance, and that it is less critical in characterizing the impact of anxiety on spatial WM performance.

DISCUSSION

GENERAL DISCUSSION AND OVERVIEW OF FINDINGS

Anxiety helps maintain a state of readiness. It facilitates threat processing and defensive responding but it also prompts cognitive changes. Studying these changes using dual-task paradigms may help to clarify behavioral performance under stress (test anxiety, decision making/planning in the battlefield or during an emergency) and emotion regulation mechanisms. In addition, this line of research can identify specific cognitive deficits associated with anxiety and anxiety disorders. Concerning the latter, the present study suggests that the cognitive and defensive components of anxiety interfere with WM tasks but to a different degree, such that anxious apprehension has more of a domain-general impact on WM, high-load verbal WM engages top-down control mechanisms that abolish anxiety-related disruption, and spatial WM is more vulnerable to the effects of anxious arousal.

As predicted, induced-anxiety impaired both verbal and spatial WM processes, but anxiety had a different impact on performance when cognitive load was considered. Results demonstrate that low-load verbal WM is more susceptible to anxiety-related disruption and spatial WM is disrupted regardless of task difficulty. Well-validated measures of anxiety (state anxiety and startle potentiation) strongly predicted variability in performance impairment, underscoring the specificity of these effects. These novel results provide a framework for understanding the interaction between anxiety and two distinct modalities of WM, by emphasizing the effect of cognitive load on performance. Further, these findings are in line with the two-component model (Vytal et al., 2012), which proposes a differential effect of anxiety on verbal versus spatial WM based on competition over two separable neural circuits [a conceptual distinction that was proposed but not substantiated in prior work (Shackman et al., 2006)].

INTEGRATION WITH CURRENT THEORIES

While there is clear support for the two-component model of anxiety, the processing efficiency theory (Eysenck and Calvo, 1992) receives only limited support and the hemispheric asymmetry hypothesis (Shackman et al., 2006) serves as only a partial explanation for these findings. First, our data do not support a key prediction of processing efficiency theory [and its offshoot, attentional control theory (ACT) (Eysenck et al., 2007)], namely, that anxious worry increases RT. However, although we did not find RT differences between any of our conditions, we found performance differences in partial support of these theories. Processing efficiency theory and ACT predict that anxiety impairs high-load WM is impaired when a subject is anxious, regardless of the task modality, yet our findings suggest that only spatial WM is disrupted under high cognitive load. Similarly, the hemispheric asymmetry hypothesis proposes that processes which rely heavily on the right hemisphere [e.g., spatial attention (Corballis et al., 2002; Manoach et al., 2004)] are disrupted by anxiety because anxious arousal consumes right hemisphere resources (Clark et al., 2003; Dalton et al., 2005). This prediction holds true to an extent; spatial WM is disrupted by anxiety (Lavric et al., 2003; Shackman et al., 2006), and it is plausible that this disruption is the result of competition for shared resources between spatial attention and automatic priming of defensive mechanisms. However, there is now ample evidence to suggest that anxiety also impairs verbal WM (Markham and Darke, 1991; Ikeda et al., 1996; Vytal et al., 2012), leaving that mechanism of impairment undefined.

The two-component theory of anxiety fills this explanatory gap by describing a specific mechanism for verbal WM disruption. Anxiety, which is comprised of a cascade of physiological and neural responses, is best characterized by two separable components: (1) an anxious apprehension component (Heller et al., 1997) that engages executive resources and includes anxiety-related cognitive processes like worry, and (2) an automatic preparatory response that primes defensive mechanisms (Lang et al., 1998), increases perceptual sensitivity (Cornwell et al., 2011), and enhances autonomic arousal (e.g., increases in heart rate and blood pressure) (Bandura, 1988). Although this distinction is not new (Heller et al., 1997) the application of such framework to modality-specific WM disruption is novel. The anxious apprehension component and automatic preparatory component engage separable neural circuits (Nitschke et al., 1999), and as a consequence, they have a differentiable impact on processes that share these same respective neural resources. Established neural correlates of verbal and spatial WM (D'Esposito et al., 1998) overlap with the anxious apprehension and preparatory component circuitry respectively. With respect to verbal WM (D'Esposito et al., 1998; Kalisch et al., 2006) and anxious apprehension (Engels et al., 2007; Paulesu et al., 2010), such regions include bilateral dorsal, medial, and left ventral PFC, and with respect to spatial WM (Manoach et al., 2004) and the preparatory component (Clark et al., 2003; Dalton et al., 2005), such regions include right dorsal/mid and ventral PFC.

Thus, it appears that when anxiety promotes adaptive responses to threat [e.g., increased heart rate (Bandura, 1988), potentiation of visual (Shackman et al., 2011) and auditory perception (Cornwell et al., 2007), amplified attention to emotionally negative stimuli (Robinson et al., 2012)], such changes commandeer neural resources that are critical to WM maintenance. These resources can be reappropriated by increasing the demands of a verbal task, in turn reducing anxiety and normalizing performance in the face of threat (Rapee, 1993; Vytal et al., 2012). Of note, both easy (e.g., 1-back) and moderately difficult (2-back) verbal WM tasks are disrupted by anxiety, indicating that even when there is partial competition for resources, anxiety continues to control shared neural real estate. Only when task demands increase sufficiently to significantly (or completely) consume resources, is the effect of anxiety on performance abolished. Top-down emotional control mechanisms and domain-general WM are mediated by the same neurocognitive mechanisms [e.g., lateral PFC (Brodmann area 9) and dorsomedial PFC (Brodmann area 6); for meta-analytic reviews of WM neuroimaging studies see Owen et al., 2005; Nee et al., 2013, for explicit emotional regulation studies see Ochsner et al., 2004; Kim and Hamann, 2007; Diekhof et al., 2011], suggesting that

down-regulation of anxiety may occur through either conscious or incidental regulation. However, increasing the demand of a spatial task does not result in normalized performance; accuracy is still impaired even under high-demand spatial WM maintenance. We propose that there are three potential reasons for this sustained impairment. First, in line with the hemispheric asymmetry hypothesis, anxiety shares a greater amount of critical resources with spatial WM processes [including spatial attention (Cornwell et al., 2008), perception, and maintenance] and therefore has a greater impact on spatial WM. Second, physiological changes associated with defensive readying (i.e., changes in spatial attention, visual acuity etc.) are more protracted (Bonanno et al., 1995) and may be less frequently and more circuitously subject to explicit regulation than cognitive responses to stress (top-down control of lower-order subcortical processes that promote survival may be more difficult than cortical control of other higher-order cortical responses). As a consequence, difficult spatial WM processes that share critical mechanisms with defensive preparations may continue to be disrupted. Third, although cognitive load can reduce anxiety and threat-related distraction (Vytal et al., 2012), defensive mechanisms remain intact under high load to promote survival, and as a consequence spatial WM impairment associated with these mechanisms may also persist.

IMPLICATIONS FOR PATHOLOGY

Clinical anxiety is associated with known disruptions in the cognitive domain, including WM (Lucas et al., 1991; Boldrini et al., 2005) spatial perception (Jacob et al., 1985; Simon et al., 1998), and spatial navigation (Cohen et al., 1996; Mueller et al., 2009) among others. These disruptions, however, are accompanied by facilitation in related domains, like visual threat detection (Bar-Haim et al., 2007), which may be supported by modulation of early sensory processes in anxiety disorders (Morgan III and Grillon, 1999; Ge et al., 2011). It follows that the greatest negative impact of this facilitation is on tasks that share resources with processes that support threat detection (e.g., a spatial WM task that requires rapid detection and sustained maintenance of perceptual information). Our findings support this claim, by demonstrating that anxiety-induction in healthy individuals results in robust impairment of spatial WM. These parallels also validate the use of threat of shock to model pathological anxiety in healthy individuals (for a review on the similarities between findings from threat of shock paradigms and pathological anxiety, see Robinson et al., under review). It is important to note however, that in addition to changes in spatial attention and perception, pathological anxiety [in particular, generalized anxiety disorder (GAD) (Brown et al., 1992)] is also associated with higher-order cognitive processes like excessive worry that involve verbally-based changes in thought (Borkovec and Inz, 1990). Here, our findings add additional insight into WM disruption; easy verbal WM task performance is impaired by anxiety, but more difficult verbal tasks result in normalized performance. These findings have critical implications for understanding the nature of disruption (as described earlier), detecting anxiety-related impairment(s), and improving treatment of different anxiety disorders.

Although anxiety can be viewed as a continuous psychological construct, with a threshold of severity separating health and pathology, anxiety disorders are comprised of categorically-separable manifestations of anxiety, with markedly different symptom profiles[1]. GAD, for example, is characterized by excessive worry (Borkovec and Inz, 1990; Brown et al., 1992), whereas panic disorder (PD) is characterized in terms of somatic symptoms that center on cardiovascular changes (Katon, 1984). By focusing on central symptoms of each patient and identifying the etiology of such symptoms, appropriate treatment methods can be better applied. For example, overloading the verbal WM system is shown to reduce threat-related cognitive distraction and reduce anxiety-related WM impairments (Vytal et al., 2012). Techniques like cognitive behavioral therapy can take advantage of this and integrate similar procedures in the treatment of patients with GAD. On the other hand, individuals with somatic anxiety symptoms (e.g., PD) may exhibit greater spatial impairments including orientation (Jacob et al., 1985; Simon et al., 1998) and WM (Boldrini et al., 2005), thus identifying cognitive markers for the disorder. In contrast to overloading the WM system, effective treatment for PD may include addressing the somatic aspects of the disorders with pharmacological interventions that alter noradrenergic function [e.g., imipramine or alprazolam (Charney et al., 1986)], compounds that selectively gate communication between amygdala and brainstem known to support physiological responses to threat [the medial part of the central nucleus of the amygdala and the dorsal vagal complex (Viviani et al., 2011)], and therapeutic interventions like progressive relaxation that target somatic symptoms (Davidson, 1978).

STRENGTHS AND LIMITATIONS

A major strength of the study was the use of a within-subject design, which increases statistical efficiency (i.e., the ability to detect an effect), and decreases the potential that group differences are driven by the individuals that comprise it rather than the experimental manipulation (because the groups are made of identical participants). Another advantage of this design was the use of an anxiety-induction manipulation where (1) subjects could serve as their own controls and (2) the emotional *state* of anxiety could be isolated without the complications of pathology or trait variable that may or may not index the state of interest. Further, the parametric nature of the design afforded the detection of different impairment patterns in spatial versus verbal WM across levels of cognitive load, an effect that is novel and one that holds important theoretical implications.

Limitations of the study included the type of stimuli used, the lack of a direct measure of anxious apprehension, and the use of a healthy sample. The stimuli used in the verbal and spatial tasks were not identical, as those in some previous studies were (Lavric et al., 2003; Shackman et al., 2006), which could account for a portion of the variability in performance between the two tasks and could introduce uncertainty in the strategies used (verbal or spatial) in each task. However, (1) the tasks were psychometrically

[1]However, it is important to note that comorbidity across different internalizing disorders suggests that a common construct links them (Watson, 2009).

matched, suggesting they were similarly susceptible to anxiety-related disruption, (2) subjects reported using verbal strategies (e.g., subvocalization) in the verbal task and spatial strategies (e.g., mentally superimposing visual representations), strategies that were only successful for the task in which they were used, suggesting that the tasks successfully tapped verbal and spatial WM, and (3) by using different stimuli, participants were not required to switch strategies on the same set of stimuli, possibly introducing interference effects and changing the nature of the task. Other task-specific potential limitations include the issue of equating difficulty between the verbal and spatial tasks in order to accurately interpret the differential effect on performance. To address this, we examined baseline (i.e., during safe) performance and found no difference between verbal and spatial WM tasks. These findings suggest that task difficulty did not differ between modalities because cognitive effort and performance accuracy was equivalent. In addition, we make claims about the presence of anxious apprehension without presenting a direct measure of this component. While the Penn State Worry Questionnaire (Molina and Borkovec, 1994) may be a viable measure, future studies should also obtain online worry ratings for comparison between experimental conditions. Finally, it is important to note that our sample consisted of healthy individuals, not anxiety patients, and any conclusions drawn regarding pathological anxiety or clinical interventions should be interpreted with caution. Although we identified mechanisms of impairment, these mechanisms may be manifested differently in anxious individuals. Future research should include patient samples to identify and contrast pathological anxiety-related cognitive impairment.

CONCLUSIONS AND FUTURE DIRECTIONS

Previous research has struggled to identify the mechanisms of cognitive impairment in anxiety, despite the obvious presence of cognitive disruption in both state and clinical anxiety. Most individuals have experienced intense apprehension, along with sweaty palms and heart pounding, that can serve to debilitate them during goal-directed behavior such as giving a public speech. Patients who suffer from social anxiety are crippled when entering a jovial room full of party-guests, or an important staff meeting at work. The impact of anxiety on cognition is undeniable. Here we systematically pinpoint where anxiety disrupts verbal and spatial WM processes, highlighting the importance of task modality and cognitive load. In sum, our findings demonstrate that (1) anxiety disrupts both verbal and spatial WM, (2) that this disruption is only present in low and medium-load verbal WM, and (3) that this disruption is present in spatial WM regardless of task difficulty. We propose that there are separable neural mechanisms of disruption that arise from competition with two different components of anxiety (anxious apprehension and priming of defensive mechanisms), resulting in the aforementioned pattern of impairment. Future research should investigate the neural underpinnings of this disruption to verify these mechanisms of impairment and extend the investigation to patient populations so that individual differences in anxiety-related impairment can be evaluated as a potential risk factor in the development of pathology.

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A biased activation theory of the cognitive and attentional modulation of emotion

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Cognition can influence emotion by biasing neural activity in the first cortical region in which the reward value and subjective pleasantness of stimuli is made explicit in the representation, the orbitofrontal cortex (OFC). The same effect occurs in a second cortical tier for emotion, the anterior cingulate cortex (ACC). Similar effects are found for selective attention, to for example the pleasantness vs. the intensity of stimuli, which modulates representations of reward value and affect in the orbitofrontal and anterior cingulate cortices. The mechanisms for the effects of cognition and attention on emotion are top-down biased competition and top-down biased activation. Affective and mood states can in turn influence memory and perception, by backprojected biasing influences. Emotion-related decision systems operate to choose between gene-specified rewards such as taste, touch, and beauty. Reasoning processes capable of planning ahead with multiple steps held in working memory in the explicit system can allow the gene-specified rewards not to be selected, or to be deferred. The stochastic, noisy, dynamics of decision-making systems in the brain may influence whether decisions are made by the selfish-gene-specified reward emotion system, or by the cognitive reasoning system that explicitly calculates reward values that are in the interests of the individual, the phenotype.

Keywords: cognition, emotion, orbitofrontal cortex, decision-making, the noisy brain, planning

INTRODUCTION

How do cognition and attention influence brain processing of emotion-provoking, that is affective, stimuli? What are the neural mechanisms?

To address this I review some of the experimental evidence on how cognition and selective attention influence the neural processing of affective stimuli.

Then I describe a top-down biased activation theory of emotion that provides a mechanism by which cognition and attention influence emotion and emotion-provoking stimuli.

The emphasis of the paper is on providing a fundamental framework at the level of brain computation for understanding how cognition and emotion influence each other, and how decisions are made between an emotional system that has its origins in gene-specified rewards, and an explicit reasoning system that allows these rewards to be deferred in favor of long-term reward value in the interests of the individual (Rolls, 2014). The approach is based on research by the author and his colleagues, and complementary research is cited below.

First, I outline an approach (Rolls, 2013b, 2014) to what emotions are, and what stimuli elicit emotions, to provide a clear foundation for what processes the cognitive and attentional inputs must influence.

A DEFINITION OF EMOTIONAL STATES

Emotions can usefully be defined (operationally) as states elicited by rewards and punishers which have particular functions (Rolls, 1999, 2005, 2013b, 2014). The functions are defined below, and include working to obtain or avoid the rewards and punishers. A reward is anything for which an animal (which includes humans) will work. A punisher is anything that an animal will escape from or avoid. An example of an emotion might thus be the happiness produced by being given a particular reward, such as a pleasant touch, praise, or winning a large sum of money. Another example of an emotion might be fear produced by the sound of a rapidly approaching bus, or the sight of an angry expression on someone's face. We will work to avoid such stimuli, which are punishing. Another example would be frustration, anger, or sadness produced by the omission of an expected reward, or the termination of a reward such as the death of a loved one. Another example would be relief, produced by the omission or termination of a punishing stimulus such as the removal of a painful stimulus, or sailing out of danger. These examples indicate how emotions can be produced by the delivery, omission, or termination of rewarding or punishing stimuli, and go some way to indicate how different emotions could be produced and classified in terms of the rewards and punishers received, omitted, or terminated.

I consider elsewhere a slightly more formal definition than rewards or punishers, in which the concept of reinforcers is introduced, and it is shown that emotions can be usefully seen as states produced by instrumental reinforcing stimuli (Rolls, 2005, 2014). Instrumental reinforcers are stimuli which, if their occurrence, termination, or omission is made contingent upon the making of a response, alter the probability of the future emission of that response. Some stimuli are unlearned reinforcers

(e.g., the taste of food if the animal is hungry, or pain); while others may become reinforcing by associative learning, because of their association with such primary reinforcers, thereby becoming "secondary reinforcers."

This foundation has been developed (Rolls, 2005) to show how a very wide range of emotions can be accounted for, as a result of the operation of a number of factors, including the following:

1. The *reinforcement contingency* (e.g., whether reward or punishment is given, or withheld) (see **Figure 1**).
2. The *intensity* of the reinforcer (see **Figure 1**).
3. Any environmental stimulus might have a *number of different reinforcement associations*. (For example, a stimulus might be associated both with the presentation of a reward and of a punisher, allowing states such as conflict and guilt to arise).
4. Emotions elicited by stimuli associated with *different primary reinforcers* will be different.
5. Emotions elicited by *different secondary reinforcing stimuli* will be different from each other (even if the primary reinforcer is similar).
6. The emotion elicited can depend on whether an *active or passive behavioral response* is possible. (For example, if an active behavioral response can occur to the omission of a positive reinforcer, then anger might be produced, but if only passive behavior is possible, then sadness, depression, or grief might occur).

By combining these six factors, it is possible to account for a very wide range of emotions (Rolls, 2005, 2014).

THE FUNCTIONS OF EMOTION

The functions of emotion also provide insight into the nature of emotion. These functions, described more fully elsewhere (Rolls, 2005), can be summarized as follows:

1. The *elicitation of autonomic responses* (e.g., a change in heart rate) and *endocrine responses* (e.g., the release of adrenaline). These prepare the body for action.
2. *Flexibility of behavioral responses to reinforcing stimuli*. Emotional (and motivational) states allow a simple interface between sensory inputs and action systems. The essence of this idea is that goals for behavior are specified by reward and punishment evaluation. When an environmental stimulus has been decoded as a primary reward or punishment, or (after previous stimulus-reinforcer association learning) a secondary rewarding or punishing stimulus, then it becomes a goal for action. The human can then perform any action (instrumental action) to obtain the reward, or to avoid the punisher. Thus there is flexibility of action, and this is in contrast with stimulus-response, or habit, learning in which a particular response to a particular stimulus is learned. The emotional route to action is flexible not only because any action can be performed to obtain the reward or avoid the

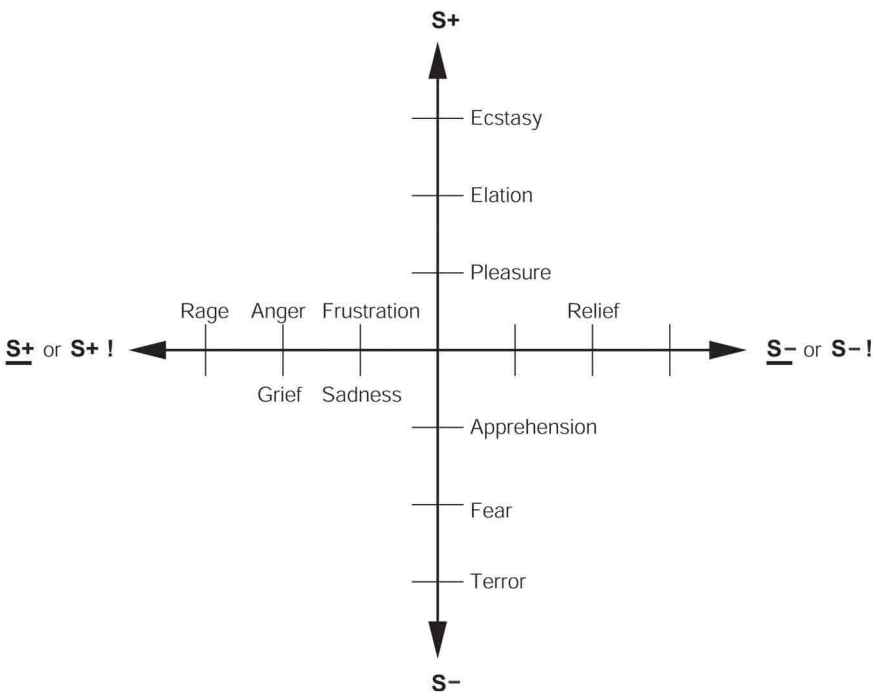

FIGURE 1 | Some of the emotions associated with different reinforcement contingencies are indicated. Intensity increases away from the center of the diagram, on a continuous scale. The classification scheme created by the different reinforcement contingencies consists of (1) the presentation of a positive reinforcer (S+), (2) the presentation of a negative reinforcer (S−), (3) the omission of a positive reinforcer (S+) or the termination of a positive reinforcer (S+ !), and (4) the omission of a negative reinforcer (S−) or the termination of a negative reinforcer (S− !). It should be understood that each different reinforcer will produce different emotional states: this diagram just summarizes the types of emotion that may be elicited by different contingencies, but the actual emotions will be different for each reinforcer (see Rolls, 2014).

punishment, but also because the human can learn in as little as one trial that a reward or punishment is associated with a particular stimulus, in what is termed "stimulus-reinforcer association learning."

Selecting between available rewards with their associated costs, and avoiding punishers with their associated costs, is a process that can take place both implicitly (unconsciously), and explicitly using a language system to enable long-term plans to be made (Rolls, 2005, 2008b). These many different brain systems, some involving implicit evaluation of rewards, and others explicit, verbal, conscious, evaluation of rewards and planned long-term goals, must all enter into the selector of behavior.

The implication is that operation by animals (including humans) using reward and punishment systems tuned to dimensions of the environment that increase fitness provides a mode of operation that can work in organisms that evolve by natural selection. It is clearly a natural outcome of Darwinian evolution to operate using reward and punishment systems tuned to fitness-related dimensions of the environment, if arbitrary responses are to be made by the animals, rather than just preprogrammed movements such as tropisms, taxes, and reflexes. This view of brain design in terms of reward and punishment systems built by genes that gain their adaptive value by being tuned to a goal for action offers I believe a deep insight into how natural selection has shaped many brain systems, and is a fascinating outcome of Darwinian thought (Rolls, 2005, 2011b, 2014).

The implication in the current context is that we are interested in processing in brain systems where instrumental rewards and punishers, and how the processing in these brain systems is modulated by cognition and by selective attention. A large amount of evidence shows that reward processing occurs in a tier of structures involving the orbitofrontal cortex (OFC) and amygdala (see **Figure 2**) (Rolls, 2014). At the preceding stages of processing, the representations are not of reward value, but instead of what taste is present and its intensity (the primary taste cortex), what odor is present (the pyriform cortex), and what visual stimulus is present (the inferior temporal visual cortex) (see **Figure 2**) (Rolls, 2014).

EFFECTS OF COGNITION ON EMOTION

To what extent does cognition influence the hedonics of stimuli that produce emotions, and how far down into the sensory system does the cognitive influence reach? Examples of the evidence on this are considered next. Further examples of the effects of cognition on emotion are described elsewhere (Grabenhorst and Rolls, 2011; Shackman et al., 2011; Lindquist et al., 2012; Ochsner et al., 2012; Sheppes et al., 2012; Rolls, 2014).

EFFECTS OF COGNITION ON OLFACTORY AND TASTE REWARD-RELATED PROCESSING

To address this, we performed an fMRI investigation in which the delivery of a standard test odor (isovaleric acid combined with cheddar cheese odor, presented orthonasally using an olfactometer) was paired with a descriptor word on a screen, which on different trials was "cheddar cheese" or "body odor." Participants rated the affective value of the test odor as significantly more pleasant when labeled "cheddar cheese" than when labeled "body odor," and these effects reflected activations in the medial OFC/rostral anterior cingulate cortex (ACC) that had correlations with the pleasantness ratings (de Araujo et al., 2005). The implication is that cognitive factors can have profound effects on our responses to the hedonic properties of affective stimuli, in that these effects are manifest quite far down into sensory processing, in that hedonic representations of odors are affected (de Araujo et al., 2005).

Similar cognitive effects and mechanisms have now been found for the taste and flavor of food, where the cognitive word level descriptor was for example "rich delicious flavor" and activations to flavor were increased in the OFC and regions to which it projects including the pregenual cingulate cortex and ventral striatum, but were not influenced in the insular primary taste cortex where activations reflected the intensity (concentration) of the stimuli (Grabenhorst et al., 2008) (see **Figure 3**).

EFFECTS OF COGNITION ON TOUCH REWARD-RELATED PROCESSING

The representation of positively affective touch and temperature in the brain

While there have been many investigations of the neural representations of pain stimuli (Grabenhorst and Rolls, 2011; Shackman et al., 2011; Kobayashi, 2012), there have been fewer investigations of the representation of pleasant touch in the brain.

In one study, the cortical areas that represent affectively positive and negative aspects of touch were investigated using functional magnetic resonance imaging (fMRI) by comparing activations produced by pleasant touch, painful touch produced by a stylus, and neutral touch, to the left hand (Rolls et al., 2003c). It was found that regions of the OFC were activated more by pleasant touch and by painful stimuli than by neutral touch, and that different areas of the OFC were activated by the pleasant and painful touches. The OFC activation was related to the affective aspects of the touch, in that the somatosensory cortex (S1) was less activated by the pleasant and painful stimuli than by the neutral stimuli (as shown by a Two-Way analysis of variance performed on the percentage change of the BOLD signals under the different stimulation conditions in the different areas). Further, it was found that a rostral part of the ACC was activated by the pleasant stimulus and that a more posterior and dorsal part was activated by the painful stimulus [and this is consistent with effects in other sensory modalities (Grabenhorst and Rolls, 2011; Rolls, 2014) (cf. Etkin et al., 2011)]. Regions of the somatosensory cortex, including S1, and part of S2 in the superior temporal plane at the mid-insula level, were activated more by the neutral touch than by the pleasant and painful stimuli. Part of the posterior insula was activated only in the pain condition, and different parts of the brainstem, including the central gray, were activated in the pain, pleasant and neutral touch conditions. The results provide evidence that different areas of the human OFC are involved in representing both pleasant touch and pain, and that dissociable parts of the cingulate cortex are involved in representing pleasant touch and pain (Rolls et al., 2003c).

Warm and cold stimuli have affective components such as feeling pleasant or unpleasant, and these components may have survival value, for approach to warmth and avoidance of cold may be reinforcers or goals for action built into us during evolution to

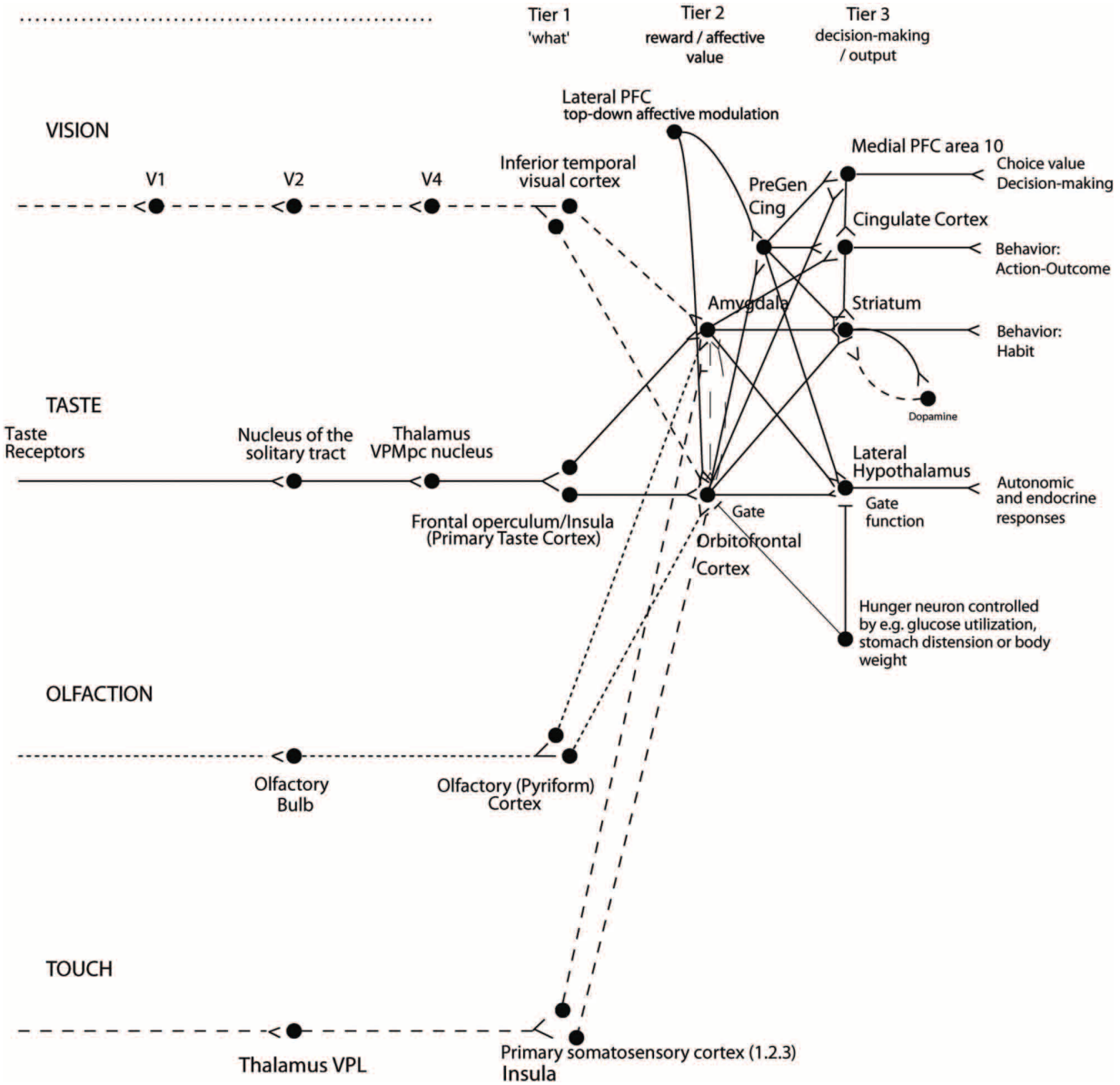

FIGURE 2 | Organization of cortical processing for computing value (in Tier 2) and making value-based decisions (in Tier 3) and interfacing to action systems. The Tier 1 brain regions up to and including the column headed by the inferior temporal visual cortex compute and represent neuronally "what" stimulus/object is present, but not its reward or affective value. Tier 2 represents by its neuronal firing the reward or affective value, and includes the orbitofrontal cortex, amygdala, and anterior including pregenual cingulate cortex. Tier 3 is involved in choices based on reward value (in particular VMPFC area 10), and in different types of output to behavior. The secondary taste cortex, and the secondary olfactory cortex, are within the orbitofrontal cortex. V1—primary visual cortex. V4—visual cortical area V4. PreGen Cing—pregenual cingulate cortex. "Gate" refers to the finding that inputs such as the taste, smell, and sight of food in regions where reward value is represented only produce effects when an appetite for the stimulus (modulated for example by hunger) is present (Rolls, 2005). Lateral PFC: lateral prefrontal cortex, a source for top-down attentional and cognitive modulation of affective value (Grabenhorst and Rolls, 2010). This is a schematic diagram, and is based on primates including humans, as rodents appear not to have homologs of some of the areas shown, including the granular prefrontal cortex, which includes much of the orbitofrontal cortex (Wise, 2008; Passingham and Wise, 2012); and because rodents have a taste system that is connected differently, without the obligatory route to the cortex that is shown (Scott and Small, 2009; Rolls, 2013a, 2014).

direct our behavior to stimuli that are appropriate for survival (Rolls, 2005). Understanding the brain processing that underlies these prototypical reinforcers provides a direct approach to understanding the brain mechanisms of emotion. In an fMRI investigation in humans, we showed that the mid-orbitofrontal and pregenual cingulate cortex and the ventral striatum have activations that are correlated with the subjective pleasantness ratings made to warm (41°C) and cold (12°C) stimuli, and combinations

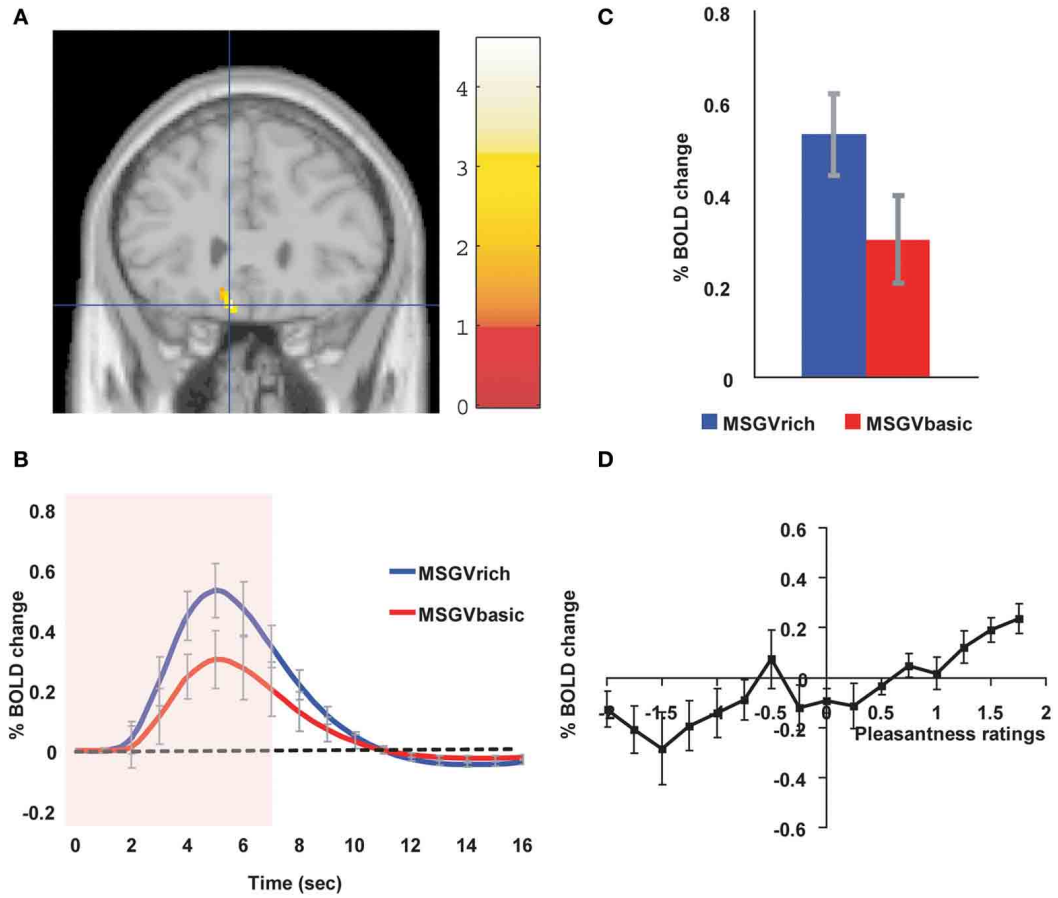

FIGURE 3 | Cognitive modulation of flavor reward processing in the brain. (A) The medial orbitofrontal cortex was more strongly activated when a flavor stimulus was labeled "rich and delicious flavor" (MSGVrich) than when it was labeled "boiled vegetable water" (MSGVbasic) ([−8 28 −20]). (The flavor stimulus, MSGV, was the taste 0.1 M MSG + 0.005 M inosine 5′monophosphate combined with a consonant 0.4% vegetable odor). **(B)** The timecourse of the BOLD signals for the two conditions. **(C)** The peak values of the BOLD signal (mean across subjects ± SEM) were significantly different ($t = 3.06$, $df = 11$, $p = 0.01$). **(D)** The BOLD signal in the medial orbitofrontal cortex was correlated with the subjective pleasantness ratings of taste and flavor, as shown by the SPM analysis, and as illustrated (mean across subjects ± SEM, $r = 0.86$, $p < 0.001$). [Reproduced with permission from Grabenhorst et al. (2008)].

of warm and cold stimuli, applied to the hand (Rolls et al., 2008b). Activations in the lateral and some more anterior parts of the OFC were correlated with the unpleasantness of the stimuli. In contrast, activations in the somatosensory cortex and ventral posterior insula were correlated with the intensity but not the pleasantness of the thermal stimuli (Rolls et al., 2008b).

A principle thus appears to be that processing related to the affective value and associated subjective emotional experience of somatosensory and thermal stimuli that are important for survival is performed in different brain areas to those where activations are related to sensory properties of the stimuli such as their intensity. This conclusion appears to be the case for processing in a number of sensory modalities, and the finding with such prototypical stimuli as pleasant and painful touch, and warm (pleasant) and cold (unpleasant) thermal stimuli, provides strong support for this principle (Rolls, 2005; Grabenhorst and Rolls, 2008, 2011; Grabenhorst et al., 2008; Rolls et al., 2008a). An implication of the principle is that by having a system specialized for the affective or reward aspects of stimuli it is possible to modify goal oriented behavior, and to do this independently of being able to know what the stimulus is (its intensity, physical characteristics etc). Thus even if a stimulus has lost its pleasantness because of for example a change of core body temperature, it is still possible to represent the stimulus, recognize it, and learn about where it is in the environment for future use (Rolls, 2005). This is a fundamental aspect of brain design (Rolls, 2005, 2008b, 2014).

Cognitive modulation of affective touch processing

There have been many studies of the top-down attentional modulation (Rolls, 2008b) of touch, with effects typically larger in secondary somatosensory and association cortical areas (e.g., parietal area 7), and smaller in S1 (Johansen-Berg and Lloyd, 2000; Rolls, 2010). However, there has been little investigation of where high-level cognition influences the representation of affective touch in the brain.

To investigate where cognitive influences from the very high level of language might influence the affective representation of touch, we performed a fMRI study in which the forearm was rubbed with a cream, but this could be accompanied by a word label that indicated that it was a rich moisturizing cream (pleasant to most people) vs. a basic cream (McCabe et al., 2008).

We found that cognitive modulation by a label at the word level indicating pleasantness/richness ("rich moisturizing cream" vs. "basic cream") influenced the representation of tactile inputs in the OFC (McCabe et al., 2008). (The cream was identical in all conditions in the study: it was only the word labels that were changed. The cream was rubbed onto the ventral surface of the forearm.) For example, a negative correlation with the pleasantness ratings of the touch as influenced by the word labels was found in the lateral OFC, a region shown in other studies to be activated by less pleasant stimuli including unpleasant odors, and losing money (O'Doherty et al., 2001; Rolls et al., 2003b,c). A positive correlation with the pleasantness of touch as influenced by the word labels was found in the pregenual cingulate cortex (McCabe et al., 2008). Convergent evidence on the functions of this region is that the pregenual cingulate region is close to where in different studies another somatosensory stimulus, oral texture, is represented (de Araujo and Rolls, 2004), correlations with pleasantness ratings are found to food and olfactory stimuli (Kringelbach et al., 2003; de Araujo et al., 2005; Grabenhorst and Rolls, 2011), and pleasant touch produces activation (Rolls et al., 2003c). We also found that activations to touch in the parietal cortex area 7 were influenced by the word labels, in that there was more activation when the rich label than when the thin label was present (McCabe et al., 2008).

Cognitive modulation of activations to the sight of touch

Cognitive modulation of effects produced by the sight of touch were investigated by a comparison of the effects of the sight of the arm being rubbed when accompanied by the label "rich moisturizing cream" vs. "basic cream." Cognitive modulation effects were found in the pregenual cingulate cortex extending into the OFC, in regions close to those where activations were correlated with the pleasantness ratings with the same two stimulus conditions. The effect of the cognitive label "rich moisturizing cream" was to make the sight of the touch more pleasant by increasing activations in these pregenual cingulate and OFC areas (McCabe et al., 2008).

TOP-DOWN EFFECTS OF SELECTIVE ATTENTION ON EMOTION

In section "Effects of Cognition on Emotion", the effects of cognition on emotion were considered, and cognition referred to for example language-level descriptions of the properties of a stimulus, such as delicious, or rich and moisturizing. In addition, paying selective attention to one property of a stimulus, such as its intensity, vs. another property, such as its pleasantness, can be thought of as a top-down attentional effect. The mechanisms though may be similar, as considered in section "A Top-Down Biased Activation Theory of Attentional and Cognitive Modulation."

TASTE, OLFACTION, AND FLAVOR

We have found that with taste and flavor (Grabenhorst and Rolls, 2008) stimuli, and olfactory (Rolls et al., 2008a) stimuli, selective attention to pleasantness modulates representations in the OFC (see **Figure 4**), whereas selective attention to intensity modulates activations in areas such as the primary taste cortex. Thus, depending on the context in which tastes and odors are presented and whether affect is relevant, the brain responds to taste, flavor, and odor, differently.

These findings show that when attention is paid to affective value, the brain systems engaged to represent the stimulus are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity.

This differential biasing by prefrontal cortex attentional mechanisms (Grabenhorst and Rolls, 2010; Ge et al., 2012) of brain regions engaged in processing a sensory stimulus depending on whether the cognitive demand is for affect-related vs. more sensory-related processing may be an important aspect of cognition and attention which have implications for how strongly the reward system is driven by stimuli including food, and thus for eating and the control of appetite (Grabenhorst and Rolls, 2008, 2011; Rolls et al., 2008a; Rolls, 2012). This important concept is addressed further below.

POSSIBLE SOURCES OF THE TOP-DOWN MODULATION OF EMOTIONAL PROCESSING

There is relatively little prior evidence on the top-down source of the bias when attention is to affective (emotional) vs. sensory aspects (e.g., the intensity) of the same stimulus (Pessoa, 2009). In a study using psychophysiological interaction (PPI) analysis, we found that two sites where selective attention to pleasantness increased the activation to taste, the OFC and a region to which it is connected, the pregenual cingulate cortex, both had functional connectivity with a quite anterior (mean $y \approx 50$) part of the lateral prefrontal cortex, illustrated in Grabenhorst and Rolls (2010). These parts of the OFC and pregenual cingulate cortex are a functionally appropriate target site for a top-down attentional modulation, in that their activations are correlated with the subjectively rated pleasantness of the taste (Grabenhorst and Rolls, 2008). Moreover, the lateral prefrontal cortex has been shown to represent current task sets and attentional demands for different types of tasks (Sakai and Passingham, 2003, 2006).

The statistics used in the calculation of PPI effects (Friston et al., 1997) do not reveal the directionality of the connectivity, for they are based on correlations. However, the directionality in this case is likely to be from the prefrontal cortex to the orbitofrontal and pregenual cingulate cortices, for the following reasons. First, the prefrontal cortex has a powerfully developed recurrent collateral system which provides the basis for the short-term memory (Rolls and Deco, 2002; Deco and Rolls, 2005a; Rolls, 2008b) that is needed to hold the subject of attention active, providing the source of the bias for top-down biased competition (Desimone and Duncan, 1995; Rolls and Deco, 2002; Deco and Rolls, 2005a; Rolls, 2008b). Second, prefrontal cortex lesions impair attention (Beck and Kastner, 2009; Rossi et al., 2009). Third, activations in areas of the lateral prefrontal cortex are related to task set, attentional instructions, and remembering

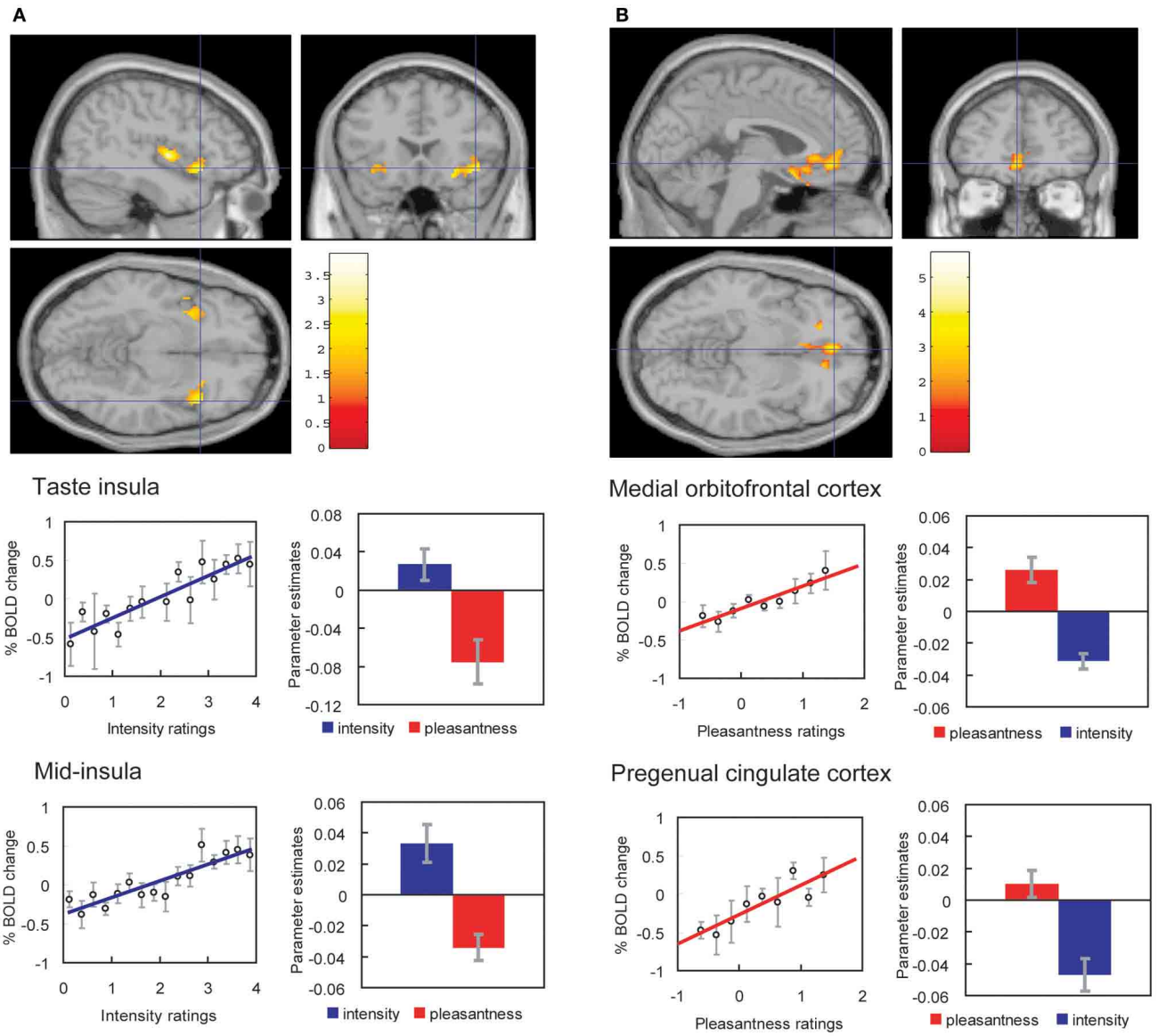

FIGURE 4 | Effect of paying attention to the pleasantness vs. the intensity of a taste stimulus. (A) Top: A significant difference related to the taste period was found in the taste insula at [42 18 −14], $z = 2.42$, $p < 0.05$ (indicated by the cursor) and in the mid insula at [40 −2 4], $z = 3.03$, $p < 0.025$. Middle: Taste insula. Right: The parameter estimates (mean ± SEM across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the taste insula $t = 4.5$, $df = 10$, $p = 0.001$. Left: The correlation between the intensity ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.91$, $df = 14$, $p << 0.001$). Bottom: Mid insula. Right: The parameter estimates (mean ± SEM across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the mid insula $t = 5.02$, $df = 10$, $p = 0.001$. Left: The correlation between the intensity ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.89$, $df = 15$, $p << 0.001$). The taste stimulus, monosodium glutamate, was identical on all trials. **(B)** Top: A significant difference related to the taste period was found in the medial orbitofrontal cortex at [−6 14 −20], $z = 3.81$, $p < 0.003$ (toward the back of the area of activation shown) and in the pregenual cingulate cortex at [−4 46 −8], $z = 2.90$, $p < 0.04$ (at the cursor). Middle: Medial orbitofrontal cortex. Right: The parameter estimates (mean ± SEM across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the orbitofrontal cortex $t = 7.27$, $df = 11$, $p < 10^{-4}$. Left: The correlation between the pleasantness ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.94$, $df = 8$, $p << 0.001$). Bottom: Pregenual cingulate cortex. Conventions as above. Right: The parameter estimates were significantly different for the pregenual cingulate cortex $t = 8.70$, $df = 11$, $p < 10^{-5}$. Left: The correlation between the pleasantness ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.89$, $df = 8$, $p = 0.001$). The taste stimulus, 0.1 M monosodium glutamate, was identical on all trials. [Reproduced with permission from Grabenhorst and Rolls (2008)].

rules that guide task performance (Sakai and Passingham, 2003; Deco and Rolls, 2005a; Sakai and Passingham, 2006; Veldhuizen et al., 2007; Beck and Kastner, 2009; Bengtsson et al., 2009; Kouneiher et al., 2009; Rossi et al., 2009). Fourth, direct anatomical connections exist between the lateral prefrontal cortex and the orbitofrontal and pregenual cingulate cortices (Price, 2006).

The conclusion that these findings suggest is therefore that a part of the lateral prefrontal cortex, not a site normally implicated in affective value and emotion, may be able to modulate emotion-/affect-related processing in the brain by a top-down attentional influence. This may be one way in which higher cognitive functions, such as a reasoning-based strategy and route to action, or verbal instruction to direct processing toward or away from emotion-related brain processing, or conscious volition, can influence the degree to which the affect-related parts of the brain process incoming (or potentially remembered) stimuli that can produce emotional responses. This is thus a part of the way in which cognition can influence, and control, emotion (Rolls, 2005, 2011a, 2014; Pessoa, 2009).

We also found that two sites where selective attention to intensity increased the activation to the taste delivery into the mouth, the anterior and mid insula, both had functional connectivity with a less anterior (mean $y \approx 37$) part of the lateral prefrontal cortex (Grabenhorst and Rolls, 2010). These parts of the insula are a functionally appropriate site for a top-down attentional modulation, in that their activations are correlated with the subjectively rated intensity of the taste (Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008). The anterior insular site may be the primary taste cortex (Pritchard et al., 1986; Yaxley et al., 1990; de Araujo et al., 2003a; de Araujo and Rolls, 2004; Rolls, 2008a), and the mid-insular site a region activated by other oral including somatosensory and fat texture inputs from the oral cavity (de Araujo et al., 2003b; de Araujo and Rolls, 2004) and perhaps by taste *per se* (Small et al., 2003) in that the activations there were correlated with the trial-by-trial subjective ratings of the taste intensity made during the scanning (Grabenhorst and Rolls, 2008). In the analyses described here, such somatosensory inputs could contribute to the attention-dependent correlations found between the mid insula and other areas.

The interpretation of this functional connectivity revealed with PPI (Friston et al., 1997) is that the prefrontal cortex and orbitofrontal/pregenual cingulate areas covary in their activations more strongly when attention is directed to pleasantness than to intensity. In this study, the implication is that when the activity in the orbitofrontal and pregenual cingulate areas is high, as it is on trials when attention is paid to pleasantness relative to trials when attention is paid to intensity, then activations in this prefrontal cortex region are also high. A large source of this variation which gives rise to the PPI effect is thus the difference in the activations on different trial types which can be captured by the correlation arising from the difference in the mean activations of both sites (orbitofrontal/pregenual cingulate cortices and prefrontal cortex) on each of the two trial types (see further O'Reilly et al., 2012). However, in addition to this source of variation, it could be that when two areas are functionally interacting strongly, there may be an additional contribution to the connectivity term produced by the trial-by-trial variation within a type of trial. For example, on trials on which pleasantness is the subject of attention, then any small variation on a particular trial in the prefrontal cortex would be expected to be reflected in the activations in the orbitofrontal/pregenual cingulate cortex. This effect would arise because when both areas are active, the neurons in each area may be operating on a relatively linear part of their activation function, producing strong coupling, whereas when one or both areas are relatively inactive, with only spontaneous firing, then the neurons may be subject to some effects produced by being close to the firing threshold, such that small changes in input may produce a smaller than linear effect on the output. This trial-by-trial variation corresponds in information theoretic analysis of neuronal covariation to a "noise" effect as compared to a "signal" effect (Oram et al., 1998; Rolls et al., 2003a; Rolls, 2008b; Rolls and Treves, 2011).

GRANGER CAUSALITY USED TO INVESTIGATE THE SOURCE OF THE TOP-DOWN BIASING OF AFFECTIVE PROCESSING

Correlations between signals, including signals at the neuronal or at the functional neuroimaging level, do not reveal the direction of the possible influence of one signal on the other. PPI analysis is based on correlations. Understanding how one brain area may influence another, for example by providing it with inputs, or by top-down modulation, is fundamental to understanding how the brain functions (Mechelli et al., 2004; Bar, 2007; Bressler and Menon, 2010). Hence, inferring causal influences from time series data has been attracting intensive interest. Recently, Granger causality has become increasingly popular due to its easy implementation and many successful applications to econometrics, neuroscience, etc., and in particular, the study of brain function (Ding et al., 2006; Bressler et al., 2008; Deshpande et al., 2010; Hwang et al., 2010; Schippers et al., 2010; Bressler and Seth, 2011; Jiao et al., 2011; Luo et al., 2011). The application of Granger causality analysis to BOLD fMRI signals which are inherently slow has been discussed elsewhere (David et al., 2008; Deshpande et al., 2010; Schippers and Keysers, 2011; Valdes-Sosa et al., 2011; Stephan and Roebroeck, 2012; Luo et al., in revision).

Granger causality is based on precedence and predictability. Originally proposed by Wiener (1956) and further formalized by Granger (1969), it states that given two times series x and y, if the inclusion of the past history of y helps to predict the future states of x in some plausible statistical sense, then y is a cause of x in the Granger sense. In spite of the wide acceptance of this definition, classical Granger causality is not tailored to measure the effects of interactions between time series x and y on the causal influences, and cannot measure systematically the effects of the past history of x on x (Ge et al., 2012). A componential form of Granger causality analysis has recently been introduced which has advantages over classical Granger analysis (Ge et al., 2012). Componential Granger causality measures the effect of y on x, but allows interaction effects between y and x to be measured (Ge et al., 2012). In addition, the terms in componential Granger causality sum to 1, allowing causal effects to be directly compared between systems.

We showed using componential Granger causality analysis applied to an fMRI investigation that there is a top-down

attentional effect from the anterior dorsolateral prefrontal cortex to the OFC when attention is paid to the pleasantness of a taste, and that this effect depends on the activity in the OFC as shown by the interaction term (Ge et al., 2012). Correspondingly there is a top-down attentional effect from the posterior dorsolateral prefrontal cortex to the insular primary taste cortex when attention is paid to the intensity of a taste, and this effect depends on the activity of the insular primary taste cortex as shown by the interaction term. The prefrontal cortex sites are those identified by the PPI analysis (Grabenhorst and Rolls, 2010) and the effects are shown schematically in **Figure 5**. Componential Granger causality thus not only can reveal the directionality of effects between areas (and these can be bidirectional), but also allows the mechanisms to be understood in terms of whether the causal influence of one system on another depends on the state of the system being causally influenced. Componential Granger causality measures the full effects of second order statistics by including variance and covariance effects between each time series, thus allowing interaction effects to be measured, and also provides a systematic framework within which to measure the effects of cross, self, and noise contributions to causality (Ge et al., 2012). The findings reveal some of the mechanisms involved in a biased activation theory of selective attention.

A TOP-DOWN BIASED ACTIVATION THEORY OF ATTENTIONAL AND COGNITIVE MODULATION

The way that we think of top-down biased competition as operating normally in for example visual selective attention (Desimone and Duncan, 1995) is that within an area, e.g., a cortical region, some neurons receive a weak top-down input that increases their response to the bottom-up stimuli (Desimone and Duncan, 1995), potentially supralinearly if the bottom-up stimuli are weak (Rolls and Deco, 2002; Deco and Rolls, 2005a; Rolls, 2008b). The enhanced firing of the biased neurons then, via the local inhibitory neurons, inhibits the other neurons in the local area from responding to the bottom-up stimuli. This is a local mechanism, in that the inhibition in the neocortex is primarily local, being implemented by cortical inhibitory neurons that typically have inputs and outputs over no more than a few mm (Rolls and Deco, 2002; Douglas et al., 2004; Rolls, 2008b). This model of biased competition is illustrated in **Figure 6B**.

This locally implemented biased competition situation may not apply in the present case, where we have facilitation of processing in a whole cortical area (e.g., OFC, or pregenual cingulate cortex) or even cortical processing stream (e.g., the linked orbitofrontal and pregenual cingulate cortex) in which any taste neurons may reflect pleasantness and not intensity. So the attentional effect might more accurately be described in this case as biased activation, without local competition being part of the effect. This *biased activation theory and model of attention*, illustrated in **Figure 6A**, is a rather different way to implement attention in the brain than biased competition, and each mechanism may apply in different cases, or both mechanisms in some cases.

The *biased activation theory of top-down attentional and cognitive control* is as follows, and is illustrated in **Figure 6A**. There are short-term memory systems implemented as cortical attractor networks with recurrent collateral connections to maintain neuronal activity (Rolls, 2008b) that provide the source of the top-down activation. The short-term memory systems may be separate (as shown in **Figure 6A**), or could be a single network with different attractor states for the different selective attention conditions. The top-down short-term memory systems hold what is being paid attention to active by continuing firing in an attractor state, and bias separately either cortical processing system 1, or cortical processing system 2. This weak top-down bias interacts

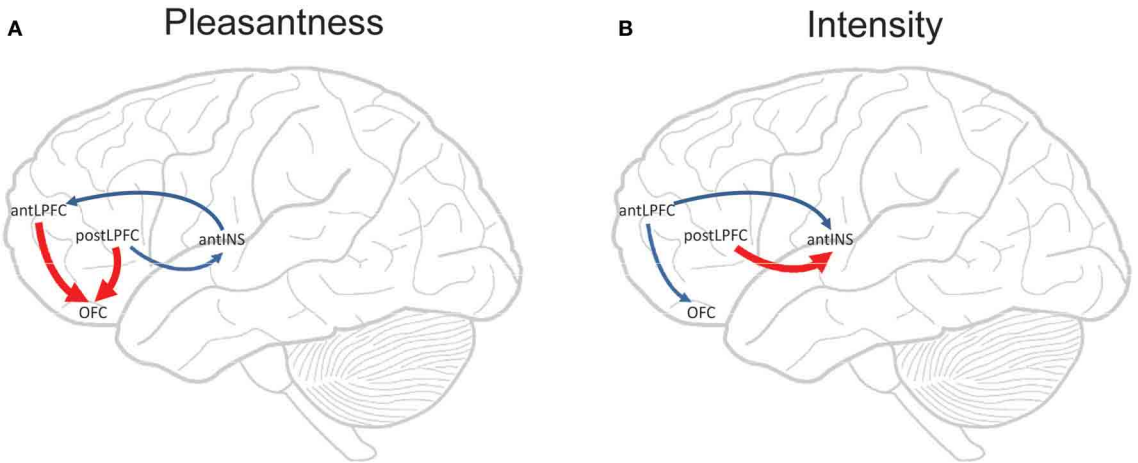

FIGURE 5 | Componential Granger causality analysis of top-down effects on taste processing from different lateral prefrontal cortex areas during attention to either the pleasantness (A) or to the intensity (B) of a taste. Significant causal influences from *t*-tests with a Bonferroni correction are marked by blue arrows (i.e., cross-componential Granger causality is greater than 0). Red arrows indicate where significant top-down effects exist in addition to significant causal influences (i.e., a significant cross-componential Granger causality that is different in the two directions). The areas are anterior (mean $y \approx 50$) and posterior (mean $y \approx 37$) lateral prefrontal cortex (antLPFC, postLPFC); orbitofrontal cortex secondary cortical taste area (OFC); and anterior insular cortex primary cortical taste area (antINS). [Reproduced with permission from Ge et al. (2012)].

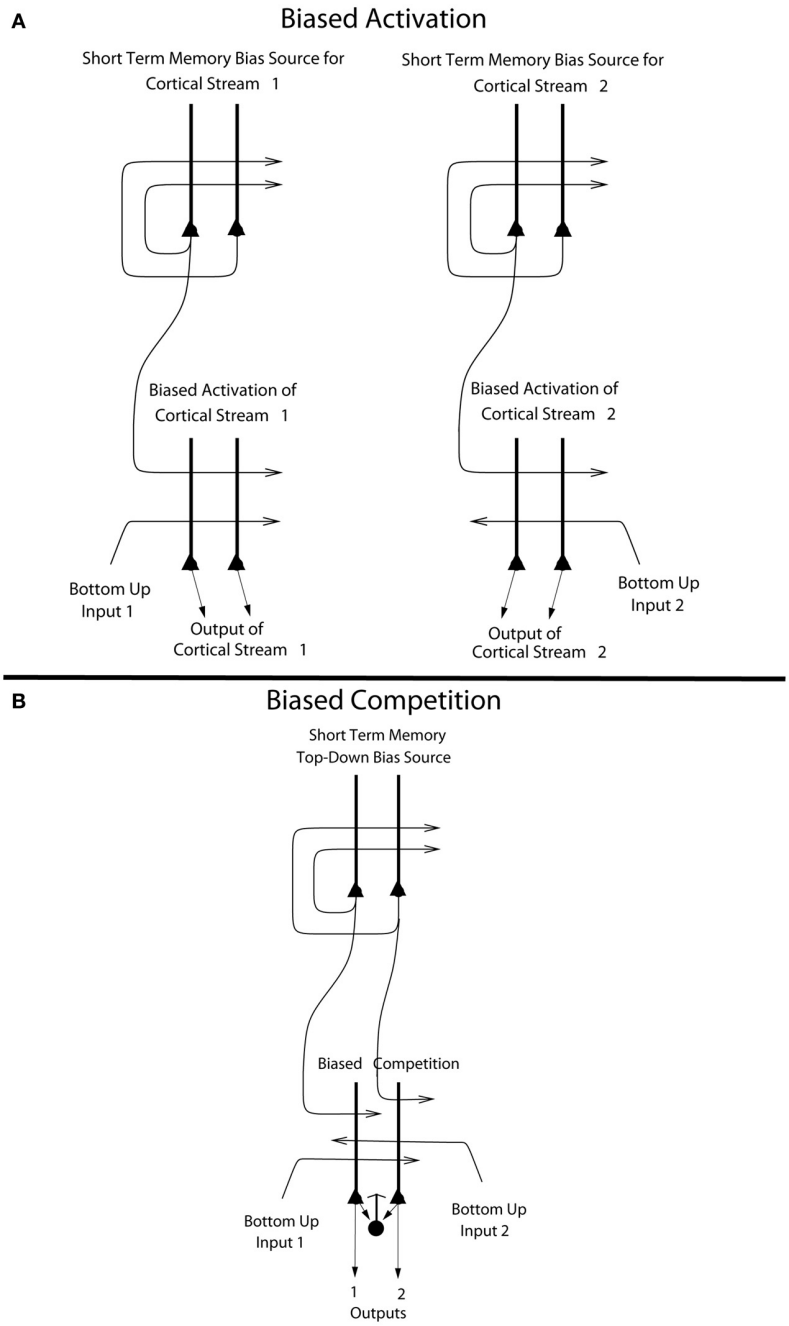

FIGURE 6 | (A) Biased activation. The short-term memory systems that provide the source of the top-down activations may be separate (as shown), or could be a single network with different attractor states for the different selective attention conditions. The top-down short-term memory systems hold what is being paid attention to active by continuing firing in an attractor state, and bias separately either cortical processing system 1, or cortical processing system 2. This weak top-down bias interacts with the bottom up input to the cortical stream and produces an increase of activity that can be supralinear (Deco and Rolls, 2005b). Thus the selective activation of separate cortical processing streams can occur. In the example, stream 1 might process the affective value of a stimulus, and stream 2 might process the intensity and physical properties of the stimulus. The outputs of these separate processing streams then must enter a competition system, which could be for example a cortical attractor decision-making network that makes choices between the two streams, with the choice biased by the activations in the separate streams (see text). **(B)** Biased competition. There is usually a single attractor network that can enter different attractor states to provide the source of the top-down bias (as shown). If it is a single network, there can be competition within the short-term memory attractor states, implemented through the local GABA inhibitory neurons. The top-down continuing firing of one of the attractor states then biases in a top-down process some of the neurons in a cortical area to respond more to one than the other of the bottom-up inputs, with competition implemented through the GABA inhibitory neurons (symbolized by a filled circle) which make feedback inhibitory connections onto the pyramidal cells (symbolized by a triangle) in the cortical area. The thick vertical lines above the pyramidal cells are the dendrites. The axons are shown with thin lines and the excitatory connections by arrow heads.

with the bottom-up input to the cortical stream and produces an increase of activity that can be supralinear (Deco and Rolls, 2005b; Rolls, 2008b). Thus the selective activation of separate cortical processing streams can occur. In the example, stream 1 might process the affective value of a stimulus, and stream 2 might process the intensity and physical properties of the stimulus.

The top-down bias needs to be weak relative to the bottom-up input, for the top-down bias must not dominate the system, otherwise bottom-up inputs, essential for perception and survival, would be over-ridden. Under such conditions, top-down attentional and cognitive effects will be largest when the bottom-up inputs are not too strong or are ambiguous, and that has been shown to be the case in realistic simulations with integrate-and-fire neurons (Deco and Rolls, 2005b; Rolls, 2008b). The weakness of the top-down biasing input is included as a part of brain design, for the top-down inputs are effectively backprojections from higher cortical areas, and these end on the apical dendrites of cortical pyramidal cells, and so have weaker effects than the bottom up inputs, which make connections lower down the dendrite toward the cell body (Rolls, 2008b) (see **Figures 6**, **7**). I suggest here that the correct connections could be set up in such a system by the following associative (Hebbian) synaptic learning process. The top-down backprojection synapses would increase in strength when there is activity in a population of short-term memory neurons that by their firing hold attention in one direction (e.g., the short-term memory system for cortical stream 1 shown in **Figure 6A**), and simultaneously there is activity in the neurons that receive the top-down inputs (e.g., in cortical stream 1 shown in **Figure 6A**).

The outputs of the separate processing streams showing biased activation (**Figure 6A**) may need to be compared later to lead to a single behavior. One way in which this comparison could take place is by both outputs entering a single network cortical attractor model of decision-making, in which positive feedback implemented by the excitatory recurrent collateral connections leads through non-linear dynamics to a single winner, which is ensured by competition between the different possible attractor states produced through inhibitory neurons (Wang, 2002, 2008; Deco and Rolls, 2006; Rolls and Deco, 2010; Deco et al., 2012). A second way in which the competition could be implemented is by that usually conceptualized as important in biased competition (Desimone and Duncan, 1995; Rolls and Deco, 2002; Deco and Rolls, 2005a,b), in which a feedforward competitive network using inhibition through local inhibitory neurons provides a way for a weak top-down signal to bias the output especially if the bottom-up inputs are weak (Rolls and Deco, 2002; Deco and Rolls, 2005b; Rolls, 2008b), and this implementation is what is shown at the bottom of **Figure 6B**. A third way in which the biased activation reflected in the output of the streams shown in **Figure 6A** could be taken into account is by a mechanism such as that in the basal ganglia, where in the striatum the different excitatory inputs activate GABA (gamma-amino-butyric acid) neurons, which then directly inhibit each other to make the selection (Rolls, 2005, 2008b).

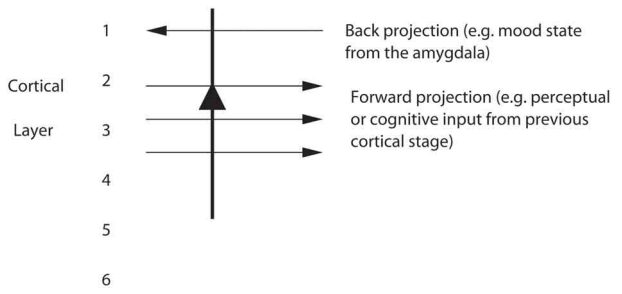

FIGURE 7 | Pyramidal cells in, for example, layers 2 and 3 of the temporal lobe association cortex receive forward inputs from preceding cortical stages of processing, and also backprojections from the amygdala. It is suggested that the backprojections from the amygdala make modifiable synapses on the apical dendrites of cortical pyramidal cells during learning when amygdala neurons are active in relation to a mood state; and that the backprojections from the amygdala via these modified synapses allow mood state to influence later cognitive processing, for example by facilitating some perceptual representations.

The difference between biased competition and biased activation may be especially important in the context of functional neuroimaging, for biased activation, in which processing in whole cortical areas is facilitated by selective attention, can be revealed by functional neuroimaging, which operates at relatively low spatial resolution, in the order of mm. In contrast, biased competition may selectively facilitate some pyramidal neurons within a local cortical area which then through the local GABA inhibitory neurons compete with the other pyramidal neurons in the area receiving bottom-up input. In this situation, in which some but not other neurons within a cortical area are showing enhanced firing, functional neuroimaging may not be able to show which local population of pyramidal cells is winning the competition due to the top-down bias. The evidence presented by Grabenhorst and Rolls (2010) is that not only the processing streams, but also even the short-term memory systems in the prefrontal cortex that provide the top-down source of the biased activation, are physically separate, as illustrated in **Figure 5A**.

A possibility arising from this model is that some competition may occur somewhere in the attentional system before the output stage, and one possible area is within the prefrontal cortex, where it is a possibility that the attractors that implement the short-term memory for attention to pleasantness (at $Y \approx 50$) may inhibit the attractors that implement the short-term memory for attention to intensity (at $Y \approx 37$), which could occur if there is some physical overlap between their zones of activation, even if the peaks are well separated. Some evidence for this possibility was found (Grabenhorst and Rolls, 2010), in that the correlation between the % BOLD activations in these two prefrontal cortex regions was $r = -0.72$ ($p = 0.0034$) on the pleasantness trials; and $r = -0.8$ ($p < 0.001$) on the intensity trials. In a biased competition model (**Figure 6B**) we would normally think of the short-term memory attractors that provide the source of the bias as being within the same single attractor network, so that there would be competition between the two attractor states through the local inhibitory interneurons. In the biased activation model (**Figure 6A**), it is an open issue about whether the attractors that provide the source of the top-down bias are in the same single network, or are physically separate making interactions between the attractor states difficult through the short-range cortical inhibitory neurons. The findings just described indicate that in the case of top-down control of affective vs. intensity processing of taste stimuli, although the

two attractors are somewhat apart in the prefrontal cortex, there is some functional inhibitory interaction between them.

The principle of biased activation providing a mechanism for selective attention probably extends beyond processing in the affective vs. sensory coding cortical streams. It may provide the mechanism also for effects in for example the dorsal vs. the ventral visual system, in which attention to the motion of a moving object may enhance processing in the dorsal stream, and attention to the identity of the moving object may enhance processing in the ventral visual stream (Brown, 2009). Similar biased activation may contribute to the different localization in the prefrontal cortex of systems involved in "what" vs. "where" working memory (Deco et al., 2004; Rottschy et al., 2012). Biased activation as a mechanism for top-down selective attention may be widespread in the brain, and may be engaged when there is segregated processing of different attributes of stimuli (Grabenhorst and Rolls, 2010).

A NEUROPHYSIOLOGICAL MECHANISM FOR TOP-DOWN ATTENTION

We have developed an integrate-and-fire neuronal model of how top-down attentional effects operate at the neuronal level (Deco and Rolls, 2005b). The model has neurons with the membrane potential driven by the dynamically modeled synaptic currents (Brunel and Wang, 2001; Rolls, 2008b; Rolls and Deco, 2010), and allows biophysical properties of the ion channels affected by synapses, and of the membrane dynamics, to be incorporated, and shows how the non-linear interactions between bottom-up effects (produced for example by altering stimulus contrast) and top-down attentional effects can account for neurophysiological results in areas MT and V4 (Deco and Rolls, 2005b). The model and simulations show that attention has its major modulatory effect at intermediate levels of bottom-up input, and that the effect of attention disappears at high levels of contrast of the competing stimulus.

The model assumes no kind of multiplicative attentional effects on the gain of neuronal responses. Instead, in the model, both top-down attention and bottom-up input information (contrast) are implemented in the same way, via additive synaptic effects in the postsynaptic neurons. There is of course a non-linearity in the effective activation function of the integrate-and-fire neurons, and this is what we identify as the source of the apparently multiplicative (Martinez-Trujillo and Treue, 2002) effects of top-down attentional biases on bottom-up inputs. The relevant part of the effective activation function of the neurons (the relation between the firing and the injected excitatory currents) is the threshold non-linearity, and the first steeply rising part of the activation function, where just above threshold the firing increases markedly with small increases in synaptic inputs (Brunel and Wang, 2001). Attention was therefore interpreted as a phenomenon that results from purely additive synaptic effects, non-linear effects in the neurons, and cooperation-competition dynamics in the network, which together yield a variety of modulatory effects, including effects that appear (Martinez-Trujillo and Treue, 2002) to be multiplicative. In addition, we were able to show that the non-linearity of the NMDA receptors may facilitate non-linear attentional effects, but is not necessary for them. This was shown by disabling the voltage-dependent non-linearity of the NMDA receptors in the simulations (Deco and Rolls, 2005b).

EFFECTS OF EMOTION ON COGNITIVE PROCESSING

Emotional states can influence memory (McIntyre et al., 2012) and perception (Pessoa, 2010). A brain system where effects of emotional state and mood on storage and recall could be instantiated is in the backprojection system from structures important in emotion such as the amygdala and OFC to parts of the cerebral cortex important in the representation of objects, such as the inferior temporal visual cortex, and more generally, to parts of the cerebral cortex involved in storing memories. It is suggested (Rolls, 1989, 2008b; Treves and Rolls, 1994) that co-activity between forward inputs and backprojecting inputs to strongly activated cortical pyramidal cells would lead to both sets of synapses being modified (see **Figure 7**). This could result in facilitation or recall of cortical representations (for example of particular faces) that had become associated with emotional states, represented by activity in the amygdala).

A theory of how the effects of mood on memory and perception could be implemented in the brain has been developed (Rolls, 1989, 1999, 2005) and tested (Rolls and Stringer, 2001). The architecture, shown in **Figure 8**, uses the massive backprojections from parts of the brain where mood is represented, such as the OFC and amygdala, to the cortical areas such as the inferior temporal visual cortex and hippocampus-related areas (labeled IT in **Figure 8**) that project into these mood-representing areas (Amaral et al., 1992). The model uses an attractor network (see Rolls, 2008b Appendix 2) in the mood module (labeled amygdala in **Figure 8**), which helps the mood to be an enduring state, and also an attractor in the inferior temporal visual cortex (IT) (or any other cortical area that receives backprojections from the amygdala or OFC). The system is treated as a system of coupled attractors (Rolls, 2008b), but with an odd twist: many different perceptual states are associated with any

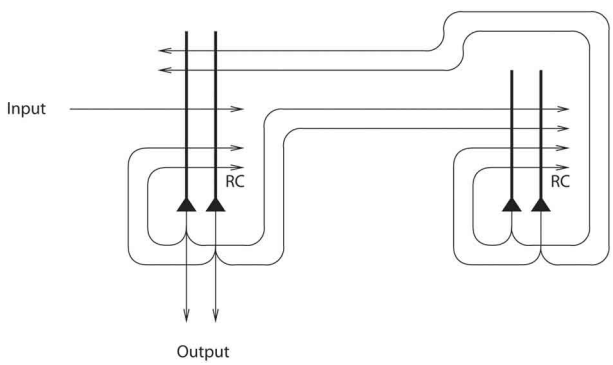

FIGURE 8 | Architecture used to investigate how mood can affect perception and memory. The IT module represents brain areas such as the inferior temporal cortex involved in perception and hippocampus-related cortical areas that have forward connections to regions such as the amygdala and orbitofrontal cortex involved in mood and emotion (after Rolls and Stringer, 2001).

one mood state. Overall, there is a large number of perceptual/memory states, and only a few mood states, so that there is a many-to-one relation between perceptual/memory states and the associated mood states. The network displays the properties that one would expect [provided that the coupling parameters *g* for the synaptic strengths between the attractors are weak (Rolls, 2008b)]. These include the ability of a perceptual input to trigger a mood state in the "amygdala" module if there is not an existing mood, but greater difficulty to induce a new mood if there is already a strong mood attractor present; and the ability of the mood to affect via the backprojections which memories or perceptual states are triggered (Rolls and Stringer, 2001).

Another interesting finding was that the forward connections to the mood module from the memory module must be relatively strong, if new inputs to the memory module are to alter the firing in the mood module by overcoming an existing mood state being kept active by the recurrent collateral connections (Rolls and Stringer, 2001). These results are consistent with the general effects needed for forward and backward projections in the brain, namely that forward projections must be relatively strong in order to produce new firing in a module when a new (forward) input is received, and backward projections must be relatively weak, if they are to mildly implement "top-down" constraints without dominating the activity of earlier modules (Renart et al., 1999a,b, 2001; Rolls, 2008b). Consistent with this, forward projections terminate on cortical neurons closer to the cell body (where they can have a stronger influence) than backprojections (which typically terminate on the distal extremities of the apical dendrite of cortical neurons, in layer 1, the top layer of the cortex (Rolls, 2008b).

An interesting property that was revealed by the model is that because of the many-to-few mapping of perceptual to mood states, an effect of a mood was that it tended to make all the perceptual or memory states associated with a particular mood more similar then they would otherwise have been (Rolls and Stringer, 2001). The implication is that the coupling parameter *g* for the backprojections must be quite weak, as otherwise interference increases in the perceptual/memory module.

In summary, emotional states may affect whether or how strongly memories are stored using the basal forebrain memory strobe (Rolls, 2005); be stored as part of many memories in for example the hippocampus (Rolls, 2005); and may influence both the recall of such memories, and the operation of cognitive processing, using backprojections in the way described in the preceding paragraphs. In turn, cognitive inputs can influence affective states, as described earlier in this paper.

CONCLUSIONS

We have thus seen that cognition can influence emotion by biasing neural activity in the first cortical region in which the reward value and subjective pleasantness of stimuli is made explicit in the representation, the OFC. The same effect occurs in a second cortical tier for emotion, the ACC. Similar effects are found for selective attention, to for example the pleasantness vs. the intensity of stimuli, which modulates representations of reward value and affect in the orbitofrontal and anterior cingulate cortices. The mechanisms for the effects of cognition and attention on emotion are top-down biased competition and top-down biased activation. Affective and mood states can in turn influence memory and perception, by backprojected biasing influences.

Emotion-related decision systems operate to choose between gene-specified rewards such as taste, touch, and beauty. Reasoning processes capable of planning ahead with multiple steps held in working memory in the explicit system can allow the gene-specified rewards not to be selected, or to be deferred (Rolls, 2014). The decisions between the selfish-gene-specified rewards, and the explicitly, cognitively, calculated rewards that are in the interests of the individual, the phenotype, may be influenced by the stochastic, noisy, dynamics of decision-making systems in the brain (Rolls and Deco, 2010; Rolls, 2013c).

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Stop feeling: inhibition of emotional interference following stop-signal trials

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Although a great deal of literature has been dedicated to the mutual links between emotion and the selective attention component of executive control, there is very little data regarding the links between emotion and the inhibitory component of executive control. In the current study we employed an emotional stop-signal task in order to examine whether emotion modulates and is modulated by inhibitory control. Results replicated previous findings showing reduced inhibitory control [longer stop-signal reaction time (SSRT)] following negative, compared to neutral pictures. Most importantly, results show decreased emotional interference following stop-signal trials. These results show that the inhibitory control component of executive control can serve to decrease emotional effects. We suggest that inhibitory control and emotion have a two-way connection in which emotion disrupts inhibitory control and activation of inhibitory control disrupts emotion.

Keywords: emotional processing, executive functions, inhibitory control, stop signal, SSRT, emotional interference

INTRODUCTION

Emotional stimuli play a major role in human lives. They are considered to receive prioritized processing and therefore affect behavior, cognition, and physiology. Maladaptive emotional processing and deficient emotion regulation are core factors in different psychopathologies and therefore it is highly important to understand their nature. One of the most studied topics among emotion scientists is the relationship between emotion and attention (e.g., Vuilleumier, 2005; Pessoa, 2009). Emotional stimuli are considered to capture attention and hence disrupt performance (i.e., elongate RT) in various tasks, such as simple discrimination tasks (Hartikainen et al., 2000; Buodo et al., 2002). This effect is termed emotional interference [i.e., elongated reaction time (RT) for negative compared to neutral trials]. Recently, a vast amount of cognitive and affective studies has been dedicated to exploring the influence of emotional information on tasks that require executive control. Executive control is considered to be a "high" order system that incorporates several attentional subsystems (Posner and Petersen, 1990; Verbruggen and Logan, 2008; Banich, 2009), which act together in order to guide behavior in accordance with internal goals (Shallice and Norman, 1986; Miyake et al., 2000; Miller and Cohen, 2001; Banich, 2009). Importantly, both emotion and executive control are crucial elements in goal-directed behavior. Therefore, studying the links between these two systems is important for understanding adaptive and maladaptive behavior. The aim of the current study is to investigate the connection between inhibitory control—a component of executive control—and emotion eliciting stimuli[1] (i.e., negative pictures).

The influence of emotional stimuli on executive control was studied mainly using selective attention tasks such as the Stroop (1935) and the flanker (Eriksen and Eriksen, 1974) tasks. These tasks measure the ability to attend to a relevant dimension and ignore irrelevant, distracting information. The findings obtained from studies that used such tasks are inconsistent. For instance, using a modified version of the flanker task, Dennis et al. (2008) found reduced executive control following presentation of fearful faces. Similarly, Padmala et al. (2011) found that negative stimuli reduced conflict monitoring and concluded that there are shared resources between executive control and emotional processing. Other studies found the opposite effect; namely, compared to neutral information, emotional information improved executive control in selective attention tasks (e.g., Kanske and Kotz, 2010, 2011a,b; for further discussion see Cohen and Henik, 2012; Kanske, 2012).

Although the effects of emotion on executive control have been widely studied, only recently have researchers begun to explore the effects of executive control on emotion. Okon-Singer et al. (2012) suggested that attentional factors, such as executive control, can exert top-down modulation on emotion (see also Bishop, 2008, for the neural mechanism responsible for regulating attention to threat-related cues; Ochsner and Gross, 2005, for a review). This top-down modulation is crucial in situations in which the emotional information is irrelevant and can disrupt goal-directed behavior. In line with this suggestion, neuroimaging studies found that activation of brain regions involved in executive control (prefrontal, especially dorsolateral, and parietal cortex) attenuates the activation in brain regions involved in emotional processing (mainly the amygdala) (Hariri et al., 2000; Liberzon et al., 2000; Pessoa, 2005; Vuilleumier, 2005; Etkin et al., 2006; Blair et al., 2007; Mitchell et al., 2008; Hart et al., 2010). There is also behavioral evidence for the top–down regulation of

[1] In the context of this manuscript, we discuss the effects of briefly presented emotional stimuli (e.g., negative pictures). It is important to note that these stimuli cause temporary emotional arousal and do not create a long-lasting emotional state or mood.

emotional stimuli. Etkin et al. (2006, 2010) used an emotional Stroop-like task and found a conflict adaptation effect (i.e., emotional conflict in the current trail was attenuated following a conflict in the previous trail). The authors concluded that executive processes (i.e., selective attention) can attenuate emotional response. Recently, we found more direct behavioral evidence for the top–down regulation of emotional stimuli (Cohen et al., 2011, 2012). We presented negative and neutral pictures following a flanker target and measured emotional interference in a following discrimination task. Participants were required to respond to the direction of a middle arrow and ignore flanking arrows. The flanking arrows could be congruent (<<<<<) or incongruent (<<><<) with the target arrow. Incongruent trials consist of a conflict and are considered to recruit executive control processes (as indicated in elongated RT in incongruent vs. congruent trials). Emotional interference was present after congruent trials, but was eliminated after incongruent trials (Cohen et al., 2012; see also Blair et al., 2007).

Looking at selective attention tasks to examine the connection between emotion and executive control might be insufficient. In line with this notion, many researchers suggested that executive control is not unitary and urged discerning between different components of control (Rafal and Henik, 1994; Harnishfeger, 1995; Miyake et al., 2000; Nigg, 2000; Banich, 2009). Selective attention tasks, such as the Stroop (Stroop, 1935; MacLeod, 1991) and the flanker (Posner and Petersen, 1990) tasks measure the ability to attend to a relevant dimension and ignore irrelevant, distracting information. The ability to ignore irrelevant information might involve inhibition (Verbruggen et al., 2004; Kalanthroff et al., 2012)—a core component of executive control (van Veen and Carter, 2006; Verbruggen and Logan, 2008). In the current paper we ask whether the inhibitory component of executive control is influenced and can modulate emotional reaction in a similar way as is found in selective attention.

INHIBITORY CONTROL

An important ingredient of executive control, and perhaps a hallmark of it, is the suppression of irrelevant information, thought, or action (van Veen and Carter, 2006; Verbruggen and Logan, 2008). This component of executive control is termed inhibitory control and is commonly associated with activation in the right inferior frontal gyrus (rIFG; Aron et al., 2003). To study this process in the laboratory, consider the stop-signal task (Logan and Cowan, 1984; Logan, 1994), which examines the ability to suppress an already initiated action that is no longer appropriate. In the classic task, participants are asked to address a visual stimulus (go signal) with a motor response as fast as possible. In about one fourth of the trials, an auditory stimulus (stop signal), which signals to participants to inhibit their motor response, comes right after the visual go signal. The duration between the go signal and the stop signal (stop-signal delay; SSD) is submitted to a tracking procedure and changes from one trial to the next based on the participant's success in inhibiting his or her response (i.e., a successful inhibition will cause the next trial to be more difficult—the SSD will be longer—and vice versa). Eventually, it is possible to estimate the stop-signal reaction time (SSRT), which is the time needed for successful inhibition. SSRT has proven to be an important measure of cognitive control (Verbruggen and Logan, 2008). Logan and Cowan (1984) and Logan et al. (1984) compared the performance in the stop-signal task to a horse race between the more automatic go process, triggered by the presentation of the go signal, and the executive stop process, triggered by the stop signal. Logan et al. (1984) argued that "response inhibition phenomena are consistent with a hierarchical theory of attention in which a high level process determines the significance of incoming stimuli and decides whether to abort the current stream of thought and action or to queue the new stimuli along with the old ones, to be processed as resources become available" (p. 290).

INHIBITORY CONTROL AND EMOTION

Few studies concentrated on the relationship between emotion and inhibitory control. Using a modified version of the stop-signal paradigm, Verbruggen and De Houwer (2007) found that emotional stimuli (negative or positive pictures) decrease the efficiency of inhibitory control (i.e., longer SSRT in emotional trials). Sagaspe et al. (2011) found prolonged RT in the presence of incidental threatening information, though SSRT was unaffected by emotion. However, these researchers did find that neural circuits engaged by inhibition are modulated by threatening information. Specifically, they found that stopping in a threatening trial was associated with activations in the orbitofrontal cortex (and not the inferior frontal gyrus usually associated with stopping). This finding implies that inhibitory control in the presence of emotional information may be different from inhibitory control in neutral situations. Pessoa et al. (2012) used the stop-signal task with high- and low-threat stimuli and found that the efficiency of inhibitory control is increased by low-threat stimuli and decreased by high-threat stimuli. This finding is in line with Pessoa et al. (2012) notion that low threat improves executive control since it increases goal-directed behavior (see also Kanske, 2012), whereas high threat attracts resources available for the task and hence disrupts executive processes.

In contrast to the mixed findings regarding the influence of emotion on selective attention, with respect to inhibitory control most findings are consistent regarding the disruptive influence of emotion on inhibitory control. A previous study showed that an emotional stimulus deteriorates performance of both go and stop processes (Verbruggen and De Houwer, 2007). However, it is not yet clear whether inhibitory control exerts a regulatory effect on emotion, similar to the effect of selective attention. This question is highly important for few reasons: (a) understanding the connection between inhibition and emotion influence on performance can deepen our knowledge regarding the connection between "high" (e.g., executive control) and "low" (e.g., emotion) cognitive systems. (b) Deficient inhibitory control underlies different psychopathologies and mood disorders, such as autism (e.g., Geurts et al., 2004), schizophrenia (e.g., Enticott et al., 2008), obsessive-compulsive disorder (e.g., Chamberlain et al., 2006), and anxiety (e.g., Derakshan et al., 2009), though it is still unknown whether disrupted inhibitory control is responsible for the abnormal emotional processing found in these disorders. Depressed patients, for example, are known to have deficient ability to inhibit processing of emotional stimuli

(e.g., Goeleven et al., 2006) and thus, in this disorder the role of disrupted inhibition is clearer. (c) Considering the fact that inhibition is at least partially involved in most executive control tasks (including selective attention tasks), the connection between inhibition and emotion could potently contribute to the overall understating of the connection between executive control and emotion.

THE CURRENT STUDY

The current study employed an emotional stop-signal task in order to examine the reciprocal links between emotion and inhibitory control. First, in no-stop-signal trials we predicted an emotional interference effect, similar to results obtained in simple discrimination tasks (Hartikainen et al., 2000; Buodo et al., 2002). Second, because we were using a design similar to the one used by Verbruggen and De Houwer (2007), we predicted a replication of their findings showing disrupted inhibitory control (i.e., longer SSRT) following negative compared to neutral pictures. Most importantly, we expected that the emotional interference would be eliminated when the previous trial was a stop trial. Namely, activation of inhibitory control processes during stop trials would reduce activation of negative stimuli on a following no-stop trial. This prediction was based on previous findings showing reduced emotional interference following executive activation using selective attention tasks (Cohen et al., 2011, 2012).

MATERIALS AND METHODS

PARTICIPANTS

Twenty-seven students of Ben-Gurion University of the Negev (Israel) participated for a small monetary payment. The study was approved by the ethical committee of the department of Psychology, Ben-Gurion University of the Negev, Israel. All participants signed an informed consent form previous to their participation in the experiment. All participants had normal or corrected-to-normal vision, were right-handed, had no history of attention deficit, or learning disabilities, and all were naive as to the purpose of the experiment. One participant was excluded from further analysis due to a high error rate on no-stop-signal trials [more than 3 standard deviations (*SD*) from the mean] and one was excluded due to report of severe depressive symptoms in a major depression inventory administered at the end of the behavioral task (MDI; Bech, 1997; Bech and Wermuth, 1998). In addition, because SSRT is an estimation of the time needed for a participant to stop on 50% of the trials, if a participant's success in inhibiting responses to stop trials was significantly different from 50%, the SSRT would not be valid and the participant would be excluded from further analysis [estimation method by Verbruggen and Logan (2009); see also Verbruggen et al. (2008)]. Three participants (females) were excluded due to the latter criterion. From the remaining 22 participants (10 females and 12 males) the youngest was 23 years old and the oldest was 29 years old (mean = 25.1 years, *SD* = 1.66).

EQUIPMENT

Data collection and stimuli presentation were controlled by a DELL OptiPlex 760 vPro computer with an Intel core 2 duo processor E8400 3 GHz. Stimuli were presented on a DELL E198PF 19″ LCD monitor. A keyboard was placed on a table between the participant and the monitor. Participants were tested individually. They sat approximately 23.5 in. from the computer screen. Stickers with "@" and "#" signs were taped on two regular keyboard keys that served as response keys.

PROCEDURE

The experiment included 12 practice trials, which were not further analyzed, and 480 experimental trials. Participants were told that the practice block would be identical to the experimental block, only that the experimental block would be longer and would not include feedback. Each trial started with a 1000 ms fixation (a black plus sign at the center of a gray screen). Fixation was followed by a picture for 100 ms. After the disappearance of the picture, a visual go stimulus appeared (i.e., @ or #). Response keys were "p" for the appearance of a "@" and "q" for a "#." Participants were asked to respond with the index fingers of both hands. The instruction indicated to participants to press the correct key as fast and accurately as possible, and emphasized not to wait for a potential stop signal. The go stimulus stayed in view for 1500 ms or until a key press. RT was calculated from the appearance of the go stimulus to the response. On a random selection of 30% of the trials, an auditory stop signal was sounded (see **Figure 1**). The stop signal was presented after a variable SSD that was initially set at 250 ms and adjusted by a staircase tracking procedure: after each successful stopping the SSD was extended by 20 ms and after each unsuccessful stopping the SSD was shortened by 20 ms. In half of the trials a neutral picture was presented and in the other half a negative picture was presented. SSD was adjusted for each valence condition (i.e., negative and neutral) separately. Trial order was random with two restrictions: we had the same number of neutral and negative stop-signal trials (72 of each), and we had the same number of neutral and negative trials that followed stop-signal trials (36 of each valence condition in the current trial for each valance condition in the previous trial).

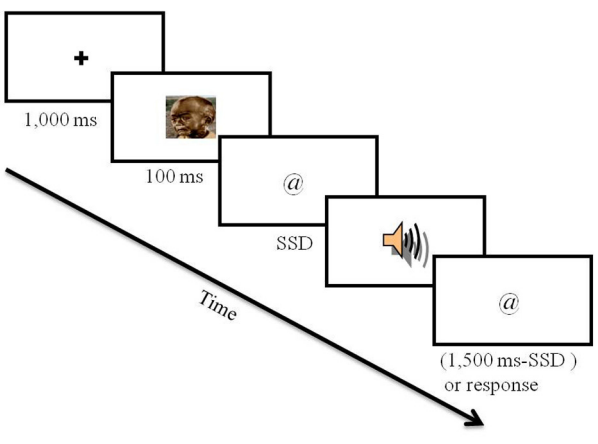

FIGURE 1 | Experimental procedure. Example of a negative stop-signal trial.

STIMULI

Participants were presented with an emotional stop-signal task. We used 40 negative (mean valence = 2.41, mean arousal = 6.16) and 40 neutral (mean valence = 5.01, mean arousal = 2.84) pictures taken from the International Affective Picture System (IAPS; Lang et al., 2001). The pictures were identical to those used by Verbruggen and De Houwer (2007). Ten neutral pictures, different from those used in the actual experiment, were used in the practice phase. The go signals were black "@" or "#" signs presented at the center of a screen on a gray background and were 0.98 in. high and 2.36 in. wide. The stop signal was an auditory tone (750 Hz, 75 ms) delivered by headphones.

RESULTS

In order to investigate our a-priori assumption that following stop-signal trials negative stimuli would not affect RT, a Two-Way analysis of variance (ANOVA) with repeated measures was applied to RT data of no-stop trials with valence (negative vs. neutral) and previous trial (no-stop vs. stop) as within-subject factors (see **Table 1**). A significant interaction between valence and previous trial was found, $F_{(1,\ 21)} = 6.325$, $p < 0.02$, *partial eta squared (PES)* = 0.231. As can be seen in **Figure 2**, following no-stop trials, RT for negative stimuli was significantly longer than RT for neutral stimuli, $F_{(1,\ 21)} = 18.905$, $p < 0.001$, $PES = 0.474$. In contrast, following stop trials, RT for negative stimuli did not differ significantly from RT for neutral trials, $F < 1$. Namely, the emotional interference effect was eliminated following stop-signal trials. This is similar to our previous findings showing attenuation of emotional interference following flanker incongruent trials (Cohen et al., 2011).

In trials without a stop signal, mean RT of correct responses was calculated for each participant in each valence condition. A One-Way ANOVA with repeated measures was applied to RT data with valence (negative vs. neutral) as a within-subject factor (see **Table 1**). As expected, RT for negative stimuli was significantly longer than RT for neutral stimuli, $F_{(1,\ 21)} = 22.191$, $p < 0.001$, $PES = 0.514$. This finding replicates the known emotional interference effect, which was previously found by using simple discrimination tasks (Hartikainen et al., 2000; Buodo et al., 2002).

As mentioned before, SSD was adjusted for each valence condition separately. Based on the assumption that chances for successful inhibition were not significantly different than 0.50, SSRT was calculated as mean RT minus median SSD for each participant in each condition (see Verbruggen and Logan, 2009; see **Table 1**). As predicted, SSRT for negative trials was longer than SSRT for neutral trials. This was significant, $F_{(1,\ 21)} = 4.301$, $p = 0.05$, $PES = 0.17$. This result replicates Verbruggen and De Houwer's (2007) findings and strengthens the claim that emotional information disrupts inhibition-related executive functions.

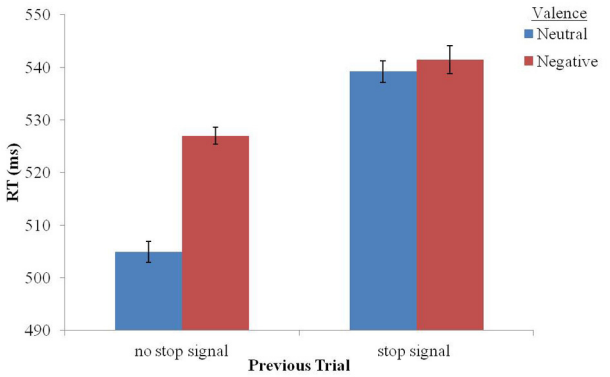

FIGURE 2 | Mean RT in the valence conditions following stop-signal trials or no stop-signal trials. Error bars represent one standard error from the mean based on Cousineau's (2005) method for within-subjects designs.

DISCUSSION

The results of the current study are straightforward: first, emotional stimuli were found to impair responding and inhibitory control (i.e., elongated SSRT). Second, activation of inhibitory control was found to attenuate the (following) emotional effect.

In no stop-signal trials, responses to the discrimination task were slower when preceded by negative stimuli than when preceded by neutral stimuli; namely, we found an emotional interference effect (Hartikainen et al., 2000; Schimmack, 2005). This basically replicated previous findings that showed that negative stimuli disrupt performance in simple discrimination tasks that do not involve conflict (Hartikainen et al., 2000; Buodo et al., 2002). This finding corresponds with LeDoux's (1995) notion that emotional stimulus saliency is increased in order to enhance its processing.

Similar to Verbruggen and De Houwer (2007), we found that stopping latencies were prolonged following presentation of negative stimuli compared to stopping latencies following

Table 1 | Reaction time (*RT in ms*), standard deviation (*SD*), and accuracy (*ACC*) of the different trials in the two valance conditions (Neutral and Negative).

	Neutral			Negative		
	RT	***SD***	***ACC***	***RT***	***SD***	***ACC***
No stop signal	517	69	0.97	533	67	0.97
Following no stop signal	505	75	0.96	527	71	0.97
Following stop signal	539	63	0.97	541	66	0.97
	SSRT	***SD***	***p(response|signal)***	***SSRT***	***SD***	***p(response|signal)***
Stop signal	187	59	0.49	210	62	0.46

neutral stimuli. Namely, the ability to stop decreased when an irrelevant negative stimulus was presented. Similar to the results found in the no-stop trials, the findings showing elongated stopping latency following negative compared to neutral stimuli also strengthen the notion that emotional stimuli capture attention and receive prioritized processing compared to non-emotional stimuli. The idea that the presentation of a negative stimulus causes a momentary freeze (as would be expected from the fight, flight, freeze theory) can be interpreted in two ways by our findings. On the one hand, Verbruggen and De Houwer (2007) suggested that a momentary freeze should have helped stopping and thus SSRT should be shortened (improved) following a negative stimulus. On the other hand, a momentary cognitive freeze that occurs during the presentation of a negative stimulus would slow down the inhibitory control process. Our results, similar to those of Verbruggen and De Houwer, show slowdown both in the inhibitory control process and in RT to no-stop trials following a negative stimulus and thus indicate that cognitive freeze did occur. These results are in line with those of other studies that found reduced performance in executive tasks following emotional stimuli (e.g., Dennis et al., 2008; Padmala et al., 2011).

Importantly, in the current paper we examined the connection between briefly (100 ms) presented emotional stimuli (i.e., IAPS negative pictures) and inhibitory control. The findings reflect effects of a transient emotional arousal (as usually found when emotional and non-emotional pictures are presented randomly within the same block; Bradley et al., 1993) and not of a sustained emotional state or mood (as found when presenting a block of emotional pictures; Bradley et al., 1996). Briefly presented IAPS pictures are known to elicit emotional arousal as measured using physiological (Lang et al., 1993), electrophysiological (Schupp et al., 2004), and brain imaging (Glascher and Adolphs, 2003) methods (see Shackman et al., 2006 for a debate regarding assessment of emotional effects). In line with these findings, in the current study the IAPS pictures caused a momentary emotional arousal which affected performance of both go and stop processes.

The most important contribution of the current study is the finding regarding the effect of inhibitory control on emotion. The novelty of our study is that it examines whether inhibitory control can attenuate the effect of a following emotional stimulus. Our results show that while RT increased following negative stimuli, this effect disappeared in trials that where preceded by a stop-signal trial; namely, the emotional interference effect was not obtained following stop-signal trials. Accordingly, we suggest that the need to inhibit a pre-potent response activated inhibitory networks, which in turn down-regulated the emotional system and eliminated its influence on behavior. Given that the current research does not allow for direct measures of emotional processes, we cannot be sure whether inhibitory processes directly inhibits emotional processes or whether it inhibits the consequences of emotional processes. Further research is needed in order to investigate these interesting possibilities.

The current study's findings correspond with our previous findings that yielded a significant emotional interference effect after flanker-congruent trials but not after flanker-incongruent trials (Cohen et al., 2011). In that study it was argued that executive control activates top-down processes that can eliminate the influence of emotions on behavior. This regulatory connection was suggested as an interpretation for the finding that emotions did not affect executive control. To differentiate from that previous study, in the current study we found a "two-way" connection in which negative stimuli interrupted inhibitory control and operation of inhibitory control attenuated the influence of emotion on performance. As mentioned earlier, the flanker task and the stop-signal task activate different aspects of executive control (though there is some overlap between the mechanisms underlying them). Whereas the flanker task is mainly used to study selective attention or conflict control, the stop-signal task examines inhibitory control. While selective attention is characterize by the need to focus on the relevant stimulus or dimension and ignore irrelevant distracters, inhibitory control is characterize by the need to stop the current course of action. On the neurological level, selective attention tasks are associated mainly with activations of the anterior cingulate cortex and the dorsolateral prefrontal cortex (Cohen et al., 1990; Botvinick et al., 1999, 2001; Carter et al., 1999; Niendam et al., 2012), while stopping is mainly associated with activation of the rIFG; ventrolateral prefrontal cortex and the presupplementary motor area (pre-SMA) (Aron et al., 2003, 2007; Rubia et al., 2003; Chambers et al., 2007; Chevrier et al., 2007). It seems that the relationship between selective attention and emotion is not identical to the relationship between inhibitory control and emotion. Specifically, it seems that emotional stimuli impair inhibitory control but have inconsistent effects on selective attention. However, converging evidence from both of these executive components strengthens the notion that activation of executive control processes regulates the impact of emotion on behavior and on cognitive processes. As mentioned in the introduction, selective attention tasks activate inhibitory processes. It is possible that activation of the inhibitory control process underlies the top-down regulation effect found when using both selective attention and stop-signal tasks.

Some implications can be drawn from the current study results. Earlier, we mentioned that many psychopathologies and mood disorder are characterized by poor inhibitory control (e.g., autism—Geurts et al., 2004; schizophrenia—Enticott et al., 2008; obsessive-compulsive disorder—Chamberlain et al., 2006; and anxiety—Derakshan et al., 2009), and poor ability to suppress processing of emotional information (e.g., depression—Goeleven et al., 2006). Further research is needed in order to investigate the connection between the deficit in inhibitory control and the deficit in emotion regulation in these patients. Attention deficit\hyperactivity disorder (ADHD) is another widespread condition that the current study results may have implications for. People with ADHD are known to have deficient inhibitory control (stop-signal inhibition was proposed to be "an endophenotype of ADHD," see Verbruggen and Logan, 2008, for review) and they also experience difficulties in emotion regulation (e.g., Walcott and Landau, 2006). The current study results imply that these two phenomena may be connected, though further research is needed in order to fully understand the connection between poor inhibitory control and the deficit in emotions regulation in individuals with ADHD.

To conclude, in the current study we demonstrated that emotional stimuli interfere with task performance, although,

following trials that required inhibitory control this effect disappears—RT of negative trials was similar to RT of neutral trials. Additionally, we replicated previous findings showing that emotional stimuli interfere with inhibitory control. These findings suggest a two-way connection between inhibitory control and emotion in which emotion both disrupts and is modulated by inhibitory control. It seems that under some circumstances "high" cognitive systems can regulate or even suppress "low" systems such as the emotional system and thus prevent it from influencing performance. This mechanism has a potentially adaptive function—it enables goal-directed behavior in the presence of briefly presented irrelevant emotional information. Further research is still needed in order to uncover the specific circumstances in which this top-down regulation occurs and the implications of deficits in this regulation mechanism for emotion dysregulation disorders.

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The impact of induced anxiety on response inhibition

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Anxiety has wide reaching effects on cognition; evidenced most prominently by the "difficulties concentrating" seen in anxiety disorders, and by adaptive harm-avoidant behaviors adopted under threatening circumstances. Despite having critical implications for daily-living, the precise impact of anxiety on cognition is as yet poorly quantified. Here we attempt to clarify the impact of anxiety on sustained attention and response inhibition via a translational anxiety induction in healthy individuals ($N = 22$). Specifically, in a within-subjects design, participants completed the Sustained Attention to Response Task (SART) in which subjects withhold responses to infrequent no-go stimuli under threat of unpredictable electrical shock (anxious) and safe (non-anxious) conditions. Different studies have argued that this task measures either (1) attention lapses due to off-task thinking or (2) response inhibition; two cognitive functions which are likely impacted by anxiety. We show that threat of shock significantly reduces errors of commission on the no-go trials relative to the safe condition whilst having no effect on go trials or overall reaction time (RT). We suggest that this is because threat of shock during SART promotes response inhibition. In particular we argue that, by virtue of frequency, subjects acquire a habitual bias toward a go response which impairs no-go performance and that threat of shock improves the ability to withhold these prepotent responses. This improved response inhibition likely falls within the range of adaptive cognitive functions which promote cautious harm avoidance under threatening conditions, although a range of alternative explanations for this effect is discussed.

Keywords: anxiety, threat, threat of shock, response inhibition, mind-wandering

INTRODUCTION

Anxiety can significantly alter cognitive function (Robinson et al., submitted). Prominent symptoms of anxiety disorders include attentional lapses and difficulty concentrating; sufferers often complain of an inability to stay focused on tasks because they are highly distractible. At the same time, in certain contexts—such as walking alone in the dark—anxiety can promote an adaptive state of improved vigilance and defense mobilization (Grillon and Charney, 2011). Whereas the effects of attentional capture by *acute* threat cues on cognitive performance is well-documented (e.g., threatening words alter performance on emotional Stroop tasks) (Algom, 2004; Pacheco-Unguetti et al., 2011; Padmala et al., 2011; Sagaspe et al., 2011; Pessoa et al., 2012), relatively little is known about the precise quantitative effects of more *sustained* anxiety states on cognitive and behavioral performance.

The present study examined the effect of sustained anxiety induced by unpredictable shock (Robinson et al., 2011; Cornwell et al., 2012) anticipation on performance of a go/no-go task designed to probe distraction (Robertson et al., 1997). In this so-called "sustained attention to response task" (SART), subjects are presented with frequent "go" stimuli, to which they have to respond, and infrequent "no-go" stimuli, to which they have to withhold responses (Robertson et al., 1997). This task was developed to measure lapses of attention and slips of action (i.e., off-task thinking) as indexed by errors of commission; e.g., inappropriate responses to the infrequent no-go trials (i.e., failed response inhibition). The impact of sustained anxiety on this task is, as yet, unknown.

Errors of commission on this task have been attributed to a number of different causes. One argument is that errors of commission represent "mind-wandering" or off-task thinking caused by boredom (Smallwood et al., 2004, 2009) and/or executive control failure (McVay and Kane, 2010). Mind-wandering involves relatively complex trains of thought which are primarily associated with the individual's current concerns (Klinger, 2009) and cause distraction from the task. However, this "mindless" theory of performance failure is not unanimously accepted. It is also argued that the task is a measure of response inhibition and impulsivity (Helton, 2008; Helton et al., 2009, 2010). Specifically, it is believed that the frequent go trials lead to a build-up of feed-forward, habitual, motor routines, which preserve task performance whilst reducing cognitive load. These responses are monitored by a supervisory system which controls "the strategic choices regarding the speed and accuracy of responses" (Helton et al., 2009). The supervisory attention system requires processing resources and can be weakened by cognitive load induced by task-relevant or -irrelevant thoughts, which leads to speeded reaction time (RT), increased RT variability, reduced response inhibition, and increased likelihood of errors of commission.

Anxiety induced by threat of shock has a wide range of effects on cognition (see Robinson et al., submitted), which leads to conflicting hypotheses regarding the impact of anxiety on this

task. Anxiety could impair performance because it impairs executive control mechanisms that help maintain goal-directed behaviors (Bishop, 2009). It could also impair performance because threat of shock promotes lapses of attention and mind-wandering (e.g., off-task thinking) due to repetitive intrusive thoughts and worries (Watkins, 2008). This hypothesis is supported by reports that a lack of concentration in high state anxiety is correlated with mind-wandering (Watts and Sharrock, 1985) and with the observation that negative (i.e., sad) mood increases mind-wandering on the SART (Smallwood et al., 2007, 2009).

However, several lines of evidence point to the opposite hypothesis; that threat of shock should *reduce* errors of commission on SART. First, anxiety can facilitate perceptual/sensory processing (Robinson et al., submitted), which could lead to improved perception and detection of the infrequent no-go trials. Second, trait anxiety has been associated with enhanced response inhibition in go/no-go experiments (Sehlmeyer et al., 2010). Indeed, anxiety induced by threat of shock can increase inhibition of motor responses (Grillon and Davis, 2007; Cornwell et al., 2008). Specifically, prepulse inhibition, the mechanism by which a week sensory stimulus can, via temporal proximity, reduce eyeblink startle response to a loud noise, is *increased* by threat of shock. In particular, threat of shock serves to increase the ability of a weak acoustic or tactile "prepulse" stimulus to *gate* startle motor responding (Cornwell et al., 2008).

In this study, we therefore sought to discriminate between these conflicting possibilities and clarify the effects of anxiety on the SART. Subjects completed the SART task under conditions where they were at risk from-, and safe from, unpredictable shock. The main analysis focused on trial by trial RT and errors of commission, but we also examined RT to the trials that preceded no-go trials (Robertson et al., 1997) as errors of commission on no-go SART trials are commonly preceded by faster responding (Robertson et al., 1997). This has been argued to reflect an automatic mode of processing and off-task thinking (Robertson et al., 1997; Smallwood et al., 2004) but could also be interpreted as evidence of feed-forward prepotent, habitual motor response, and speed/accuracy trade-off (Helton, 2008). Finally, we examined self-report of off-task thinking (Smallwood et al., 2007) by asking subjects whether they were focusing on the task or if they experienced off-task thinking (anxious or otherwise).

Thus, a reading of the prior literature leads to conflicting hypotheses. On the one hand, anxiety could reduce the ability to maintain attention across trials through increased attentional lapses and anxiety-related thoughts manifested as increased RT variability and enhanced rates of errors of commission. On the other hand, anxiety could reduce errors of commission by improving sensory perception and/or response inhibition. Here, we aimed to distinguish between these two possibilities by examining the effect of anxiety induced by threat of shock on performance during SART.

METHODS

PARTICIPANTS

Twenty two healthy volunteers (11 males, 11 females) between the ages of 20 and 34 (mean 27) were compensated for completing the study. Inclusion criteria were: (1) no past or current psychiatric disorders according to SCID-I/P (First et al., 2002), (2) no history of a psychiatric disorder in any first-degree relatives; (3) no medical condition that interfered with the objectives of the study as established by a physician, and (4) no use of illicit drugs or psychoactive medications according to history and confirmed by a negative urine screen. All participants gave written informed consent approved by the National Institute of Mental Health (NIMH) Human Investigation Review Board.

PROCEDURE

Following attachment of the electrodes, nine startle stimuli (habituation) were delivered every 18–25 s. This was followed by a shock work-up procedure to set up the shock intensity at a level highly annoying and mildly painful. Next, subjects performed a variant of SART (Robertson et al., 1997) when safe from shock and when anticipating shock.

SART

Participants were asked to respond to frequent "go" stimuli ("=") by pressing the space bar and to withdraw their response to rare "no-go" stimuli ("O"). These stimuli were randomly distributed and were presented for 250 ms at a rate of one every 2000 ms and there was no response deadline. There were a total of eight continuous 106-s SART blocks, four safe blocks, and four threat blocks that alternated. In each block, the go stimuli were presented on either 47 or 48 occasions while the no-go stimulus occurred four or five times per block for a total of 190 go and 18 no-go trials (adding up to 9.5% of total trials) per safe or threat condition. Three startle stimuli were delivered in each block to assess subjects' psychophysiological concomitants of anxiety during shock anticipation. The first SART block was a safe condition in half the subjects and it was a threat condition in the other half. Subjects were asked to give equal weight to speed and accuracy. A single shock was presented mid-block prior the final trial of two separate threat conditions, thus there were two shocks within a period of ∼15 min; a sustained state of anxiety.

QUESTIONNAIRES

Subjective reports of on- and off-task thoughts as well as subjective anxiety were assessed after each block. Immediately after a block ended, subjects were asked to retrospectively rate their level of anxiety on a scale ranging from 1 (not at all anxious) to 10 (extremely anxious). On- and off-task thinking was evaluated by asking subjects about their thoughts at the time the block ended. They had to select one of the three choices indicating that they were (1) thinking about the task, (2) thinking about something unrelated (but not an anxious thought), or (3) having anxious thoughts. The sum total of each thought category was determined for each participant under each condition and the mean anxiety rating recorded for each condition.

STIMULATION AND PHYSIOLOGICAL RESPONSES

Stimulation and recording were controlled by a commercial system (Contact Precision Instruments, UK). The acoustic startle stimulus was a 40 ms duration 103-dB (A) burst of white noise presented through headphones. The eyeblink reflex was recorded with electrodes placed under the left eye. The electromyographic

(EMG) signal was amplifier with bandwidth set to 30–500 Hz and digitized at a rate of 1000 Hz. The shock was administered on the left wrist.

DATA ANALYSIS

Following rectification and smoothing of the EMG signal, peak startle/eyeblink magnitude was determined in the 20–100-ms timeframe following stimulus onset relative to a 50-ms prestimulus baseline. The startle magnitude scores were averaged within the safe and the threat condition. Performance accuracy was determined for each condition (threat/safe) trial type (go/no-go) by dividing the number of correct trials by the total number of each trial type. The one trial following a shock was excluded from analyses. During the go condition, correct responses were any trial in which there was a response and in the no-go condition, correct trials are the ones in which no response was provided. RTs for correct go trials and incorrect no-go trials (errors of commission) were averaged across each condition. Response variability was determined by calculating the standard deviation in RT for (correct) go trials for each subject. To examine pre-error responses (Robertson et al., 1997), RTs were averaged across the four stimuli before no-go trials (**Table 1**), averaged across condition, and stratified by whether the subsequent no-go trial was or was not successful. The startle magnitude and subjective anxiety scores were averaged across blocks within each condition. Data were analyzed with repeated measures analyses of variance (ANOVA) and *T*-tests.

RESULTS

SART PERFORMANCE

Accuracy was analyzed using a condition (safe, threat) × trial type (go, no-go) ANOVA. Consistent with previous results (Robertson et al., 1997), subjects were less accurate in responses to no-go trials compared to go trials [main effect of trial type; $F_{(1,\ 21)} = 8.6$, $p = 0.008$] as well as less accurate under safe relative to threat [$F_{(1,\ 21)} = 4.7$, $p = 0.04$]. However, accuracy to no-go trials was differently affected by the safe/threat conditions, leading to a significant condition × trial type interaction [$F_{(1,\ 21)} = 8.9$, $p = 0.007$]. The interaction was driven by a significant increase in no-go trial accuracy under threat relative to safe [$F_{(1,\ 21)} = 6.8$, $P = 0.017$; **Figure 1**]. Such a change in accuracy was not present for go trials [$F_{(1,\ 21)} = 0.004$, $P = 0.9$]. There was no significant difference in RT for correct go trials [$t_{(21)} = 0.3$, $P = 0.8$] or failed no-go trials [in which a response was recorded; $t_{(20)} = 1.7$, $P = 0.1$; note that this is a small number of trials so interpretation is limited; degrees of freedom in *t*-test is 20 because one subject had 100% accuracy]. RT variability was comparable across both safe and threat (SEM = 14 and 16 ms respectively) and a comparison of the standard deviation of each subject's go trials under safe and threat was not significant [$t_{(21)} = -0.04$, $p = 0.97$].

Table 1 | Behavioral measures; RT = reaction time (ms).

	Threat				Safe			
	No-Go		Go		No-Go		Go	
Accuracy	0.79	(0.05)	0.90	(0.02)	0.70	(0.06)	0.90	(0.02)
RT	370	(46)	361	(17)	295	(18)	359	(14)
	No-Go fail		No-Go success		No-Go fail		No-Go success	
Pre RT	293	(9)	357	(23)	316	(14)	364	(16)

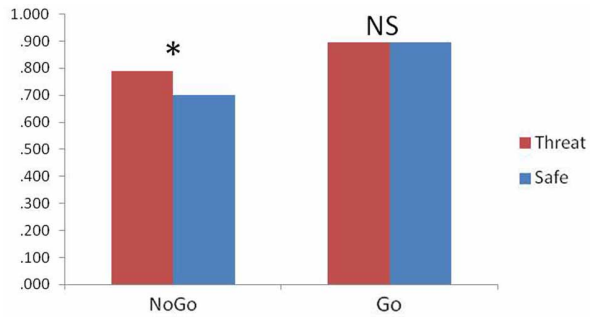

FIGURE 1 | Response Accuracy; threat of shock significantly improved no-go accuracy (*$p < 0.05$), while having no effect upon go accuracy (NS = not significant), error bars represent standard error of the mean.

The pre-no-go trial RT were analyzed in a condition (safe, threat) × accuracy (fail, success) ANOVA. Results show a significant main effect of accuracy [$F_{(1,\ 18)} = 15$, $p = 0.001$] due to faster RT preceding failed compared to successful no-go responses that was not affected by the threat of shock {no condition × accuracy interaction; [$F_{(1,\ 18)} = 0.4$, $p = 0.54$]}. However, these results should also be treated with caution because they comprise a relatively small number of trials, particularly for failed no-go trials. Overall behavioral measures for each trial type and condition are presented in **Table 1**.

ANXIETY MEASURES

There was a significant increase in state anxiety ratings under the threat (mean 5 ± 2) vs. safe (mean 2 ± 2) conditions [$t_{(21)} = 6.8$, $P < 0.001$]. This was associated with a comparable significant increase in raw startle response under threat (38) relative to safe (18) $t_{(21)} = 3.3$, $p = 0.005$.

PROBES OF ON-AND OFF-TASK THINKING

Following each block of the task, subjects thought equally about the task under threat and safe [$T_{(21)} = 0.38$, $p = 0.7$], but had more anxious thoughts under threat relative to safe [$T_{(21)} = -3.2$, $p = 0.005$], and more unrelated thoughts under safe relative to threat [$T_{(21)} = 4.2$, $p < 0.001$].

DISCUSSION

The main result of this study is that anxiety induced by threat of shock *reduced* errors of commission without affecting response speed or variability. These findings do not therefore support the hypothesis that threat of shock increased off-task thinking; as this would be expected to impair performance. Rather, we argue that induced-anxiety improved response inhibition.

We think that the most plausible explanation for better no-go accuracy during threat of shock is improved motor response

inhibition. This is consistent with a number of different lines of research. Firstly, from a theoretical perspective, anxiety activates inhibitory behaviors. In fact, freezing is a well-established measure of anxiety (Gray and McNaughton, 2003). Secondly, event-related potential studies have suggested that trait anxiety is associated with enhanced motor response inhibition during no-go trials (Righi et al., 2009; Sehlmeyer et al., 2010). Thirdly, induced anxiety also increases prepulse inhibition of startle, that is, the ability to inhibit a startle motor response following a prepulse stimulus (Grillon and Davis, 2007; Cornwell et al., 2008). Indeed, the proportion of no-go trials in the SART is very low compared to the frequent go trials. As such, the task may be more a test of reactive stopping than proactive stopping (Aron, 2011). Specifically, by virtue of being more frequent, the go targets may acquire a bias toward habitual responding. Hence, no-go trials may be less about deciding *not to go* than *countermanding an initiated prepotent* response (Aron, 2011). Thus, anxiety may improve the ability to inhibit habitual responding. Such facilitation is of clear adaptive value as it may reduce the likelihood of an inappropriate motoric urge or impulsive response when threat looms.

The pattern of performance during SART could, however, potentially be due to the fact that anxiety facilitated detection of the no-go stimuli. Two potential mechanisms could lead to such an improvement: enhanced perception or focused attention. Substantial evidence shows that induced-anxiety facilitates perceptual/sensory processing (reviewed in Robinson et al., submitted). Such facilitation could help detect no-go trials. However, there is also evidence that anxiety increases the selectivity of attention. According to Easterbrook (1959)'s attentional breadth theory, anxiety narrows attention, reducing distraction by task-irrelevant peripheral stimuli. This view has been supported by several studies in which anxiety evoked by the anticipation of shocks leads to improved target detection (Agnew and Agnew, 1963; Tecce and Happ, 1964; Hu et al., 2012). Nevertheless, it seems unlikely that performance improvement under threat of shock was due to a better ability to detect or attend to stimuli on such a simple task with low perceptual load. First, several authors have noted that "Participants have no difficulty seeing and identifying the target" during SART (Cheyne et al., 2009; Helton et al., 2009). Second, as evidenced by the present data, participants only have difficulty withholding a response to the no-go trials; go trials, which are of equivalent perceptual demand, are uninfluenced. Third, on tasks specifically designed to probe vigilance, threat of shock actually serves to *impair* perception on high-load visual scanning tasks, whilst leaving low-load tasks intact (Cain et al., 2011). Thus, although firm conclusion must await further studies, it seems unlikely that the greater accuracy on no-go trials during threat of shock was driven by facilitated perception of or attention toward no-go stimuli.

Another possible explanation for improved performance during threat of shock is a non-specific increase in awakeness/arousal [i.e., alertness on a sleep wake spectrum (Oken et al., 2006)]. Anxiety increases arousal (Baas et al., 2006; Cornwell et al., 2007) and arousal can help maintain sustained attention (Oken et al., 2006). However, a key component of arousal is that it tends to decrease over time; and effect which is thought to underlie a phenomenon known as "vigilance decrement" (Helton, 2008; Warm et al., 2008; Helton et al., 2009). In particular, traditional sustained attention tasks are of long duration (longer than the SART) and require subjects to detect very rare targets. Such tasks are typically associated with a progressive decrement in performance thought to be driven, in turn, by progressively decreasing arousal (Helton, 2008; Helton et al., 2009). Errors of commission on the SART have, however, been shown to *decrease* over time when the test is repeated (Helton, 2008; Helton et al., 2009) which, if anything, would indicate *increasing* arousal as the task progressed. Helton and others have in fact argued that, rather than measuring sustained attention *per se*, performance on the SART reflects a strategic decision regarding speed/accuracy trade-off (Helton, 2008). This hypothesis is based on the observation that, over time, errors of commission go down while RT goes up (Helton, 2008). The present study, as well as previous studies (Robertson et al., 1997; Smallwood et al., 2004), provide further support for this speed accuracy trade-off argument by demonstrating that errors of commission are preceded by faster RT than non-errors. Thus, more cautious RT leads to greater accuracy. However, this effect does not vary across safe/threat conditions and hence unlikely explains the improved performance under threat. In other words, threat seems to improve accuracy at no cost to speed, providing no evidence for a speed/accuracy trade-off.

It should be noted that the effect seen here is distinct from that seen when discrete threatening or aversive cues are utilized in go/no-go tasks. For instance cues which have been paired with shocks as well as aversive faces [more analogous to "fear" than "anxiety" (Grillon, 2008)] serve to impair inhibitory control (Padmala et al., 2011; Sagaspe et al., 2011; Pessoa et al., 2012). Indeed, anxiety can impair inhibitory control in the context of affective targets in Stroop like paradigms (Pacheco-Unguetti et al., 2011). The key difference between these studies and the present study is that in the present task the stimuli are affectively neutral. Indeed, for the purposes of harm avoidance, it makes adaptive sense to allocate resources toward threatening stimuli in the context of anxiety (even at the expense of impaired inhibition). At the same time, it makes sense to improve the overall ability to inhibit responding in the absence of threatening stimuli. Thus, the overall behavior is likely the result of an interaction between the sustained state (anxiety), the valence of the stimuli being processed (e.g., aversive vs. neutral stimuli) and the motor response.

In summary, we present novel data demonstrating that anxiety induced by threat of shock can improve the ability to withhold responses to infrequent targets on a go/no-go task. We argue that this effect reflects facilitated inhibition of habitual motor responses, which may be a part of a broader pattern of anxiety improving cognitive and perceptual processes, perhaps for the sake of better improving harm avoidance (Robinson et al., submitted). It should be noted that errors of commission during SART have been typically used as evidence of mind-wandering (Robertson et al., 1997; Smallwood et al., 2004, 2009). However, errors of commission are only indirect measures of mind-wandering and can be affected by other processes, such as changes in perceptual processing or response inhibition. We believe that reduced errors of commission in the present study did not reflect reduced

off-task thinking during threat of shock but better response inhibition, although we *also* believe SART may be useful to study off-task thinking and more specifically anxious thoughts. Future studies may attempt to use more comprehensive thought sampling methodologies (Smallwood and Schooler, 2006) to tap into subjective experiences, as well as attempt to clarify the neural substrates of this effect using fMRI and EEG, in both healthy and patient populations.

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Failure to filter: anxious individuals show inefficient gating of threat from working memory

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Dispositional anxiety is a well-established risk factor for the development of psychiatric disorders along the internalizing spectrum, including anxiety and depression. Importantly, many of the maladaptive behaviors characteristic of anxiety, such as anticipatory apprehension, occur when threat is absent. This raises the possibility that anxious individuals are less efficient at gating threat's access to working memory, a limited capacity workspace where information is actively retained, manipulated, and used to flexibly guide goal-directed behavior when it is no longer present in the external environment. Using a well-validated neurophysiological index of working memory storage, we demonstrate that threat-related distracters were difficult to filter on average and that this difficulty was exaggerated among anxious individuals. These results indicate that dispositionally anxious individuals allocate excessive working memory storage to threat, even when it is irrelevant to the task at hand. More broadly, these results provide a novel framework for understanding the maladaptive thoughts and actions characteristic of internalizing disorders.

Keywords: anxiety disorders, attention, contralateral delay activity (CDA), emotion-cognition interactions, event-related potential (ERP), individual-differences, trait anxiety, working memory

INTRODUCTION

Anxiety disorders are debilitating, highly prevalent, and associated with substantial morbidity and mortality (Sareen et al., 2005; Collins et al., 2011; Kessler et al., 2012; Taylor et al., 2012). High levels of dispositional anxiety and behavioral inhibition are a well-established risk factor for anxiety, depressive, and other psychiatric disorders (Lahey, 2009; Kotov et al., 2010; Blackford and Pine, 2012; Clauss and Blackford, 2012), highlighting the importance of understanding the neurocognitive underpinnings of this key risk factor. Indeed, alterations in core cognitive processes, such as executive control and working memory, are central to neurocognitive theories of anxiety (Bishop, 2007, 2008; Eysenck et al., 2007; Eysenck and Derakshan, 2011; Berggren and Derakshan, in press).

Difficulties controlling the processing of threat are a central feature of dispositional anxiety and the anxiety disorders; anxious individuals frequently allow threat-related information to unduly control their thoughts and actions. In particular, there is considerable evidence that anxious individuals are biased to allocate excess attention to threat-related cues when they are present in the immediate environment (e.g., words, faces; Cisler and Koster, 2010), even when this comes at the expense of task-goals and on-going behavior (Bishop et al., 2004, 2007; Etkin et al., 2009). This attentional bias to threat has been proposed to be a specific causal risk factor for the development and maintenance of anxious psychopathology (Bar-Haim et al., 2007; Hofmann et al., 2012; MacLeod and Mathews, 2012; Shechner et al., 2012).

Importantly, many of the maladaptive thoughts and actions characteristic of anxious individuals occur when threat-related cues are absent from the immediate external environment (e.g., anticipatory apprehension, behavioral avoidance, and intrusive thoughts)—a key clinical feature that is not addressed by research focused on attentional biases to threat cues. This raises the possibility that dispositional anxiety reflects a broader regulatory deficit that encompasses problems governing threat's access to working memory. Working memory is the "blackboard of the mind" (Goldman-Rakic, 1996, p. 13473), a limited capacity workspace where information is actively maintained, recalled, and manipulated (Cowan, 2005; Baddeley, 2012). The internal representation of task sets and other kinds of goals in working memory plays a critical role in sustaining goal-directed attention, information processing (e.g., memory retrieval), and action in the face of competition with potential sources of distraction or interference (Miller and Cohen, 2001; Postle, 2006; D'Ardenne et al., 2012). This framework suggests that the maladaptive cognitive-behavioral profile characteristic of anxious individuals reflects a failure to prevent threat from gaining access to working memory. Allowing threat-related distracters access to working memory would potentially allow them to bias the stream of information processing after they are no longer present in the external environment. Ultimately, the unnecessary entry of threat into working memory may promote worry, intrusive thoughts, and other anxiety-related cognitions that disrupt on-going behavior (Thiruchselvam et al., 2012).

Here, we used a well-validated neurophysiological measure of working memory storage, *contralateral delay activity* (CDA; Vogel and Machizawa, 2004), to directly test whether dispositionally anxious individuals have difficulty preventing threat-related distracters from gaining access to working memory. The amplitude of the CDA, an event-related potential (ERP) that persists throughout the retention period of visual working memory tasks, is highly sensitive to the number of items maintained in working memory (Vogel and Machizawa, 2004; McCollough et al., 2007; Ikkai et al., 2010; Voytek and Knight, 2010). We measured CDA during a working memory task in which subjects were instructed to selectively retain one or more emotional faces while ignoring others (Sessa et al., 2011). Faces were either threat-related (i.e., fearful; Whalen, 1998; Davis and Whalen, 2001) or emotionally-neutral. This procedure allowed us to quantify the number of task-irrelevant distracter faces that gained access to working memory, indexed by increased CDA amplitude (Vogel et al., 2005). Critically, it also made it possible to measure the extent to which higher levels of dispositional anxiety, measured using the well-validated State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), are associated with problems gating threat-related distracters from working memory.

METHODS

SUBJECTS

Thirty-four (22 female) students from the University of Wisconsin, Milwaukee community participated in exchange for course extra-credit ($M = 21.83$ years, $SD = 5.34$). Subjects provided written informed consent prior to the experiment. The study was approved by the University of Wisconsin, Milwaukee's Institutional Review Board. One subject was removed due to chance performance. Nine subjects were excluded from analyses due to excessive ocular artifacts, a rate that is consistent with prior research using similar tasks (e.g., ∼35%; Sessa et al., 2011). A total of 24 subjects remained for further analysis.

QUANTIFYING DISPOSITIONAL ANXIETY

All subjects completed the trait version of the STAI (Spielberger et al., 1983), a 20-item measure of trait or dispositional anxiety (e.g., *Some unimportant thought runs through my mind and bothers me*, *I take disappointments so keenly that I can't put them out of my mind*, *I worry too much over something that really doesn't matter*). The STAI has been shown to exhibit high internal-consistency reliability ($\alpha = 0.89$) and test-retest stability ($r = 0.88$; Barnes et al., 2002). The distribution of scores in the present sample ($M = 38.2$, $SD = 9.43$, range of 20–53) was similar to published norms for mixed-sex undergraduate populations (Spielberger et al., 1983).

WORKING MEMORY TASK

We used a lateralized change detection task to estimate the number of threat-related (i.e., fearful) and emotionally-neutral faces stored in working memory, as indexed by the CDA. As detailed below, the use of lateralized stimulus displays was mandated by our focus on CDA (**Figure 1**; Vogel and Machizawa, 2004; Perez and Vogel, 2012). The trial sequence was adapted from a report by Sessa et al. (2011) and began with a fixation-cross (500 ms). Next, a pair of arrows indicating the to-be-remembered hemifield was presented above and below the fixation-cross (200 ms). Following a brief interstimulus interval (200–400 ms), an array of 2 or 4 faces was presented (500 ms). Participants were instructed to attend to one or two target faces, which were surrounded by red (or yellow) borders in the cued hemifield, and to ignore distracter faces, which were surrounded by yellow (or red) borders. The pairing of colors with targets or distracters was counterbalanced across participants.

CDA was quantified during the subsequent retention period (900 ms). This was followed by a probe array. Subjects were instructed to make a response indicating whether or not a target face had changed identity (equiprobable; button contingencies counterbalanced across subjects). The probe array was presented until a response was registered. On change trials, the identity of one of the target faces changed while the expression remained invariant. The fixation-cross was displayed during inter-trial intervals (800–1200 ms). Set-sizes of 1 and 2 were used because previous research has shown that working memory capacity saturates at approximately 2 faces (Jackson and Raymond, 2008; Jackson et al., 2009).

DESIGN

To assess the influence of expression and individual differences in anxiety on the ability to prevent task-irrelevant faces from entering working memory, the task included conditions in which threat-related distracters (1 Neutral Target and 1 Fear Distracter [NT1FD1]) or neutral distracters were present (1 Neutral Target and 1 Neutral Distracter [NT1ND1]). These conditions allowed us to calculate "filtering efficiency" scores (detailed below; Jost et al., 2011), reflecting the degree of unnecessary storage, for each expression. To confirm that CDA was sensitive to the number of faces retained in working memory, the task also included conditions in which set size was varied and only task-relevant targets were presented (i.e., 1 Neutral Target [NT1], 2 Neutral Targets [NT2], 1 Fear Target [FT1], 2 Fear Targets [FT2], and 1 Neutral Target paired with 1 Threat Target [NT1FT1]). Subjects completed 32 practice trials before beginning the experimental trials, which included 180 trials/condition for a total of 1260 trials organized into twenty 63-trial blocks. The condition order was pseudo-randomized across blocks within-subjects.

FACE STIMULI

Face stimuli consisted of 52 black-and-white images (26 unique models; half expressing fear) from the MacBrain Face Stimulus Set (http://www.macbrain.org/faces) or Ekman and Friesen's (1976) set. Images were digitally manipulated to remove non-face features (e.g., hair, clothing) and equate luminance. Faces were presented in rectangular borders (2.4° wide × 2.8° tall) at a viewing distance of ∼65 cm. Both the memory array and probe array contained faces that were placed in fixed locations surrounding a fixation cross. Horizontal distance between the face stimuli and the fixation cross was 3°. Vertical distance between top and bottom face was 1.5°.

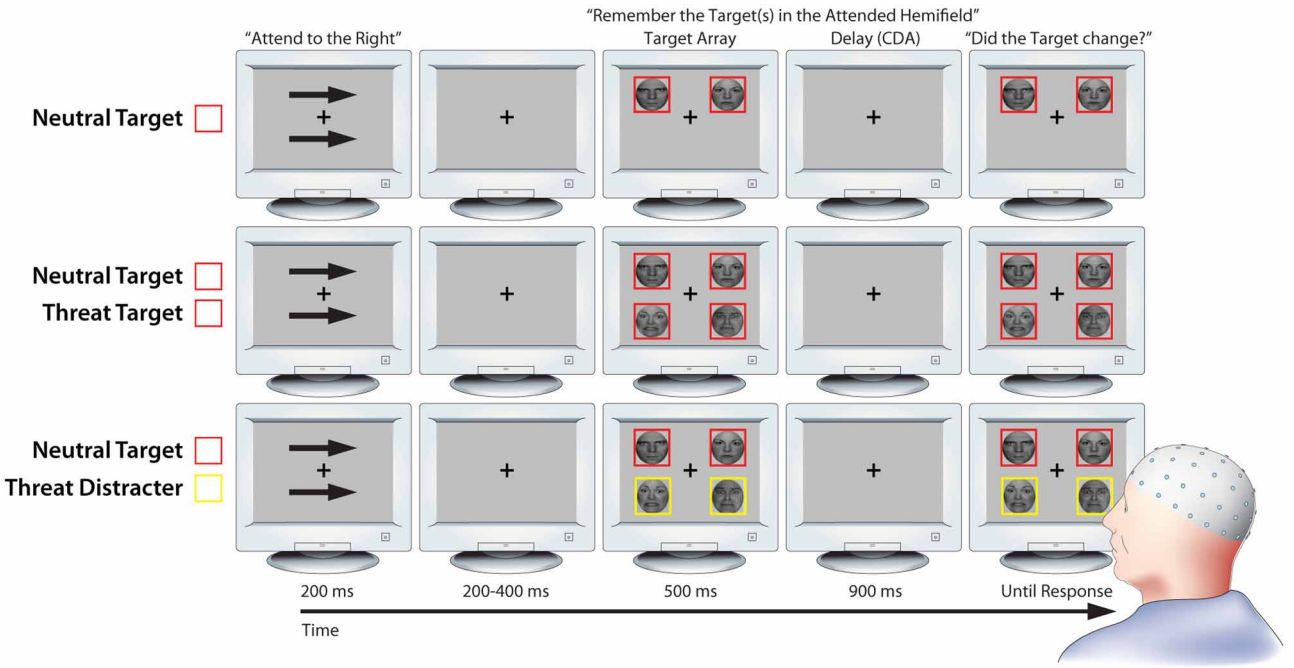

FIGURE 1 | Working memory task. Rows depict three key conditions from the lateralized change detection (i.e., working memory) task (from top to bottom: NT1, NT1FT1, NT1FD1). As detailed in the Methods section, lateralized presentation was necessary for isolating contralateral delay activity (CDA). Attention was directed to one hemifield by the arrow cues; identical stimuli were presented in the uncued hemifield to control for non-specific perceptual and preparatory motor activity when calculating CDA. Delay-spanning CDA was extracted from the 900 ms delay epoch. For ease of interpretation, the schematic is not to scale. Portions of this figure were reprinted by permission from Macmillan Publishers Ltd.: *Nature Reviews Neuroscience* (Houdé and Tzourio-Mazoyer, 2003; Peelen and Downing, 2007).

ERP DATA ACQUISITION AND PREPROCESSING

ERPs were recorded using a DC amplifier and a 32-channel cap with shielded leads (Advanced Neuro Technology B.V., Netherlands) referenced to the left mastoid. Impedances were kept below 10 kΩ. Data were low-pass filtered (~69.12 Hz) and sampled at 256 Hz. The vertical electrooculogram (VEOG) was measured using a pair of bipolar-referenced electrodes placed above and below the right eye. The horizontal electrooculogram was recorded using a pair of bipolar-referenced electrodes placed 1 cm from the outer canthi of the eyes.

Offline, ERP data were re-referenced (mean of the left and right mastoids), filtered (Butterworth band-pass of 0.1–30 Hz; 24db/octave), segmented (–200 to 1400 ms from the onset of the target array), and baseline-corrected (200 ms). Because the CDA critically depends on lateralized visual processing, we elected to reject all trials in which there was evidence that subjects failed to attend to the center of the visual field, rather than use artifact-correction algorithms that could potentially mask shifts in visual attention (Shackman et al., 2009; McMenamin et al., 2010, 2011). Accordingly, trials where VEOG exceeded ±80 μV and/or other channels exceeded ±60 μV were automatically rejected. Nine subjects with excessive artifact (>35% trials) were excluded from analyses, consistent with other studies using similar tasks (e.g., Sessa et al., 2011). For the remaining subjects, an average of 79.87% ($SD = 0.08$) of trials were retained. Importantly, the retained and excluded subjects did not significantly differ in either the mean level of dispositional anxiety or estimated working memory capacity, $ts < 0.68$, $ps > 0.51$.

CDA

To isolate CDA, contralateral waveforms were created by averaging the activity recorded in the left hemisphere when attending to cued stimuli in the right visual field, and activity over the right hemisphere when attending to cued stimuli in the left visual field. Ipsilateral waveforms were created by averaging the activity recorded in the left hemisphere when attending to uncued stimuli in the left visual field, and activity over the right hemisphere when attending to uncued stimuli in the right visual field (see **Figure 1**). CDA was calculated as the difference between contralateral and ipsilateral activity during the retention interval (500–900 ms; **Figure 1**). In contrast to other neurophysiological measures of delay-spanning activity, these procedures for isolating CDA have the advantage of removing nonspecific perceptual (i.e., elicited by physically-identical stimuli in the uncued visual field) and motor preparatory activity (Vogel and Machizawa, 2004; Vogel et al., 2005). Averaged waveforms were created for each condition and hemisphere using electrode clusters (P3/4, P7/8, O1/2, and T7/8). Consistent with prior work, error trials were excluded when calculating CDA for the conditions in which only targets were presented (Vogel et al., 2005), but were not excluded when calculating CDA for the conditions in which a mixture of targets and distracters was presented

(Lee et al., 2010). Error trials were used for the mixed conditions because decrements in performance likely reflect the storage of distracters in working memory (Lee et al., 2010). For visualization purposes, grand averaged waveforms were low-pass filtered (10 Hz).

CONFIRMATORY ANALYSES

To confirm that task-relevant threat-related targets are associated with enhanced storage (Sessa et al., 2011) and that larger target arrays (i.e., set sizes) are associated with increased working memory storage, we performed a series of analyses using CDA, as well as behavioral estimates of working memory capacity and reaction time (RT). Working memory capacity was estimated using Pashler's (1988) formula: $K = S \times (H - \mathrm{FA})/(1 - \mathrm{FA})$, where K is the estimated number of items maintained in WM, S is the set-size of the memory array, H is the hit-rate, and FA is the false alarm rate. Pashler's K was used because it was developed for working memory tasks using whole-display probes; whereas the more commonly used Cowan's K (Cowan, 2001) was developed for single-probe displays (see Rouder et al., 2011 for a detailed discussion). Analyses were performed using SPSS (version 18.0.0; IBM Inc., Armonk, NY).

HYPOTHESIS TESTING (FILTERING EFFICIENCY)

To test whether dispositionally anxious individuals fail to regulate threat's access to working memory, CDA "filtering efficiency" scores (Jost et al., 2011) were separately computed for the threat and neutral distracter conditions. Filtering efficiency for threat-related distracters was calculated as the difference in amplitude between trials in which two targets were presented (1 Neutral Target and 1 Fear Target [NT1FT1]) and physically-identical trials in which a neutral target was paired with a fear distracter (NT1FD1). Because CDA is a negative-going potential, difference scores were scaled by −1 to aid interpretation. An efficiency of zero indicates a complete failure of filtering (i.e., equivalent storage of two targets compared to the combination of a target and a threat-related distracter). Likewise, filtering efficiency for neutral distracters was calculated as the difference in amplitude between trials in which two neutral targets (NT2) were presented and trials in which a neutral target was paired with a neutral distracter (NT1ND1) (scaled by –1).

Hypothesis testing on relations between dispositional anxiety (i.e., STAI) and filtering efficiency was performed using a series of regressions. A single outlier was excluded from the analyses of neutral filtering efficiency. Results were similar with the outlier included (not reported). To assess the specificity of relations between dispositional anxiety and CDA filtering efficiency, we computed additional regressions controlling for nuisance variation in mean-centered age, sex, and maximum working memory capacity (i.e., the maximal Pashler's K across any of the five "pure" target conditions). Robust regressions, which minimize the influence of outlying observations (e.g., Shackman et al., in press; Wager et al., 2005), yielded equivalent results. Although hypothesis testing focused on CDA filtering efficiency, exploratory analyses of RT filtering efficiency were also performed. RT filtering efficiency was computed using the same formulas described for CDA, but without the −1 scalar.

RESULTS

THREAT-RELATED TARGETS ARE ASSOCIATED WITH ENHANCED STORAGE

As a precursor to hypothesis testing, we examined the influence of threat on working memory storage when it is task-relevant. Consistent with previous research (Sessa et al., 2011), task-relevant threat targets (FT1, FT2) were associated with enhanced storage compared to emotionally-neutral targets (NT1, NT2), evidenced by enhanced CDA, increased K, and slower responses ($Fs_{(1,\ 23)} > 6$, $ps < 0.03$; **Figure 2** and **Table 1**). As expected, larger target arrays were associated with increased storage, as indexed by the same three measures ($Fs_{(1,\ 23)} > 6.3$; $ps < 0.03$).

INEFFICIENT FILTERING OF THREAT-RELATED DISTRACTERS

Threat-related distracters gained unnecessary access to working memory, as indexed by increased CDA amplitude for the threat-distracter condition (NT1FD1) compared to a single neutral target (NT1), $t_{(23)} = 2.40$, $p = 0.03$ (**Figure 3**). On average, subjects were able to filter threat-related distracters, albeit inefficiently. Specifically, the amplitude of CDA was significantly smaller for the threat-distracter condition (NT1FD1) compared to those in which two targets were presented (NT1FT1), $t_{(23)} = -3.61$; $p = 0.001$. Unlike threat, neutral-distracters were efficiently filtered; CDA amplitude did not differ between the neutral-distracter (NT1ND1) and single target conditions (NT1), $t_{(23)} = 1.4$; $p = 0.18$ (**Figure 3**) but was significantly smaller than the two neutral target condition (NT2), $t_{(23)} = -2.61$, $p = 0.02$.

ANXIOUS INDIVIDUALS FAIL TO FILTER THREAT-RELATED DISTRACTERS

To test whether anxious individuals exhibit difficulties gating threat-related distracters from working memory, we used the CDA to compute filtering efficiency scores (see the Methods section; Jost et al., 2011). An efficiency of zero indicates a complete failure of filtering, that is, comparable levels of storage in the physically-identical distracter and two-target conditions. Analyses of CDA filtering efficiency demonstrated that anxious individuals were less efficient at preventing threat-related distracters from gaining access to working memory, $R^2 = 0.24$, $p < 0.03$ (**Figure 4**). Similar effects were obtained after controlling for nuisance variation in age, sex, and maximum working memory capacity (partial $R^2 > 0.31$, $p < 0.01$) or the number of artifact-free trials contributing to the CDA analyses (partial $R^2 = 0.20$, $p = 0.03$). Dispositional anxiety was unrelated to the efficiency of filtering emotionally-neutral distracters ($R^2 < 0.01$, $p > 0.05$). To confirm that our results were not unduly influenced by outlying values, we recomputed the key analyses using robust regression techniques. This revealed nearly identical results: higher levels of dispositional anxiety predicted reduced efficiency for filtering threat-related distracters ($R^2 = 0.25$, $p < 0.01$), but not neutral distracters ($R^2 < 0.01$, $p > 0.05$).

Likewise, dispositional anxiety did not predict CDA amplitude when threat-related targets were relevant (FT1 and FT2) to the task, $R^2 < 0.02$, $p > 0.05$. Consistent with these results, anxiety significantly predicted threat filtering efficiency after controlling for either variation in neutral filtering efficiency or

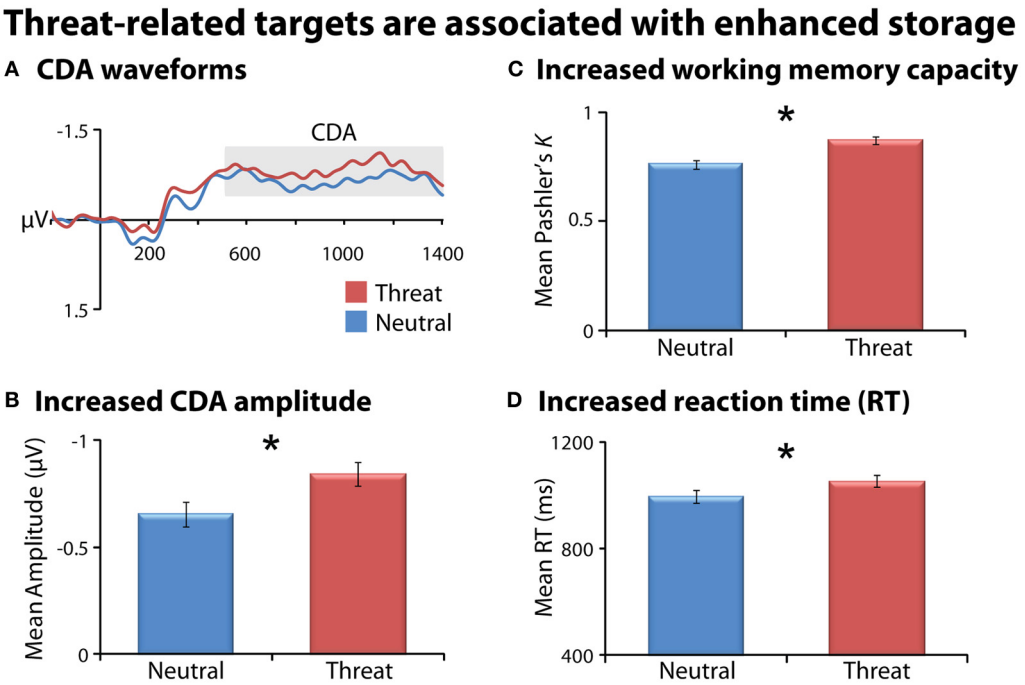

FIGURE 2 | Task-relevant threat targets are associated with enhanced storage. Means are collapsed across set-size (NT1/NT2 and FT1/FT2). Contralateral delay activity (CDA) waveforms (panel **A**). Mean CDA amplitude was extracted using the entire delay interval (500–1400 ms; gray box). Threat (red) was associated with increased CDA amplitude (panel **B**), working memory capacity (panel **C**), and reaction time (RT; panel **D**) compared to neutral (blue). Asterisks denote significant pairwise mean differences ($p < 0.05$). Error bars indicate the nominal probability of the null hypothesis being rejected by chance: $p < 0.05$ (non-overlapping bars) or $p > 0.05$ (overlapping bars). Bars were computed as described in Shackman et al. (2010). Note that for CDA results, negative is plotted up corresponding to increased amplitude.

Table 1 | Means and standard deviations for accuracy, working memory capacity (*K*), and reaction time (in milliseconds) for each condition.

Condition	Accuracy (proportion correct)	Working memory capacity (*K*)	RT (ms)
1 Neutral target	0.83 (0.10)	0.74 (0.17)	900.65 (179.42)
2 Neutral targets	0.66 (0.07)	0.78 (0.35)	1108.33 (268.45)
1 Fear target	0.86 (0.09)	0.79 (0.16)	976.05 (209.37)
2 Fear targets	0.70 (0.07)	0.96 (0.32)	1139.68 (260.42)
1 Neutral target and 1 Fear target	0.69 (0.08)	0.92 (0.34)	1104.41 (251.72)
1 Neutral target and 1 Fear distracter	0.80 (0.11)	0.70 (0.19)	995.99 (215.20)
1 Neutral target and 1 Neutral distracter	0.79 (0.10)	0.69 (0.17)	993.00 (187.31)

the CDA associated with task-relevant threat targets (partial $R^2 > 0.24$, $ps < 0.05$). Exploratory analyses of RT filtering efficiency revealed a similar pattern. Specifically, higher levels of dispositional anxiety predicted reduced filtering efficiency for threat-related ($R^2 = 0.22$, $p = 0.02$), but not neutral distracters ($R^2 < 0.01$, $p > 0.05$). Maximum working memory capacity did not predict filtering efficiency for either the threat or neutral distracter conditions (R^2s < 0.03, $ps < 0.05$), likely reflecting the rather limited variation in capacity for faces (Jackson and Raymond, 2008; Jackson et al., 2009; Sessa et al., 2011).

DISCUSSION

The present results provide compelling new evidence that dispositionally anxious individuals allocate unnecessary working memory storage to threat-related cues when they are irrelevant to the task at hand. This effect was not evident for emotionally-neutral distracters and could not be explained by individual differences in working memory capacity, the size of the CDA evoked by task-relevant threat targets, or the efficiency of filtering emotionally-neutral distracters. Parallel results were obtained for RT. Taken together these data indicate that dispositional anxiety is associated with a specific deficit in preventing threat-related distracters from gaining access to working memory. These results reinforce work emphasizing the importance of cognitive control deficits in anxiety and mood disorders (Eysenck et al., 2007; Eysenck and Derakshan, 2011; Owens et al., 2012). More generally, our results provide a novel neurobiological framework for conceptualizing the neural mechanisms that underlie the intrusive thoughts and maladaptive actions characteristic of anxious individuals when threat is absent.

Our findings demonstrate that anxiety is associated with inefficient gating of threat-related distracters from working

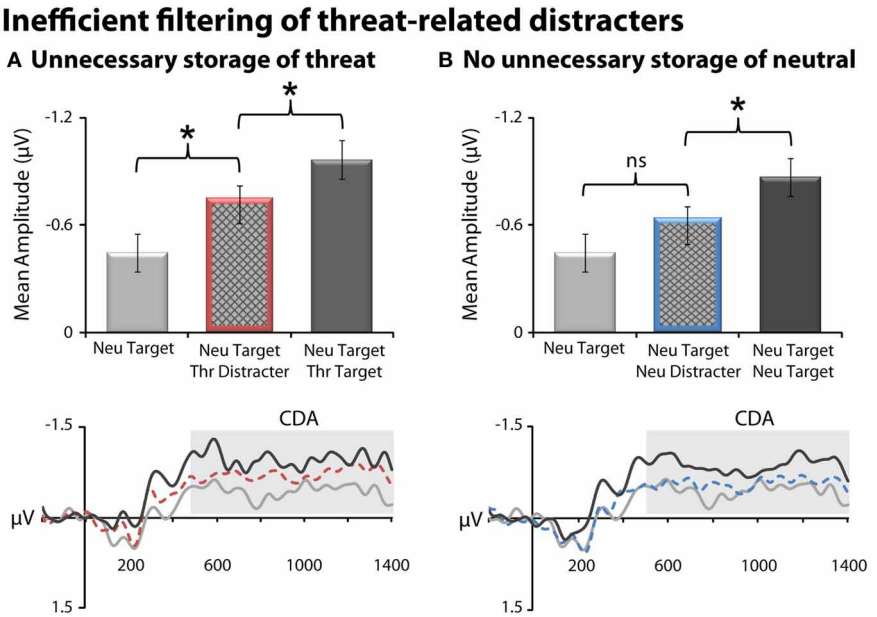

FIGURE 3 | Threat-related distracters were inefficiently filtered from working memory, as indexed by contralateral delay activity (CDA). **(A)** Threat distracters. Mean CDA amplitude was significantly increased (i.e., more negative) on trials with a threat-related distracter (red bar) (NT1FD1) compared to those with a single neutral target (light gray) (NT1). On average, subjects were able to filter threat-related distracters, albeit inefficiently; mean CDA amplitude was significantly decreased on trials with a threat-related distracter (NT1FD1) compared to those with two physically-matched targets (dark gray) (NT1FT1). CDA waveforms for the three conditions are shown at the bottom. Mean CDA amplitude was extracted using the entire delay interval (500–1400 ms; gray box). **(B)** Neutral distracters. Mean CDA amplitude was not significantly increased on trials with a neutral distracter (blue bar) (NT1ND1) compared to those with a single neutral target (light gray) (NT1). Asterisks denote significant pairwise mean differences ($p < 0.05$). Error bars indicate the nominal probability of the null hypothesis being rejected by chance: $p < 0.05$ (non-overlapping bars) or $p > 0.05$ (overlapping bars). Bars were computed as described in Shackman et al. (2010). Note that negative potentials are plotted up corresponding to increased CDA amplitude.

memory, but they do not directly address the neural mechanisms underlying this deficit. Prior work using simple geometric stimuli suggests that CDA reflects the activity of a capacity-limited buffer instantiated in the posterior parietal cortex (PPC; Todd and Marois, 2004, 2005; Xu and Chun, 2006). Presently, the specific neural mechanisms underlying anxious individuals' inability to adequately gate threat's access to this buffer remain unknown. Our results are compatible with alterations in any of three distinct functional circuits. A key challenge for future research will be to directly test these hypotheses.

One possibility is that the unnecessary storage of threat-related distracters in PPC reflects the amygdala's influence on the visual cortical regions responsible for processing threat-related cues, such as the faces used in our study. Among anxious and behaviorally inhibited individuals, the amygdala is more reactive to potential threat (Schwartz et al., 2003; Etkin and Wager, 2007; Blackford et al., 2012). The amygdala is poised to bias attention to threat via excitatory projections to the visual cortex (Vuilleumier et al., 2004; Freese and Amaral, 2009). Indeed, functional connectivity between these two regions is increased when attending to threat cues (Noesselt et al., 2005; Mohanty et al., 2009) and threat-induced recruitment of the amygdala precedes enhanced activation of visual cortex (Sabatinelli et al., 2009; Pourtois et al., in press). Variation in amygdala activation also predicts the reorienting of attention to threat-related cues (Gamer and Büchel, 2009) and the trial-by-trial detection of threat—an effect mediated by activation in the visual cortex (Lim et al., 2009). Collectively, these data suggest that difficulties regulating threat's access to working memory could be a downstream consequence of anxious individuals' bias to over-allocate covert and overt attention to threat (Bar-Haim et al., 2007).

A second possibility is that the unnecessary occupation of working memory by threat reflects problems monitoring the competition between targets and threat-distracters for attention. Adjudication of this competition is thought to depend upon conflict-monitoring processes instantiated in the midcingulate cortex (MCC; Botvinick, 2007; Shackman et al., 2011). When conflict is detected in the MCC, it triggers prefrontal regulatory signals aimed at biasing competition to favor task-relevant cues over potential sources of distraction, such as the threat-distracters used in the present study (Miller and Cohen, 2001; Etkin et al., 2010). These biasing signals could be directed at the visual cortex (Miller and Cohen, 2001) or the amygdala (Etkin et al., 2011). At present, it remains unclear whether anxious individuals are less efficient at monitoring threat-related conflicts (Bishop et al., 2004; Etkin et al., 2010; Shackman et al., under review).

A third possibility is that anxious individuals' bias to allocate unnecessary storage to threat-distracters reflects a gating deficit. Consistent with recent computational models (Frank and O'Reilly, 2006; Moustafa et al., 2008; Wiecki and Frank, 2010),

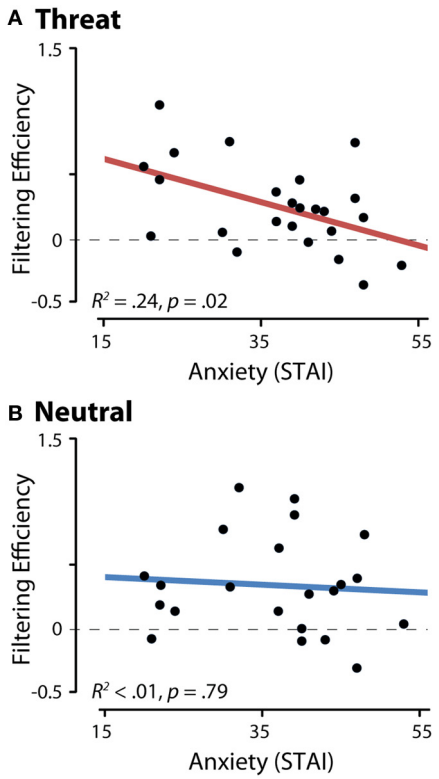

FIGURE 4 | Dispositionally anxious individuals are inefficient at filtering threat distracters, as indexed by contralateral delay activity (CDA). (A) Threat-related distracters. **(B)** Neutral distracters. A filtering efficiency of zero (broken gray line) indicates a complete failure of filtering (i.e., comparable levels of storage in the distracter and two-target conditions, NT1FT1—NT1FD1 and NT2-NT1ND1).

the basal ganglia and dorsolateral prefrontal cortex (dlPFC) exhibit gating-like signals that are associated with reduced distracter-evoked activity in visual cortex and reduced storage of distracters in the PPC (Postle, 2005; McNab and Klingberg, 2008; Suzuki and Gottlieb, 2013) during emotionally-neutral working memory tasks. Furthermore, patients with lesions involving the basal ganglia (i.e., left putamen) show selective deficits in gating distracters when performing emotionally-neutral working memory tasks (Baier et al., 2010). Whether similar mechanisms support the regulation of threat-related or other emotionally-salient distracters is unknown. Nevertheless, robust projections from the amygdala to the basal ganglia (Freese and Amaral, 2009) suggest one way in which high levels of dispositional anxiety could promote threat's access to working memory. Functional interactions between the amygdala and dlPFC could provide an alternate pathway (Lim et al., 2009).

From a translational perspective, our results provide a framework for conceptualizing the intrusive and distressing thoughts, worries, and memories that are a central feature of anxiety and mood disorders, including generalized anxiety, obsessive compulsive, posttraumatic stress, and major depressive disorders (Beck et al., 2005; Nolen-Hoeksema et al., 2008). High levels of dispositional anxiety are associated with a similar pattern of dysregulated cognition (e.g., Eysenck, 1984; Eysenck and van Berkum, 1992). Inefficient filtering of threat-related information from working memory potentially explains many of these features. That is, once it resides in working memory, threat-related information could continue to elicit distress and maladaptively bias attention and action after it is no longer present in the external environment.

Importantly, this framework also provides a potential mechanistic explanation for the intrusive, distressing memories that are a hallmark of both dispositional anxiety and many disorders on the internalizing spectrum (Krueger and Markon, 2006). In particular, it has become clear that items can enter working memory via either perceptual encoding, as with the threat-related distracters used in the present study, or retrieval from long-term memory (Jonides et al., 2008). From this perspective, working memory reflects the temporary activation of recently perceived items or the temporary re-activation of representations stored in long-term memory (Oberauer, 2002; Jonides et al., 2008; Lewis-Peacock et al., 2012). This suggests that intrusive memories, such as those prominent in posttraumatic stress disorder, could result from problems preventing distressing long-term memories from gaining access to working memory.

On the basis of the present results and other data, we have proposed that the maladaptive profile of thoughts and behaviors exhibited by anxious individuals in the absence of overt threat could reflect a more fundamental deficit in controlling threat's access to working memory. Although it is clear that much work remains, this hypothesis provides a clear roadmap to the most fruitful avenues for understanding the neurocognitive mechanisms underlying these symptoms. In particular, as with any preliminary study, it will be important to replicate our findings using a larger sample (Yarkoni, 2009). Given that our conclusions were based on a convenience sample, it will be essential to test our hypothesis in high-risk and patient populations and to directly assess the degree to which threat-related filtering efficiency predicts differences in the severity or frequency of distressing thoughts and maladaptive behaviors. It may be that the presentation of gating deficits differs across internalizing disorders (Owens et al., 2012). Methodologically, it will be important to develop improved procedures for minimizing ocular artifacts, which led to substantial attrition in the present study and in other studies using similar paradigms (Sessa et al., 2011). Extending our approach to incorporate simpler cues (e.g., color patches or oriented bars) that have been aversively-conditioned may prove helpful in this regard and would have the added benefit of increasing integration with the large body of cognitive neuroscience research and theory developed around such stimuli (see Owens et al., 2012 for a related application).

Dispositional anxiety is an important risk factor for the development of anxiety, depressive, and other psychiatric disorders.

The present study provides novel evidence that dispositional anxiety reflects a failure to adequately regulate the access of threat to working memory, the capacity-limited workspace that underlies adaptive, goal-directed behavior. These results set the stage for a more detailed understanding of the distressing thoughts and memories that afflict anxious individuals when threat is absent—a defining, but poorly understood feature of the internalizing spectrum of disorders. Future research aimed at clarifying the neural underpinnings of this regulatory deficit promises to enhance our understanding of the mechanisms that confer risk for the development of psychopathology.

AUTHOR CONTRIBUTIONS

Daniel M. Stout conceptualized the study. Daniel M. Stout, Christine L. Larson, and Alexander J. Shackman designed the study. Daniel M. Stout collected data and performed data processing. Daniel M. Stout analyzed data. Daniel M. Stout, Alexander J. Shackman, and Christine L. Larson contributed to data interpretation. Daniel M. Stout and Alexander J. Shackman wrote the paper. Alexander J. Shackman and Daniel M. Stout created the figures and table. Christine L. Larson supervised the study. All authors contributed to revising the paper.

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Trait anxiety modulates fronto-limbic processing of emotional interference in borderline personality disorder

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Previous studies of cognitive alterations in borderline personality disorder (BPD) have yielded conflicting results. Given that a core feature of BPD is affective instability, which is characterized by emotional hyperreactivity and deficits in emotion regulation, it seems conceivable that short-lasting emotional distress might exert temporary detrimental effects on cognitive performance. Here we used functional magnetic resonance imaging (fMRI) to investigate how task-irrelevant emotional stimuli (fearful faces) affect performance and fronto-limbic neural activity patterns during attention-demanding cognitive processing in 16 female, unmedicated BPD patients relative to 24 age-matched healthy controls. In a modified flanker task, emotionally negative, socially salient pictures (fearful vs. neutral faces) were presented as distracters in the background. Patients, but not controls, showed an atypical response pattern of the right amygdala with increased activation during emotional interference in the (difficult) incongruent flanker condition, but emotion-related amygdala deactivation in the congruent condition. A direct comparison of the emotional conditions between the two groups revealed that the strongest diagnosis-related differences could be observed in the dorsal and, to a lesser extent, also in the rostral anterior cingulate cortex (dACC, rACC) where patients exhibited an increased neural response to emotional relative to neutral distracters. Moreover, in the incongruent condition, both the dACC and rACC fMRI responses during emotional interference were negatively correlated with trait anxiety in the patients, but not in the healthy controls. As higher trait anxiety was also associated with longer reaction times (RTs) in the BPD patients, we suggest that in BPD patients the ACC might mediate compensatory cognitive processes during emotional interference and that such neurocognitive compensation that can be adversely affected by high levels of anxiety.

Keywords: borderline personality disorder, cognition-emotion interaction, anxiety, fMRI, amygdala, anterior cingulate cortex

INTRODUCTION

Borderline personality disorder (BPD) is a severe mental disorder characterized by behavioral impulsivity, instability in interpersonal relationships, repetitive suicidal behavior, aggression, particularly autoaggressive behavior, and identity disturbance (Lieb et al., 2004; Mauchnik and Schmahl, 2010). Most of these behavioral patterns are assumed to result from affective instability, which in turn might reflect a general emotional hyperreactivity, but also dysfunction in emotion regulation. The ability to regulate negative emotions successfully allows an individual to adaptively respond to stressful experiences, with deficits in emotion regulation often leading to considerable psychological distress (Gross and Muñoz, 1995; Davidson et al., 2000; Gross, 2002; Ochsner and Gross, 2005). Moreover, emotion regulation abilities also affect an individual's social interactions (Lopes et al., 2005). Notably, BPD patients exhibit particularly pronounced deficits in emotion processing in response to aversive interpersonal events, such as perceived rejection, criticism or separation (Stiglmayr et al., 2005; Gunderson and Lyons-Ruth, 2008). On the other hand, the disturbances of social interaction in BPD (Preißler et al., 2010) might also, to some extent, be a consequence of primarily impaired emotion regulation, leading to a vicious circle (Schmahl and Bremner, 2006; Domes et al., 2009). Behaviorally oriented treatments for BPD like Dialectic-Behavioral Therapy (DBT) or Systems Training for Emotional Predictability and Problem Solving (STEPPS) often focus on emotion regulation and its disturbance (e.g., Linehan, 1993; Blum et al., 2008). Therefore, a better understanding of the underlying neural mechanisms might help to further improve therapeutic strategies for this debilitating psychiatric disorder (Brendel et al., 2005; Koenigsberg et al., 2009).

Despite well-documented clinical and experimental evidence for affective instability in BPD, the underlying neural mechanisms are up to now not quite well understood, with previous studies yielding, at least in part, conflicting results (for a recent meta-analysis see Ruocco et al., 2013). Most functional neuroimaging studies of emotional processing in BPD have focused on a fronto-limbic network that includes the amygdala, the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), the hippocampus, and the dorsolateral prefrontal cortex (DLPFC). This network is likely to be involved in the processing of social and emotional information, thereby contributing crucially to emotion regulation (Ochsner and Gross, 2005; Phillips et al., 2008). A dysregulation of this network, most prominently in an interpersonal context, is thought to mediate important aspects of the BPD symptomatology (Brendel et al., 2005; Schmahl and Bremner, 2006; Dell'Osso et al., 2010). A recent metaanalysis of studies investigating negative emotion processing suggests that BPD patients exhibit decreased amygdala and subgenual cingulate, but increased insula activity during processing of negative emotions relative to presumably neutral conditions (Ruocco et al., 2013). On the other hand, several studies have reported higher amygdala activation in BPD patients compared to healthy subjects in response to socially relevant negative emotional stimuli, especially fearful facial expressions (Herpertz et al., 2001; Donegan et al., 2003; Minzenberg et al., 2007; Silbersweig et al., 2007; Koenigsberg et al., 2009). In addition to the observed emotional hyperreactivity, studies focusing on cognition-emotion interactions (e.g., emotion regulation tasks, emotional Stroop paradigms or exposure to autobiographical memories) also suggest that dorsolateral and medial prefrontal regions, including the ACC, might exert an inefficient regulatory functioning in BPD patients (Schmahl et al., 2003, 2004; Minzenberg et al., 2007; Wingenfeld et al., 2009). Taken together, these findings point to a weakened inhibitory control of amygdala reactivity by prefrontal cortical structures in BPD patients (Lieb et al., 2004; Lis et al., 2007; Mauchnik and Schmahl, 2010). Studies demonstrating reduced white matter integrity relevant to a fronto-limbic circuitry and altered functional coupling between the amygdala and the OFC (Grant et al., 2007; New et al., 2007; Rusch et al., 2010) have provided further converging evidence for a disturbance fronto-limbic circuitry in BPD. In line with this idea, emotional stimuli have been shown to interfere with cognitive processing in BPD. Patients with BPD exhibit reduced inhibitory control when confronted with aversive information, which is accompanied by reduced mPFC and increased amygdala activation in fMRI (Silbersweig et al., 2007). In addition, the recruitment of prefrontal cortical control mechanisms during emotional Stroop performance is deficient in BPD patients (Wingenfeld et al., 2009).

Several studies suggest that BPD might be inherently associated with more general cognitive deficits that are not specific to emotion processing (Bazanis et al., 2002; Monarch et al., 2004; Ruocco, 2005; Judd, 2012), but might ultimately also result in deficient regulation of negative emotions. Posner et al. for example, reported alterations of an attentional network involved in conflict resolution and cognitive control in BPD patients (Posner et al., 2002). In this case, impaired inhibition and attentional control might constitute the primary mechanisms of impaired emotion regulation and affective instability in BPD. It should be noted, on the other hand, that cognitive performance in BPD patients is highly variable *intra*individually, a phenomenon that has been linked to reduced prefrontal processing efficiency (MacDonald et al., 2006) and, in the case of BPD, might result from the affective instability of the patients (Beblo et al., 2006). This is in line with the notion that inhibitory control in BPD patients is particularly impaired when the irrelevant information to be suppressed is emotionally aversive in nature (Arntz et al., 2000; Korfine and Hooley, 2000; Domes et al., 2006; Sieswerda et al., 2007). It is thus conceivable that alterations of cognitive processing in BPD might rather result from a primary alteration of emotion processing or its regulation, like the well-documented preferential processing of negative emotions in BPD patients (Barnow et al., 2009; Domes et al., 2009; Dyck et al., 2009; Staebler et al., 2009), particularly in interpersonal contexts (Benjamin et al., 1989; Sieswerda et al., 2007). Compatibly, a direct investigation of voluntary emotion regulation in BPD has indeed yielded both increased amygdala activation and decreased recruitment of the OFC in BPD patients relative to healthy controls (Schulze et al., 2011). It seems thus conceivable that cognitive processing in BPD patients is primarily altered under conditions of emotional distress, as the high intensity of the associated affective processes might exhaust the cognitive resources required for successful emotion regulation. In line with this notion, BPD patients have been shown to exhibit an increased amygdala response to faces with negative emotional and even emotionally neutral expressions (Donegan et al., 2003), and despite the fact that multiple negative emotions are found to be elevated in BPD (Jacob et al., 2009; Staebler et al., 2009), amygdala hyperreactivity in BPD patients is most prominently observed in response to fearful faces (Minzenberg et al., 2007). Moreover, BPD patients also exhibit altered mPFC-amygdala connectivity during fear processing (Cullen et al., 2011). On the other hand, self-report measures usually demonstrate elevated trait anxiety in BPD patients, and the individual degree of anxiety also correlates with behavioral measures of reduced inhibition of negative stimuli during cognitive tasks (Domes et al., 2006).

Previous studies demonstrating altered cognitive processing of negative emotional faces have typically used tasks that required an explicit processing of the negative emotional information, such as gender discrimination (Minzenberg et al., 2007) or the emotional Stroop task (Wingenfeld et al., 2009). To better understand how the (inconsistently reported) general alterations of cognitive function in BPD might be brought about, it might be helpful to disentangle the cognitive task at hand from emotional stimuli. In the present study, we used event-related functional magnetic resonance imaging (fMRI) to investigate how incidental, i.e., task-irrelevant emotional interference, might affect behavioral performance and neural mechanisms in an attention-demanding cognitive task in BPD patients. Emotional stimuli have previously been demonstrated to interfere with PFC-dependent cognitive processing in attention-demanding tasks like the Eriksen flanker task (Eriksen and Eriksen, 1974) in the healthy population (Fenske and Eastwood, 2003; Larson et al., 2006; Wiswede et al., 2009; Richter et al., 2011). The presentation of unpleasant

pictures from the International Affective Picture System (IAPS) prior to each flanker stimulus has been shown to lead to an increased error related negativity (ERN) compared to trials with neutral or pleasant pictures (Wiswede et al., 2009), and genetically mediated individual differences in aggression and anger have been linked to altered recruitment of the dACC and the OFC in a comparable task using angry vs. neutral faces (Richter et al., 2011). Because emotional reactivity and attentional bias in BPD patients are particularly pronounced during processing of fearful faces (Minzenberg et al., 2007; Jovev et al., 2012) we adapted the modified flanker task with emotional distracters in the background (Richter et al., 2011) to the use of fearful vs. neutral faces as irrelevant background pictures. The effective completion of the task used here required participants to suppress the irrelevant emotional information and focus attention on the relevant cognitive (flanker) task.

Based on current models of BPD and the previously described functional differences in fronto-limbic networks, we expected that BPD patients might exhibit increased amygdala activations to fearful and possibly to neutral faces and reduced DLPFC- and ACC-dependent cognitive control as compared to controls. Specifically, we hypothesized that reduced dACC and DLPFC activation in the patients would be most prominent during incongruent flanker trials with emotional distracter stimuli. Because previous results indicate that trait anxiety might act as a modifier of inhibitory control of emotional information in BPD (Domes et al., 2006), we further hypothesized that neural signatures of emotional interference in the context of fearful vs. neutral distracters might be correlated with individual levels of trait anxiety. To this end, individual differences in anxiety levels were therefore assessed using the State-Trait Anxiety Inventory (STAI, Spielberger and Lushene, 1966), and trait dimensions of anxiety were included as covariates in all analyses and specifically addressed by brain-behavior correlations, in which we aimed to correlate activations of the dACC, a structure presumably involved in cognitive conflict processing, and of the rACC, a brain region supposedly more directly involved in emotion processing, with trait anxiety. In line of their differential role in neurocognitive networks (Margulies et al., 2007), we tentatively hypothesized that dACC activation might correlate negatively with trait anxiety, whereas the rACC might show an inverse pattern.

METHODS

PARTICIPANTS

Demographic and clinical characteristics of the study groups are presented in **Table 1**. Subjects gave written informed consent prior to study participation. The study was approved by the ethics committee of the Charité Universitätsmedizin Berlin. Gender differences in neural correlates have been reported for emotion processing (Hamann and Canli, 2004), and gender seems to play an important role in the neurobiology of BPD (Schmahl and Bremner, 2006); therefore only female subjects were included in the study. Participants were all right-handed and between 20 and 46 years old. Borderline patients were recruited at the Department of Psychiatry, Charité Universitätsmedizin Berlin and all met DSM-IV criteria for BPD. All participants were screened with the German version of the Structural Clinical Interview for DSM-IV (SCID-I and II; First et al., 1996, 1997; German version Wittchen et al., 1997), and symptom severity was assessed with the Symptom Checklist (SCL-90-R; Franke, 2002) and the Borderline Symptom List (BSL; Bohus et al., 2001). Diagnosis of BPD was confirmed by a consultant psychiatrist with extensive experience in the diagnosis and treatment of BPD.

Table 1 | Demographic and clinical characteristics.

	BPD	*HC*	Statistics
Age	25.56 (4.70)	26.83 (5.35)	$z = -0.596$, n.s.
Smoking	yes = 12	yes = 14	$X^2_{(1)} = 1.172$, n.s.
LPS (sum subtest 3 + 4)	58.13 (11.05)	61.54 (7.10)	$z = -0.911$, n.s.
MWT-B (IQ)	100.25 (12.53)	106.75 (10.32)	$t_{(38)} = 1.8$, n.s.
STAI-trait (trait anxiety; sum)	63.5 (6.70)	32.58 (5.48)	$z = -5.308$, $p < 0.001$
BIS (sum)	79.00 (13.71)	61.92 (8.24)	$t_{(38)} = -4.82$, $p < 0.001$
SCL-90-R (GSI)	1.93 (0.69)	0.29 (0.21)	$z = -5.304$, $p < 0.001$
BSL (sum)	194.68 (59.29)	31.13 (18.55)	$z = -5.302$, $p < 0.001$
BSL: affect regulation (sum)	33.13 (9.34)	4.21 (4.54)	$z = -5.229$, $p < 0.001$
BDI (sum)	28.81 (9.11)	3.96 (2.77)	$t_{(16.87)} = -10.59$, $p < 0.001$

Mean scores of psychometric measures for the BPD and HC group. Standard deviations are given in parentheses. Statistics: in case of categorical data Chi-square-tests were applied; for continuous data not significant departing from normal distribution independent sample t-tests (t-values reported) were computed; otherwise Mann–Whitney-U-Tests were used (z-values are reported). LPS, Leistungsprüfsystem; MWT-B, Mehrachwahlwortschatztest form B; STAI-trait, State-Trait-Anxiety Inventory II (trait anxiety scale); BIS, Barratt Impulsiveness Scale; SCL-90-R (GSI), Symptom-Checklist (Global Severity Index); BSL, Borderline Symptom List; BDI, Beck Depression Inventory.

Exclusion criteria were a history of psychotic disorder, major depression at time of participation, current mania or hypomania, a diagnosis of ADHD, and substance dependence within the last six months prior to study participation. Patients had to be free from psychotropic medication for at least 2 weeks prior to participation (6 weeks in case of fluoxetine), and previous use of depot neuroleptics lead to exclusion for at least 6 months. Control subjects should not meet criteria for any current or past Axis I or Axis II disorder (as screened with the SCID I and II). In both patients and healthy controls any neurological disorder and any current medical condition influencing cerebral metabolism (e.g., diabetes, systemic corticosteroid medication) was also considered as an exclusion criterion. One patient was further excluded from further analysis due to below-chance level performance in the (neutral) congruent flanker condition. The final study sample comprised 16 patients diagnosed with BPD and 24 healthy control subjects (HC). The BPD and control samples were carefully matched with respect to age, smoking

status, and intelligence as assessed with the "Multiple-Choice Vocabulary Intelligence Test" ("Mehrfachwahl-Wortschatz-Intelligenztest," MWT-B; Lehrl, 2005) and subtests 3 and 4 of the "Performance Testing System" ("Leistungsprüfsystem," LPS-3 and LPS-4; Horn, 1983) (see **Table 1**). Intelligence measures were considered to be a more appropriate measure than mere years of education, as patients often had disruptions of their educational and professional careers resulting from disorder-related periods of prolonged illness and/or hospitalization.

In the BPD group, two patients met the DSM-IV criteria for posttraumatic stress disorder (PTSD) at the time of participation. Further comorbid Axis I psychiatric diagnoses in this sample included the following: past major depression ($n = 10$), substance abuse ($n = 7$), panic disorder ($n = 1$), social phobia ($n = 1$), obsessive–compulsive disorder ($n = 1$), bulimia nervosa ($n = 2$). Comorbid Axis II disorders were: avoidant personality disorder ($n = 3$), dependent personality disorder ($n = 1$), obsessive-compulsive personality disorder ($n = 1$) and histrionic personality disorder ($n = 1$).

Participants completed complementary well-established questionnaires to assess individual differences in psychopathology. Trait anxiety was assessed using the State-Trait-Anxiety Inventory (STAI; Spielberger and Lushene, 1966). We chose to use trait rather than state anxiety as a measure of individual anxiety levels, as BPD patients, due to their affective instability, might show less reliable responses in the STAI-state, and we were also concerned that state anxiety might even show considerable fluctuations in these patients during the course of the experimental session. We further employed the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995; German version Preuss et al., 2003) to assess impulsivity and the Beck Depression Inventory (BDI II; Hautzinger et al., 1994) to quantify depressive symptoms.

EXPERIMENTAL PARADIGM

Participants were scanned while performing a modified version of the Eriksen Flanker task (Eriksen and Eriksen, 1974) with task-irrelevant emotional and neutral distracters (Richter et al., 2011). The flanker stimulus consisted of a central arrowhead, pointing either to the right or left, flanked by four surrounding arrowheads or four dashes on either side. Flanking arrowheads could point either in the same (congruent condition) or opposite direction (incongruent condition) of the central arrowhead. In these conditions, subjects were instructed to respond as fast and accurately as possible to the pointing direction of the target with a button press on the respective side while ignoring the direction of the surrounding arrowheads. Task-irrelevant pictures of neutral or fearful faces were presented in the background of the flanker stimulus (Richter et al., 2011). The experiment consisted of seven experimental conditions, including four primary conditions of interest with the combinations of congruent/incongruent flanker stimuli and emotional/neutral face stimuli. To improve the estimation accuracy of the stimulus-specific BOLD responses, we included a baseline condition, in which the target flanker was surrounded by dashes only, and a blurred face was presented in the background, thus not eliciting a conflict. Furthermore, two stop conditions (congruent and incongruent) were included, in which the response to the target item should be inhibited. Stop trials were included as a behavioral measure of motor impulsivity, but were not considered further in the present analyses and will be reported separately.

Each trial lasted 1500 ms, beginning with the presentation of a neutral or emotional face stimulus for 650 ms, followed by a 200 ms presentation of the flanker stimulus, during which the face stimulus was blurred, and ending with the respective face stimulus for another 650 ms. Example stimuli and the sequence of one trial are displayed in **Figure 1**. Flanker stimuli were presented at the location of the face's eyes, thereby requiring subjects to keep the face within the focus of attention. During stop trials a regular flanker stimulus was presented for 100 ms followed by 100 ms of the presentation of a "0" at the site of the target stimulus. The stop conditions were combined with either an emotional or neutral face. Face stimuli were obtained from the Karolinska Directed Emotional Faces database (KDEF; Lundqvist et al., 1998). The experiment lasted approximately 20 min, consisting of 50 trials of each of the emotion x congruency conditions, and 20 emotional and 20 neutral baseline and stop trials respectively, resulting in 280 trials in total. Conditions were presented in random order and response direction (direction of the target stimuli: left/right) was balanced across all conditions. Interstimulus intervals were jittered near-exponentially between 2 and 8 s. Stimuli were displayed, and responses were collected using the Presentation software (Neurobehavioral Systems Inc, Albany, CA) and a fiber optic response device (fORP, Current Design Inc, Philadelphia, PA).

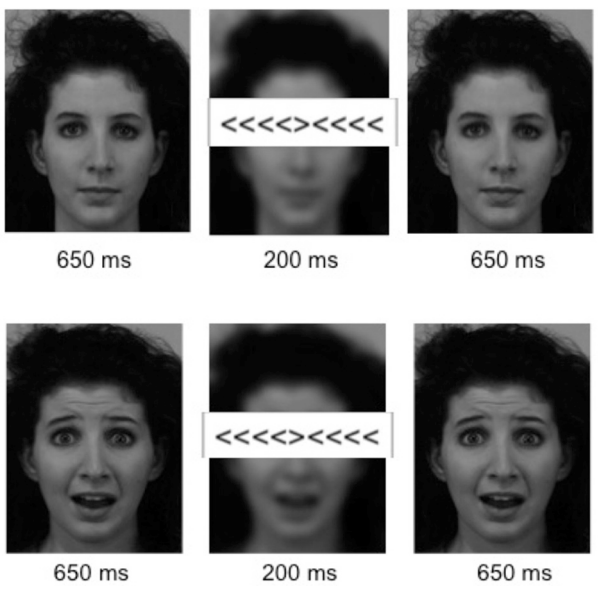

FIGURE 1 | Stimuli. Example stimuli for an incongruent flanker condition with a neutral **(Top)** and an emotional **(Bottom)** background pictures. Six hundred and fifty milliseconds presentation of the neutral/fearful face stimulus were followed by 200 ms in which the flanker stimulus appeared at the height of the eyes and the background picture was blurred, ending with another presentation of the face stimulus for 650 ms.

MRI DATA ACQUISITION

MRI data were acquired on a 3 Tesla Siemens Tim Trio MR tomograph located at the Dahlem Institute for Neuroimaging of Emotion (D.I.N.E.; Cluster Languages of Emotion, Free University of Berlin) with a 12-channel phased array head coil. Because we were interested in both the amygdala and inferior prefrontal structures that typically require opposite tilting of the slice block, we decided to orient the slices in a strict transversal orientation. As displayed **Figure S1**, both the amygdala and the rACC regions-of-interest (ROIs) overlapped in post part with the brain mask, suggesting that signal dropout was negligible.

Functional MRI data were acquired using a gradient, T2*-weighted echoplanar imaging pulse sequence (GE-EPI). Thirty-seven adjacent axial slices were acquired along the AC-PC plane in ascending order covering the whole brain, with a 64×64 matrix and 192 mm field of view (in-plane voxel size $3 \times 3\,mm^2$, slice thickness = 3 mm, inter-slice gap = 0.3 mm, $TR = 2000$ ms, $TE = 30$ ms, flip angle = 70°). Structural data were acquired using a 3D T1-weighted MPRAGE sequence (isotropic voxel size $1 \times 1 \times 1$ mm) in a 256 mm field of view (256×256 matrix, 176 slices, $TR = 1900$ ms, $TE = 2.52$ ms).

DATA PROCESSING AND ANALYSIS

Behavioral data analyses

Behavioral data consisted of mean RTs (for correct responses) and accuracy rates for each subject and were analyzed using SPSS 18 (SPSS Inc, Chicago). These variables were entered into repeated measures analyses of variance (ANOVA), as far as the assumption of normal distribution was met, and subjected to non-parametric test-statistics otherwise. Stop trials were analyzed separately for the dependent variable false alarm rate (failed inhibition of response). The stop trial conditions particularly served the purpose to obtain an additional behavioral measure of impulsivity and were consequently not a factor of interest in the fMRI analyses. All statistical tests employed are listed in **Table 2**.

Fmri data analyses

Image preprocessing and fMRI data analyses were performed using Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running on Matlab 7.7 (Mathworks Inc., Natick, MA). Data were corrected for acquisition delay and head motion, and subjects' individual T1-weighted MPRAGE images were coregistered to the mean image obtained from motion correction. The MPRAGE image was then segmented using the algorithm implemented in SPM, and EPIs were transformed into the Montreal Neurological Institute (MNI) template space using the normalization parameters obtained from segmentation. Finally, normalized images were smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum. A temporal high-pass filter with a cut-off frequency of 1/128 Hz was applied to the data to remove low-frequency noise. Serial correlations in time series were removed using an autoregressive model of first order [AR(1)]. For statistical analysis a two-stage mixed effects model was applied. In the first stage, individual general linear models (GLMs) were estimated containing separate covariates for the four conditions of interest [congruent and incongruent flanker condition × fearful and neutral background pictures] and further covariates of no interest for low-level baseline trials, stop trials, error trials, the six rigid-body transformations obtained from motion correction and a single constant representing the mean over scans. Second-level random effects analyses were then computed over the single subjects' contrasts. Only BOLD responses to trials with correct responses were modeled as effects of interest.

In the second stage of the model, single subjects' contrasts of the four conditions were included in two separate within-subject repeated measures ANOVAs for the BPD and the HC group, with the factors subject, flanker (congruent and incongruent), and emotion (fearful and neutral). In the second level analyses, individual differences in anxiety were expected to affect attentional orienting and neural responses to fearful face stimuli, possibly irrespective of diagnosis (Reeck et al., 2012). Similarly, impulsivity has been demonstrated to affect electrophysiological correlates of cognitive monitoring in a flanker task with stop trials in both healthy controls and BPD patients (Ruchsow et al., 2008a,b). As we were interested in both diagnosis-related between-group differences independent of anxiety and impulsivity, but also in the specific influences of trait anxiety, covariates representing individual levels of trait anxiety and impulsivity (obtained from the STAI-trait and BIS questionnaires) were included in all statistical models. Because only two additional factors can be modeled besides the subjects factor in this kind of SPM second level analysis, separate between-subjects ANOVAs were computed for factors group (BPD and HC) and emotion (fearful and neutral); group and congruency (congruent and incongruent) as well as for group and the emotion by congruency interaction [(inc_emo > cong_emo) > (inc_neut > cong_neut)].

Whole-brain voxel-wise comparisons are reported $p < 0.001$, uncorrected, with a minimum cluster size of 10 adjacent voxels. To adjust α-error probabilities for brain regions known to be involved in the paradigm used in this study (Richter et al., 2011), literature-based probabilistic ROIs (Schubert et al., 2008) were generated for all brain regions *a priori* hypothesized, namely the amygdala, the dorsal ACC (dACC), the rostral ACC (rACC), the DLPFC, and the fusiform face area (FFA). The significance level for activation in these ROIs was set at $p < 0.05$, family-wise error (FWE)-corrected for the ROI volumes. Directional t-tests were inclusively masked with the respective F-contrast, thresholded at $p < 0.05$. Correspondence between macroscopic brain anatomy as well as cyto-architectonics and activation foci were determined using a maximum probability map approach (Eickhoff et al., 2006a) as provided by the probabilistic cyto-architectonical brain atlas for SPM (Eickhoff et al., 2005) and areas were labeled according to the publications describing these probabilistic maps (Geyer et al., 1996, 1999; Amunts et al., 1999, 2000, 2005; Morosan et al., 2001; Geyer, 2004; Caspers et al., 2006; Choi et al., 2006; Eickhoff et al., 2006b,c; Malikovic et al., 2007; Rottschy et al., 2007; Scheperjans et al., 2008; Kurth et al., 2010). Literature-based probabilistic ROIs for α-error adjustment were created using a previously described algorithm (Schubert et al., 2008; see Supplementary Information for details).

Table 2 | Mean response times (RT) and accuracy in the four conditions of interest (congruency × emotion) in the Borderline (BPD) and the control group (HC).

A. Behavior: descriptives

	RT		Accuracy		FA rate stop trials	
	BPD	***HC***	***BPD***	***HC***	***BPD***	***HC***
Neutral					0.213 (0.27)	0.215 (0.27)
Congruent	598.94 (132.25)	665.17 (155.66)	0.961 (0.08)	0.985 (0.03)	–	–
Incongruent	736.69 (160.24)	764.33 (180.83)	0.876 (0.13)	0.949 (0.06)	–	–
Fearful					0.259 (0.26)	0.196 (0.24)
Congruent	601.38 (131.07)	670.04 (152.64)	0.977 (0.05)	0.988 (0.03)	–	–
Incongruent	758.31 (166.05)	788.96 (192.73)	0.843 (0.14)	0.949 (0.06)	–	–

B. Behavior: statistics

REACTION TIMES

Factor	F_{df}	***p***	**Partial Eta squared**
Congruency	81.516_1	0.000	0.682
Emotion	17.783_1	0.000	0.319
Group	0.923_1	0.343	0.024
Congruency*emotion	6.190_1	0.017	0.140
Congruency*group	1.819_1	0.185	0.046
Emotion*group	0.183_1	0.671	0.005
Congruency*emotion*group	0.001_1	0.972	0.000

ACCURACY

Mann–Whitney test

	ME_{cong}	ME_{emo}	$IE_{congemo}$
Mann–Whitney U	147.000	142.500	110.500
Wilcoxon W	283.000	278.500	246.500
Z	−1.245	−1.369	−2.254
R	−0.197	−0.216	−0.356
Exact sig. [2*(1-tailed sig.)]	0.222	0.174	0.023

Wilcoxon signed ranks test

	(cong-neut + inc-neut)/2 − (cong-emo + inc-emo)/2	**(inc-neut + inc-emo)/2 − (congneut + cong-emo)/2**	**inc-neut - cong-neut − inc-emo - cong-emo**
Z	−0.873	−4.581	−1.413
R	−0.138	−0.724	−0.065
Asymp. sig. (2-tailed)	0.383	0.000	−0.158

FALSE ALARMS

Mann–Whitney test

	ME_{emo}
Mann–Whitney U	126.000
Wilcoxon W	426.000
Z	−1.860
R	−0.294

(Continued)

Table 2 | Continued

Wilcoxon signed ranks test	
	stop_neut_prop_FA – stop_emot_prop_FA
Exact sig. [2*(1-tailed sig.)]	0.070
Z	−0.742
R	−0.117
Asymp. sig. (2-tailed)	0.458

Standard deviations are given in parentheses. Abbreviations: ME_{cong}, main effect of congruency; ME_{cong}, main effect of emotion; $IE_{congemo}$, interaction effect congruency x emotion.

Brain-behavior correlations

For selected core symptoms of BPD the relationship between symptom severity and fMRI activation patterns was investigated by the means of brain-behavior-correlations. Since we used fearful facial expressions as background pictures, the STAI as a measure of trait anxiety was considered to be the most relevant psychometric scale. To avoid circularity in the data analysis (Kriegeskorte et al., 2010), correlations between psychometric data and BOLD-responses were carried out in *a priori* defined ROIs only. Because of their well-characterized role in emotional processing the rACC and amygdala were chosen as ROIs. Further we chose the dACC as a relevant region for contrasts reflecting the interaction of the cognitive process with the fearful face processing. GLM parameter estimates (corrected for the effects of no interest) were extracted from the ROIs for the fearful > neutral contrast (for incongruent and congruent conditions separately) and the incongruent > congruent contrast (for fearful and neutral faces separately) and Pearson's correlations were calculated with the STAI-trait scores in the HC and BPD groups separately. Robustness of correlation values was examined by calculation of Cook's distances (Di), a measure of the influence that single values exert on a correlation (Cook and Weisberg, 1982). In case of single values exceeding an *a priori* defined threshold of Di>4/n (Bollen and Jackman, 1990), the respective subject was excluded and the correlation coefficient recalculated. In order to compare correlation coefficients between groups a bootstrap approach with Monte Carlo approximation was chosen (Efron, 1979). One thousand bootstrap samples of size 16 were generated by independent, random draws with replacement from the original sample and the correlation was calculated for each bootstrap sample. This procedure was applied for the BPD and HC group separately, resulting in 1000 estimates for the correlation coefficient per group and contrast. With the resulting distributions of the correlation coefficients an estimate of the correlation coefficient's standard deviations could be computed. These were used to calculate effect sizes (Cohen's d) for the group differences. Additionally the bootstrap-correlations were entered into Mann–Whitney-U-Tests (BPD vs. HC; all *p*-values were Bonferroni-corrected). Only correlation coefficients significantly differing from zero in at least one of the groups were tested for group differences. *Note:* Brain-behavior correlations were also performed for impulsivity, but those results will be reported separately, together with the stop trial results.

RESULTS

BEHAVIOR

Descriptive statistics for RTs, accuracy rates and false alarm rates for both groups are presented in **Table 2A**, and the inferential statistics, including effect sizes are presented in **Table 2B**.

Reaction times

The distribution of RTs did not depart significantly from the predicted normal distribution in either of the conditions (as assessed with the Kolmogorov–Smirnov-Test with Lilliefors significant correction; KS-test; Lilliefors, 1967), neither in the control nor the Borderline group (smallest *p*-value in the KS-test: $p = 0.11$). The ANOVA on RTs yielded a significant main effect of congruency and of emotion [$F_{(1,\ 38)} = 81.51$, $p < 0.001$ and $F_{(1,\ 38)} = 17.78$, $p < 0.001$, respectively], as well as a significant congruency by emotion interaction [$F_{(1,\ 38)} = 6.19$, $p = 0.017$], with RTs being longer in incongruent compared to congruent and emotional compared to neutral trials, yielding their maximum in the incongruent emotional condition. Neither the group main effect [$F_{(1,\ 38)} = 0.923$, $p = 0.34$] nor the emotion by group, congruency by group nor the three-way interaction reached significance [$F_{(1,\ 38)} = 0.183$, $p = 0.671$; $F_{(1,\ 38)} = 1.82$, $p = 0.185$; and $F_{(1,\ 38)} = 0.001$, $p = 0.972$, respectively]. These results indicate the occurrence of a behavioral conflict effect as well as a differential effect of emotion on the processing of congruent and incongruent flanker stimuli, which did not differ significantly between the BPD and control group.

Accuracy

The KS-test on accuracy rates indicated a significant deviation from the normal distribution, thus a non-parametric test procedure was adopted, testing within-subjects effects and between-subjects effects using Wilcoxon-Signed-Ranks-Tests and Mann–Whitney-Tests, respectively. After Bonferroni correction only the main effect of congruency yielded significance ($z = -4.581$, $p < 0.01$).

Stop trials

The KS-test on FA rates indicated a significant deviation from the normal distribution, thus a non-parametric test procedure was adopted. Neither the main effect of emotion, nor the main effect of group, nor the emotion by group interaction effect reached significance. This (objective) measure of impulsivity did consequently not indicate any differences in behavioral impulsiveness between the BPD and HC groups.

BRAIN RESPONSES

Table 3 displays the results of all ROI-based analyses in the dACC, rACC, amygdala, DLPFC, and FFA ($p < 0.05$, small-volume FWE corrected). **Tables 4–8** display the results of whole-brain voxel-wise comparisons ($p < 0.001$, uncorrected).

Within-group effects: effect of emotion

Contrasting the fearful with the neutral condition the control group showed increased BOLD signal in the left amygdala,

Table 3 | Brain activations; ROI-based analyses.

Roi, hemisphere			Within subject comparisons				Between subject comparisons		
		Group	e > n	n > e	i > c	inter	emo	cong	inter
dACC (bilat.)	L/R	HC	–	–	0, 17, 43 $p = 0.010$*	–	BPD > HC −12, 26, 34 $p = 0.044$*	–	–
		BPD	–	–	−6, 20, 43 $p = 0.078$	–			
rACC (bilat.)	L/R	HC	–	6, 50, 1 $p = 0.086$	–	–	–	–	–
		BPD	–	–	–	–			
Amygdala	L	HC	−18, −10, −14 $p = 0.003$**	–	–	–	–	–	–
		BPD	−21, −1, −14 $p = 0.021$*	–	–	–			
	R	HC	–	–	–	–		–	–
		BPD	30, −1, −14 $p = 0.040$*	–	–	24, −4, −23 $p = 0.007$**			
DLPFC	L	HC	−42, 11, 2 5 $p < 0.001$*	–	−45, 5, 28 $p = 0.006$**	–	BPD > HC −27, 29, 31 $p = 0.099$	–	–
		BPD	–	–	–	–			
	R	HC	45, 17, 25 $p = 0.001$**	24, 32, 34 $p = 0.042$*	45, 8, 28 $p < 0.001$**	–	–	–	–
		BPD	45, 26, 13 $p = 0.041$	–	–	–			
FFA	L	HC	−42, −52, −17 $p < 0.001$**	–	–	–	–	–	–
		BPD	−39, −46, −17 $p < 0.001$**	–	–	–			
	R	HC	33, −67, −11 $p < 0.001$**	–	–	–	–	–	–
		BPD	39, −61, −14 $p = 0.054$	–	–	–			

*Results of the ROI-based analyses. Peak coordinates are reported. dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FFA, fusiform face area; *FWE-correctable at $p < 0.05$; **FWE-correctable at $p < 0.01$.*

Table 4 | Brain responses; fearful > neutral.

Brain structure (area %)	*H*	Cluster size	*Z* (peak)	MNI coordinates		
				x	*y*	*z*
HC						
Lingual gyrus (BA17: 20%)	R	569	5.46**	3	−82	−2
Fusiform gyrus (V4v: 70%)			4.98**	30	−70	−11
Lingual gyrus (V3v: 60%)			4.56	21	−79	−5
Middle temporal gyrus (V5: 30%)			3.72	57	−67	1
Inferior temporal gyrus			3.67	51	−73	−5
Fusiform gyrus	L	204	4.86*	−42	−52	−17
Lingual gyrus (V4: 30%)			4.39	−21	−79	−14
Inferior occipital gyrus			3.82	−39	−67	−11
Inferior frontal gyrus (p. tria. BA45: 40%)	L	168	4.59	−48	23	−2
Inferior frontal gyrus (p. oper. BA44: 30%)			3.14	−45	14	7
Middle occipital gyrus	R	158	4.54	30	−76	22
Middle temporal gyrus (PGp: 40%)			3.88	51	−76	13
Superior occipital gyrus			3.38	27	−64	31
Superior temporal gyrus	R	118	4.81*	45	−31	4
Middle temporal gyrus			4.14	57	−52	4
Inferior frontal gyrus (p. tria. BA44: 40%)	L	115	4.88*	−42	11	25
Inferior parietal lobule (7A: 50%)	L	110	4.38	−30	−55	49
Angular gyrus			3.24	−36	−55	37
Inferior frontal gyrus (p. tria.)	R	88	4.77*	45	17	25
Middle temporal gyrus	L	70	4.19	−48	−46	7
Thalamus (temporal: 49%)	R	36	4.99*	3	−13	1
Amygdala (SF: 50%)	L	24	3.89	−18	−10	−14
Amygdala (LB: 10%)	L	18	4.53	−33	2	−26
Middle occipital gyrus	L	14	3.49	−51	−76	−2
Putamen	L	11	3.69	−30	−10	−8
BPD						
Inferior temporal gyrus	L	257	4.61	−39	−46	−17
Fusiform gyrus (V4v: 60%)			4.04	−27	−76	−14
Lingual gyrus			3.87	−24	−52	−11
Inferior occipital gyrus			3.83	−45	−73	−11
Lingual gyrus (BA18: 60%)	R	154	4.58	18	−82	−14
Calcarine gyrus (BA17: 60%)	L		3.88	−9	−91	−2
Inferior frontal gyrus/insula	R	30	4.41	45	26	10
Precuneus (7A: 10%)	L	24	3.94	−9	−67	31
Middle occipital gyrus (BA18: 30%)	R	16	3.48	30	−91	16
Precuneus	R	15	3.72	15	−58	25
Precuneus (5M: 40%)	R	11	3.55	6	−46	67

*Clusters of activation for >10 contiguous voxels with p < 0.001, uncorrected. Z, z-score of local maximum; *FWE-correctable at p < 0.05; **FWE-correctable at p < 0.01; Cluster size: in voxels; H, Hemisphere; BA, Brodmann area; hOC4v/hOC5v, human occipital cortex 4/5 ventral; V4/V5, visual area 4/5; SPL, superior parietal lobule; 7A, posterior Superior Parietal Cortex; BA7, anterior part; hIP3, human intraparietal area 3; IPC, Inferior Parietal Cortex; PGa, rostral part of BA39 (angular gyrus), extending from the Inferior parietal sulcus to the temporo-occipital junction; Amygdala SF, superficial; CM, centromedial; LB, laterobasal; 5M, medial area of BA5.*

the inferior frontal gyrus, the middle temporal gyrus, fusiform gyrus, intra-parietal sulcus, and middle occipital gyrus. The BPD group did not show a reliable activation of the left amygdala as well as the fusiform gyrus, lingual gyrus, the inferior frontal gyrus, precuneus and middle and inferior occipital gyri (**Tables 3**, **4**). Emotion-related activation of the FFA survived small-volume correction in the left and right FFA in the HC group (peaks at [−42, −52, −17] and [33, −67, −11]) and in the left FFA in the BPD patients (peak at [−39, −46, −17]). Both groups also showed ROI-correctable activation of the left amygdala during presentation of emotional relative to neutral faces (HC: peak at [−18, −10, −14]; BPD peak at [−21, −1, −14]; see **Table 3** and **Figures 2A,B**, left panel).

Table 5 | Brain responses; neutral > fearful.

Brain structure (area %)	*H*	Cluster size	*Z* (peak)	MNI coordinates		
				x	*y*	*z*
HC						
Inferior occipital gyrus (BA17: 90%)	R	28	4.96*	24	−100	−2
Middle frontal gyrus		16	3.72	24	32	34
Caudate nucleus		12	3.95	9	20	4
BPD						
Superior frontal gyrus (BA6: 30%)	R	13	3.91	15	23	61

*Clusters of activation for >10 contiguous voxels with $p < 0.001$, uncorrected. Z, z-score of local maximum; *FWE-correctable at $p < 0.05$; **FWE-correctable at $p < 0.01$; Cluster size: in voxels; H, Hemisphere; BA, Brodmann Area.*

In the neutral > fearful faces comparison, healthy controls showed activation increases in the visual cortical and DLPFC structures, as well a trendwise activation in the rACC (**Tables 3**, **5**). The BPD patients, on the other hand, showed an increased activation of the dorsomedial PFC in this contrast.

Within-group effects: effect of congruency

When compared to congruent flanker stimuli, incongruent flanker trials were associated with increased activation in largely overlapping regions in the HC and BPD groups, comprising the inferior and superior parietal lobule, the superior, middle and inferior frontal gyrus, the inferior temporal gyrus, insula, and dACC (**Table 6**). Corrections for the ROI volumes revealed a significant signal increase in the dACC in healthy controls and a trendwise activation in BPD patients in response to the incongruent flanker stimulus (HC: peak at [0, 17, 43]; BPD: peak at [−6, 20, 43]; see **Table 3**, **Figure 3**), whereas activations in the DLPFC were significant after FWE correction in healthy controls only (**Table 3**). In the congruent > incongruent comparison, both groups showed activation increases in several brain structures (see Supplementary Information: **Table S2** for details). Healthy controls demonstrated greater BOLD signal in both the left and right amygdalae (see **Figure 2A**, right panel) and the rACC in the congruent condition, whereas BPD patients did not show this activation difference in the amygdala, but only in the rACC (see supplementary **Table S2**). Additionally the BPD group showed a significant activation for the right FFA ROI (Supplementary **Table S2**).

Within-group effects: interaction congruency-emotion

Testing for the congruency by emotion interaction effect, the corresponding contrast yielded increased activations in the intraparietal sulcus and the right amygdala in BPD patients. The effect in the right amygdala was robust when correcting for the amygdala ROI volume (**Figure 2B**, right panel; **Table 3**). This effect was not found for the HC group. Coordinates and *z*-values are presented in **Tables 3**, **7**.

Between-group effects: group interactions

There were no regions showing higher activation differences in the HC compared to the BPD group as a function of emotion (fearful > neutral), congruency (incongruent > congruent) nor of the congruency by emotion interaction effect. In the fearful > neutral contrast, BPD patients exhibited a higher BOLD signal in the, precuneus, the rACC and in a cluster comprising the dACC and parts of the DLPFC. The elicited activation differences in the dACC were robust after ROI-based FWE correction (peak at [−12, 26, 34]; see **Table 3**), and the DLPFC cluster showed a trend toward significance when correcting for the respective ROI volume (peak at [−27, 29, 31], FWE-corrected $p = 0.071$; **Table 8** and **Figure 4**). The congruency by group interaction contrast revealed higher signal differences (incongruent > congruent) in the BPD as compared to the HC group in the left pallidum. BPD patients showed higher activation differences for the emotion by congruency interaction effect [(inc-emo > cong-emo) > (inc-neut > cong-neut)] in the temporoparietal junction (angular gyrus), cuneus, precuneus, middle and superior occipital gyri as compared to healthy controls (**Table 8**).

Brain-behavior correlations: effects of trait anxiety

Based on their well-characterized roles in emotion regulation and cognitive control, respectively, we focused our brain-behavior correlations on the rACC and dACC. Pearson correlations of the STAI-trait scores and BOLD responses in the emotional conditions of the congruency effect (incongruent > congruent) yielded significant negative relationships between the two variables in both rACC and dACC ROIs in the BPD group (see **Figure 5**). Thus, trait anxiety was inversely associated with activation differences between the incongruent and congruent flanker condition when fearful faces were presented as distracters. Notably, these negative correlations were restricted to the patient group, with healthy controls showing no significant relationship between BOLD signal and STAI-trait scores in any of these contrasts or regions. The effect sizes reflecting the group difference in these correlation coefficients were high in both cases ($d = 1.51$ and $d = 3.71$ for the rACC and dACC, respectively) and did differ significantly ($p < 0.001$ for dACC and rACC). Correlation coefficients, bootstrap results and test statistics are given in **Table 9** and **Figure 5**.

In order to assess potential behavioral effects of trait anxiety on performance in the cognitive task, STAI-trait scores were correlated with RT differences of the incongruent fearful

Table 6 | Brain responses; incongruent > congruent.

Brain structure (area %)	*H*	Cluster size	*Z* (peak)	MNI coordinates		
				x	*y*	*z*
HC						
Inferior parietal lobule (hIP3:40%)	R	903	6.77**	36	−46	49
Superior parietal lobule (SPL/7P: 30%)			6.76**	24	−67	52
Supramarginal gyrus (IPC/PFt: 70%)			6.15**	48	−31	46
Superior occipital gyrus			5.85**	27	−64	34
Angular gyrus (hIP3: 30%)			5.74**	30	−58	43
Middle occipital gyrus			3.72	42	−85	10
Superior parietal lobule (SPL/7A: 50%)	L	741	6.72**	−21	−64	49
Inferior parietal lobule (hIP2: 40%)			5.65**	−42	−37	37
Middle occipital gyrus			5.22**	−27	−73	28
Inferior parietal lobule (BA2: 60%)			4.76*	−45	−37	52
Inferior frontal gyrus (BA44: 30%)	R	121	5.58**	45	5	28
Superior medial gyrus		94	4.02	0	17	43
Superior medial gyrus	L		3.99	−6	14	46
Inferior temporal gyrus	R	63	4.55	57	−55	−11
Precentral gyrus	L	60	4.44	−45	2	31
Superior frontal gyrus	R	55	4.19	24	2	49
Superior frontal gyrus	L	40	3.95	−24	−4	55
Middle frontal gyrus			3.49	−24	5	46
Insula	R	33	4.02	36	20	4
Inferior temporal gyrus	L	33	3.95	−48	−67	−5
BPD						
Superior parietal lobule (SPL/7P: 70%)	R	428	5.42**	15	−70	55
Superior occipital gyrus			5.03*	24	−64	43
Inferior parietal lobule (IPC/PFt: 40%)			4.50	45	−37	49
Middle occipital gyrus			4.40	30	−73	31
Inferior parietal lobule (hIP3: 30%)			4.40	39	−49	49
Middle occipital gyrus (IPC/PGp: 30%)			4.01	39	−79	22
Inferior parietal lobule (hIP1: 40%)	L	138	4.35	−36	−43	40
Inferior parietal lobule (SPL/7PC: 50%)			4.20	−33	−49	49
Superior parietal lobule (SPL/7PC: 60%)			3.99	−33	−52	64
Superior parietal lobule (SPL/7A: 50%)	L	74	5.21**	−15	−64	52
Middle frontal gyrus	R	64	4.02	36	2	61
Superior frontal gyrus	L	47	4.07	−21	−1	49
Middle frontal gyrus (BA6: 30%)			3.69	−30	−1	64
Insula	R	46	5.10**	33	23	−2
Insula	L	35	4.21	−33	17	1
Inferior frontal gyrus (BA44: 30%)	R	19	3.68	48	8	31

*Clusters of activation for >10 contiguous voxels with $p < 0.001$, uncorrected. Z, z-score of local maximum; *FWE-correctable at $p < 0.05$; **FWE-correctable at $p < 0.01$; Cluster size: in voxels; H, Hemisphere; BA, Brodmann Area; hIP1-3, human intraparietal area 1-3; SMA, supplementary motor area; hOC5, human occipital lobe; V5, visual area 5; 7A,7P, posterior Superior Parietal Cortex, anterior and posterior part of BA7; 7PC, anterior Superior Parietal Cortex; IPC, Inferior Parietal Cortex; Pft, dorsal supramarginal gyrus, rostralmost sector of the IPC.*

and congruent fearful conditions (RT_inc-emo - RT_cong-emo; analogously to the contrast of the BOLD-signal). A positive relationship between trait anxiety and RT differences was observed in both groups ($r = 0.44$ and $r = 0.19$ for BPD and HC, respectively), but reached significance in the BPD group only ($p = 0.045$, one-tailed).

DISCUSSION

The present study aimed to assess the impact of task-irrelevant emotional information on cognitive processing in patients with BPD. Our results extend previous observations of a dysregulated fronto-limbic circuitry in BPD. By including anxiety and impulsivity as covariates (see "Methods" section for details),

Table 7 | Brain responses; interaction congruency by emotion.

Brain structure (area %)	*H*	Cluster size	*Z* (peak)	MNI coordinates		
				x	*y*	*z*
HC						
Thalamus (Temporal: 20%)		14	3.85	3	−1	1
BPD						
Inferior parietal lobule (hIP1: 30%)	R	25	3.94	36	−52	34
Amygdala (LB: 90%)	R	12	3.72	24	−4	−23
Caudate nucleus	L	11	3.71	−15	11	7

Clusters of activation for >10 contiguous voxels with p < 0.001, uncorrected. Z, z-score of local maximum; Cluster size: in voxels; H, Hemisphere; hIP1, human intraparietal area 1; Amygdala LB, laterobasal.

Table 8 | Brain responses; BPD > HC.

Brain structure (area %)	*H*	Cluster size	*Z* (peak)	MNI coordinates		
				x	*y*	*z*
EMOTION						
Dorsal anterior cingulate cortex	L	26	4.44	−15	26	31
Middle frontal gyrus			3.48	−27	29	31
Precuneus	L	16	3.87	−12	−67	31
Precuneus	R	16	3.70	15	−67	28
Superior frontal gyrus	R	15	3.99	15	35	43
Rostral anterior cingulate cortex	L	11	3.92	−6	35	7
Superior medial gyrus	R	10	4.23	12	62	25
CONGRUENCY						
Pallidum	L	18	4.15	−21	2	1
INTERACTION EMOTION CONGRUENCY						
Angular gyrus (hIP3: 40%)	R	82	4.15	30	−52	43
Inferior parietal lobule (hIP1: 50%)			3.34	39	−49	34
Middle occipital gyrus			3.24	33	−61	37
Middle occipital gyrus	L	19	4.35	−33	−70	31
Cuneus	R	14	3.87	21	−64	37
Precuneus			3.28	15	−70	40
Superior occipital gyrus	R	14	3.51	21	−76	28
Cuneus			3.51	12	−79	31

Clusters of activation for >10 contiguous voxels with p < 0.001, uncorrected. Z, z-score of local maximum; Cluster size: in voxels; H, Hemisphere; hIP1/hIP3, human intraparietal area 1/3.

we were able to distinguish disorder-related between-group differences and diagnosis-specific correlations of psychopathology and brain activity. Patients showed an interaction between stimulus congruency in the flanker task and emotional interference from the fearful faces in the right amygdala that was not observed in the healthy control group. Furthermore, patients exhibited an emotion-related activation in the rACC/mPFC as well as the dACC that was also absent in controls. Moreover, a disease-specific negative relationship was observed between ACC activity in the emotional incongruent condition and trait anxiety.

EMOTIONAL INTERFERENCE IN THE FLANKER TASK IN HEALTHY CONTROLS

As evident from the RT and accuracy data, a behavioral conflict effect was elicited by the incongruent trials, and emotional salience of the background pictures showed a more pronounced effect on the processing of incongruent as compared to congruent flanker stimuli. At a neural level, performance of the flanker task was associated with increased activation of the dACC in incongruent relative to congruent trials in the healthy controls, replicating previous results (Botvinick et al., 2004; Fan et al., 2008). Also in line with earlier studies, the amygdala showed higher activation

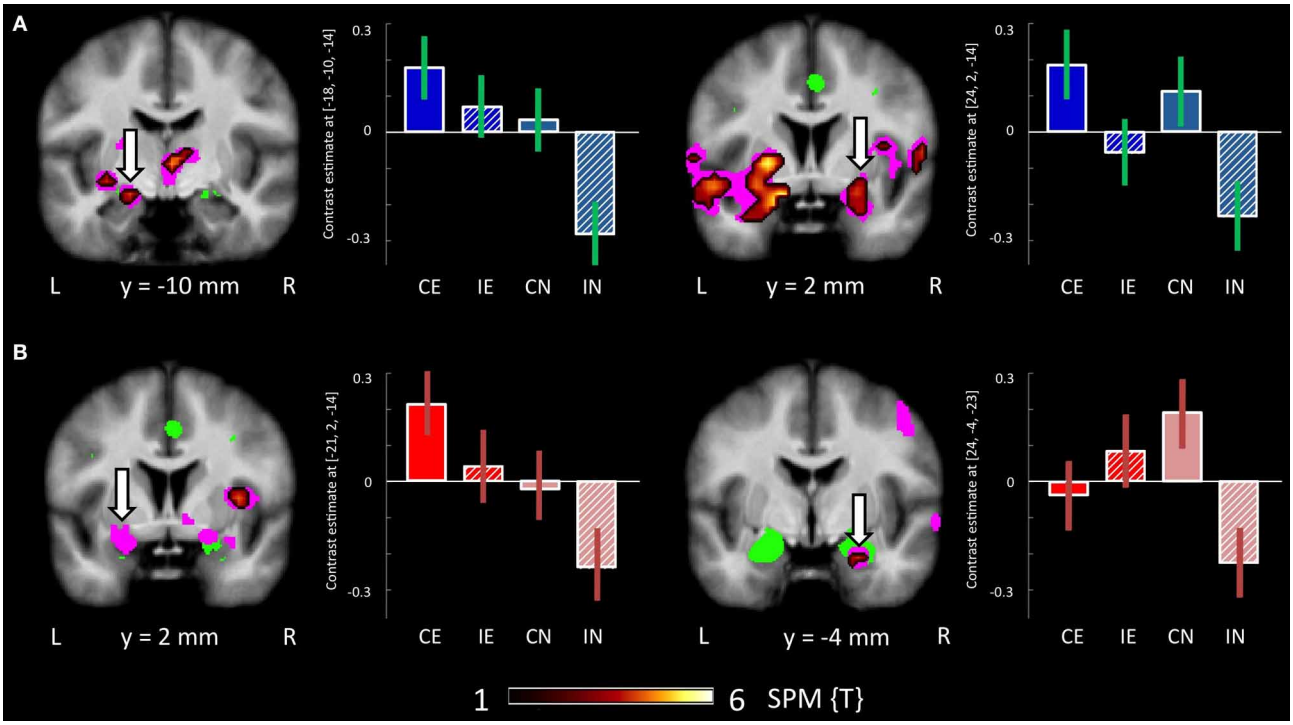

FIGURE 2 | Brain responses: effect of emotion and congruency in the amygdalae. (A) Effects in HCs. Left panel: Activation in the left amygdala for the fearful > neutral contrast in the HC group. Right panel: Activation in the right amygdala for the congruent > incongruent contrast in the HC group. **(B)** Effects in BPD patients. Left panel: Activation in the left amygdala for the fearful > neutral contrast in the BPD group. Right panel: Emotion by congruency interaction in the amygdala in BPD patients. Plots depict contrast estimates for the respective peak voxel (±90% confidence intervals). Conditions: CE, congruent emotional; IE, incongruent emotional; CN, congruent neutral; IN, incongruent neutral.

during the presentation of fearful as compared to neutral faces in the HC group (Bush et al., 2000; Whalen et al., 2001; Phan et al., 2004). Results in healthy controls thus confirm the expected effect of the flanker stimuli as well as of the fearful face stimuli, indicating the effectiveness of the current task design.

DYSREGULATION OF FRONTO-LIMBIC INTERACTIONS IN BPD

BPD patients, like healthy controls exhibited the behavioral flanker effect with higher error rates and lower RTs in the incongruent condition (**Table 2**). This was mirrored by fMRI activation of the dACC, the parietal cortex and the dorsolateral and ventrolateral prefrontal cortex in the comparison of incongruent to congruent flanker stimuli, which was also observed in both groups. The dACC is a region consistently found to be activated in tasks involving cognitive or response conflict (Botvinick et al., 2004; Fan et al., 2008). It is believed to play an important role as part of a distributed attention network, with its functions ranging from the modulation of attention and executive functions by influencing sensory systems or response selection, over competition monitoring and error detection to complex motor control (Bush et al., 2000; Botvinick et al., 2004; Mohanty et al., 2007). Activation of the dACC in the BPD patients and HCs during incongruent flanker trials indicates that conflict processing or conflict detection, irrespective of the emotionality of the distracter, does not differ substantially in the patient group. Similarly, both groups showed increased amygdala activation to fearful as compared to neutral faces, also in line with a well-documented responsivity of the amygdala to emotional stimuli, most prominently fearful faces (Costafreda et al., 2008). Therefore, our results do not support the notion that cognitive mechanisms related to attention and conflict processing might be fundamentally altered in BPD patients (Posner et al., 2002). Instead, we observed alterations in more confined subprocesses of emotional interference on cognitive conflict processing.

The amygdala has repeatedly been implicated in the processing of negative emotional states, including fear processing and the recognition of emotional stimuli, especially facial expression of fear (Whalen et al., 2001; Adolphs, 2002; Amaral, 2002; Pessoa et al., 2002; Phan et al., 2002, 2004; Murphy et al., 2003; Fitzgerald et al., 2006; Phelps, 2006). A dysfunction in amygdala reactivity or its regulation in BPD was therefore hypothesized in our study as it might represent an important neural mechanism underlying increased emotional sensitivity and deficient regulation of negative emotions in BPD. In line with this hypothesis we indeed observed differential activation patterns as a function of emotion processing and emotional interference in the bilateral amygdalae. While a significant activation of the left amygdala as a function of emotionality (fearful vs. neutral faces) was found in both groups (**Figure 2**), healthy controls also showed an increased signal in the left and right amygdala when comparing the congruent with

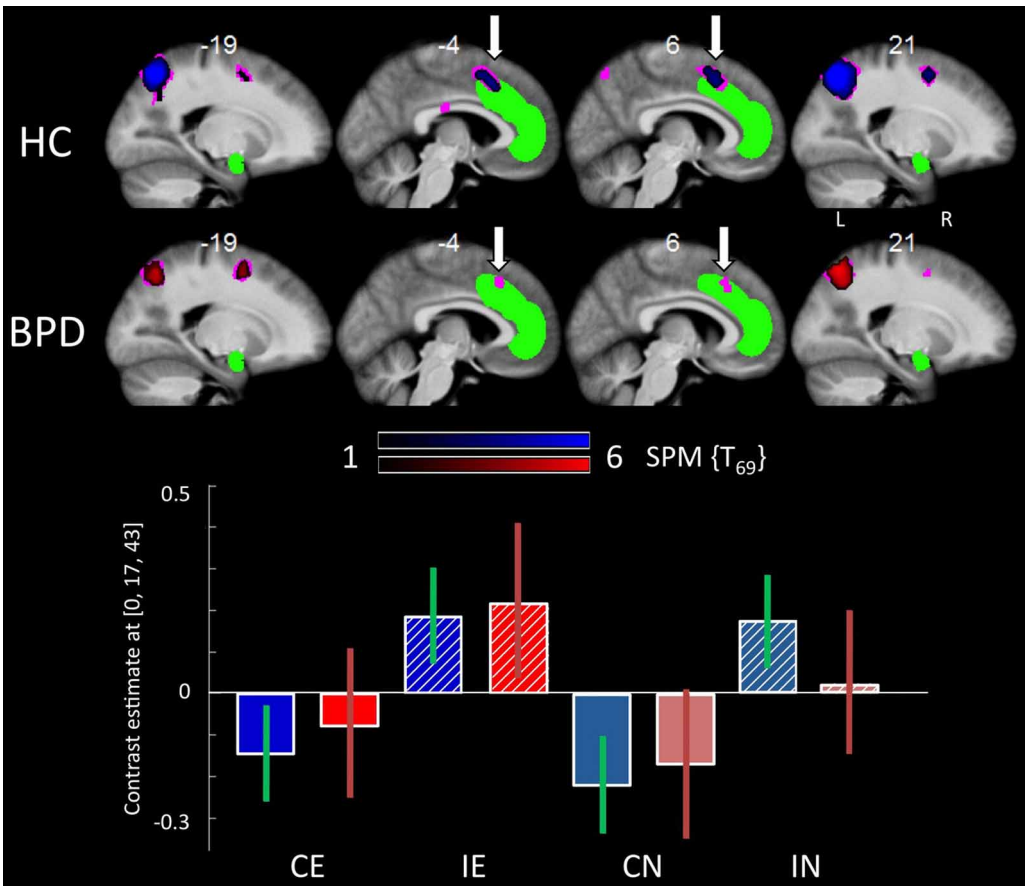

FIGURE 3 | Brain responses: effects of congruency. Top panel: Activation in the dACC for the incongruent > congruent contrast in the HC group (upper line) and the BPD group (lower line). **Bottom panel:** Plots depict contrast estimates for the respective dACC ROI analysis peak voxel (±90% confidence intervals) for the HC (in blue) and BPD group (in red) in the four conditions. Abbreviations: CE, congruent emotional; IE, incongruent emotional; CN, congruent neutral; IN, incongruent neutral.

the incongruent flanker condition, irrespective of emotionality. This amygdala activation as a function of congruency was not observed in the BPD patients. This result has to be interpreted with caution due to the lack of a significant effect in the congruency by group interaction, but we tentatively suggest that it might reflect a diminished down-regulation of amygdala activation in the incongruent condition in BPD patients, or, more generally, decreased task-specific modulation of amygdala activity in BPD (Ruocco et al., 2013). On the other hand, the BPD group exhibited a significant interaction of emotion and congruency in the right amygdala, which was not observed in healthy control participants. Previous investigations of amygdala function in the processing of emotional stimuli suggest that the left amygdala is generally recruited more frequently (Costafreda et al., 2008). The right amygdala, on the other hand, appears to be more sensitive to subliminally presented emotional stimuli (Morris et al., 1999; Costafreda et al., 2008), and meta-analyses suggest that, more generally, the left and right amygdalae differ in the temporal dynamics of their responses to emotionally salient stimuli (Sergerie et al., 2008). In the present study, BPD patients exhibited a stronger response of the right amygdala in the emotional incongruent condition as compared to the emotional congruent condition (**Figure 2B**, right panel). Given the responsivity of the right amygdala to subliminally presented emotional stimuli (Costafreda et al., 2008; Sergerie et al., 2008), we suggest that patients might be able to suppress right amygdala activity by means of emotion regulation in the congruent condition, but not under higher cognitive resource demand of the incongruent condition. An increased responsivity to subliminal negative emotional stimuli in BPD has also been demonstrated in a recent study on attentional bias to fearful faces that was observed in BPD patients during very rapid presentation of the stimuli (Jovev et al., 2012). The notion that the emotion by congruency interaction in the amygdala seen in the patients was not observed in the healthy controls might suggest that, in the healthy population, a right amygdala response, albeit being potentially relatively automatic (Morris et al., 1999), can be suppressed by a demanding cognitive task. In BPD, on the other hand, this suppression of the fast, automatic, right amygdala response might require additional neurocognitive resources and therefore be impaired during performance of demanding tasks. A further aspect of the observed pattern of right amygdala activation in the patient group is the

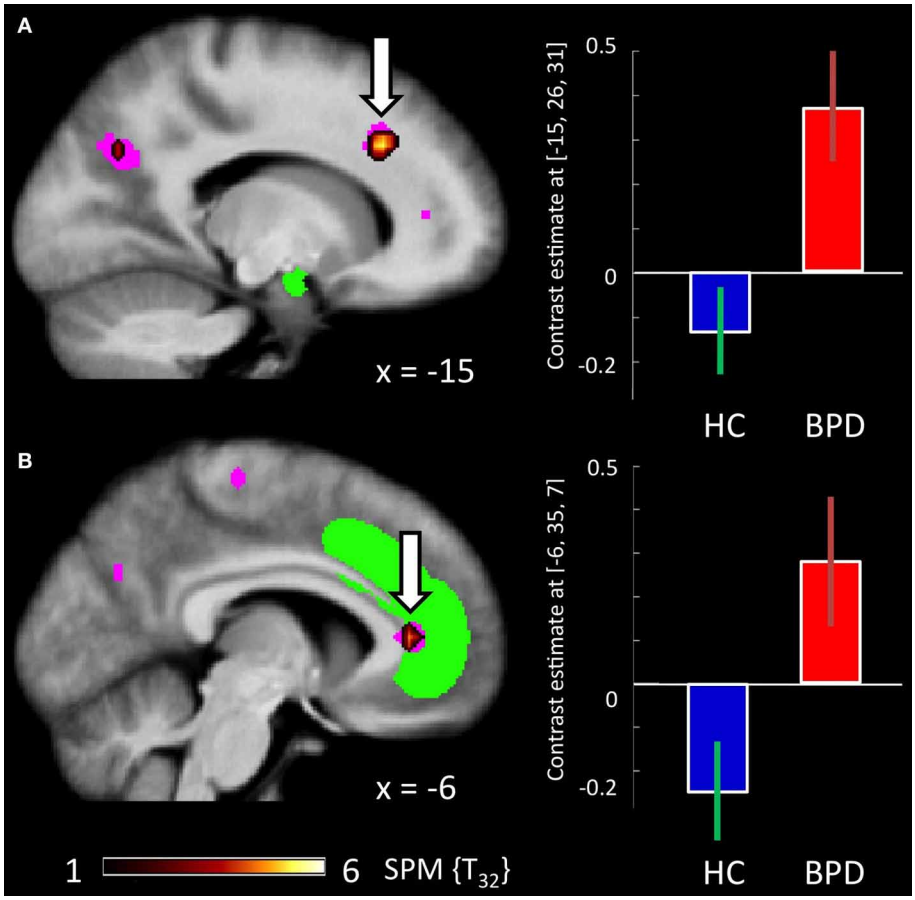

FIGURE 4 | Brain responses: group by emotion interaction. (A) $BPD_{emo>neut} > HC_{emo > neut}$ in the dACC. **(B)** $BPD_{emo>neut} > HC_{emo > neut}$ in the rACC. Plots depict contrast estimates for the peak voxel of the respective contrast (±90% confidence intervals) in healthy controls (in blue) and BPD patients (in red).

presence of a robust right amygdala response to neutral face stimuli in the congruent condition. One limitation in this context is that participants did not explicitly rate the emotional expressions of the face stimuli. Our finding is, however, compatible with a previously observed negativity bias in BPD patients that is accompanied by an increased amygdala response to neutral facial expressions in BPD (Wagner and Linehan, 1999; Donegan et al., 2003) and with BPD patients showing a heightened emotional sensitivity to facial expressions in general (Lynch et al., 2006).

THE ROLE OF THE ACC IN EMOTION REGULATION AND THE MODULATORY INFLUENCE OF TRAIT ANXIETY

The most prominent between-group difference as a function of emotional salience was observed in the dACC and, to a lesser extent, in the rACC/mPFC. BPD patients exhibited somewhat lower dACC activation in the incongruent relative to the congruent flanker condition (albeit not in a direct comparuison with the healthy controls; see **Figure 3**). On the other hand, an increased dACC—and rACC/mPFC—activation was observed in the patients during presentation of emotional faces (**Figure 4**), a pattern that showed a trend into the opposite direction in the HC group (**Figure 4**). Given the comparable behavioral performance in both group, we suggest that this result is indicative of a putatively disorder-specific neural mechanism in BPD patients, leading to an atypical recruitment of an extended ACC region that encompasses both the dACC involved in attentional control and the more rostral region of the pregenual ACC, a portion of the rACC/mPFC complex that has been linked to cognitive processing of emotions, such as the appraisal of fear responses (Mohanty et al., 2007; Etkin et al., 2011).

In addition to the overall increased response of the extended ACC in fearful relative to neutral trials, brain behavior correlations of the STAI-trait scores with both dACC and rACC activation in the emotional high conflict condition (incongruent vs. congruent flanker trials with fearful distracters) revealed a significant negative relationship between trait anxiety and ACC activation during emotional high conflict trials in the BPD, but not in the HC group [*Note:* while the correlation was nominally negative in the HCs as well, it did not approach significance]. Previous studies had demonstrated diminished rACC responses in BPD patients (Minzenberg et al., 2007; Wingenfeld et al., 2009), a finding that could not be confirmed by our study, but instead,

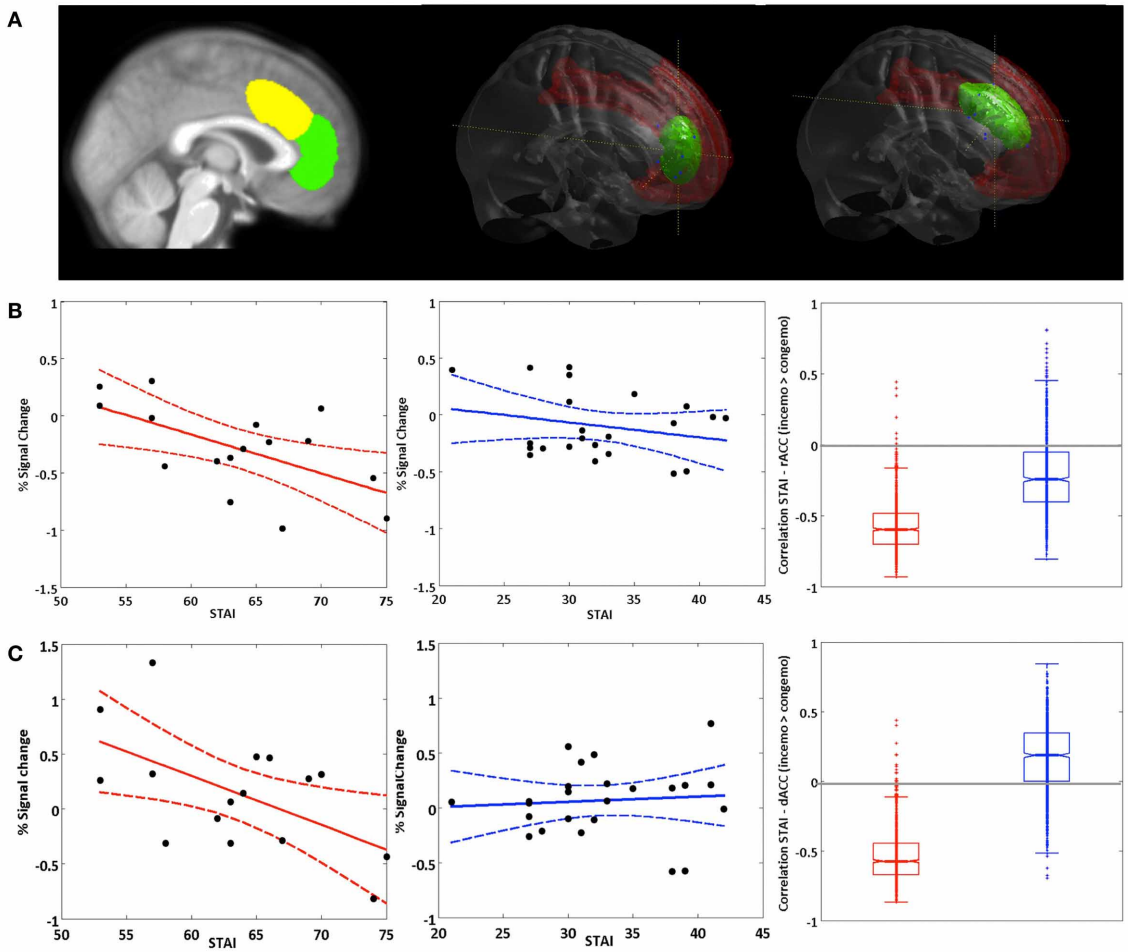

FIGURE 5 | Brain-behavior correlations: STAI (trait). (A) Left panel: Non-overlapping ROIs for the dACC (yellow) and rACC (green). Middle and right panel: rendered dACC and rACC ROI. **(B)** Correlation of the STAI trait score with activation in the rACC and **(C)** activation in the dACC in the fearful condition for the contrast inc > cong (solid lines represent regression lines, dashed lines 95% prediction bounds). Left panel: BPD group. Middle panel: HC group. Right panel: Boxplot for the bootstrap-sample correlations (BPD group: red, HC group: blue).

Table 9 | Brain-behavior correlations; STAI (trait).

Region	Contrast	Correlation		Bootstrap *SD*		Statistics	
		BPD	*HC*	*BPD*	*HC*	Mann–Whitney test	Cohen's d
rACC							
Fearful	Incongruent > congruent	−0.60*	−0.24	0.18	0.26	$z = -30.20$, $p < 0.001$	1.62
Neutral	Incongruent > congruent	0.31	0.13				
dACC							
Fearful	Incongruent > congruent	−0.57*	0.08	0.19	0.25	$z = -37.13$, $p < 0.001$	3.71
Neutral	Incongruent > congruent	−0.28	−0.33				

*Pearson correlation coefficients for the BPD and HC group. For the Bootstrap samples Standard deviations of the samples are given. Mann–Whitney tests were calculated for the bootstrap sample (n = 16; N = 1000); Cohen's d was calculated with empirical correlation values (with pooled SD of SD estimates from the bootstrap samples); *Significant at p < 0.05.*

our results indicate a disease-specific modulatory effect of trait anxiety on ACC function in BPD. One reason for this apparently diverging result might be the degree of emotion processing elicited by performance of the task at hand in the different studies. In both the gender discrimination task employed by Minzenberg et al. and the emotional Stroop task used by Wingenfeld et al. explicit processing of the emotional information was required for successful task performance. In our study, on the other hand,

the face stimuli were completely task-irrelevant, and any attention directed to them could have interfered with performance. We tentatively suggest that patients were largely successful at allocating additional cognitive resources to ACC-dependent emotion regulation and, by upregulating activity of the rACC (and dACC), they were able to compensate for their reduced processing efficiency (possibly similarly to patients with deficits in PFC-dependent cognitive control; see MacDonald et al., 2006) and thus performed the task with a performance largely comparable to that of healthy controls. On the other hand, the patients' ability to recruit ACC regions in situations requiring a higher focus of attention seems thus to be detrimentally affected by their individual degree of trait anxiety. As evident from the brain-behavior correlations, the individual STAI-trait scores were specifically associated with the differential activation in the ACC in the incongruent as compared to the congruent condition with emotional distracters. It thus seems that the impact of higher anxiety on ACC activation in the BPD group only becomes relevant, when the task is sufficiently demanding, and the influence emotional distracters exert over cognitive processing therefore needs to be suppressed. Compatibly, trait anxiety showed a positive correlation with RTs in the BPD group, suggesting that higher anxiety might act as an endogenous attention setting (Reeck et al., 2012) and thereby lead to dysfunctional allocation of cognitive resources to processing of the emotional distracters and adversely affect the ACC-mediated compensatory mechanisms. The observed negative relationship between anxiety and ACC activation is compatible with previous results suggesting a relationship between anxiety and deficient inhibition as well as altered processing of negative information in BPD patients (Domes et al., 2006). While Domes and colleagues observed most pronounced effects of anxiety for state rather than trait anxiety, our results suggest that, at the level or brain activity and subtle RT differences, trait differences of individual anxiety might exert qualitatively similar effects.

While the negative correlation between ACC activation and trait anxiety was restricted to the patient group here, a recent study also reported a similar result in healthy participants (Klumpp et al., 2011). In that study, trait anxiety inversely predicted the response of the rACC to attended relative to unattended angry faces, while no comparable negative correlation was observed for fearful faces. The authors suggested that the attended angry faces might pose a stronger perceived direct threat than the fearful faces. In the present study, faces were always unattended, and no relationship between ACC activation and trait anxiety was observed in the HC group. In BPD patients, on the other hand, the face stimuli were apparently sufficiently salient that the negative relationship of trait anxiety and ACC activity was observed to faces that were not attended and most likely signaled an indirect rather than a direct threat. This observation is compatible with the notion that BPD patients exhibit a cognitive processing bias toward emotionally negative, socially salient stimuli (Barnow et al., 2009; Dyck et al., 2009).

While we had initially hypothesized that trait anxiety might differentially correlate with dACC vs. rACC activation, we observed that the increased activation in the emotional condition irrespective of congruency as well as the negative correlation of the BOLD signal in the emotional incongruent condition with trait anxiety were observed in both the dACC and the rACC. Such an apparently cooperative activation of the dACC, a brain structure that is primarily thought to be involved in cognitive conflict processing, and the pregenual ACC, a region that is thought to belong to a network of regions associated with the regulation of affective processing (Bush et al., 2000; Mohanty et al., 2007; Etkin et al., 2011), may at first appear somewhat counterintuitive, as the two structures are generally thought to belong to distinct networks that are, at least during rest, often found to be negatively correlated (Margulies et al., 2007). However, studies of emotion regulation have shown that dACC activation is commonly found during voluntary, explicit regulatory processes like reappraisal, whereas rACC activation might reflect automatic shifting of attention toward or away from aversive emotional information (Phillips et al., 2008). In the present study, it seems conceivable that participants might have employed a mixed strategy comprising both voluntary and automatic emotion regulation strategies. Moreover, it has recently been suggested that the dissociation of a "cognitive" dACC and an "affective" rACC might no longer be as strongly tenable as previously, with both subregions of the ACC being involved in the regulation of affective processing and in the appraisal of emotional material (Etkin et al., 2011). Specifically, the dACC has been implicated in emotional conflict processing, and activation of the rACC has been linked to appraisal and regulation of emotions, with previous studies having shown diminished rACC responses in BPD patients that were accompanied by increased amygdala activity (Minzenberg et al., 2007).

EMOTIONAL OR SOCIAL INTERFERENCE—OR BOTH?

In the present study, when viewing fearful pictures as compared to neutral ones increased activation was observed not only in the amygdala but also fusiform cortex and primary visual processing areas in both groups. Besides modulating emotional responses, the amygdala is thought to interact with sensory processing via backprojections to and a modulation of fusiform cortex and early sensory processing regions (Ledoux, 2000; Vuilleumier et al., 2004; Sabatinelli et al., 2005; Vuilleumier, 2005; Phelps, 2006; Vuilleumier and Pourtois, 2007), thereby enhancing activity in these regions and biasing further perceptual processing through attentional amplification. A subregion of the fusiform cortex has been shown to selectively respond to face stimuli and has thus been commonly referred to as the FFA (Vuilleumier et al., 2004; Vuilleumier, 2005; Vuilleumier and Pourtois, 2007). The observed upregulation of the visual processing stream in response to fearful face stimuli is consistent with the previous literature (Vuilleumier et al., 2001; Sabatinelli et al., 2005) and is indicative of an enhanced representation of fearful as compared to neutral faces in the FFA. In contrast to previous studies (Herpertz et al., 2001; Koenigsberg et al., 2009) we did not find a greater signal increase in the FFA or primary visual areas for BPD as compared to healthy controls. Patients though did show an effect in the FFA with greater signal intensities in the congruent vs. incongruent trials that mirrored the amygdala response pattern observed in the healthy controls. Previous studies suggest that FFA activity often follows the same pattern as that one observed in the amygdala

(Vuilleumier et al., 2004; Vuilleumier, 2005). Here, however, Borderline patients exhibited a response pattern to task-irrelevant faces as a function of task difficulty that did not correspond to that of the (right) amygdala, where a complex interaction between congruency and emotional salience of the background pictures was observed. Given the previously reported amygdala response even to neutral faces in BPD (Donegan et al., 2003) and the well-known difficulties in social interactions of BPD patients (Lopes et al., 2005; Koenigsberg et al., 2009; Preißler et al., 2010; Dziobek et al., 2011), we cannot exclude that the response pattern observed here might be specific to face stimuli or possibly social stimuli in general. Future studies should employ other aversive stimuli, such as (non-social) IAPS pictures (Wiswede et al., 2009), to differentiate between effects of social processing and unspecific emotional interference.

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

The sample size in the present study was modest, though comparable to that of most functional imaging studies of psychiatric populations. Nevertheless a failure to detect possible differences at a behavioral level might be explained by a lack of statistical power, given a complex factorial design like the present one. Also, because our sample consisted of only female patients with relatively typical clinical presentation, we cannot make conclusive inferences for male BPD patients who make up a smaller proportion of all BPD patients and often exhibit atypical clinical features.

A further limitation is that the contribution of comorbid psychiatric disorders in the patient group to the experimental findings remains unclear. However, comorbid disorders are typically observed in the BPD population and exclusion of any comorbidities would have led to the sampling of a non-representative patient group. It should also be noted that the sample did not include any patients with a comorbid generalized anxiety disorder and only one patient with co-morbid panic disorder, making it unlikely that Axis I anxiety disorders can explain the present results.

It must also be note that the present study focused exclusively on fearful faces and anxiety as a negative emotion, but we cannot exclude a different outcome when investigating other negative or positive emotions. While most pronounced emotional interference was to be expected after presentation of fearful faces in BPD patients, future studies should also address the effects of other negative and also on positive emotions on cognitive processing, particularly in the light of a general bias toward negative emotions in BPD. This line of research could also be pursued in other patient groups with affective dysregulation, such as patients with posttraumatic-stress disorder or bipolar disorder.

CONCLUSIONS

In the present functional neuroimaging study, we directly investigated the interference of task-irrelevant emotional information on an attention-demanding cognitive process in BPD. Our results demonstrate that BPD patients exhibit an atypical response of the right amygdala, which might be related to an increased implicit processing of irrelevant negative emotional information. Behaviorally, patients were able to compensate for this, possibly by enhanced recruitment of dACC and rACC structures involved in emotion regulation. The observed disorder-specific negative relationship between trait anxiety and ACC response in the emotional incongruent condition further suggests that anxiety might be an important factor determining the vulnerability of cognitive processing to emotional interference in Borderline patients.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/Human_Neuroscience/10.3389/fnhum.2013.00054/abstract

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Prefrontal control of attention to threat

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Attentional control refers to the regulatory processes that ensure that our actions are in accordance with our goals. Dual-system accounts view temperament as consisting of both individual variation in emotionality (e.g., trait anxiety) and variation in regulatory attentional mechanisms that act to modulate emotionality. Increasing evidence links trait variation in attentional control to clinical mood and anxiety disorder symptoms, independent of trait emotionality. Attentional biases to threat have been robustly linked to mood and anxiety disorders. However, the role of variation in attentional control in influencing such biases, and the neural underpinnings of trait variation in attentional control, are unknown. Here, we show that individual differences in trait attentional control, even when accounting for trait and state anxiety, are related to the magnitude of an attentional blink (AB) following threat-related targets. Moreover, we demonstrate that activity in dorso-lateral prefrontal cortex (DLPFC), is observed specifically in relation to control of attention over threatening stimuli, in line with neural theories of attentional control, such as guided activation theory. These results have key implications for neurocognitive theories of attentional bias and emotional resilience.

Keywords: anxiety, attentional blink, biased competition, cognitive control, emotion, facial expression, fMRI, prefrontal cortex

INTRODUCTION

Facial expressions provide critical information about potential threat. For example, angry expressions convey aggressive intent or disapproval, and fearful expressions convey the presence of environmental danger (Whalen, 1998). Accordingly, it is thought that threat-related faces receive a prioritized access to limited cognitive resources (Vuilleumier, 2005).

A normative function of such attentional prioritization is to help the organism respond effectively to significant danger (Lazarus, 1991). However, exaggerated biases in processing innocuous threat-related information are implicated in the etiology and maintenance of mood and anxiety disorders. Specifically, it has been suggested that the attentional system of clinically anxious individuals may be distinctively sensitive to and biased in favor of threat-related stimuli in the environment (Mathews and Mackintosh, 1998; Mogg and Bradley, 1998). While attentional bias to threat (i.e., differential attentional allocation toward threatening vs. neutral stimuli) is a robust finding in anxious populations (Bar-Haim et al., 2007 for meta-analysis), the mechanisms underpinning human variation in such bias remain unclear.

Perhaps unsurprisingly, given the well-established link between the emotional traits of neuroticism and behavioral inhibition and mood disorders (Kotov et al., 2010 for meta-analysis), much of the experimental work examining individual variation in attentional bias for threat has focused on trait negative emotionality. This work has shown increased attentional bias to threat in high anxious, non-clinical individuals (Bar-Haim et al., 2007 for meta-analysis). Likewise, neuroimaging studies of individual differences in facial threat processing have focused on individual differences in negative emotionality (e.g., trait anxiety, harm avoidance). Such studies have generally observed enhanced activity in the amygdala [a structure known to be critical for fearful responding and fear learning, (Johnson et al., 2009)] to unattended threat-related faces and scenes with increasing anxiety (Bishop et al., 2004; Ewbank et al., 2009) or harm avoidance (Most et al., 2006); and have led to the development of neuro-cognitive models positing a key role for the amygdala in mediating attentional bias (Vuilleumier, 2005).

According to "dual system" accounts, temperament is not only composed of individual variation in emotional reactivity (e.g., trait anxiety) but also comprises dispositional differences in self regulatory control mechanisms that act to modulate emotional reactivity (Posner and Rothbart, 2009). Trait attentional control reflects stable individual differences in the efficiency of executive attention. Key aspects of trait attentional control include the ability to flexibly control attentional allocation and to effortfully maintain or disengage attention (Posner and Rothbart, 2009; Bridgett et al., 2012).

There is increasing evidence that variation in attentional control prospectively predicts the development and maintenance of mood and anxiety disorders, both independently of and in interaction with negative emotionality (Oldehinkel et al., 2007; Verstraeten et al., 2009; Sportel et al., 2011; Van Oort et al., 2011; Yap et al., 2011). Further, twin studies show shared genetic influences on both trait attentional control and mood and anxiety symptoms (Lemery-Chalfant et al., 2008), suggesting links at an etiological level. Despite the clear protective effect of attentional

control on mood and anxiety symptomatology, previous research on threat-related processing has largely neglected the role of individual variation in attentional control in attenuating attentional bias to threat (but see Derryberry and Reed, 2002; Lonigan and Vasey, 2009) and in influencing prefrontal attentional control mechanisms (but see Gyurak et al., 2012). Recently, Cisler and Koster (2010) suggested that poor attentional control may be a potential mechanism mediating certain elements of attentional bias for threat, in particular, difficulties in "disengaging" attention from threat. Attentional dwell time paradigms, which allow measurement of the (dis)engagement of attentional resources from an initial target, by examining its impact on identification of a subsequent target, represent an ideal paradigm to test this hypothesis (Ward et al., 1997).

An extensively studied effect in the literature on rapid serial visual presentation (RSVP) is the attentional blink (AB) (Raymond et al., 1992). In studies of the AB a deficit in the identification of a second target, (T2), is typically observed, if that target appears in a rapid stream of distractors within ∼500 ms of an initial target (T1). The AB is thought to arise from attentional demands of T1 for selection, working memory encoding, episodic registration, and response selection, which prevents this high-level central resource from being applied to the second target when the time between the presentation of T1 and T1 (T1–T2 lag) is short (Dux and Marois, 2009). T1 processing also transiently impairs the redeployment of these attentional resources to subsequent targets (Dux and Marois, 2009). Recent studies show that a threat-related or negative T1 target (e.g., an angry face) relative to a neutral T1 can lead to an enhanced AB (i.e., greater difficulty in reporting the T2 identity) for a subsequent neutral T2 target (Mathewson et al., 2008; Koster et al., 2009; de Jong et al., 2010). If variation in regulatory temperament is important in controlling the bias toward threatening stimuli, then individual variation in attentional control should predict the impact of threat-related T1 stimuli on subsequent neutral T2 identification (i.e., the magnitude of the threat-related AB). Indeed, recently, we demonstrated behaviorally that individuals with poor attentional control showed impaired target processing in an RSVP task following presentation of an irrelevant emotional distractor, if the target appeared within 200 ms of the distractor (Peers and Lawrence, 2009). However, the neural basis of this effect remains unclear.

To bypass the sluggish temporal resolution of fMRI, here we move away from the standard AB paradigm and instead use the closely related 2-target paradigm, known to tap a common attentional limitation (Ward et al., 1997; Dux and Marois, 2009). In addition, T1 and T2 target stimuli were selected from different visual categories (faces and scenes, respectively) that activate anatomically distinct regions—fusiform face area (FFA) (Kanwisher et al., 1997), and parahippocampal place area (PPA) (Epstein and Kanwisher, 1998). This allowed us to examine, for the first time, the brain regions mediating the influence of variation in trait attentional control on the magnitude of the threat-related AB.

We predicted that weaker attentional control would be associated with an enhanced AB following a threat-related relative to a neutral T1 (Peers and Lawrence, 2009). Further, we predicted that regions of prefrontal cortex implicated in top-down attentional control (Miller and Cohen, 2001; Duncan, 2010) would mediate the influence of variation in trait attentional control on the magnitude of the threat-related AB. Specifically, we predicted that individuals with better attentional control would show greater prefrontal cortex activity on trials in which threatening information was successfully inhibited. Given the proposed role of the amygdala in prioritizing threat-related material (Vuilleumier, 2005), AB for threat may also be related to heightened amygdala activity. It is possible that any amygdala activity associated with the threat AB could also correlate with anxious temperament. This potential effect in the amygdala may occur either in addition to any attentional control effects or in the absence of such effects of control (Mathews et al., 2004; Bishop et al., 2007).

MATERIALS AND METHODS

PARTICIPANTS

Nineteen healthy volunteers (9 female, all right-handed, aged 19–40, mean age 27 years) with normal, or corrected to normal, vision participated. No participant had a history of neurological disease or head injury or was currently on medication affecting the CNS. One additional participant was excluded due to scanner malfunction. The study was approved by Suffolk Local Research Ethics Committee. All volunteers provided written informed consent and received a small honorarium.

Participants were selected from an initial sample of 55 volunteers who had completed a number of mood and personality questionnaires. These included the attentional control scale (ACS) (Derryberry and Reed, 2002), which contains 20 items such as "When I am trying to focus my attention, I am easily distracted" (reverse scored), rated on a four point Likert scale from 1 (almost never) to 4 (always); and the trait anxiety subscale of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) (seven items, score range 0–21). Two recent studies (Sulik et al., 2009; Bridgett et al., 2012) have demonstrated that both self-report measures of attentional control and performance on cognitive control tasks like the Stroop task are indicators of a single latent attentional control construct. The HADS anxiety scale has excellent reliability and correlates highly with other measures of trait anxiety such as the Spielberger (1983) Trait Anxiety Inventory (Bjelland et al., 2002) and the Carver and White (1994) Behavioral Inhibition Scale (BIS) (Brunborg et al., 2010). Selection from this sample was carried out on the basis of scores on these scales to ensure a range of attentional control and anxiety scores in the fMRI sample. ACS scores ranged from 45 to 70 (mean 57.1, SD 6.2) whilst HADS anxiety scores ranged from 2 to 18 (mean 5.5, SD 2.5) and were comparable to published norms of healthy populations (Crawford et al., 2001).

Immediately prior to scanning, participants completed a measure of state anxiety—the State form of the Spielberger State-Trait Anxiety Inventory (STAI) (range, 21–42, mean 29.92, SD 6.88) (Spielberger, 1983).

TASK

We modified the 2-target attentional dwell task, (based on Ward et al., 1997), to examine the influence of individual differences in attentional control and state/trait anxiety on the allocation

of attentional resources to threat-relevant (fearful) and neutral initial targets (T1), based on their impact on processing of a subsequent neutral T2 target (scene) following closely in time. Trials comprised a single masked fearful or neutral face followed by a single masked neutral scene (T2) presented in unpredictable locations (**Figure 1**).

STIMULI

Two classes of stimuli were used, faces and scenes, which have been shown to selectively activate distinct brain areas—FFA (Kanwisher et al., 1997) and PPA (Epstein and Kanwisher, 1998), respectively. The use of these classes of stimuli allowed us to localize the neural responses of the T1 and T2 stimuli and to assess the BOLD response to the T2 stimulus uncontaminated by T1 activity. The face stimuli were taken from two standardized databases: the Pictures of Facial Affect (POFA) and Caucasian images from the Japanese and Caucasian Facial Expressions of Emotion (JACFEE) (www.paulekman.com). They comprised eight females and seven males displaying both neutral and fearful expressions. Scene stimuli were selected from a large database of pictures of visual scenes which have previously been shown to evoke activation in regions of "parahippocampal place area" (PPA) (Epstein and Kanwisher, 1998). The stimulus set comprised 15 black and white images of "inside" locations and 15 images of "outside" locations. The "outside" locations were a mixture of natural landscapes (seven scenes) and urban locations (eight scenes). Face and scene masking stimuli were developed by superimposing examples of the faces or scenes on top of one another to produce a stimulus with low level contours, resembling the stimulus category, but which did not look like any of the individual items specifically. Previous work, with face stimuli at least, (Peers et al., 2005) has shown that this type of mask has similar psychometric properties to that of a pattern mask used with letters.

PROCEDURE

The experiment was run on a Dell desk-top computer. The participants viewed the stimuli via a Christie video projector seen through a mirror positioned 90 mm from their eyes. Participants' responses were collected using a 4-button serial response box. Experiments were programmed using E-prime (Psychology Software Tools, Inc.).

BLOCK STRUCTURE

The scanning session comprised 4 blocks of 128 trials. Each block was separated into three task conditions: either a single task "attend face only" condition, a single task "attend scene only" condition or a dual task, "attend both face and scene" condition. The single task conditions were included to ensure participants could selectively attend and that we could reliably detect FFA and PPA activity in this paradigm but are not discussed further. Each block of trials started with a sub-block (32 trials) of one of the single task conditions followed by two sub-blocks (64 trials) of the dual task condition, followed by a sub-block of the other single task condition. All participants completed the "attend face only" condition first in blocks 1 and 4 and the "attend scene only" condition first in blocks 2 and 3. Instructions displayed at the beginning of each task informed participants of the task to

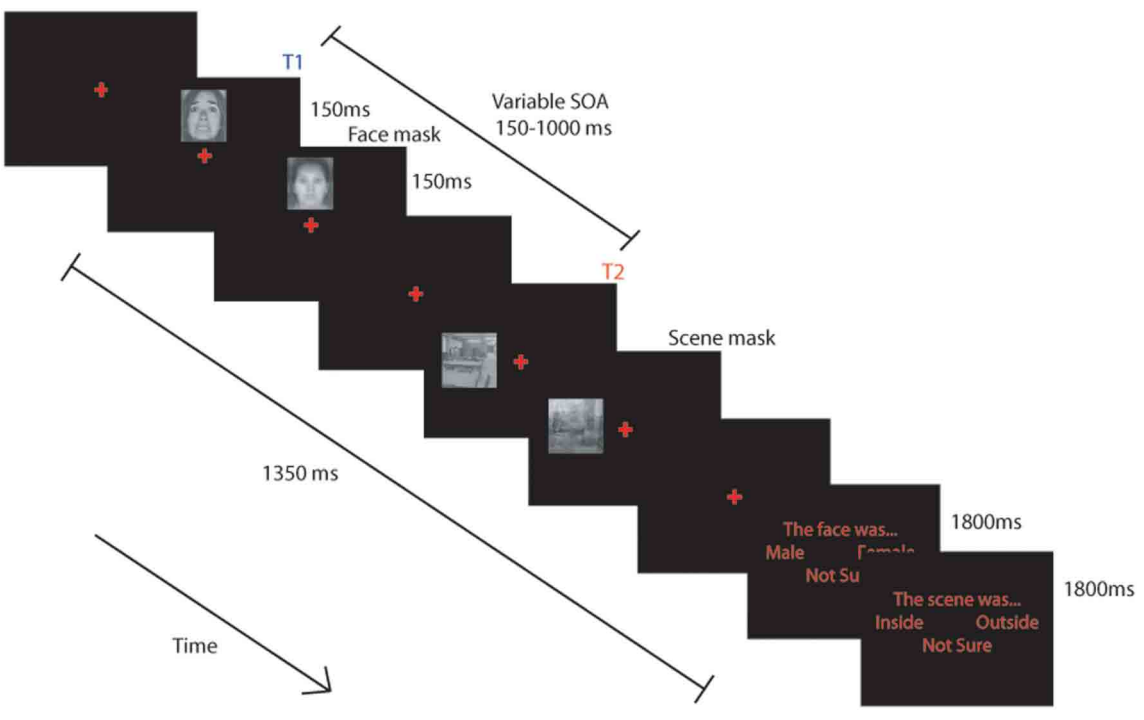

FIGURE 1 | Schematic representation of the task used. BOLD signal was modeled from the onset of each trial and included the response phase. (see text for details).

be completed. These appeared on the screen for 5 s with arrows pointing to the possible locations of targets and instructed the participant to "attend face," "attend scene," or "attend face and scene" (**Figure 1**).

TRIAL STRUCTURE

Each trial followed essentially the same pattern, with only the initial instruction and the response requirements manipulated across conditions. In the single task conditions participants were requested to attend only to either the face or the scene. When they were to attend to the face they were requested to indicate whether it was male or female and when they were to attend to the scene they were to indicate whether it was inside or outside. Trials commenced with presentation of a red central fixation cross ($\sim 0.7° \times 0.7°$) on a black screen for a variable duration between 150–300 ms. A target face stimulus ($\sim 2.5° \times 3.2°$) was then presented randomly $\sim 2.3°$ above or below the cross for 150 ms before being replaced by the face mask for 150 ms. After an stimulus onset asynchrony (SOA) of 150, 300, 450, or 1000 ms following presentation of the face, a scene ($\sim 3.2° \times 3.2°$) was presented randomly $\sim 3°$ to the left or right of the central cross for 150 ms before being replaced by a scene mask for an equivalent duration. The experiment was fully counterbalanced for face gender (male and female) and expression (fearful or neutral), scene location (inside or outside) and SOA.

TASK DEMANDS

In the "attend face only" and "attend face and scene" conditions, a response screen was presented 1350 ms after the onset of the face stimulus, which instructed participants to press the leftmost button to indicate a male face was present, the rightmost button to indicate a female face, and either of the central buttons if they were "not sure." The response screen was displayed for 1800 ms. The response screen for the scenes (in the "attend scene only" and "attend face and scene" conditions), presented 3150 ms after the onset of the face, instructed participants to press the leftmost button to indicate that the scene was "inside," the rightmost button for "outside" scenes, and either of the central buttons if they were "not sure." Responses were collected for both decisions during the 1800 ms presentation of the response screen. A 500 ms rest period was provided between trials.

Participants were instructed to only attend to the stimuli indicated by the task instruction, and to try to ignore other stimuli. They were informed that on each trial the face would appear first either above or below the cross and that the scene would then appear either to the left or right. They were told that in dual task trials they would always be requested to make the decision about the face before the decision about the scene and were requested to respond to items only when the response cue was present.

All participants attempted a short version of the task outside the scanner on a separate visit and were then given eight trials of practice on each of the tasks on the day of scanning outside the scanner.

LOCALIZER

An independent localizer scan was performed in the same participants to define FFA and PPA at the end of the scanning session. Participants were required to perform a 1-back matching task, in which four 16 s blocks of each stimulus type (scenes, neutral faces, fearful faces, and objects) were presented in a pseudo-random order. Each block consisted of 20 stimuli (18 different images and two repeats) presented centrally on the screen for 300 ms with a 500 ms gap between stimuli. Images were selected from those used in the dwell time task, with additional faces drawn from the NimStim Face Stimulus Set (Tottenham et al., 2009). Object stimuli were selected from a set of objects previously used in localizer tasks (Epstein and Kanwisher, 1998). Participants were instructed to view each of the stimuli and to press any button when they saw an immediate repetition of an image.

IMAGE ACQUISITION

MRI scanning was performed on a Siemens Tim Trio 3-Tesla MR scanner. Whole brain data were acquired with T2*-weighted echo-planar imaging (EPI) sensitive to blood oxygenation level-dependent (BOLD) contrast. Each image volume consisted of 32 sequentially acquired axial oblique 3 mm thick slices (interslice gap = 25%; FOV = 192 mm × 192 mm; matrix size = 64 × 64; flip angle = 78°; voxel bandwidth 2232 Hz/Px; TE 30 ms; TR 2000 ms). Four functional runs of the dwell time task, each of 380 volume acquisitions, were acquired together with one localizer run of 154 volumes. The first six volumes of each run were discarded to allow for T1 equilibration. T1 weighted structural images were acquired at a resolution of 1 mm^3.

IMAGE ANALYSIS

Data were pre-processed and analyzed using SPM5 (Wellcome Trust Centre for Neuroimaging, London, UK). Functional images were first corrected for motion by realigning all images with respect to the first, and for differences in slice timing by re-sampling all slices in time to match the middle slice. Each participant's structural image was co-registered to the mean of the realigned functional images and then segmented to separate out gray matter, which was normalized to the gray matter in a template image in MNI stereotactic space. The realigned EPI images were then spatially normalized using the structural normalization parameters, re-sampled into 3 mm cubic voxels and spatially smoothed with an 8 mm FWHM isotropic Gaussian kernel. A high-pass filter of 1/128 Hz was used to remove low-frequency noise, and an AR(1) model corrected for temporal autocorrelations.

Random effects statistical analysis was undertaken in two stages. In the first stage, event types for each functional run were modeled by convolving onset times of trials with a canonical hemodynamic response function. Thus, the BOLD signal for each trial captured both presentation and behavioral response. For the localizer task, a block-design was used. Parameters for each regressor were estimated using a subject-specific model, with movement parameters in the three directions of motion and 3° of rotation included as confounds, and covariates representing the mean session effects. Linear contrasts were used to obtain subject-specific estimates for each of the effects of interest. These estimates were entered into the second stage of analysis treating subjects as a random effect, using one-sample *t*-tests across

subjects. Additionally, regression analyses were carried out using participants' attentional control scores as a covariate.

We defined a priori regions of interest (ROIs) (see **Figure 2**) independently of the data under examination, based on a separate localizer scan or on coordinates reported in previous studies. Functional localizer ROIs (fROIs) (Kawabata Duncan and Devlin, 2011) for the fusiform face area (FFA; (176 mm^3 in extent) parahippocampal place area (PPA; left PPA 2304 mm^3, right PPA 3165 mm^3), superior temporal sulcus (STS; 2832 mm^3), and amygdala (2104 mm^3) were defined as the group-level peak clusters nearest the previously published co-ordinates for these regions in the independent localizer contrasts (faces > scenes and objects) (for FFA and amygdala), (fear faces > neutral faces) (for the STS) and (scenes > faces and objects) (for the PPA)[1]. These were created using the MarsBar toolbox (Brett et al., 2002). In addition an early visual cortex (earlyVC; 729 mm^3) f-ROI was created in the same way using a comparison of all visual events in the localizer against rest. Prefrontal ROIs sampled using 10 mm radius spheres centered on coordinates

[1]The robustness of these ROI's was examined by examining comparisons of the two single task conditions in the main experiment, these revealed the expected finding of significant activity in the FFA for the attend faces vs. attend scenes, and significant activity in the PPA and early VC for the reverse contrast.

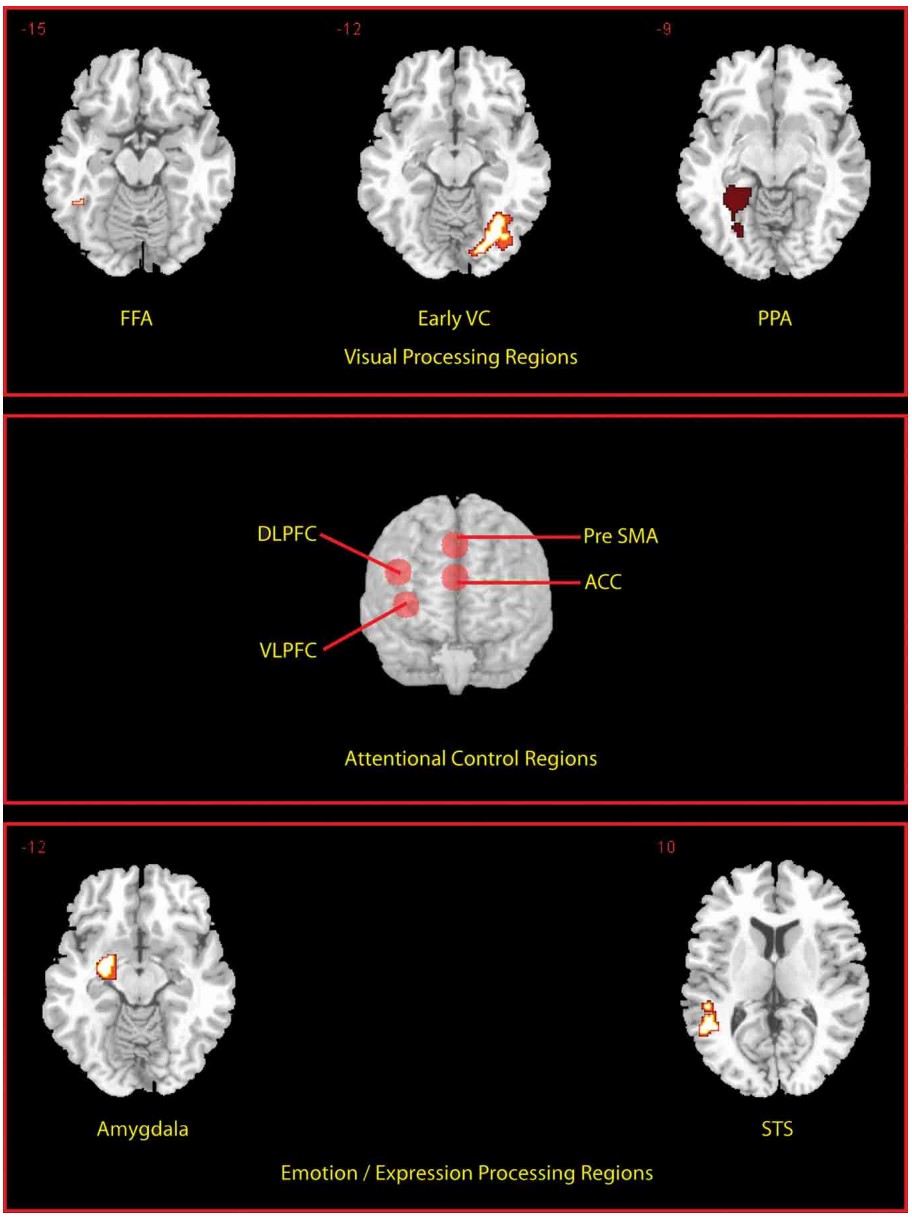

FIGURE 2 | Locations of a priori defined ROIs. Transverse slices for the peak voxel of each of the fROI's are shown. Prefrontal ROIs are rendered on to the anterior surface of a whole brain.

based on a meta-analysis of multiple-demand regions (Duncan, 2010) were produced for dorso-lateral prefrontal cortex; DLPFC center (±42, 24, 25), ventrolateral prefrontal cortex; VLPFC (±36, 18, 1), anterior cingulate; ACC, (0, 31, 21), and pre-supplementary motor area; pre-SMA (0, 20, 45). Activations are reported if they exceeded the family-wise error threshold of $p < 0.05$ small volume correction (SVC) for ROIs. Activations occurring outside the ROI were reported if they exceeded the family-wise error threshold of $p < 0.05$ whole-brain corrected and were larger than 10 voxels in extent.

RESULTS

BEHAVIORAL RESULTS

T1 performance

Proportion of correct reports of T1 target gender did not differ as a function of expression $t = -0.69$, df $= 18$, $p = 0.50$, with values of 0.73, and 0.74 for neutral and fearful faces, respectively. To ensure that T1 had been attended to, subsequent behavioral and fMRI analyses were restricted to trials in which T1 had been correctly reported (T2|T1).

Influence of emotion and attentional control on T2 performance

The temporal dynamics of attention were assessed using a repeated-measures ANCOVA with T1 expression (neutral vs. fearful) and T1–T2 SOA (150, 300, 450, and 1000 ms) as a function of ACS score (**Figure 3A**). This revealed a near significant effect of SOA $F_{(3, 51)} = 2.45.18$, $p\eta^2 = 0.13$, $p = 0.07$, as well as a significant T1 expression by SOA, $F_{(3, 51)} = 2.83$, $p\eta^2 = 0.14$, $p = 0.048$ interaction and crucially a three-way expression by SOA by ACS interaction, $F_{(3, 51)} = 3.12$, $p\eta^2 = 0.16$, $p = 0.034$, indicating a robust AB, an enhanced blink for threat relative to neutral faces, and a change in the profile of the blink associated to neutral and fearful faces with ACS score.

"High" and "low" ACS groups, based on median splits (with five participants falling on the median removed from the sample), were used to explore the three-way interaction. Trials were separated in to "short" (150, 300 ms) and "long" (450, 1000 ms) SOAs based on our previous findings that attentional control effects in RSVP were confined to SOA's less than 400 ms, (Peers and Lawrence, 2009). More broadly, interference effects in the dwell time paradigm are limited to T1–T2 SOAs of 400 ms or less, see Ward et al. (1997), Dux and Marois (2009). Paired samples *t*-tests comparing T2 accuracy for fearful vs. neutral face trials at "short" and "long" SOAs were carried out separately. These revealed a significant effect in the low ACS group at short SOAs $t = -3.09$, df $= 6$, $p < 0.05$, but no equivalent effect in the high ACS group $t = 0.81$ df $= 6$, $p = 0.45$, and no effect in either group at long SOAs (low ACS $t = -0.08$ df $= 6$, $p = 0.94$, high ACS $t = -1.75$, df $= 6$, $p = 0.13$), confirming a deeper AB for negative than for neutral T1 faces in the low ACS group only (**Figure 3B**). Corroborating the median split analysis, in the entire sample a significant correlation was observed between ACS score and threat-related relative to neutral AB magnitude at short lags $r = 0.61$, df $= 17$, $p < 0.01$.

Influence of emotion and trait and state anxiety on T2 performance

No significant correlations were observed between ACS and either state or trait measures of anxiety (STAIs, $r = -0.32$, $p = 0.18$; HAD-A, $r = -0.04$, $p = 0.87$) allowing us to examine effects of anxiety separately from those of ACS. Repeated-measures ANCOVAs carried out using STAI or HAD-A as covariates revealed significant effects of SOA but no other main effects or interactions, suggesting these anxiety measures did not influence performance. Crucially, the correlation between ACS and threat-related relative to neutral AB at short SOAs remained even when controlling for either STAIs ($r = 0.61$, df $= 16$, $p < 0.01$) or HAD-A ($r = 0.65$, df $= 16$, $p = 0.01$). Furthermore, HAD-A did not moderate the relationship between ACS and the threat relative to neutral AB at short SOAs ($t = 0.21$, df $= 15$, $p = 0.84$).

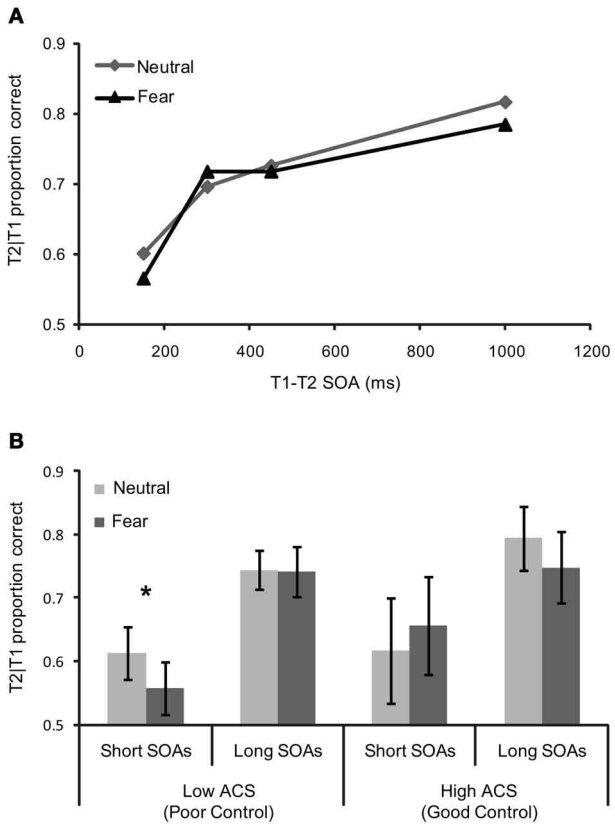

FIGURE 3 | Behavioral performance for (A) whole sample ($n = 19$)—T2 scenes task in the dual task condition as a function of the SOA between T1 (the face) and T2 (the scene), and (B) mean T1/T2 performance (±S.E.) for short and long SOAs as a function of T1 expression in high ($n = 7$) and low ACS ($n = 7$) groups. The significant effects are marked with an asterisk.

fMRI DATA

Behaviorally we observed a modulation of the AB to threat related faces by trait attentional control. The key aim of our study was therefore to examine the neural correlates underpinning T2 interference from T1 threat and the effect of trait attentional control in modulating this, and as such we focus our results on the relevant contrasts specified below. Behavioral performance on the task provides a means for us to compare neural activity associated with successful disengagement from the T1 stimulus (i.e., "unblinked"

trials or hits, when both T1 and T2 are correctly reported) with unsuccessful disengagement from T1 ("blinked" trials or misses). Data for short and long SOAs were collapsed as there were few blinked responses at long lags and thus any analyses would be underpowered.

ROI BASED ANALYSES

Below we report analyses carried out in each of our pre-defined ROIs, including the prefrontal (DLPFC, VLPFC, ACC, pre-SMA) regions, the category-selective FFA and PPA, and the amygdala and STS. Only significant results are reported.

Main effect of (un)successful dwell performance

No significant activity differences were seen in any of our ROIs when T2 hits vs. misses were compared for either the neutral-face or fear-face T1 conditions or no effects of attentional control were observed. The reverse contrast (misses vs. hits i.e., "attentional blinks") showed no differences in the neutral-face condition. However, increased activity in the pre-SMA ($x, y, z = 9, 21, 42$, $Z = 3.69$, Psvc $= 0.009$) was seen for fear-face misses vs. hits. A previous study (Yeung et al., 2006) of task switching found that activity in pre-SMA increased as a function of interference between tasks. Similarly here the increased pre-SMA activity may reflect increased demands on conflict or error monitoring processes when the fearful face disrupts T2 performance.

Effects of attentional control and emotion

Attentional control was not found to modulate activity in any region for neutral misses relative to hits ("neutral AB"). However, critically and in line with our predictions, it was found to modulate activity for both fearful misses relative to hits ("fear blinks") and fear blinks relative to neutral blinks. Strong negative correlations with attentional control were observed in right DLPFC for fear blinks (cluster peak $x, y, z = 45, 21, 21$, $Z = 3.09$, Psvc $= 0.04$) and fear blinks relative to neutral blinks (cluster peak $x, y, z = 42, 18, 21$, $Z = 3.6$. Psvc $= 0.01$), respectively. These negative correlations were also observed in STS, for both fear blinks (cluster peak $x, y, z = 45, -24, 0$, $Z = 3.16$, Psvc $= 0.04$) and fear blinks relative to neutral blinks (cluster peak $x, y, z = 45, -33, 0$, $Z = 3.01$, Psvc $= 0.05$).

To examine the strength of the relationships between activity in these areas and ACS whilst addressing the potential issues of non-independence (Kriegeskorte et al., 2010), average unstandardized beta values within each of the entire pre-defined ROIs were calculated for each individual. Significant correlations between ACS and DLPFC were observed for both fear blinks $r = -0.40$, df $= 17$, $p = 0.04$ and fear blinks relative to neutral blinks $r = -0.49$, df $= 19$, $p = 0.02$ (**Figure 4A**) and between ACS and STS, $r = -0.57$, df $= 17$, $p = 0.006$ for fear blinks and $r = -0.591$, df $= 17$, $r = 0.004$ for fear blinks relative to neutral blinks (**Figure 4B**).

Plots of high and low ACS groups suggest that the effects in both the DLPFC (**Figure 4C**) and STS (**Figure 4D**) are driven by relatively increased activity in the high ACS group when the target is perceived. Additionally whilst the high ACS group show reductions in activity when an item is blinked the low ACS group appear to show increases in activity. Following this up repeated-measures ANOVAs reveal significant performance by group interactions in both the DLPFC, $F_{(1, 11)} = 4.42$, $p\eta^2 = 0.29$, $p = 0.05$, and STS $F_{(1, 11)} = 10.28$, $p\eta^2 = 0.48$, $p = 0.008$, as well as a main effect of group in the DLPFC, $F_{(1, 11)} = 5.31$, $p\eta^2 = 0.33$, $p = 0.042$. Paired samples t-tests revealed no significant change in activity between seen and unseen T2 target trials in either the DLPFC ($t = -1.1$, df $= 5$ $p = 0.32$) or STS ($t = -1.95$, df $= 5$, $p = 0.11$) in the low ACS group. However, the high ACS group showed significantly reduced activity in both DLPFC ($t = 2.67$, df $= 6$, $p = 0.037$) and STS ($t = 2.63$, df $= 6$, $p = 0.039$) on fear trials when the target was blinked.

Effects of anxiety

In line with our behavioral findings, trait anxiety was not found to modulate activity in any of our regions, for fear blinks, or fear blinks relative to neutral blinks. Furthermore, negative correlations between average beta values in DLPFC and STS and ACS for fear blinks relative to neutral blinks remained when controlling for both trait anxiety (HAD-A) (DLPFC $r = -0.45$, $p = 0.03$, df $= 16$, STS $r = -0.57$, $p = 0.007$, df $= 16$) and amygdala reactivity (DLPFC $r = -0.47$, $p = 0.04$, df $= 15$, STS $r = -0.59$, $p = 0.007$, df $= 16$).

Direct comparison of the influence of attentional control on DLPFC vs. amygdala activity

Finally a William's test comparing the size of the correlations between ACS and DLPFC reactivity with that between ACS and amygdala activity showed a trend to significance ($t = 1.53$, df $= 15$, $p = 0.06$) suggesting individual differences in ACS were more strongly correlated with DLPFC than amygdala activity.

WHOLE BRAIN ANALYSES

Complementary whole brain analyses were carried out for each of the above contrasts. No significant activity was observed once whole brain correction was applied.

DISCUSSION

A wealth of research demonstrates attentional biases toward threat in anxiety disorders (Bar-Haim et al., 2007). The majority of research to date has focused on the role of trait negative emotionality (indexed by trait anxiety, behavioral inhibition, neuroticism, etc.) in such biases. There has been relative neglect of the role of individual differences in regulatory temperament dimensions, including attentional control (Posner and Rothbart, 2009), despite increasing evidence that variation in attentional control prospectively predicts the development and maintenance of mood and anxiety disorder symptomatology, both independently (additively), and in interaction with negative emotionality.

We found that variation in attentional control was related to attentional "disengagement" from threat. That is, people with lower ACS scores showed a selective enhancement of the AB following a threat-related vs. neutral T1. In concordance with this, activity in DLPFC was modulated by individual differences in attentional control for threat but not neutral ABs. Individuals with higher ACS scores showed greater DLPFC activity for unblinked threat trials, whilst the DLPFC did not show such a modulatory effect in those with lower ACS scores. We discuss these findings and their implications, in turn.

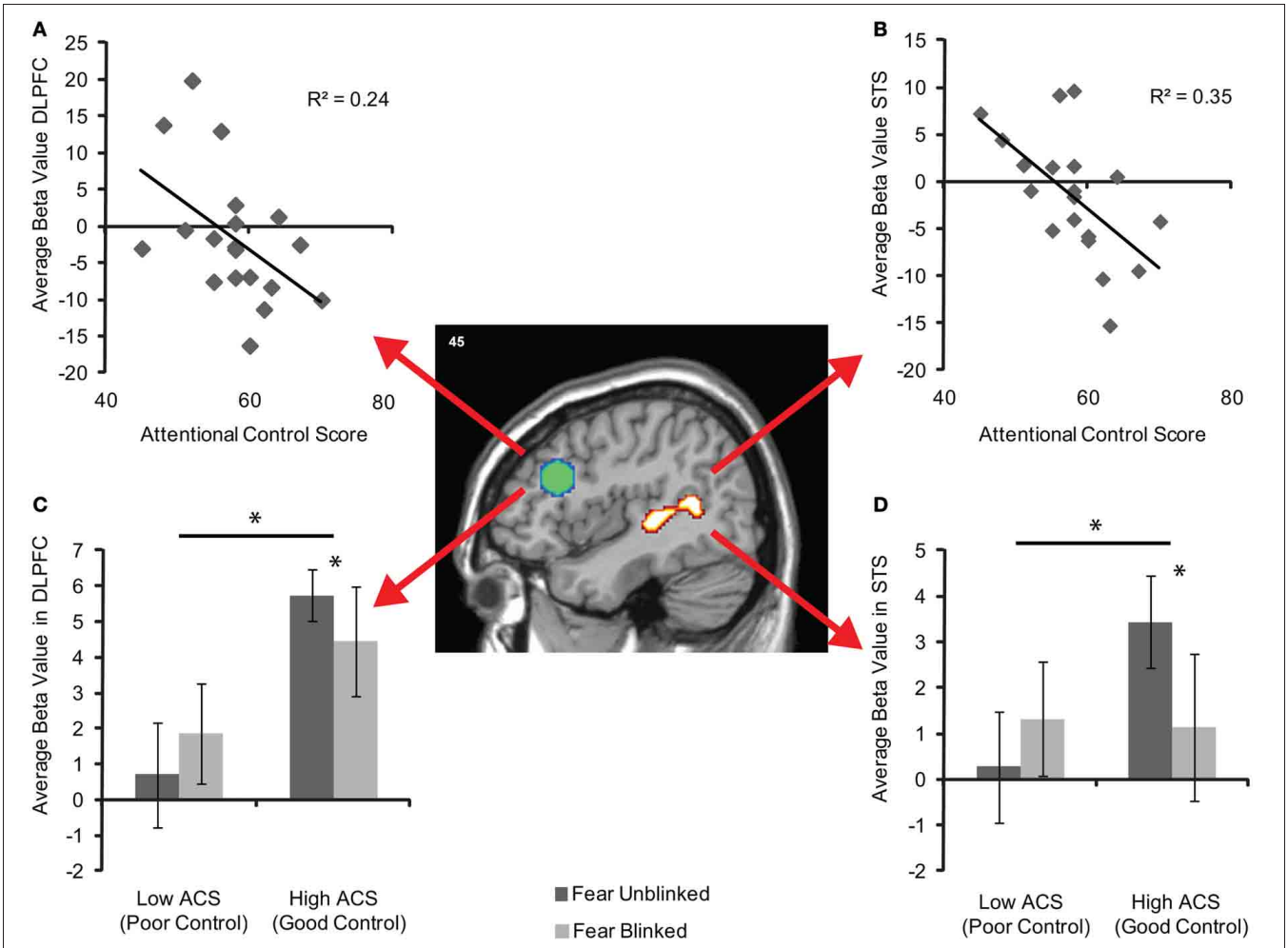

FIGURE 4 | Brain activity in the independently-defined DLPFC (green sphere based on previous coordinates) and STS (activity cluster based on localizer scan) regions of interest for fear blinked > unblinked trials. **(A)** Shows average unstandardized beta values in DLPFC, and **(B)** in STS, across participants as a function of attentional control score across the entire sample ($n = 19$). **(C)** Shows mean (±S.E.) activity in DLPFC, and **(D)** in STS for each AB trial type of the high ($n = 7$) and low ($n = 7$) ACS groups. The significant main effects and interactions are marked with an asterisk.

IMPACT OF VARIATION IN ATTENTIONAL CONTROL ON TEMPORAL ATTENTION TO THREAT

Theoretical accounts of the AB suggest that the reduction in T2 performance following T1 presentation is the result of transient increases in attentional demands required to allow for selection, working memory encoding, episodic registration and response selection of the T1 stimulus, meaning these resources are not available for redeployment to T2 at short T1–T2 intervals (Ward et al., 1997; Dux and Marois, 2009). de Jong et al. (2010) showed a larger AB following a threat related (vs. neutral) T1, that was independent of anxiety. They interpreted their findings as being consistent with an automatic prioritized processing of threat stimuli. However, whilst we too observe no effects of individual differences in anxiety on AB to threat, we found that a relatively larger AB for T1 threat stimuli was only seen in individuals with poor attentional control. In individuals with good attentional control, there was no advantage for threat-related T1 targets relative to neutral T1s in modulating the AB. Our findings are thus inconsistent with strong automaticity accounts of threat processing (see also Stein et al., 2010).

Findings by Stein et al. (2009) and Schupp et al. (2007) help clarify our results. Stein et al. found that the effect of fearful faces on the AB is task-dependent. When the emotional expression of the face stimuli had to be indicated, fearful faces induced a stronger AB than did neutral faces. However, with identical physical stimulation, the enhancement of the AB by fearful faces disappeared when participants had to judge face gender. They concluded that fearful faces attract more attentional resources, leaving less processing capacity for a T2 appearing at short T1–T2 intervals, but only when T1 emotion is selectively attended as part of current task goals. Consistent with this, Schupp et al. (2007) found, using high temporal resolution ERPs that implicit (task-irrelevant) emotion and explicit attention acted synergistically at later processing stages, but independently at perceptual encoding stages under RSVP conditions. Our results indicate that the emotional aspects of negative stimuli do not necessarily have to

be explicitly task relevant in order to attract greater attentional resources in individuals with poor temperamental attentional control.

According to models of attentional control, such as biased competition (Desimone and Duncan, 1995) and its development in guided activation theory (Miller and Cohen, 2001), individual differences in interference from task irrelevant information arise from variation in the ability to actively maintain representations that guide control of tasks. These representations provide a top-down excitatory bias to groups of neurons processing task-relevant information. Because their activity is heightened relative to neurons processing task-irrelevant information, distracting information has less effect. Thus, we might expect that individuals with poorer attentional control may have difficulty in actively maintaining or implementing task representations (Posner et al., 2002). In the absence of strong top down control, we argue, these individuals are unable to prevent emotion potentiated attention effects during the capacity-limited later-stage processing underlying the AB (Woodman and Vogel, 2008; Martens et al., 2010). This difficulty appears relatively specific however: poor attentional control was not associated with reduced dual-task performance *per se*, only impacting on performance in the presence of emotional T1 targets. This is presumably because top-down excitatory biases are especially important for exerting attentional control when task-irrelevant information can effectively compete with task-relevant information [in this case face gender (Kaul et al., 2011)] for priority in processing. Such mechanisms may be particularly relevant in order to focus task demands on face gender, as opposed to expression, processing, since emotion expression processing is relatively automatic (Pessoa, 2005).

Here we did not observe any effects of anxious temperament on T2 performance following threat-related T1s (Georgiou et al., 2005; Koster et al., 2006), nor did attentional control interact with anxiety to predict performance (Derryberry and Reed, 2002; Lonigan and Vasey, 2009). Because many studies linking anxiety traits to attentional biases focused on individuals with high trait vulnerability (Bar-Haim et al., 2007) it may be that our modestly sized sample did not have sufficient range to ascertain relations between anxious temperament traits and attentional bias for threat. Also, our study may not have been adequately powered to detect interactions between anxiety and attentional control. Further, we did not use individual concern-specific (Mathews and MacLeod, 1985), but rather generic threat stimuli. Despite these limitations, it should be noted, however, that most previous studies did not routinely measure trait attentional control. One conclusion from our results is that variation in emotional interference from task-irrelevant threat does not result solely (or perhaps even primarily) from variation that is unique to trait negative emotionality. Theoretical models of individual differences in attentional bias for threat, therefore, need to take into account the overlap between attentional control and negative emotionality, which are related, but distinguishable, facets of self-control (Evans and Rothbart, 2009). Such a suggestion does not preclude the possibility that anxiety may uniquely influence other aspects of threat processing. According to Cisler and Koster (2010), attentional control ability underlies difficulty in "disengagement" from threat, whereas anxiety influences facilitation. Our findings are consistent with these proposals if disengagement is operationalized as sustained resource allocation to task-irrelevant threat.

Our findings are perhaps most consistent with the cognitive model of Mathews and Mackintosh (1998). On this account, a balance between opposing influences of an anxiety-linked threat-evaluation system and an independent task control system determines the extent of any attentional bias for task-irrelevant threat. In situations where threat evaluation is low, the major influence on attentional bias is likely to be variation in the strength of top-down task control. Our findings do not support, however, a recent account positing that trait anxiety, even in unselected populations, is directly linked to impoverished recruitment of attentional control mechanisms to inhibit distractor processing (Bishop, 2009).

ROLE OF PREFRONTAL CORTEX IN CONTROL OF EMOTIONAL INTERFERENCE

Neurally we observed a modulation of activity in the DLPFC for blinked relative to unblinked trials that was specific to the condition in which a threat T1 was present. Individuals with better attentional control showed reduced DLPFC activity for fear blinks, an effect not seen in those with lower ACS scores. These data are consistent with neural models of cognitive control (Miller and Cohen, 2001; Duncan, 2010). These models suggest that DLPFC maintains the representations that guide control of tasks, providing excitatory feedback to groups of neurons processing task relevant aspects of the stimulus and reducing the influence of distracting information. Thus, for those with better control, who were less susceptible to the emotional AB, a blink following a fearful face was associated with reduced activity in DLPFC, a region previously linked to variation in selective attention and task control (Polk et al., 2008; Leber, 2010).

Interestingly, if anything, the reverse appears to be the case in those with poorer control. In those with lower ACS scores, increases in prefrontal activity alongside corresponding increases in STS [a region which responds to threat expressions (Pessoa et al., 2002)] were observed for fear AB trials, compatible with the notion that despite DLPFC engagement these individuals may be less able to suppress the processing of the task irrelevant "threat" aspects of the face stimulus (compare Eysenck and Derakshan, 2011). In line with these findings, Schmitz et al. (2010) found that attentional selection was redistributed in older adults from posterior perceptual to goal-directed DLPFC mechanisms due to an age-related "leakiness" of early perceptual features and thus enhanced demands on late-stage selection processes.

A few previous studies have observed increased recruitment of DLPFC in the presence of irrelevant emotional distraction. Compton et al. (2003) found increased DLPFC activity during an emotional Stroop task, and argued that this was related to increased engagement of task control mechanisms in the face of emotional distraction (see also Denkova et al., 2010). However, that study did not look at individual differences in attentional control, or link activity to performance. Bishop et al. (2007) found that variation in attentional control (controlling for anxiety) was related to DLPFC activity to threat-related distractors under low (but not high) perceptual load, and linked DLPFC activity to late selection mechanisms, but no effects of attentional

control on performance were seen in that study. Fales et al. (2008) found that depressed individuals showed reduced DLPFC activity when ignoring fear faces (relative to neutral) in a spatial attention paradigm, and a similar finding for high anxious individuals was reported by Bishop et al. (2004) (see also Most et al., 2006), but again, in the absence of anxiety effects on performance. Our findings are the first to demonstrate a clear role for DLPFC in attentional control over emotional interference effects, and link them to variation in temperamental attentional control.

Although not the primary focus of our experiment, and with the caveat that our fMRI sequence may not have been optimal to maximize signal from the amygdala, amygdala activity was not related to the presence of a threat-related AB. Further, we saw no modulation of amygdala activity for threat-related ABs by individual differences in attentional control or trait anxiety. The amygdala has often been considered to be a source of "emotional attention" underpinning attentional biases for threatening stimuli (Vuilleumier, 2005) and to underpin the influence of anxiety on such processing biases (Bishop et al., 2004), although previous studies have frequently found anxiety influences on the amygdala in the absence of performance effects.

It may be that the current paradigm (threat related T1) taps those aspects of attentional bias ("disengagement") that are most strongly associated with prefrontal control mechanisms (Cisler and Koster, 2010). Paradigms that emphasize e.g., rapid shifts of attention to threat-stimuli may be more effective in engaging the amygdala, which might mediate facilitated attention to threat (Cisler and Koster, 2010; but see Tsuchiya et al., 2009). For example, Carlson et al. (2009) found amygdala activity related to spatial orienting to masked fearful faces in a dot-probe task. Using a related paradigm to the current one, in which threatening (or arousing) T2 stimuli follow a neutral T1, it has been found that AB effects are smaller for emotional vs. neutral T2 stimuli (Anderson, 2005), especially in anxious individuals (Fox et al., 2005), and this effect may result from more rapid early detection of threat. An initial study (Anderson and Phelps, 2001) found that lesions encompassing (but not restricted to) the amygdala abolish the advantage for emotional T2s (Anderson and Phelps, 2001; see also Schwabe et al., 2011 for complementary fMRI findings, who also found evidence that regions of prefrontal cortex including dorsal anterior cingulate mediated the influence of a threat T1). However, a recent study in more selective amygdala lesioned individuals failed to replicate this effect (Bach et al., 2011). Moreover, a few recent fMRI studies have, in addition to the amygdala, implicated regions of prefrontal cortex in potentiating performance for threat related T2 stimuli. Lim et al. (2009) found that the influence of the amygdala on visual cortical responses for fear conditioned T2 stimuli was mediated via regions of the medial frontal gyrus (see also De Martino et al., 2009). Most notably, Piech et al. (2011) recently found that amygdala lesions did not influence performance on an emotional AB task in which emotional distractors impair the detection of subsequent targets (Most et al., 2005), a task which is sensitive to individual differences in attentional control (Peers and Lawrence, 2009). Hence it appears that attentional regions in prefrontal cortex are closely linked to both the interfering effects of a threat T1 on a neutral T2, and potentially, though we did not address the issue in the current study, the advantage of a threat T2 in the AB.

CONCLUDING REMARKS

To conclude, we find that variation in prefrontal control mechanisms is related to variation in the sustained processing of task-irrelevant threat in an attentional dwell-time paradigm. The protective role of frontally driven attentional control against irrelevant threat in a non-clinical population fits well with findings from longitudinal studies, which suggest that individual differences in attentional control predict later psychological adjustment (e.g., Van Oort et al., 2011). Our findings suggest a possible mechanism by which attentional control could contribute to the development of resilience, and more generally speak to the importance of studying individual variation in neural mechanisms of attentional control.

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The role of affect and reward in the conflict-triggered adjustment of cognitive control

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Adapting to changing task demands is one of the hallmarks of human cognition. According to an influential theory, the conflict monitoring theory, the adaptation of information processing occurs in a context-sensitive manner in that conflicts signal the need for control recruitment. Starting from the conflict monitoring theory, here the authors discuss the role of affect in the context of conflict-triggered processing adjustments from three different perspectives: (1) the affective value of conflict *per se*, (2) the affective modulation of conflict-triggered processing adjustments, and (3) the modulation of conflict adaptation by reward. Based on the current empirical evidence, the authors stress the importance of disentangling effects of affect and reward on conflict-triggered control adjustments.

Keywords: cognitive control, conflict adaptation, affect, reward, conflict monitoring

Cognitive control refers to the human ability to intentionally carry out a weak response in the face of a dominant but inappropriate response (e.g., Miller and Cohen, 2001). Within the last decade, there have been tremendous research activities within the neuroscientific and psychological disciplines, to learn more about the specific mechanisms underlying such cognitive flexibility. The first main challenge was to identify and understand the processes that inform the cognitive system when and how to implement control without relying on an omniscient homunculus (e.g., Monsell, 1996). In this context, Botvinick et al. (1999, 2001, 2004) in their influential conflict monitoring theory suggested a conflict monitoring module that automatically detects response conflicts in the ongoing processing stream by monitoring the amount of energy over conflicting response nodes.[1] The elegancy of the assumption is that such a conflict detector does not have to *know* the correct response; it simply registers the *need* for additional control as a consequence of the simultaneous activation of conflicting response tendencies. This conflict information is then sent forward to a control module that biases processing selectivity in accordance with the current task demands. Thus, the detection of a response conflict in trial_N triggers the increase of control in trial_{N+1}. Behaviorally, this assumption receives support from findings of sequential conflict adjustments in response interference tasks (see Egner, 2007), with the particular finding of smaller response interference effects in trials following conflict than in trials without prior response conflict (e.g., Gratton et al., 1992; Stürmer et al., 2002; Kerns et al., 2004). On a neuronal level, this conflict-control loop is implemented in the anterior cingulate cortex (ACC), that has repeatedly been shown to get activated by response conflicts (Botvinick et al., 1999; Cohen et al., 2000; MacDonald et al., 2000), and the dorsolateral prefrontal cortex (DLPFC) that presumably increases attention to task relevant information, thereby reducing the influence of task irrelevant information (e.g., Kerns et al., 2004; Kerns, 2006).

THE ROLE OF AFFECT, REWARD, AND AROUSAL IN SEQUENTIAL CONTROL ADJUSTMENTS

Recently, Botvinick (2007)—in an attempt to integrate findings showing that the ACC is not only activated by response conflicts but also by monetary loss, social exclusion, pain, and negative performance feedback (e.g., Rainville, 2002; Eisenberger et al., 2003; Nieuwenhuis et al., 2004; Singer et al., 2004)—suggested that the ACC might monitor for any aversive event in general. Aversive signals, from this perspective might then either serve as avoidance learning signal for future action selection (e.g., Holroyd and Coles, 2002; Nieuwenhuis et al., 2004) or as a trigger for processing adjustments (e.g., Kerns et al., 2004; Akcay and Hazeltine, 2007). The idea that the ACC monitors affective and cognitive conflict is not new and has been ascribed to segregate parts of the ACC, namely the ventral ACC for affective conflict and the dorsal ACC for cognitive conflict (Bush et al., 2000). Interestingly, in a recent review, Shackman et al. argued against this segregate model

[1] In this review we will focus on conflict-triggered control adjustments, but acknowledge that other signals, e.g., errors (Holroyd and Coles, 2002), may also induce processing adaptations.

and gathered strong evidence that the anterior midcingulate cortex (aMCC) is conjointly activated by negative affect, pain, and cognitive control (Shackman et al., 2011b). This fits perfectly with the idea that this region of the ACC serves the function of an aversive signal detector in general, as suggested by Botvinick (2007). Importantly, the claim of the ACC as an aversive signal detector has several implications: first, if the ACC registers aversive events, then conflicts *per se* should produce an aversive and thus, most likely affective signal, too. Second, aversive signals should trigger processing adjustments even in the absence of response conflicts if avoidance is not an option, whereas positive signals, on the other hand, should reduce processing adjustments.

So far, there exists evidence for both kinds of modulations. Accordingly, we will start our overview by reviewing the existing literature dealing with the affective value of conflict *per se*. Subsequently, we will present and aim to dissociate affective modulations from reward-based modulations of conflict-triggered processing adjustments, as previous affect and reward studies revealed inconsistent findings (see **Table 1** for an overview).

THE AFFECTIVE VALUE OF CONFLICTS

In two recent studies we could provide evidence in favor of the aversive nature of conflicts. In Dreisbach and Fischer (2012), we adopted the affective priming paradigm (Fazio et al., 1986; Fazio, 2001), in which positive and negative primes ease the affective evaluation of positive and negative targets accordingly. Here, congruent and incongruent Stroop color words served as primes (e.g., RED written in red or in green) and distinct positive and negative words and pictures (e.g., love vs. hate) as targets. Participants' task was to evaluate the affective valence of the targets. In two experiments we found a significant interaction of prime congruency and target valence, showing that—as predicted—positive targets were evaluated faster after congruent Stroop primes whereas negative targets were evaluated faster after incongruent Stroop primes. The results were taken as first empirical evidence for the aversive nature of conflicts. Comparable results have also been reported for action compatible common household objects (Brouillet et al., 2011). In a further study (Fritz and Dreisbach, in press) the authors investigated whether the aforementioned conflict priming effect was actually due to the affective valence inherent in conflict primes or simply due to a match of processing fluency between prime and target (since positive stimuli as well as congruent primes can be processed faster than negative stimuli and incongruent primes). To this end, only neutral targets were presented (words and Chinese characters) and participants' task was to judge spontaneously the affective valence of the (neutral) targets. Results of two experiments showed that neutral targets were more often judged as positive after congruent and more often as negative after incongruent Stroop primes. Results were thus perfectly in line with the first study (Dreisbach and Fischer, 2012) and show that conflict stimuli do not simply share basic processing characteristics with affective stimuli but do indeed convey affective valence.

More indirect evidence for the aversive nature of conflict comes from studies showing that conflict stimuli promote avoidance behavior (Kool et al., 2010; Schouppe et al., 2012). For example, in the Schouppe et al. study, participants were asked to move a manikin on the screen either toward or away from a Stroop color word (depending on its color). The Stroop color words could either be congruent (e.g., BLUE printed in blue), stimulus incongruent (BLUE printed in yellow with blue and yellow affording the same manual response) or response incongruent (BLUE printed in brown, with blue and brown affording different manual responses). The authors found a significant reduction of the stimulus interference effect in the avoidance condition as compared to the approach condition, leading them to the general conclusion that stimulus conflict stimulates avoidance behavior. Interestingly, however, this effect was not found for the response interference condition, which raises the question of how important response execution actually is in order to elicit aversive reactions.

To the best of our knowledge, so far there is only one study that failed to find evidence for the aversive nature of conflict. Schacht et al. (2010) used a Simon conflict task and registered peripheral reactions such as skin conductance response, pupil diameter, and corrugator activation, all of which are known to be sensitive to arousal or affect manipulations. Even though the typical Simon conflict was found in the behavioral data as well as in the N2 component of the EEG, a conflict signal frequently observed in response conflict tasks (Yeung et al., 2004), the peripheral measures were not differentially affected by conflict and non-conflict stimuli.

Taken together, most evidence so far speaks in favor of the aversive nature of conflicts. Furthermore, from the fact that in both conflict priming studies, the primes did not afford an overt response (Dreisbach and Fischer, 2012; Fritz and Dreisbach, in press), together with the observation that only stimulus incongruence (but not response incongruence) enhanced avoidance behavior (Schouppe et al., 2012), it seems that response execution is not that critical a process for conflict to occur as originally assumed in the conflict monitoring model where conflict is computed over the response layer (see Botvinick et al., 2001). However, Botvinick et al. themselves, in their seminal paper, already considered the possibility of conflict at representational levels other than the response level. In fact, they state that conflict in general occurs due to the "simultaneous activation of incompatible representations" (Botvinick et al., 2001, p. 68). In any case, empirical evidence so far suggests that the aversive character of conflicts does not necessarily depend on response execution.

AFFECTIVE MODULATION OF SEQUENTIAL CONFLICT ADAPTATION

Another, closely related line of research deals with the effect of affect on conflict-triggered processing adjustments. The first group to directly address this issue was van Steenbergen et al. (2009). They administered an arrow flanker task and arbitrarily presented gain or loss cues after a random subset of trials. It turned out that gain cues following conflict trials eliminated the typical conflict adaptation effect and altered early visual distracter processing (see also van Steenbergen et al., 2012). This was taken as evidence that these cues counteracted the assumed negative valence of conflicts (see Dreisbach and Fischer, 2012; Fritz and Dreisbach, in press) as a consequence of which the conflict adaptation was abolished. These results fit well with a recent study

Table 1 | Overview of the reviewed studies.

	Paradigm	Manipulation (affect/reward)	Results
AFFECTIVE VALUE OF CONFLICTS			
Brouillet et al. (2011)	Affective priming task	Action-compatible/incompatible trials served as primes prior to the evaluation of target valence	Action-compatible/incompatible trials facilitated the evaluation of positive/negative targets
Dreisbach and Fischer (2012)	Affective priming task	Stroop-trials served as primes prior to the affective evaluation of affective targets	Incongruent/congruent primes facilitated the evaluation of negative/positive targets
Fritz and Dreisbach (in press)	Affective priming task	Stroop-trials served as primes prior to the affective evaluation of neutral targets	Incongruent/congruent primes increased negative/positive judgments of neutral targets
Kool et al. (2010)	Demand selection task	Decks of cards with either high vs. low probability of a task switch served as manipulation of cognitive demand	Anticipated cognitive demand resulted in avoidance behavior (cards from the high demand pile are chosen less frequently)
Schacht et al. (2010)	Simon task	Simon conflict as trigger signal for physiological responses	Simon conflict elicited an EEG conflict signal (N2), but no effects in peripheral measures
Schouppe et al. (2012)	Stroop task	Approach/avoidance responses toward/away from congruent and incongruent Stroop stimuli	Reduced stimulus conflict in the avoidance condition
AFFECTIVE MODULATION OF CONFLICT ADAPTATION			
Dreisbach and Fischer (2011)	Fluency task	Number words written in easy and hard to read fonts served as manipulation of aversiveness to trigger processing adjustments	Non-fluent words triggered sequential processing adjustments without any response conflict
Padmala et al. (2011)	Face Stroop	Phasic affect induction (presentation of neutral vs. highly negative pictures with high arousal levels between trials)	Eliminated conflict adaptation for negative pictures (increased interference after conflict trials)
van Steenbergen et al. (2010)	Flanker task	Sustained mood-induction with controlled valence-arousal dimensions	Stronger conflict adaptation after the induction of sad and anxious mood states (irrespective of arousal)
MODULATION OF CONFLICT ADAPTATION BY PERFORMANCE NON-CONTINGENT REWARD			
Stürmer et al. (2011)	Simon task	Random presentation of reward and loss cues (Experiment 1)	No effect of random reward and loss cues on conflict adaptation (Experiment 1)
van Steenbergen et al. (2009)	Flanker task	Monetary gain or loss cues as arbitrary reward feedback presented after flanker trials	Gain cues after conflict eliminated conflict adaptation
van Steenbergen et al. (2012)	Flanker task	Monetary gain or loss cues as arbitrary reward feedback presented after flanker trials	Gain cues after conflict eliminated conflict adaptation, conflict related theta oscillations sustained longer after loss
MODULATION OF CONFLICT ADAPTATION BY PERFORMANCE CONTINGENT REWARD			
Braem et al. (2012)	Flanker task/Task switching	Performance-dependent reward cues (for fast and correct responses) were presented in 25% of flanker trials (Experiment 1). Switching between Simon and Flanker task (Experiment 2)	Increased conflict adaptation following reward cues (Experiment 1). Reward increased switch costs following conflict trials (Experiment 2)
Stürmer et al. (2011)	Simon task	Performance-dependent reward (for 25% fastest responses) and loss cues (25% slowest responses) (Experiment 2)	Increased conflict adaptation following reward cues (Experiment 2)

from our laboratories (Dreisbach and Fischer, 2011) where we manipulated the fluency of processing of target words by using either easy or hard to read font. Since there is ample evidence that the experienced ease of processing serves as an affective signal (see Winkielman et al., 2003 for a review), this manipulation made it possible to look into sequential processing adjustments, triggered by aversive (i.e., non-fluent) stimuli even in the absence of any response conflict. Participants had to judge the magnitude of number words that were either written in an easy (fluent) or hard (non-fluent) to read font. Indeed, a significant adaptation effect was found: the fluency effect (non-fluent minus fluent) was smaller after non-fluent than after fluent trials, suggesting that the aversive valence of non-fluent stimuli indeed triggered processing adjustments in terms of increased effort even without

any response conflict involved. Finally, in a further study by van Steenbergen et al. (2010), the authors orthogonally manipulated mood and arousal between participants and found a significant interaction of mood and conflict adaptation in the Flanker task: more specially, subjects experiencing calm (positive, low arousal) and happy mood (positive, high arousal) showed a reduced conflict adaptation effect and subjects in a sad (negative, low arousal) and anxious mood (negative, high arousal) showed enhanced conflict adaption, respectively. Arousal, thus, did not have any effects.

So far, results seem to suggest that negative mood (van Steenbergen et al., 2010) or negative stimuli (Dreisbach and Fischer, 2011) promote sequential processing adjustments while positive mood and unconditional reward eliminate conflict adaptation (van Steenbergen et al., 2009, 2010, 2012). However, there is one study that does not fit into the picture. Padmala et al. (2011) presented neutral or highly negative pictures with high arousal levels between picture-word Stroop trials and found reduced conflict adaptation following highly arousing negative pictures. This result obviously stands in sharp contrast to the stronger conflict adaptation effect found by van Steenbergen et al. under sustained negative affect. It remains a question of future research, whether this discrepancy is due to the differential affect manipulations (e.g., Shackman et al., 2006, 2011a) or due to different arousal levels between studies.

MODULATION OF CONFLICT ADAPTATION BY REWARD

In contrast to arbitrary reward contingencies of the van Steenbergen studies, reward *conditional* on actual task performance, which on first glance might be closely related to positive affect, appears to have the opposite effects on sequential conflict adaptation. Braem et al. (2012), presented reward cues for fast and correct responses in a flanker task[2] and hypothesized that conditional reward should *enhance* active connections between stimulus and response, as a consequence of which, conflict adaptation should be amplified. This prediction was derived from the associate learning account of conflict adaptation (Verguts and Notebaert, 2008, 2009; see also Thorndike, 1927). In their theory, and in line with Botvinick's theory, the authors also assume that the ACC detects conflict over the output layer. However, instead of directly sending signals to the DLPFC, the ACC projects to the locus coeruleus which then sends a Hebbian learning signal presumably via increases in noradrenergic activity over the cortex as a consequence of which connections between currently active representations within DLPFC are strengthened. More generally spoken, it is suggested that conflict triggers an autonomic arousal response that strengthens currently active task representations in working memory. By this, the model is able to produce not only the typical sequential conflict adaptation data pattern in terms of reduced response interference on trials following conflict trials, but also the typically observed increased conflict induced switch costs, an effect that the original conflict model would not necessarily predict (Braem et al., 2012, Experiment 2). Importantly, for the present purpose, the associative-learning model predicts that positive signals should serve as a reinforcement signal thereby *strengthening* connections between currently active task representations and thus rather *amplify* conflict-triggered processing adjustments. Results were in line with the authors' hypotheses: conflict adaptation was enhanced following reward cues. Interestingly, within such a reward context, on trials without reward cues *no* conflict adaptation was observed. Unfortunately, no punishment condition was included which makes it hard to decide which of the two data patterns, the *absence* of conflict adaptation following no reward in a reward context or the *presence* of conflict adaptation following reward cues, drives the effect. Support for the authors' interpretation in terms of reinforcement learning[2] comes from the fact that the effect was further modulated by the sensitivity toward reward (reward responsiveness). Obviously, the results of Braem et al. (2012) thus stand in sharp contrast to the van Steenbergen et al. (2009, 2012) studies reported above. The only difference between both is that the gain cue in van Steenbergen's studies (2009, 2012) was entirely random and not contingent on behavior whereas in the Braem study, participants were informed that on a predetermined number of trials, reward could be earned for fast and correct responding. This might have rendered the gain cue in the van Steenbergen study a simple positive affect cue that counteracted the aversive nature of the preceding conflict, whereas the reward cue in Braem's study informed about the successful completion of the preceding response. Fortunately, there is one study that directly investigated the effects of random versus performance contingent gains and losses on conflict adaptation. Stürmer et al. (2011) presented gains and losses randomly and non-contingent on the respective performance in one experiment and compared the effects to a second experiment, where only the 25% fastest and the 25% slowest responses were rewarded and punished, respectively. It turned out that random gains and losses had *no* effect on conflict adaptation (Experiment 1). In contrast, gains contingent on fast and correct responses enhanced conflict adaptation effects (Experiment 2). The results of the Stürmer et al.'s study (2011) are thus in line with Braem et al. (2012) and support the assumption that reinforcement that is contingent on actual task performance *strengthens* active connections between task representations and the response. Random gains irrespective of task performance, on the other side, seem to have either *no* effect (Stürmer et al., 2011) or even *eliminate* conflict adaptation (van Steenbergen et al., 2009). This assumption might also explain other seemingly contradictory results from two studies in a related field using the AX continuous performance task, a paradigm well-suited to study processes of goal maintenance. Whereas positive affective pictures (non-contingent on performance) *reduced* goal maintenance (Dreisbach, 2006), in the same paradigm, reward *improved* goal maintenance (Locke and Braver, 2008).

Given the findings of eliminated conflict adaptation under positive affect and unconditional reward (van Steenbergen et al., 2009, 2010, 2012) one might therefore speculate that random

[2]In fact, the authors ran a second experiment using the task switching paradigm. For task switching, the associative learning account (ALA) makes the opposite prediction, namely that reward increases switch cost following conflict trials because on task switches following a reward signal, the formerly relevant task and its corresponding connections become strengthened as a result of the reinforcement signal. The results were as predicted by ALA.

gains also produce a positive affective reaction that, however, is different from the affective reaction due to successful task performance. One possible reason could be that performance contingent reward increases the intrinsic reinforcement signal in response to correct responses (Satterthwaite et al., 2012). Such intrinsic reinforcement signals are elicited within the ventral striatum, a key region of dopamine function, are stronger for correct than incorrect responses and are further modulated by task difficulty (Satterthwaite et al., 2012). From this perspective, successful conflict resolution itself might trigger an intrinsic reinforcement signal (cf. Braem et al., 2012) which might further be enhanced by external performance contingent reward. Non-contingent random reward, on the other side, might actually counteract the intrinsic reward signal, as it presumably conveys the information that task performance is not a value by itself.

CONCLUSION

In this short review, we first presented evidence from different studies showing that conflict signals are registered as aversive. Second, while most studies seem to suggest that positive affect as subjective experience *reduces* conflict-triggered processing adjustments, reward as motivational manipulation, on the other hand, appears to *strengthen* conflict-triggered processing adjustments. Based on the present literature we suggest that unconditional reward reduces the intrinsic reward signal whereas positive mood reduces the negative experience of the conflict signal—both resulting in reduced conflict adaptation. Reward contingent on task performance, by contrast, may serve as reinforcement signal, enhancing bindings between currently active task representations and response—thereby increasing conflict adaptation. We thus close this review by emphasizing the importance to empirically and theoretically disentangle effects of affect and reward on processes of cognitive control in general and on conflict adaption in particular (see also Chiew and Braver, 2011).

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When does hearing laughter draw attention to happy faces? Task relevance determines the influence of a crossmodal affective context on emotional attention

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Prior evidence has shown that a person's affective context influences attention to emotional stimuli. The present study investigated whether a crossmodal affective context that is induced by remembering an emotional sound modulates attention to visual emotional stimuli. One group of participants had to remember a positive, negative, or neutral sound during each trial of a dot probe paradigm. A second group of participants also had to encode the valence of the sound. The results revealed that attention was preferentially deployed to stimuli that were emotionally congruent to the affective context. However, this effect was only evident when participants had to encode the valence of the affective context. These findings suggest that a crossmodal affective context modulates the deployment of attention to emotional stimuli provided that the affective connotation of the context is task-relevant.

Keywords: affective context, crossmodality, emotional attention, task relevance, attentional bias

INTRODUCTION

Numerous studies have shown that attention is preferentially deployed to emotional stimuli (Yiend, 2010) and especially to negative events (Rozin and Royzman, 2001). Many researchers assume that this negativity bias has an evolutionary benefit since the detection of dangers is relevant to survival (Öhman et al., 2001). Recently, however, it has been discussed whether a negativity bias is adaptive at all times (Rothermund et al., 2008). For instance, strong attentional biases to negative events are related to deficits in psychological adaptation (Gotlib et al., 2005). Some researchers have therefore suggested that the deployment of attention needs to be flexible in order to be adaptive (Brandtstädter and Rothermund, 2002).

In line with this reasoning, Smith et al. (2006) have proposed that the accessibility of positive or negative information in memory determines whether positive or negative emotional stimuli receive preferred attention. According to their reasoning, highly accessible negative information signals to watch out for dangers, thereby tuning attention to negative events. In contrast, the accessibility of positive information indicates safety, permitting attention to be deployed to positive, potentially rewarding information. Indeed, when participants had to indicate the valence of predominantly positive or negative pictures, they preferentially deployed attention, as indexed by the P1 component of event-related brain potentials (ERPs), to pictures that matched the valence of the majority of the presented pictures. Relatedly, Becker and Leinenger (2011) have found an attentional bias toward mood-congruent stimuli. Moreover, Grecucci et al. (2010) have demonstrated that holding emotional words in memory directs attention toward emotionally congruent faces.

The present research aims to extend these findings by investigating whether inducing an affective context in one modality affects the allocation of attention to affectively congruent and incongruent stimuli presented in a different modality. For instance, when a person hears laughter, is attention biased to visually presented positive stimuli such as happy faces? In real life, people are constantly presented with information in different modalities and people appear to integrate this information (Spence, 2007). Moreover, previous research has shown that visual and auditory emotional stimuli modulate the attentional capture of an acoustic probe, as indexed by ERP-component P3, in a similar way (Keil et al., 2007). In addition, Brosch et al. (2008) have shown that emotional sounds bias the deployment of visual attention to neutral events that appear in the same spatial location. However, these findings do not allow any conclusions on whether auditory emotional information biases attention toward certain classes of information such as emotionally congruent visual input. Observing a general, modality-independent influence of an affective context on emotional attention would suggest that contextual influences on emotional attention are much more powerful and general than when they would be limited to an exact

overlap of the modality of affective context and emotional input (cf. Scherer and Larsen, 2011).

To address this issue, we investigated whether remembering an emotional sound modulates the attentional bias toward positive and negative visual stimuli. Moreover, we included a condition in which we examined whether the influence of an auditory context is dependent on the task relevance of the affective connotation of the context. Recent evidence has suggested that affective information needs to be task-relevant in order to observe an attentional bias toward emotional stimuli (e.g., Hahn and Gronlund, 2007; Van Dillen et al., 2011). If this is also true for contextual influences, then the impact of an affective context should depend on the relevance of the affective connotation for the task at hand.

We used a standard dot probe task (MacLeod et al., 1986) to examine the orienting of attention. In this task, one positive or negative picture and one neutral picture were simultaneously presented at two different locations on the screen, immediately followed by a target. If individuals selectively orient to a certain type of picture, responses should be faster to targets at the location previously occupied by that picture. Before each trial of the dot probe task, we induced an affective context by presenting a neutral, positive, or negative sound that participants had to remember during the dot probe task trial. According to prominent models of attention (Folk et al., 1992; Folk and Remington, 1999), attentional capture is contingent upon top–down settings and holding information in working memory therefore biases attention toward matching information (Downing, 2000; Soto et al., 2007). After each trial of the dot probe task, we presented a second sound that could match the first sound or not. In experimental condition one, participants had to indicate whether the sound was identical or different to the first sound. In condition two, they had to indicate whether the sounds were identical or the valence of the sounds was the same. By this, participants had to encode both the sound and its affective connotation.

MATERIALS AND METHODS

PARTICIPANTS

Sixty native Dutch-speaking volunteers (30 women) took part in the experiment. Thirty participants were assigned to experimental condition one and thirty different participants were assigned to condition two. Participants had normal or corrected-to-normal vision. Participants were naive as to the purpose of the experiment and gave written consent prior to participating in this study.

APPARATUS AND MATERIALS

Auditory stimuli

Forty-five sounds were either extracted from a sound database (http://www.findsounds.com) or were recorded for the goal of this study. Sounds consisted of screaming, mumbling, or laughing for a duration of 1500 ms and were performed by women. We restricted both sound and visual stimuli to women to avoid gender influences. We selected eight sounds for each sound category (positive, neutral, or negative), based on a pretest in which 47 participants provided ratings of valence and arousal on a seven-point Likert scale ranging from "1" (not at all pleasant/arousing) to "7" (completely pleasant/arousing). Participants also assessed whether a man or a woman had produced the sound. Three criteria were used for the selection: first, all participants had to rate the producer of the sound as female. Second, the valence ratings had to be significantly different between all sound categories (positive: $M = 5.16$, $SD = 0.23$; neutral: $M = 3.63$, $SD = 0.14$; negative: $M = 1.54$, $SD = 0.21$), $ps < 0.001$. Finally, we sought to match the arousal level of positive sounds ($M = 4.63$, $SD = 0.24$) as closely as possible to the arousal level of negative sounds ($M = 4.96$, $SD = 0.42$), $t_{(7)} = 2.28$, $p = 0.06$.

Visual stimuli

Twenty-four pictures were obtained from the Karolinska Directed Emotional Faces database (KDEF, Lundqvist et al., 1998). We selected eight pictures for each picture category (positive, neutral, or negative). These pictures depicted a woman's face with either a laughing, neutral, or fearful expression. Selection was based on a validation study by Goeleven et al. (2008) in which participants evaluated all pictures on emotional content and provided ratings for arousal on a nine-point Likert scale ranging from "1" (not at all arousing) to "9" (completely arousing). We selected the pictures on the basis of two criteria. First, the emotional expression of the picture was unambiguously correctly identified (i.e., more than 70% correct identifications) in the study by Goeleven et al. Second, the arousal level of positive pictures ($M = 3.93$, $SD = 0.30$) matched that of negative pictures ($M = 3.83$, $SD = 0.32$), $t_{(7)} = 0.86$, $p = 0.42$.

PROCEDURE

Experimental condition 1

The experiment was programmed and presented using the INQUISIT Millisecond Software package (Inquisit 3.0, 2011) on an Asus Barebone Computer. The participants sat at a viewing distance of 54 cm from a 17-in. CRT monitor. On each trial, participants had to perform a combination of an auditory working memory task with a visual dot probe paradigm. First, an emotional sound was presented over a headphone and participants were asked to remember this sound. Then, participants saw two cue pictures and had to respond to a subsequently presented visual target in the dot probe task. Immediately afterward, participants were tested on their recollection of the remembered sound by judging whether a second sound presented at this point was identical or different to the first sound.

As can be seen in **Figure 1**, each trial started with a white fixation cross ($0.6 \times 0.6°$ visual angle) presented against a black background in the middle of the screen. After 500 ms an emotional sound appeared along with the message "Remember this sound!" on the screen. Hereafter, two white rectangles ($14.4 \times 13.5°$ visual angle) were presented, one to the left and one to the right of the fixation cross. The middle of each of these two peripheral rectangles was 8.8° visual angle from fixation. After 500 ms, two pictures ($12.1 \times 11.3°$ visual angle) were presented in the rectangles for 500 ms. After picture offset, a target appeared. The target consisted of a black square ($1.1 \times 1.1°$ visual angle) presented in the center of one of the two rectangles. Participants had to respond by pressing one of two keys (target left: "4"; target right: "5") with the index and middle finger of their right hand on the numeric pad of an AZERTY keyboard. After a response was registered or 1500 ms had elapsed since target onset, a fixation

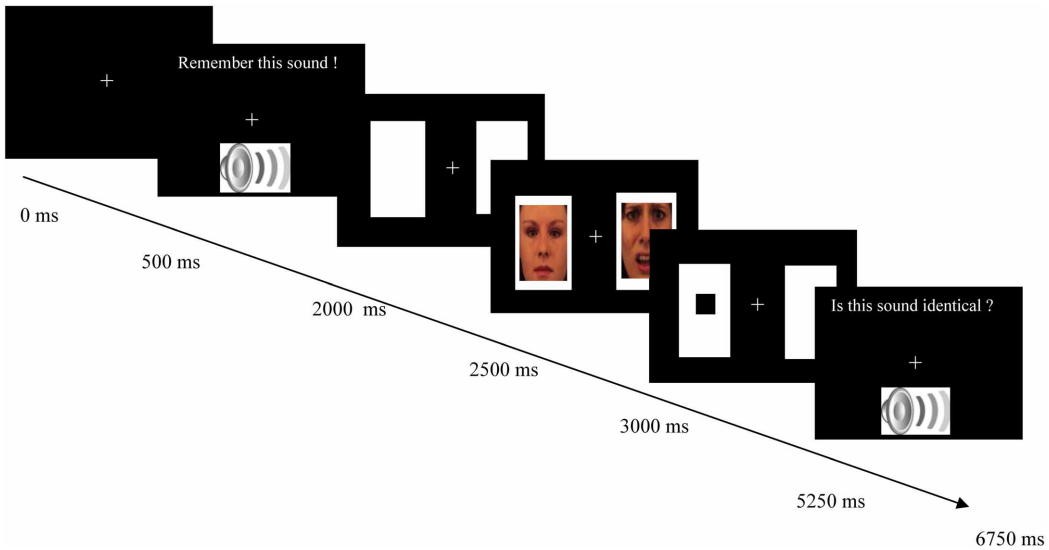

FIGURE 1 | Schematic overview of an example trial of the combined auditory working memory task and the visual dot probe task. The first two boxes displays the onset of the working memory task in which an emotional auditory stimulus was presented that had to be remembered during the dot probe task. The next three boxes depict the dot probe task in which the presentation of two cues was followed by a probe (black square) that had to be localized. The cues consisted of an emotional picture, which was either positive or negative, and a neutral picture. The last box displays the second part of the working memory task in which a second auditory stimulus was presented. Participants had to evaluate whether this sound was identical to the first sound. In experimental condition 2, a different message appeared together with the second sound, namely "Is this sound similar in emotional value?" on half of the trials. On those trials participants had to evaluate whether the second sound was similar to the first sound in valence, which was either neutral, negative, or positive.

screen was presented for 750 ms. Then, a second emotional sound was presented together with the question "Is this sound identical?" Participants had to respond by pressing one of two keys (same sound: "s"; different sound: "d") with the index and middle finger of their left hand. Feedback on the correctness of their response was displayed for 500 ms after their response had been registered. The next trial started after 500 ms.

The experiment consisted of 180 trials, 60 trials for each of the three sound valence categories: neutral, positive, or negative. The second sound was identical to the first sound in 50% of all trials. In each trial of the dot probe task a neutral picture was presented with an emotional picture. The emotional picture was positive in half of the trials and negative in all other trials. Half of all trials were *emotionally valid* trials, in which the target appeared on the same side as the emotional picture. In *emotionally invalid* trials the target appeared on the same side as the neutral picture. The order of trials was determined randomly and for each participant separately. Participants in condition 1 performed 10 practice trials and participants in condition 2 performed 12 practice trials.

Experimental condition 2

The procedure for participants in condition 2 was identical to condition 1, except that the memory task changed. During the instructions, participants were informed that sounds would be positive, neutral, or negative in emotional value. In 50% of the trials, participants had to indicate whether the second sound matched the first sound in affective connotation. The message that appeared on the screen was "Is this sound similar in emotional value?". Participants had to respond to this question in the same way as in condition 1 (i.e., same emotional value: "s"; different emotional value: "d"). To prevent those participants would only memorize the valence but not the sound, participants indicated whether the sounds were identical or different in the other half of the trials. By this, participants did not know which judgment they had to perform until the second sound was presented.

RESULTS

DATA PREPARATION

Trials with errors on the dot probe task were removed (experimental condition 1: 1.13%, condition 2: 3.90%). Participants made errors on the working memory task in 4.21% of the trials in condition 1 and in 8.00% of the trials in condition 2. Dot probe trials followed by an erroneous response in the working memory task were not included in the analyses. Data from one participant in the first condition were removed because she gave an incorrect response in over 25% of dot probe task trials. In line with Vogt et al. (2011a), dot probe reaction times (RTs) shorter than 150 ms or larger than three standard deviations above the individual mean were discarded as outliers (condition 1: 3.86%; condition 2: 0.01%).

OVERALL EFFECTS

We performed a 3 (sound valence: positive, neutral, negative) × 2 (picture valence: positive, negative) × 2 (emotional cue validity: valid, invalid) repeated measures analysis of variance (ANOVA) on the RTs of the dot probe task with experimental condition as between-subject factor. There was a significant effect

of emotional cue validity, $F_{(1, 57)} = 4.80$, $p = 0.014$, $\eta_p^2 = 0.08$. Responses were faster on trials in which the target appeared at the location of the emotional picture ($M = 434$ ms, $SD = 15$ ms) than at the location of the neutral picture ($M = 442$ ms, $SD = 14$ ms). Importantly, the main effect of experimental condition did not reach significance, $F_{(1, 57)} = 0.50$, $p = 0.48$, $\eta_p^2 = 0.01$, meaning that reaction times in experimental condition 1 were not different from condition 2 (condition 1: $M = 428$ ms, $SD = 20$ ms; condition 2: $M = 448$ ms, $SD = 20$ ms). The main effects of sound valence and picture valence did not reach significance either, Fs < 2.50, ps > 0.11.

The interaction between picture valence and emotional cue validity was significant, $F_{(1, 57)} = 6.50$, $p = 0.013$, $\eta_p^2 = 0.10$. Responses were faster on trials where the location of the negative picture was valid ($M = 432$ ms, $SD = 15$ ms) compared to invalid ($M = 445$ ms, $SD = 14$ ms), $t_{(58)} = 3.32$, $p = 0.002$. This was not the case for positive pictures (valid: $M = 435$ ms, $SD = 15$ ms; invalid: $M = 440$ ms, $SD = 14$ ms), $t_{(58)} = 1.00$, $p = 0.32$. The analyses also revealed a significant interaction between emotional cue validity and experimental condition, $F_{(1, 57)} = 8.21$, $p = 0.006$, $\eta_p^2 = 0.13$. Responses were faster in condition 2 on emotionally valid trials ($M = 438$ ms, $SD = 26$ ms) compared to emotionally invalid trials ($M = 458$ ms, $SD = 23$ ms), $t_{(29)} = 2.73$, $p = 0.011$. This difference was not significant in condition 1 (valid: $M = 429$ ms, $SD = 21$ ms; invalid: $M = 427$ ms, $SD = 19$ ms), $t_{(28)} = 0.98$, $p = 0.33$.

Crucially, the interaction between sound valence, picture valence, and emotional cue validity was significant, $F_{(2, 114)} = 6.91$, $p = 0.001$, $\eta_p^2 = 0.11$. This interaction was qualified by the four-way interaction effect between sound valence, picture valence, emotional cue validity, and experimental condition, $F_{(2, 114)} = 4.00$, $p = 0.021$, $\eta_p^2 = 0.07$. None of the other two- or three-way interactions reached significance, Fs < 1.15, ps > 0.31.

To further explore the latter effect, we conducted separate ANOVAs for each condition. The three-way interaction between sound valence, picture valence, and emotional cue validity was significant in the second condition, $F_{(2, 58)} = 7.52$, $p = 0.001$, $\eta_p^2 = 0.21$, but not in the first, $F_{(2, 56)} = 0.62$, $p = 0.54$, $\eta_p^2 = 0.02$. We then calculated indices for attentional biases by subtracting RTs on emotionally valid trials from RTs on emotionally invalid trials for positive and negative pictures separately (Vogt et al., 2010) (see **Table 1**; **Figure 2**). In condition 1, significant attentional biases to either positive or negative pictures were not revealed, ts < 1.40, ps > 0.19. In contrast, in condition 2, participants displayed a significant attentional bias to positive pictures when they remembered positive sounds ($M = 35$ ms, $SD = 76$ ms), $t_{(29)} = 2.79$, $p = 0.009$, and to negative pictures when they remembered negative sounds ($M = 24$ ms, $SD = 47$ ms), $t_{(29)} = 2.47$, $p = 0.019$. The negativity bias was also significant when participants remembered neutral sounds

Table 1 | Mean attentional bias indices for positive and negative pictures and standard deviations (in ms) as a function of emotional sound valence in condition 1 and 2.

	Affective context					
	Positive sound		Neutral sound		Negative sound	
	M	*SD*	*M*	*SD*	*M*	*SD*
CONDITION 1						
Positive pictures	−6	26	−10	25	−9	20
Negative pictures	1	21	6	26	1	25
CONDITION 2						
Positive pictures	35*	76	13	53	4	37
Negative pictures	10	31	32*	49	24*	47

Note: Attentional bias indices for positive and negative pictures were calculated by subtracting RTs on emotionally valid trials from emotionally invalid trials

*$p < 0.05$.

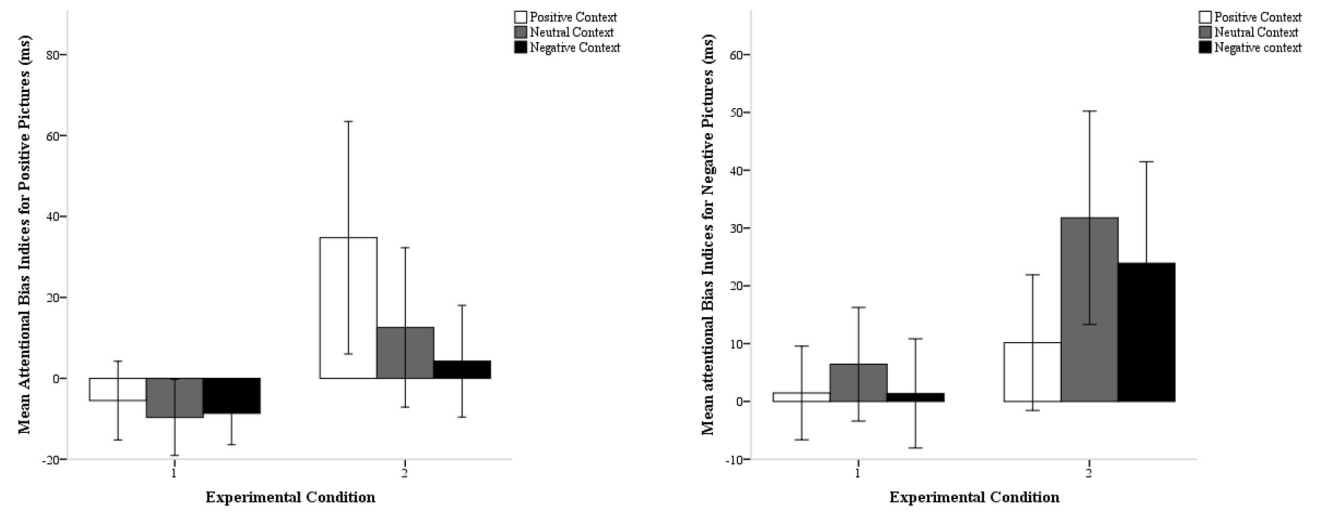

FIGURE 2 | Mean attentional bias indices for positive pictures and negative pictures as a function of sound valence (positive, neutral or negative) in both experimental conditions. Error bars represent 95% confidence intervals.

($M = 32$ ms, $SD = 49$ ms), $t_{(29)} = 3.52$, $p = 0.001$. Planned comparisons revealed that the positivity bias was significantly larger in a positive context ($M = 35$ ms, $SD = 77$ ms) than in a negative ($M = 4$ ms, $SD = 37$ ms) or neutral context ($M = 13$ ms, $SD = 53$ ms), $ts > 2.31$, $ps < 0.03$. The negativity bias was significantly larger in a negative context ($M = 24$ ms, $SD = 47$ ms) than in a positive context ($M = 10$ ms, $SD = 31$ ms), $t_{(29)} = 2.40$, $p = 0.023$, but not significantly larger than in a neutral context ($M = 32$ ms, $SD = 49$ ms), $t_{(29)} = -0.87$, $p = 0.39$.

DISCUSSION

The aim of this study was to examine whether remembering emotional sounds modulates the allocation of spatial attention to emotional pictures. We found that an affective auditory context modulated visual attention, when the task required participants to encode the valence of the affective context. In this case, more attention was allocated to pictures that were emotionally congruent to the remembered sound. These results add to recent findings on the influence of affective contexts on attention (Smith et al., 2006; Grecucci et al., 2010).

Importantly, in our study, the influence of an affective context extended to another modality. The auditory affective context modulated attention to positive or negative emotional stimuli in the visual modality. This suggests that the influence of an affective context on emotional attention involves representations that are modality-independent and abstract rather than modality-specific (Peelen et al., 2010). In a neuroimaging study by Klasen et al. (2011), the ventral Posterior Cingulate Cortex (vPCC) has been suggested as a neurological basis for supramodal representations of emotion. These supramodal representations of emotion information would be independent from low-level sensory features and help to determine the relevance of incoming information, through links with the Anterior Cingulate Cortex (ACC) (Vogt, 2005). Alternatively, however, the present results might also be compatible with an embodiment view on the representation of emotional categories. Horstmann 2010; (Horstmann and Ansorge, 2011) has argued that emotional categories are represented as *multimodal* sensory-motor representations. Therefore, activating an emotional category in one modality causes the activation of information belonging to this category in other modalities. However, the fact that emotional sounds do only bias attention to matching visual input when the emotional value had to be encoded in an abstract way (i.e., by encoding its valence) suggests that an abstract representation of the emotional information is crucial in order to find these effects on the attentional level. Future evidence is needed to examine the processes underlying crossmodal emotional effects.

Moreover, previous studies (e.g., Smith et al., 2006) only investigated the effects of an affective context by exposing one group of participants to a positive context and another group to a negative context. Our data provide evidence that an affective context influences attention on a trial-by-trial basis. This shows that context effects do not require enduring and rather static mood manipulations (e.g., Becker and Leinenger, 2011), but that attention can be influenced flexibly by the short-term availability of emotional information in memory.

Notably, the affective context did not influence attention when participants did not encode the valence of it. In contrast to previous studies in which participants performed a dot-probe task with emotional cues (e.g., Mogg and Bradley, 1998; Yiend, 2010), participants did not show any bias to emotional stimuli in this condition. However, participants simultaneously had to perform a second task in our study. Previous studies have shown that the processing of emotional stimuli is impaired when another, non-affective task demands cognitive control (e.g., Hahn and Gronlund, 2007; Van Dillen and Koole, 2009). Importantly, the results of this study also show that the affective connotation of the affective context has to be encoded in order to find an influence of the affective context. Interestingly, in the study by Smith et al. (2006), participants had to categorize the emotional pictures that were used for inducing an affective context in terms of emotional valence (i.e., whether they were positive or negative). These results add to findings suggesting that attentional biases to emotional events are driven by the relevance of emotional information for participant's current goals or tasks (e.g., Hahn and Gronlund, 2007). For instance, Vogt et al. (2011b) found that experiencing disgust is accompanied by an attentional bias to disgusting pictures, but also by a bias to pictures representing cleanliness, suggesting that the goal to alleviate an aversive emotion drives emotional attention in aversive emotional states. These findings propose that the influence of emotion on cognition is not automatic in the sense of goal-independent and stimulus-driven as often assumed (e.g., Öhman et al., 2001). In contrast, they corroborate the idea that representations in memory which are determined by the individual's current goals and tasks guide emotional attention (Grecucci et al., 2010; Pessoa and Adolphs, 2010; Vogt et al., 2012; see also Folk et al., 1992).

Four potential limitations of the study need to be addressed. First, we induced a crossmodal affective context by presenting auditory stimuli and measured attentional allocation to visual emotional stimuli. Future research should address whether our findings generalize to other combinations of sensory modalities (e.g., the influence of a visual affective context on attention to auditory or multimodal emotional stimuli). Second, as neutral pictures were presented twice as often compared to positive or negative pictures, the general attentional bias to emotional events can be interpreted as evidence for enhanced attention toward novel stimulus classes (Yantis and Jonides, 1984). However, this cannot explain why an affective context modulates attention toward emotionally congruent stimuli. Third, in line with prior studies using dot probe paradigms and emotional cues we implemented a cue exposure time of 500 ms (e.g., Bar-Haim et al., 2007). Therefore, our results do not allow conclusions on the fast and early allocation of attention. Importantly, we might therefore have measured disengagement-related processes rather than attentional engagement. Moreover, with an exposure time of 500 ms, we cannot exclude possible influences of strategic processes on attention. However, we assume that the use of specific strategies on attention to the emotional cues was limited because emotional cues predicted the correct location of the target in only half of the trials. Fourth, our results revealed that participants preferentially attended to negative stimuli in a neutral context. Though this observation is in line with previous research

suggesting that attention is generally biased toward negative stimuli (Baumeister et al., 2001), it could suggest that contextual influences are not the sole determinant of attentional allocation to emotional stimuli. However, we cannot exclude that participants experienced neutral events and negative facial expressions as emotionally congruent. Future research should further examine how both characteristics of emotional stimuli and the affective context distinctively contribute to emotional attention.

In sum, the present study suggests that attention to emotional stimuli is influenced by affective contexts provided that the emotional value of this context is task-relevant. We hope that future research will further explore the relation between emotion and attention across modalities.

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The neurobiology of emotion–cognition interactions: *fundamental questions and strategies for future research*

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Recent years have witnessed the emergence of powerful new tools for assaying the brain and a remarkable acceleration of research focused on the interplay of emotion and cognition. This work has begun to yield new insights into fundamental questions about the nature of the mind and important clues about the origins of mental illness. In particular, this research demonstrates that stress, anxiety, and other kinds of emotion can profoundly influence key elements of cognition, including selective attention, working memory, and cognitive control. Often, this influence persists beyond the duration of transient emotional challenges, partially reflecting the slower molecular dynamics of catecholamine and hormonal neurochemistry. In turn, circuits involved in attention, executive control, and working memory contribute to the regulation of emotion. The distinction between the 'emotional' and the 'cognitive' brain is fuzzy and context-dependent. Indeed, there is compelling evidence that brain territories and psychological processes commonly associated with cognition, such as the dorsolateral prefrontal cortex and working memory, play a central role in emotion. Furthermore, putatively emotional and cognitive regions influence one another via a complex web of connections in ways that jointly contribute to adaptive and maladaptive behavior. This work demonstrates that emotion and cognition are deeply interwoven in the fabric of the brain, suggesting that widely held beliefs about the key constituents of 'the emotional brain' and 'the cognitive brain' are fundamentally flawed. We conclude by outlining several strategies for enhancing future research. Developing a deeper understanding of the emotional-cognitive brain is important, not just for understanding the mind but also for elucidating the root causes of its disorders.

Keywords: ACC, amygdala, anxiety, depression, emotion control and regulation, EEG/ERP, fMRI, PFC

Until the 20th century, the study of **emotion** and **cognition** was largely a philosophical matter. Although modern perspectives on the mind and its disorders remain heavily influenced by the introspective measures that defined this earlier era of scholarship, the last several decades have witnessed the emergence of powerful new tools for assaying the brain and a remarkable acceleration of research to elucidate the interplay of emotion and cognition (Pessoa, 2013; Braver et al., 2014; Dolcos and Denkova, 2014). The immediate goal of our Special Research Topic was to survey recent advances in understanding how emotional and cognitive processes interact, how they are integrated in the brain, and the implications for understanding the mind and its disorders (Okon-Singer et al., 2014b; **Figure 1**). Here, we consider ways in which this rapidly growing body of work begins to address some more fundamental questions about the nature of cognition–emotion interactions, highlighting key points of consensus. By focusing attention on the most important outstanding questions, we hope to move the field forward. First, we hope that answers provided by our contributors will stimulate discussion. Second, we hope that juxtaposing clear theoretical goals against the current state of the science will motivate new and impactful research. Clearly, our understanding of emotion–cognition interactions remains far from complete. Indeed, we are reminded of Ekman and Davidson's comment: "There are many promising findings, many more leads, [and] a variety of theoretical stances" (Ekman and Davidson, 1994, p. 3). We conclude by outlining several strategies for enhancing future research. With continuing effort, some of the fundamental questions will be decisively addressed. In some cases, the questions themselves will evolve, as in other areas of the biological sciences.

HOW DOES EMOTION INFLUENCE COGNITION?

Many of our contributors highlighted evidence that the perception of emotionally-salient stimuli and the experience of emotional states can profoundly alter cognition.

EMOTIONAL CUES GRAB EXOGENOUS ATTENTION AND MODULATE ENDOGENOUS ATTENTION

There is abundant evidence that emotionally-salient cues—snakes, spiders, and angry faces—strongly influence attention

FIGURE 1 | The top 200 scientific terms used in the Special Research Topic. The typeface is scaled proportional to the frequency of each term. The figure was generated using http://www.wordle.net.

(e.g., Siman-Tov et al., 2009; Lerner et al., 2012; Pourtois et al., 2013; Carretié, 2014) the ability to selectively respond to relevant aspects of the environment while inhibiting potential sources of distraction and competing courses of action (Desimone and Duncan, 1995; Miller and Cohen, 2001). The focus of attention is determined by the pervasive competition between exogenous (often termed 'stimulus-driven' or 'bottom–up') and endogenous (often termed 'goal-directed' or 'top–down' attention) mechanisms (Egeth and Yantis, 1997).

With respect to exogenous attention, a number of contributors describe new evidence that emotionally-charged cues are more attention-grabbing than neutral cues and highlight recent efforts to specify the mechanisms underlying this bias (Holtmann et al., 2013; McHugo et al., 2013; Peers et al., 2013; Stollstorff et al., 2013). Along the way, McHugo et al. (2013) provide a useful tutorial on methods for quantifying the capture of attention by emotional cues (e.g., dot-probe, emotional attentional blink).

Importantly, attention can also be guided in an endogenous fashion by internal goals (e.g., rules, instructions, and plans) as well as moods and motivational states (e.g., feeling anxious or hungry). Mohanty and Sussman (2013) discuss evidence demonstrating that emotion and motivation can guide attention to congruent cues (e.g., food when hungry). In particular, they show that subcortical regions proximally involved in determining value and orchestrating emotional states (e.g., amygdala, substantia nigra) can facilitate endogenous attentional processes implemented in frontoparietal regions and can strengthen activation in relevant sensory regions (e.g., face-selective regions of the fusiform gyrus when anticipating an angry face). This extended network, encompassing sensory, attentional, and emotional circuits, facilitates the rapid detection of emotionally-significant information.

ATTENTIONAL BIASES TO EMOTIONAL CUES ARE PLASTIC

Anxious individuals tend to allocate excess attention to threat and there is evidence that this cognitive bias causally contributes to the development and maintenance of anxiety disorders (Bar-Haim et al., 2007; Hakamata et al., 2010; MacLeod and Mathews, 2012; Singer et al., 2012; Van Bockstaele et al., 2013; MacLeod and Clarke, 2015). Extreme anxiety and behavioral inhibition often emerges early in development (Fox et al., 2005a; Blackford and Pine, 2012; Fox and Kalin, 2014), raising important questions about the degree to which childhood attentional biases to threat are plastic and can be influenced by early experience (Shechner et al., 2012; Bar-Haim and Pine, 2013; Henderson et al., 2014; MacLeod and Clarke, 2015).

Here, Kessel et al. (2013) provide tantalizing correlative evidence that emotional biases in attention are influenced by caregiver style. Using an innovative combination of behavioral and electrophysiological techniques, they show that although temperamentally inhibited children allocate more attention to aversive cues, this is reduced among the offspring of parents who rely on encouragement, affection, and appreciation to reinforce positive behavior. A key challenge for future research will be to test whether targeted interventions aimed at cultivating more salubrious parenting styles have similar consequences. Prospective designs (e.g., before and after exposure to a negative life event or trauma) would provide another powerful approach for understanding the plasticity of emotional attention (Admon et al., 2009, 2012).

EMOTION EXERTS PERSISTENT EFFECTS ON ATTENTION

Emotions are often conceptualized as fleeting and most imaging and psychophysiological studies of emotion focus on transient responses to punctate emotional challenges. Yet, there is growing evidence that emotions can have lingering consequences for

cognition and behavior (Davidson, 2004; Suls and Martin, 2005; Hajcak and Olvet, 2008; Qin et al., 2009).

Here, for example, Vaisvaser et al. (2013) combined serial measures of emotional state, neuroendocrine activity, and resting-state brain activity to demonstrate that alterations in amygdala–hippocampal functional connectivity persist for more than 2 h following exposure to intense social stress. Along conceptually similar lines, Morriss et al. (2013) use electrophysiological techniques to show that endogenous attention is potentiated for several seconds following brief emotional challenges (i.e., standardized emotional images).

Several threads of evidence highlight the importance of understanding the mechanisms that govern variation in the speed of recovery from emotional perturbation. In particular, individual differences in emotional recovery (a) strongly predict personality traits, such as neuroticism, that confer increased risk of developing psychopathology (e.g., Blackford et al., 2009; Schuyler et al., 2014); and (b) are sensitive to adversity and chronic stress exposure, two other well-established risk factors (Lapate et al., 2014). An important challenge for future research will be to identify the neural circuitry and molecular pathways that support the enduring effects of emotion on endogenous attention and to clarify the intermediate processes that link variation in emotional recovery to mental health and disease.

DISTRACTING EMOTIONAL CUES READILY PENETRATE THE GATE PROTECTING WORKING MEMORY

Endogenous attention is tightly linked with working memory (Postle, 2006; D'Esposito and Postle, 2014; Sreenivasan et al., 2014). The transient representation of task-sets, goals, and other kinds of information in working memory plays a crucial role in sustaining goal-directed attention and guiding behavior in the face of potential distraction (Miller and Cohen, 2001). In short, information held in working memory is a key determinant of our momentary thoughts, feelings, and behavior. Importantly, the capacity of working memory is strongly determined by the ability to filter or gate irrelevant information (Vogel et al., 2005; McNab and Klingberg, 2007; Awh and Vogel, 2008).

Here, Stout et al. (2013) used a well-established electrophysiological marker of working memory storage (i.e., contralateral delay activity; Vogel and Machizawa, 2004) to show that threat-related distractors (i.e., task-irrelevant fearful faces) are stored in working memory and that this filtering inefficiency is exaggerated in dispositionally-anxious individuals. Once in working memory, emotional information is poised to hijack endogenous attention and other kinds of top–down control mechanisms. From a psychiatric perspective, this emotional gating deficit may help to explain the persistence of heightened negative affect (e.g., anxiety, sadness) among patients with emotional disorders (Grupe and Nitschke, 2013; Cohen et al., 2014; Stout et al., 2014). An important challenge for future studies will be to use hemodynamic imaging techniques, such as fMRI, to clarify the neural circuitry underlying emotional gating deficits. A variety of evidence suggests that the pulvinar may play an important role (Pessoa and Adolphs, 2010; Arend et al., 2014).

DISTRACTING EMOTIONAL CUES DISRUPT COGNITIVE CONTROL AND WORKING MEMORY

Classically, cognition and emotion have been viewed as oppositional forces (Damasio, 2005a; Okon-Singer et al., 2007, 2011; Shackman et al., in press). From this perspective, moods and other kinds of emotional states are responsible for short-circuiting cognition.

Consistent with this view, Kalanthroff et al. (2013) show that emotional distractors disrupt cognitive control. Cognitive control encompasses the range of processes (e.g., endogenous attention, inhibition, and learning) that are engaged when habitual responses are not sufficient to sustain goal-directed behavior, as in stop-signal, go/no-go, Stroop, and Eriksen flanker tasks (Shackman et al., 2011b). Here, the authors demonstrate that the brief presentation of emotional images disrupts performance in the stop-signal task, a widely used index of inhibitory control (see also Pessoa et al., 2012).

Likewise, Iordan et al. (2013) review evidence that emotional distractors disrupt working memory. Converging with other work focused on emotion-related distraction (Bishop, 2007; Etkin, 2012; Bishop and Forster, 2013; Etkin et al., 2013; Okon-Singer et al., 2014a; van Ast et al., 2014), they suggest that degraded performance reflects two processes: (a) increased engagement of regions involved in processing socio-emotional information and orchestrating emotional expressions (e.g., amygdala), and (b) a reduction of delay-spanning activity in frontoparietal cortex.

EMOTION STRENGTHENS SOME COGNITIVE PROCESSES WHILE WEAKENING OTHERS

With the ascent of evolutionary theory in the 19th century (Darwin, 1872/2009, 1872), many scientists adopted the view that emotions are functional and enhance fitness (Susskind et al., 2008; Todd et al., 2012; Sandi, 2013; Schwabe and Wolf, 2013; Todd and Anderson, 2013); in short, that emotions are more adaptive than not and "that there is typically more cooperation than strife" between emotion and cognition (Levenson, 1994).

Consistent with this more nuanced perspective, the contributions from Clarke and Johnstone (2013), Morriss et al. (2013), Robinson et al. (2013a, 2013b), Vytal et al. (2013) provide evidence that experimentally-elicited anxiety facilitates some kinds of information processing, while degrading others. In particular, they provide considerable evidence that anxiety: (a) enhances vigilance, potentiating early sensory cortical responses to innocuous environmental stimuli, increasing the likelihood that emotionally salient information will be detected; and (b) disrupts working memory.

The molecular basis of emotion's deleterious impact on working memory is reviewed by Shansky and Lipps (2013). Building on pioneering work by Arnsten and Goldman-Rakic (1998) and Arnsten (2009), the authors describe evidence that stress strongly influences catecholamine (i.e., dopamine and norepinephrine) and glucocorticoid levels in the prefrontal cortex (PFC) in ways that degrade delay-spanning neuronal activity.

Shansky and Lipps (2013) also describe important new evidence that sex hormones, such as estrogen, can exacerbate the impact of stress on prefrontal function. Along these lines, Sacher

et al. (2013) review human imaging studies showing that the structure and function of brain circuits involved in emotion generation and regulation are strongly and dynamically modulated by cyclic fluctuations in sex hormones (see also Sacher et al., 2012). Taken together, these observations underscore the plasticity of emotion–cognition interactions and provide promising clues about the origins of well-established sex differences in the prevalence of stress-related disorders, such as anxiety and depression (Kessler et al., 2012; Kendler and Gardner, 2014).

EMOTIONAL STATES PROMOTE MOOD-CONGRUENT THOUGHTS AND ACTIONS

Moods and other, more transient emotional states tend to encourage congruent thoughts and actions (e.g., Lerner et al., 2015), a process that is necessarily mediated by enduring changes in brain activity and connectivity (cf. Vaisvaser et al., 2013). Here, Van Dessel and Vogt (2012) demonstrate that mood increases the amount of attention allocated to mood-congruent cues. Schick et al. (2013) provide evidence that individuals at risk for developing depression interpret motivationally ambiguous cues in a less positive light. Harlé et al. (2013) describe a novel Bayesian computational framework for understanding the mechanisms underlying mood-congruency effects. An important advantage of this framework is that it generates explicit mechanistic hypotheses. For example, the model predicts that anxiety facilitates behavioral avoidance because it leads to inflated expectations about the need for avoidant behavior and increased expectations of punishment or error. Furthermore, fitting model parameters to observable behavior affords an opportunity to identify the underlying determinants of mood-congruency effects in healthy and clinical populations.

EMOTIONAL TRAITS INFLUENCE COGNITIVE PERFORMANCE, EVEN WHEN EMOTIONAL CUES, AND CHALLENGES ARE ABSENT

Emotional traits are often conceptualized as diatheses for emotional states (Matthews et al., 2009). Thus, individuals with high levels of neuroticism or negative emotionality are thought to be prone to exaggerated anxiety in the face of trait-relevant cues, contexts, and challenges (e.g., punishment, negative feedback), as illustrated in the contributions from Kessel et al. (2013), Moser et al. (2013), and Proudfit et al. (2013). Yet, a considerable body of neurophysiological evidence indicates that emotional traits are embodied in the on-going activity and connectivity of the brain (Canli et al., 2005; Fox et al., 2008; Shackman et al., 2009; Rohr et al., 2013; Birn et al., 2014a,b). Likewise, the sustained levels of heightened vigilance and distress characteristic of individuals with anxiety disorders are most apparent in the absence of clear and imminent threat (Davis et al., 2010; Lissek, 2012; Grupe and Nitschke, 2013). These observations raise the possibility that emotional traits could influence cognition in the absence of explicit emotional distraction or challenge (Watson and Clark, 1984; Bolger and Schilling, 1991; Suls and Martin, 2005).

Here, Berggren et al. (2013) provide compelling evidence that trait anxiety is associated with degraded cognitive control, indexed using an anti-saccade task under load. This new observation adds to a growing literature showing that "hot" emotional traits can influence "cold" cognition (Shackman et al., 2006; Eysenck et al., 2007; Bishop, 2009; Berggren and Derakshan, 2013, 2014; Cavanagh and Shackman, 2014), a point that we develop more fully in the subsequent section focused on the integration of emotion and cognition.

HOW DOES EMOTION INFLUENCE EMOTION?

An important but rarely addressed question in psychology and psychiatry concerns the potential influence of emotions on one another and concomitant motivational states. For example, are we less likely to experience excitement or joy on a day where we're feeling frazzled, depressed, or worn out (Arnsten, 1998, 2009; Pizzagalli, 2014)?

EMOTION ALTERS REINFORCER SENSITIVITY

Building on earlier work by Bogdan and Pizzagalli (2006), Pizzagalli et al. (2007), Bogdan et al. (2010), and Berghorst et al. (2013) demonstrate that experimentally-elicited anxiety selectively reduces sensitivity to reward, suggesting a mechanism that may contribute to the high rate of comorbidity between anxiety and anhedonia (Southwick et al., 2005). Notably, this effect was only observed in the subset of subjects who were most responsive to the anxiety induction (i.e., threat of noxious electric shock). Given evidence that many individuals will never experience a mood or anxiety disorder (Kessler et al., 2012), this paradigm may provide a means of identifying those at greatest risk. Methodologically, this observation underscores the necessity of including independent measures of emotion in studies of emotion–cognition interactions (Shackman et al., 2006).

HOW DOES COGNITION INFLUENCE AND REGULATE EMOTION?

Humans frequently regulate their emotions and they do so using a variety of implicit and explicit cognitive strategies (Gross, 1998a,b; Gross and Thompson, 2007; Gross et al., 2011; Webb et al., 2012; Okon-Singer et al., 2013). Implicit strategies are unintentional and appear to occur without effort or insight. In contrast, explicit strategies are voluntary and demand a degree of effortful control.

Several contributors to our Special Research Topic described new insights into the mechanisms supporting the cognitive regulation of emotion and the role of emotion regulation in psychiatric disorders, such as depression.

ATTENTION REGULATES EMOTION

Perhaps the most basic strategy for reducing distress is attentional avoidance; that is, to simply look away from the source of distress (Xing and Isaacowitz, 2006). Overt attentional redeployment is a potent means of regulating the engagement of subcortical structures, such as the amygdala, that play a key role in orchestrating emotional states (Pessoa et al., 2002; Dalton et al., 2005; Dalton et al., 2007; van Reekum et al., 2007; Urry, 2010; Okon-Singer et al., 2014a).

Here, Aue et al. (2013b) employed an innovative combination of eyetracking, psychophysiology, and fMRI to explore visual avoidance in spider phobics. Taking an individual differences approach, they demonstrate that enhanced activation in

the amygdala and dorsal striatum to spider images was predictive of increased visual avoidance among arachnophobes. Peripheral measures of autonomic arousal showed a similar pattern, suggesting that arachnophobes endogenously redirect attention as a means of regulating their extreme fear, a strategy that might be non-adaptive in the long term (Grupe and Nitschke, 2013). A key challenge for future research will be to clarify the order of these effects (i.e., fear → attention avoidance → reduced fear), perhaps by leveraging the millisecond temporal resolution afforded by facial electromyography (e.g., Lee et al., 2009; Heller et al., 2014). Elucidating the mechanisms supporting the recursive interplay of emotion and attention and the mutual influences of different processing biases (Aue et al., 2013a) would inform our understanding of disorders, like post-traumatic stress, that are characterized by dysregulated emotion and aberrant attention to emotionally-salient cues (e.g., Admon et al., 2013; Wald et al., 2013) and set the stage for developing improved interventions (MacLeod and Mathews, 2012; Bar-Haim and Pine, 2013; MacLeod and Clarke, 2015).

THE CHOICE OF COGNITIVE REGULATION STRATEGY DEPENDS ON THE SITUATION

Sheppes and Levin (2013) emphasize that humans frequently use effortful cognitive strategies to cope with and regulate their emotions (e.g., Egloff et al., 2006; Ehring et al., 2010). For example, they may try to distract themselves or they may try to reappraise the situation in a more positive light. Sheppes and Levin (2013) provide evidence that not only do individuals have the capacity to flexibly choose emotion regulation strategies, but that they do so in ways that are strongly influenced by the emotional context (e.g., choosing to reappraise when presented with mild negative pictures, and to distract themselves in face of highly aversive stimulation).

WORKING MEMORY REGULATES EMOTION

Some strategies for regulating emotional distress, such as reappraisal, require the effortful maintenance of an explicit regulatory goal. Rolls (2013) reviews evidence suggesting that this critically depends on working memory. More broadly, he suggests that goals, attentional sets, and other kinds of declarative knowledge held in working memory play a central role in regulating the output of emotional systems.

HOW ARE EMOTION AND COGNITION INTEGRATED?

Humans tend to experience cognition and emotion as fundamentally different. Emotion is infused with feelings of pleasure or pain and manifests in readily discerned changes in the body, whereas cognition often appears devoid of substantial hedonic, motivational, or somatic features. These apparent differences in phenomenological experience and peripheral physiology led many classical scholars to treat emotion and cognition as distinct mental faculties (de Sousa, 2014; Schmitter, 2014). But contemporary theorists have increasingly rejected the claim that emotion and cognition are categorically different (Damasio, 2005b; Duncan and Barrett, 2007; Lindquist and Barrett, 2012; Barrett and Satpute, 2013; Pessoa, 2013), motivated in part by recent imaging evidence demonstrating the overlap of emotional and cognitive processes in the brain (e.g., Shackman et al., 2011b; Raz et al., 2012, 2014). The neural integration of emotion and cognition should not be surprising—after all, the human brain did not evolve to optimize performance on laboratory measures of 'cold' cognition or to passively respond to experimental manipulations of emotion, such as threat of shock. Our brain, like that of other animals, is the product of evolutionary pressures that demanded neural systems capable of using information about pleasure and pain, derived from stimuli saturated with hedonic and motivational significance, to adaptively regulate attention, learning, somatic arousal, and action.

A number of contributors highlighted advances in our understanding of the neural mechanisms that serve to integrate emotion and cognition.

CANONICAL TERRITORIES OF THE 'COGNITIVE' BRAIN REGULATE EMOTION

The dorsolateral prefrontal cortex (dlPFC) is a canonically 'cognitive' region of the brain, well known for its critical role in reasoning and higher cognition (e.g., endogenous attention, working memory, and cognitive control; Roberts et al., 1998; Miller and Cohen, 2001; D'Esposito and Postle, 2014). Yet, there is growing evidence that the dlPFC plays a key role in the top–down control of emotion and motivated behavior (Fox et al., 2005b; Koenigs et al., 2008; Zaretsky et al., 2010; Buhle et al., 2013; Frank et al., 2014; Treadway et al., 2014).

Here, Clarke and Johnstone (2013) and Iordan et al. (2013) provide tantalizing, albeit correlational, evidence that dlPFC acts to protect the contents of working memory from emotional distraction. This converges with work by Peers et al. (2013) and Stollstorff et al. (2013) indicating that dlPFC plays a key role in regulating the focus of attention in the face of potentially distracting emotional cues.

Rolls (2013) extends this perspective to decision-making, arguing that behavior reflects a pervasive, dynamic competition between two kinds of brain systems: (a) emotional systems, including circuits centered on the amygdala and ventral striatum, that have been genetically programmed by our phylogenetic history (e.g., fear elicited by danger, joy elicited by sweets and fat); and (b) cognitive systems, such as the frontoparietal network, that are informed by our ontogenetic history and governed by our declarative knowledge and explicit goals (i.e., *pick the healthy orange, not the unhealthy candy bar*; cf. Hare et al., 2008, 2009). Rolls emphasizes that the lateral PFC can override the output of emotion circuitry, biasing behavior in favor of our explicit goals. John et al. (2013) articulate a complementary perspective, reviewing evidence that the PFC and amygdala functionally interact via a complex anatomical network of recurrent cortical and thalamic projections and intra-amygdalar microcircuits (see also Pessoa and Adolphs, 2010; Pessoa, 2012; Pessoa et al., 2012; Birn et al., 2014a,b; Treadway et al., 2014).

Evidence linking the dlPFC to mood and anxiety disorders, as in the papers contributed by Crocker et al. (2013) and Warren et al. (2013), underscores the importance of developing a more sophisticated understanding of the role played by 'cognitive' regions in normal and disordered emotion.

CANONICAL TERRITORIES OF THE 'COGNITIVE' BRAIN ARE REGULATED BY EMOTION

Regulation is a two-way street. Just as 'cognitive' systems (e.g., dlPFC) regulate emotion, 'emotion' systems (e.g., amygdala) are well positioned to regulate 'cognitive' systems via their influence over the brainstem neurotransmitter systems that govern the quality of information processing (e.g., neuronal signal-to-noise) in cortical regions, as highlighted in the review contributed by Shansky and Lipps (2013). Via these mechanisms, the amygdala is endowed with the capacity to transiently assume enhanced control over attention and behavior in situations that favor immediate responses over slower, more deliberate reasoning (Davis and Whalen, 2001; Arnsten, 2009).

ADAPTIVE AND MALADAPTIVE BEHAVIOR REFLECTS THE INTEGRATED CONTRIBUTIONS OF EMOTION AND COGNITIVE CONTROL

Oftentimes, cognitive control is associated with laboratory tasks that require the detection and adjudication of response conflict, as with incongruent trials of the Stroop, Eriksen Flanker, and go/no-go tasks. Yet, it is clear that control processes are engaged by a much broader range of cognitive and emotional challenges (e.g., Pochon et al., 2008; Shenhav et al., 2013). In particular, control is engaged when there is uncertainty about the optimal course of action (e.g., probabilistic learning), when potential actions are associated with the possibility of error or punishment, or when there is competition between alternative courses of action (e.g., flee/freeze, go/no-go). These features are hallmarks of dangerous environments, both in the real world and in laboratory studies of fear, anxiety, and pain. Consequently, it has long been thought that control processes are engaged in threatening environments in order to monitor risk, optimize learning, and avoid potentially catastrophic actions (Norman and Shallice, 1986; Gray and McNaughton, 2000). These theoretical considerations raise the possibility that the neural circuitry underlying 'cognitive' control also contributes to the negative emotions elicited by potential threat. Indeed, there is compelling evidence from functional imaging studies that negative affect and cognitive control paradigms consistently activate an overlapping region of the midcingulate cortex (MCC; Shackman et al., 2011b; Lin et al., 2014). This overlap is consistent with anatomical evidence suggesting that the MCC represents a hub where information about pain, threat, and other more abstract forms of potential punishment and negative feedback are synthesized into a biasing signal that modulates regions involved in expressing fear and anxiety, executing goal-directed behaviors, and biasing the focus of selective attention (Shackman et al., 2011b; Cavanagh and Shackman, 2014). Taken together, these observations suggest that anxiety and other emotions are tightly integrated with control processes implemented in the MCC and other brain regions.

Along these lines, Morrison et al. (2013) show that even simple, phylogenetically-ancient kinds of motivated behavior, such as the reflexive withdrawal from pain or the learned avoidance of pain-related contexts, are dynamically shaped by complex, hierarchically-organized networks of feedforward and feedback connections that serve to integrate 'emotional' (e.g., value, risk) and 'cognitive' computations (e.g., prediction error, attention allocation, action selection) in ways that support adaptive behavior (for convergent perspectives, see the contributions from Rolls, 2013, and John et al., 2013).

Dreisbach and Fischer (2012) describe other evidence consistent with this integrative perspective. In particular, they show that 'cognitive' conflict is aversive. This converges with a growing body of evidence demonstrating that conflict and other prompts for increased control (e.g., errors, punishment), are experienced as unpleasant and facilitate avoidance (Botvinick, 2007; Kool et al., 2010; Dreisbach and Fischer, 2012; Schouppe et al., 2012; Lindström et al., 2013; Proudfit et al., 2013; Shenhav and Buckner, 2014).

If negative emotions are indeed integrated with control processes, we would expect that anxiety and control should covary. That is, one would expect a degree of functional convergence between measures of anxiety and control-related activity in the MCC or other regions (i.e., convergent validity; Campbell and Fiske, 1959). Consistent with this possibility, Moser et al. (2013) provide compelling meta-analytic evidence that error-related signals generated in the MCC are enhanced among anxiety patients and individuals with heightened negative emotionality. This indicates that negative emotionality, a fundamental dimension of childhood temperament and adult personality (Caspi et al., 2005), involves systematic differences in the way that the brain responds to prompts for cognitive control.

McDermott et al. (2013) describe important new evidence, gleaned from the study of Romanian orphans, that MCC control signals are plastic. In particular, they demonstrate that MCC-generated control signals are profoundly shaped by early experience in ways that confer risk or resilience for later socio-emotional problems. This underscores the need to clarify the neurodevelopmental mechanisms that serve to integrate emotion and cognition in the laboratory and in daily life.

UNDERSTANDING THE INTERPLAY OF EMOTION AND COGNITION: STRATEGIES FOR FUTURE RESEARCH

Despite substantial progress, a number of important questions about the interaction of emotion and cognition remain unanswered. In this final section, we highlight three strategies for enhancing research in the cognitive-affective sciences (for more general recommendations about best research practices, see Button et al., 2013a,b,c; David et al., 2013; Chalmers et al., 2014; Ioannidis et al., 2014a,b).

UNDERSTANDING THE SIGNIFICANCE OF EMOTIONAL-COGNITION INTERACTIONS IN THE LABORATORY REQUIRES MORE SOPHISTICATED MEASURES OF BEHAVIOR IN THE REAL WORLD

Most investigations of emotion, cognition, and their interplay rely on a small number of well-controlled, but highly artificial paradigms for manipulating emotion and cognition (e.g., static aversive images and threat of shock to elicit anxiety; Coan and Allen, 2007). Although these methods have afforded a number of critical insights, their real-world significance remains poorly understood. For example, are attentional biases to threat, as indexed by the dot-probe or other laboratory assays, predictive of elevated behavioral inhibition or distress in daily life? Is amygdala activation to fearful faces predictive of heightened social reticence

or risk avoidance outside the scanner (see Admon et al., 2009 for preliminary affirmative evidence)? Does the eliciting stimulus (e.g., faces or aversive images) matter? Are measures of functional connectivity or network-based metrics (e.g., node centrality; cf. McMenamin et al., 2014) more predictive than regional activation of behavior in the real world?

Given the limitations of ambulatory measures of brain activity—there is no 'fMRI helmet' as yet—addressing these fundamental questions requires pairing assays of brain and behavior obtained in the laboratory with measures of thoughts, feelings, and behavior obtained in the field. Recent work combining fMRI with ecological momentary assessment (EMA) techniques, in which surveys are repeatedly delivered to participants' mobile devices, highlights the value of this approach for identifying the neural systems underlying naturalistic variation in mood and behavior, a central goal of psychology, psychiatry, and the behavioral neurosciences (Forbes et al., 2009; Berkman and Falk, 2013; Lopez et al., 2014; Wilson et al., 2014). The widespread dissemination of smart phone technology affords additional, largely unrealized opportunities for objectively and unobtrusively quantifying daily behavior (e.g., assessments of activity and context based on accelerometer and geographical positioning system data (Gosling and Mason, 2015). In short, combining EMA with laboratory assays provides a critical means of testing theoretical validity and clinical relevance (e.g., *does activation of the ventral striatum support craving and approach?*), a novel strategy for assessing and dissociating the functional significance of new assays and derivative measures (e.g., functional connectivity between the striatum and PFC), and an impetus for the development of laboratory probes that more closely resemble the challenges we routinely encounter in life (e.g., appetitive social cues and temptations).

UNDERSTANDING THE INTERPLAY OF EMOTION AND COGNITION REQUIRES A DYNAMIC NETWORK PERSPECTIVE

Emotion and cognition emerge from the dynamic interactions of large-scale brain networks. Put simply, fear, joy, attention, working memory, and other psychological constructs cannot be mapped to isolated brain regions because no one region is both necessary and sufficient. Likewise, similar profiles of impairment can emerge from damage to different regions located within in the same functional network (Karnath and Smith, 2014; Oler et al., in press). This is not a new or contentious idea; pioneers like Mesulam, Goldman-Rakic, and LeDoux highlighted the importance of distributed neural circuits more than two decades ago and there is widespread agreement amongst basic and translational researchers (Goldman-Rakic, 1988; LeDoux, 1995; Mesulam, 1998; Bullmore and Sporns, 2012; LeDoux, 2012; Uhlhaas and Singer, 2012; Anticevic et al., 2013).

Thus, understanding the interplay of emotion and cognition requires that we accelerate the transition from localization strategies (i.e., mapping isolated brain structures to function; sometimes termed 'neo-phrenology') to a network-centered approach. This will require harnessing the kinds of analytic tools (e.g., functional connectivity fingerprinting, graph-theoretic and machine-learning approaches) that are necessary for elucidating how adaptive and maladaptive behavior emerges from functional coalitions of brain regions (Kinnison et al., 2012; Raz et al., 2012, 2014; Anticevic et al., 2013; McMenamin et al., 2014; Uddin et al., 2014). A key challenge for future research will be to harness new techniques (e.g., EEG/fMRI fusions, sliding window analyses of functional connectivity, EEG source models of connectivity) for understanding how network activity dynamically changes across the broad range of time scales on which emotion and cognition interact (Pessoa and Adolphs, 2010; Shackman et al., 2011a; Johnson et al., 2012; Raz et al., 2012, 2014).

Computationally explicit strategies (i.e., where quantitative parameters of an abstract computational model are fit to behavioral or physiological measures), already common in the neuroeconomics literature, and information-based approaches, such as multivoxel pattern analysis (MVPA), that are increasingly common in the cognitive neuroscience literature, provide powerful tools for discovering the functional significance of regions and networks associated with emotional and cognitive perturbations and disorders (e.g., Hartley and Phelps, 2012; Montague et al., 2012; Lewis-Peacock and Norman, 2013). For example, traditional univariate fMRI analyses use regression to predict the activity of voxels, one-by-one, given some mental state (e.g., experiencing pain). While this strategy has proven enormously generative, it does not provide strong evidence as to whether overlapping patterns of fMRI activation (e.g., during physical and social pain; Wager et al., 2013; Woo et al., 2014) reflect the same mental representation. MVPA provides a means of addressing this problem. MVPA classifies mental states given a pattern of activity across voxels; in effect, treating each voxel as a weighted source of information about mental state. This contributes to the identification of the combinatorial code (i.e., pattern of activity across voxels) instantiating a particular mental state (e.g., experiencing anxiety) and to test whether that neural signature is reinstated at other times (e.g., performing a cognitive control task), an essential step in elucidating the functional contributions of territories that are commonly recruited by cognitive and emotional challenges (e.g., dlPFC, MCC, anterior insula).

Embracing a network perspective also reminds us that the functional circuitry underlying the interplay of emotion and cognition is likely to be complex and need not recapitulate the simpler pattern of direct projections revealed by invasive anatomical tracing techniques [cf. the contributions from John et al. (2013), Morrison et al. (2013), and Rolls (2013)]. Indeed, there is ample evidence of robust functional connectivity between brain regions that lack direct structural connections and increasing evidence that regulatory signals can rapidly propagate across complex, indirect pathways in ways that enable emotion (e.g., motivational salience or value) to be integrated with perception and other kinds of on-going information processing (Vincent et al., 2007; Ekstrom et al., 2008; Honey et al., 2009; Pessoa and Adolphs, 2010; Adachi et al., 2012; Birn et al., 2014a). Deciphering the functional significance of this 'connectomic' complexity is likely to require more advanced analytic approaches, such as probabilistic machine-learning techniques (Murphy, 2012). The combination of ongoing advances in computational methods as well as developments in brain imaging acquisition techniques (e.g., those supported by

the U.S. BRAIN initiative) will undoubtedly contribute to these efforts.

UNDERSTANDING THE INTERPLAY OF EMOTION AND COGNITION REQUIRES MECHANISTIC RESEARCH

Most of the contributors to the Special Research Topic used non-invasive techniques, such as fMRI, to trace associations between emotion and cognition, on the one hand, and brain function on the other. Aside from unresolved questions about the origins and significance of the measured signals (e.g., Logothetis, 2008), the most important limitation of these techniques is that they do not address causation. A crucial challenge for future studies is to develop a mechanistic understanding of the distributed networks that support the interplay of emotion and cognition. This can be achieved by combining mechanistic techniques (e.g., optogenetics) or invasive analyses of neuromolecular pathways in animal models with the same whole-brain imaging strategies routinely applied in humans (Borsook et al., 2006; Lerman et al., 2007; Fox et al., 2010, 2012; Lee et al., 2010; Desai et al., 2011; Casey et al., 2013; Narayanan et al., 2013; Roseboom et al., 2014). Similar strategies can be used with patients with circumscribed brain damage (e.g., Nomura et al., 2010; Gratton et al., 2012; Motzkin et al., 2014). Combining fMRI or EEG with non-invasive perturbation techniques (e.g., transcranial magnetic stimulation or transcranial direct current stimulation) or pharmacological manipulations provides another opportunity for understanding how regional changes in brain activity alter network function and, ultimately, behavior (Paulus et al., 2005; Guller et al., 2012; Chen et al., 2013; Reinhart and Woodman, 2014). Prospective longitudinal designs represent another fruitful approach to identifying candidate mechanisms, especially in relation to the development of neuropsychiatric disorders (Admon et al., 2013).

CONCLUSION

The last decade has witnessed an explosion of interest in the interplay of emotion and cognition. The research embodied in this Special Research Topic highlights the tremendous advances that have already been made. In particular, this work demonstrates that emotional cues, emotional states, and emotional traits can strongly influence key elements of on-going information processing, including selective attention, working memory, and cognitive control. Often, this influence persists beyond the duration of transient emotional challenges, perhaps reflecting slower changes in neurochemistry. In turn, circuits involved in attention and working memory contribute to the voluntary regulation of emotion. The distinction between the 'emotional' and the 'cognitive' brain is blurry and context-dependent. Indeed, there is compelling evidence that territories (e.g., dlPFC, MCC) and processes (e.g., working memory, cognitive control) conventionally associated with cognition play a central role in emotion. Furthermore, putatively emotional and cognitive regions dynamically influence one another via a complex web of recurrent, often indirect anatomical connections in ways that jointly contribute to adaptive behavior. Collectively, these observations show that emotion and cognition are deeply interwoven in the fabric of the brain, suggesting that widely held beliefs about the key constituents of 'the emotional brain' and 'the cognitive brain' are fundamentally flawed.

Developing a deeper understanding will require a greater emphasis on (a) assessing the real-world relevance of laboratory assays, including measures of brain activity; (b) a network approach to characterizing the neurobiology of emotion–cognition interactions, and (c) mechanistic research. Adopting these strategies mandates collaboration among researchers from different disciplines, with expertise in different species, populations, measurement tools, analytic strategies, and conceptual approaches.

Addressing the interplay of emotion and cognition is a matter of theoretical as well as practical importance. In particular, many of the most common and costly neuropsychiatric disorders—anxiety, depression, schizophrenia, substance abuse, chronic pain, autism, and so on—involve prominent disturbances of cognition *and* emotion (Millan, 2013). Fundamentally, they are disorders of the emotional-cognitive brain. Collectively, these disorders far outstrip the global burden of cancer or cardiovascular disease (Collins et al., 2011; Whiteford et al., 2013; DiLuca and Olesen, 2014), underscoring the importance of accelerating efforts to understand the neural systems underlying the interaction and integration of emotion and cognition.

GLOSSARY OF TERMS NOT DEFINED IN THE MAIN TEXT

Affect: The experience or expression of emotion (see also Barrett et al., 2007).

Anxiety: A sustained state of heightened apprehension in response to uncertain, distal, or diffuse threat (Davis et al., 2010).

Cognition: Cognition is a fuzzy category that conventionally includes processes involved in knowing or 'thinking,' including attention, imagination, language, learning, memory, and perception (for discussion, see Duncan and Barrett, 2007).

Emotion: Like 'cognition,' 'emotion' is a fuzzy, contentious category that conventionally includes valenced processes (e.g., action tendencies, attention, overt behavior, subjective feelings, and alterations in peripheral physiology) that are triggered by specific external or internal stimuli (e.g., actual or remembered threat for fear); often taken to include states of anger, disgust, fear, happiness, and sadness (e.g., Ekman and Davidson, 1994; Duncan and Barrett, 2007; Gendron and Barrett, 2009; LeDoux, 2012, 2014).

Mood: A low-intensity emotional state that persists in the absence of an explicit triggering stimulus (Ekman and Davidson, 1994).

Motivation: Internal states that are elicited by reinforcers and serve to organize behavioral direction (i.e., approach or avoidance) and intensity. Emotional states involve alterations in motivation (e.g., increased avoidance in the case of fear). However, motivation can be altered by homeostatic processes, such as hunger and satiety, that are not conventionally considered emotional (Rolls, 1999).

Neuroticism/Negative Emotionality: A fundamental dimension of childhood temperament and adult personality; individuals with high levels of Neuroticism/Negative Emotionality are susceptible to more intense or long-lasting negative emotions, including anger,

anxiety, fear, guilt, and sadness (Watson and Clark, 1984; Caspi et al., 2005).

Reinforcer: Rewards and punishments; anything an organism will work to approach or avoid (Rolls, 1999).

AUTHOR CONTRIBUTIONS

All the authors supervised the Special Research Topic. Hadas Okon-Singer and Alexander J. Shackman wrote the paper. All the authors edited and revised the paper.

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