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Emotional arousal and multiple memory systems in the mammalian brain

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Emotional arousal induced by stress and/or anxiety can exert complex effects on learning and memory processes in mammals. Recent studies have begun to link study of the influence of emotional arousal on memory with earlier research indicating that memory is organized in multiple systems in the brain that differ in terms of the "type" of memory they mediate. Specifically, these studies have examined whether emotional arousal may have a differential effect on the "cognitive" and stimulus-response "habit" memory processes sub-served by the hippocampus and dorsal striatum, respectively. Evidence indicates that stress or the peripheral injection of anxiogenic drugs can bias animals and humans toward the use of striatal-dependent habit memory in dual-solution tasks in which both hippocampal and striatal-based strategies can provide an adequate solution. A bias toward the use of habit memory can also be produced by intra-basolateral amygdala (BLA) administration of anxiogenic drugs, consistent with the well documented role of efferent projections of this brain region in mediating the modulatory influence of emotional arousal on memory. In some learning situations, the bias toward the use of habit memory produced by emotional arousal appears to result from an impairing effect on hippocampus-dependent cognitive memory. Further research examining the neural mechanisms linking emotion and the relative use of multiple memory systems should prove useful in view of the potential role for maladaptive habitual behaviors in various human psychopathologies.

Keywords: emotion, memory, amygdala, striatum, hippocampus, learning, anxiety, stress

The influence of "emotional arousal" including in particular the effects of stress and anxiety on learning and memory has received extensive investigation (for reviews see Joels et al., 2006; Shors, 2006). Consistent with the hypothesis that emotional arousal can serve to modulate memory processes in a bi-directional manner, both enhancing and impairing effects of stress and anxiety have been observed in lower animal and human studies. In addition, investigation of brain regions that in part mediate the modulatory effects of emotional arousal on memory has focused largely on various limbic system structures, in particular the basolateral amygdala (BLA) (for review see McGaugh, 2004). Studies examining the organization of memory in the mammalian brain indicate the existence of multiple memory systems, raising the question of whether emotional arousal may differentially influence the use of different brain systems in a given learning situation. This hypothesis is examined in the present brief review, in which dissociable roles of the hippocampus and dorsal striatum in "cognitive" and "habit" memory, respectively, are first described. This is followed by a discussion of recent studies in lower animals indicating a differential influence of emotional arousal on the *relative* use of multiple memory systems. Evidence that the BLA mediates the influence of emotional arousal on multiple memory systems in lower animals is presented. Finally, recent work examining the effects of stress on the use of multiple memory systems in humans is described, and the hypothesis that the modulatory influence of emotional arousal on cognitive and habit memory systems may be relevant to understanding various human psychopathologies is briefly considered.

NEUROBIOLOGICAL EVIDENCE FOR MULTIPLE MEMORY SYSTEMS: HIPPOCAMPUS AND DORSAL STRIATUM

Extensive evidence from studies employing a variety of mammalian species indicates that memory is organized in multiple brain systems that differ in terms of the type of memory they mediate (for reviews see Squire et al., 1993; Packard and Knowlton, 2002; White and McDonald, 2002; Squire, 2004). Neurobiological evidence that the brain contains multiple memory systems has led to the proposal of several "dual-memory" theories designed to define the psychological operating principles that distinguish different forms of memory (for review see Kesner, 1998). Each of these theories was derived primarily from a comparison of the pattern of spared and impaired learning and memory functions observed following damage to the hippocampal system. In addition, the operating principles described in many dual-memory theories, particularly those derived from the animal literature, are heavily influenced by the classical debate between "cognitive" (e.g., Tolman, 1932) and "stimulus-response" (e.g., Thorndike, 1933; Hull, 1943) animal learning theorists. For example, the memory functions of the mammalian hippocampal system have been described as essentially neo-Tolmanian in nature, while the types of learning spared following hippocampal system damage are often readily interpreted by Hullian-like

S-R or "habit" learning theories (e.g., Hirsh, 1974; O'Keefe and Nadel, 1978; Mishkin and Petri, 1984).

In rats, evidence for the multiple memory systems hypothesis is found in experiments comparing the effects of manipulations of the hippocampal system and caudate-putamen (i.e., dorsal striatum). In studies using pairs of tasks with similar motivational, sensory, and motoric processes, lesions of the rat hippocampal system and dorsal striatum result in a double dissociation of task acquisition (Packard et al., 1989; Packard and McGaugh, 1992; McDonald and White, 1993; Kesner et al., 1993). For example, lesions of the fimbria-fornix impair acquisition of "win-shift" behavior in the radial maze, a learning task that requires rats to remember which maze arms have been visited within a daily training session (Packard et al., 1989). However, fornix lesions facilitate acquisition of a simultaneous visual discrimination "win-stay" radial maze task, in which food baited maze arms are signaled by a light cue (Packard et al., 1989). In contrast, lesions of the dorsal striatum impair acquisition of the win-stay radial maze task, but have no effect on acquisition of win-shift behavior (Packard et al., 1989; McDonald and White, 1993). Another early experiment in rats demonstrating a double dissociation between the mnemonic functions of the hippocampal system and dorsal striatum used two versions of a two-platform water maze task. In this task, two rubber balls protruding above the water serve as cues. One ball (correct) is on a rectangular platform that can be mounted to escape the water, and the other ball (incorrect) is mounted on a thin rod and thus does not provide escape. The two balls also differ in visual appearance (i.e., vertical versus horizontal black/white stripes). In a cognitive version of the task, the correct platform is located in the same location on every trial, but the visual appearance of the ball varies. Thus, this version of the task requires rats to learn to approach the correct ball on the basis of spatial location, and not visual pattern. In the S-R habit version of the task, the correct platform is located in different spatial locations across trials, but the visual pattern is consistent. Thus, this task can be acquired by learning an approach response to the visual cue (i.e., pattern discrimination). Lesions of the fornix, but not the dorsal striatum, impair acquisition of the cognitive task; whereas lesions of the dorsal striatum, and not hippocampus, impair acquisition of the habit task (Packard and McGaugh, 1992).

A further example of the differential roles of the hippocampus and dorsal striatum in memory involves the use of a plus-maze task that served as a "battleground" for the debate between cognitive and S-R learning theorists during the late 1940's–early 1950's (for review see Restle, 1957). The plus-maze apparatus allows an animal to approach a goal box (e.g., east or west) from one of two start boxes (e.g., north or south). In a "dual-solution" version of the task, rats are trained to start from the same start box (e.g., south) and obtain food in a consistently baited goal box (e.g., west). In describing the manner in which rats acquire this task, cognitive learning theorists argued that rats learn the spatial location of the food reward (i.e., "place" learning). However, stimulus-response learning theorists argued that rats instead learn to make a specific body turn at the choice point (i.e., "response" learning). The use of these two possible learning mechanisms can be assessed in a probe trial administered after training, in which rats are started from the opposite start box (e.g., north). On the probe trial, rats that approach the spatial location that contained food during training are designated "place" learners, whereas rats that make the same body turn that was reinforced during training are designated "response" learners.

Although intact rats can use both types of learning in performing the task (depending in part on intra- and extra-maze environmental conditions; for review see Restle, 1957), the multiple memory systems hypothesis raises the possibility that these two types of learning may have distinct neural substrates. This hypothesis was addressed in a plus-maze study designed to differentiate the role of the hippocampus and the dorsal striatum in memory (Packard and McGaugh, 1996). Rats were trained in a daily session from the same start box to obtain food from a consistently baited goal box. Following a week of daily training the animals were given a probe trial to assess the use of place or response learning. Prior to the probe trial, rats received intra-dorsal striatal or intra-hippocampal injections of either vehicle saline or the local anesthetic lidocaine, a compound that produces a localized and reversible neural inactivation via a blockade of voltage-gated sodium channels. Rats receiving vehicle injections into the hippocampus or dorsal striatum were predominantly place learners on the probe trial. Intra-hippocampal, but not intra-striatal injections of lidocaine blocked expression of place learning. Thus, the functional integrity of the hippocampus, but not dorsal striatum is necessary for expression of place learning.

In order to assess whether the dorsal striatum might be selectively involved in response learning, we took advantage of previous findings indicating that with extended training in the plus-maze intact rats "switch" from the use of place learning to response learning (for review Restle, 1957). Accordingly, we trained the rats for an additional week and then administered a second probe trial. Rats receiving vehicle injections into either the hippocampus or dorsal striatum were predominantly response learners on the second probe trial, confirming previous reports of a shift from the use of place information to response learning with extended training. Intra-hippocampal injections of lidocaine had no effect on the expression of response learning. In contrast, rats receiving intra-striatal lidocaine displayed *place* learning (i.e., a blockade of the use of response learning observed in control rats). These findings provide further evidence for the differential roles of the hippocampus and the dorsal striatum in memory. They also suggest that, in this dual-solution task, place learning is acquired earlier than response learning and that with extended training the control of learned behavior "shifts" from the hippocampus to the dorsal striatum.

Finally, in addition to lesion studies, double dissociations between the roles of the hippocampus and the dorsal striatum in memory have also been observed following post-training intracerebral drug injections (e.g., Packard and White, 1991; Packard et al., 1994; Packard and Teather, 1997, 1998). For example, post-training intra-hippocampal injections of dopaminergic agonists selectively enhance memory in a win-shift radial maze task, while similar injections into the dorsal striatum selectively enhance memory in a win-stay radial maze task (Packard and White, 1991). Moreover, post-training intra-hippocampal injections of the glutamatergic NMDA receptor antagonist AP5 selectively

impair memory in a hidden platform water maze task, while similar injections into the dorsal striatum selectively impair memory in a visible platform water maze task (Packard and Teather, 1997). In both the hippocampus and the dorsal striatum, the effects of the post-training treatments are time-dependent; injections delayed 2 h post-training have no effect on memory. The time-dependent nature of these post-training injections strongly implicates these brain regions in the modulation of memory processes (McGaugh, 1966), and the task-dependent nature of the treatments indicate selective roles for the hippocampus and dorsal striatum in different types of memory.

Finally, when taken together, double dissociations between the mnemonic functions of the hippocampus and the dorsal striatum in cognitive and habit memory have also been demonstrated in other mammalian species, including monkeys (e.g., Teng et al., 2000; Fernandez-Ruiz et al., 2001) and humans (e.g., Martone et al., 1984; Heindel et al., 1988; Butters et al., 1994; Knowlton et al., 1996).

EMOTIONAL AROUSAL AS A FACTOR INFLUENCING THE USE OF MULTIPLE MEMORY SYSTEMS

In view of the numerous studies supporting a multiple systems view of memory organization in the mammalian brain, there has been an increasing interest in examining various factors that might influence the *relative* use of these different systems. In this context we have conducted several experiments assessing the effects of "emotional arousal" produced by acute stress or drug-induced anxiety on the use of cognitive and habit memory systems. For example, in one study (Kim et al., 2001), rats were exposed to a pre-training stress regimen (restraint stress and intermittent tail-shock) and trained in a dual-solution water maze task in which a visible escape platform is always located in the same spatial location. Training in this task appears to involve a parallel activation (McDonald and White, 1994) of hippocampus-dependent cognitive memory (swim to the same spatial location) and dorsal striatal-dependent habit memory (swim to the visible cue). On a probe trial given after task acquisition, the use of these two learning strategies is assessed by moving the visibly cued platform to a new spatial location and observing whether rats continue to swim to the old location or, alternatively, continue to approach the visible cue. Rats that were administered the pre-training stress-regimen acquired the task at a normal rate. However, on a probe trial 24 h after training, the previously stressed rats displayed a predominant use of habit learning, approaching the cued platform in its new location and showing significantly fewer visits to the old spatial location (Kim et al., 2001). These findings suggest that, in a task in which both hippocampus-dependent and dorsal striatal-dependent learning is adequate for acquisition, acute stress may bias rats toward the use of striatal-dependent habit memory.

We have expanded on these findings by examining the effects of drug-induced anxiety on the relative use of multiple memory systems. Accordingly, we selected doses of the α-2 adrenoreceptor antagonists yohimbine and RS 79948–197 that have been shown to possess anxiogenic properties in rats (e.g., Handley and Mithani, 1984; Guy and Gardner, 1985; White and Birkle, 2001). Using a water maze version of the dual-solution plus-maze task described earlier, we observed that pre-training peripheral injections of either drug produced a robust use of response learning relative to place learning (Packard and Wingard, 2004). A similar bias toward the use of response learning in the dual-solution water maze task is also observed if the drugs are injected prior to memory retrieval (i.e., prior to the probe trial), and importantly the effects of pre-training or pre-retrieval injections of RS 79948–197 are not due to state-dependency (Elliot and Packard, 2008). In addition, pre-training exposure to an ecologically valid stressor (trimethlythiazoline, a component of fox feces odor) also biases rats toward the use of dorsal-striatal response learning in the dual-solution water plus-maze task (Packard and Carlin, unpublished data). Taken together, experiments involving the administration of acute stress or anxiogenic drug injections in lower animals suggest that, at least in some learning situations, robust levels of emotional arousal may bias the brain toward the use of a habit memory system. Interestingly, lower levels of trait anxiety have been recently shown to correlate positively with place recognition memory and with a preference for the use of hippocampus-dependent place learning in rats (Hawley et al., 2011).

EMOTIONAL AROUSAL AND MULTIPLE MEMORY SYSTEMS: ROLE OF BASOLATERAL AMYGDALA

The studies reviewed above suggest that acute stress or peripheral anxiogenic drug injections may influence the relative use of multiple memory systems. However, they do not directly identify the neuroanatomical structure(s) that confer the ability of emotional arousal to favor habit learning and memory. In this context we have focused on investigating a potential role for the BLA. There are at least two lines of evidence from animal studies that support the hypothesis that the BLA may mediate a modulatory influence of emotional arousal on different memory systems. First, this brain structure has been historically linked to emotional behavior in mammals (e.g., Kluver and Bucy, 1939), and in rats intra-BLA injection of various drugs induces an anxiogenic behavioral and physiological profile (e.g., Nagy et al., 1979; Scheel-Kruger and Petersen, 1982; Sanders and Shekhar, 1991). Second, decades of research has implicated the BLA as a critical brain site for the memory modulatory effects of drugs that influence several transmitter systems, including those activated by emotional arousal (for review see McGaugh, 2004). According to the hypothesis that the BLA functions as a "general" memory modulatory system, efferent projections of the BLA influence the consolidation of memory in other brain structures. Consistent with this idea, extensive evidence indicates that the BLA modulates memory processes occurring in both the hippocampus and the dorsal striatum (Packard et al., 1994, 1996; Packard and Teather, 1998; Roozendaal and McGaugh, 1996, 1997).

In order to examine whether the bias toward habit memory produced by peripheral anxiogenic drug administration may involve the BLA, rats trained in the dual-solution plus-maze tasks received injections of RS 79948–197 directly into this brain structure. On the later drug-free probe trial, these rats showed a significant use of response learning relative to control rats (Packard and Wingard, 2004). This finding indicates that intra-BLA injections of RS 79948–197 mimic the effects of peripheral

administration of the drug. Moreover, we subsequently demonstrated that the dose of RS 79948–197 that produces this memory modulatory influence is also anxiogenic when injected into the BLA (Wingard and Packard, 2008).

One question raised by these findings in the dual-solution plus-maze task concerns whether intra-BLA injections bias rats toward the use of habit learning by *directly* facilitating striatal-dependent response learning, or in a perhaps more *indirect* manner by impairing hippocampus-dependent place learning. In order to address this question, we trained rats in "single-solution" versions of the water plus-maze task that *required* rats to use either response or place learning. In the single-solution plus-maze tasks, the start points used varied between North and South. In the response task, the spatial location of the escape platform varied equally across trials (East or West) and the same body turn response (e.g., left) was consistently reinforced. In the place task, the escape platform was always located in the same spatial location (e.g., West) and the body turn responses (left and right) were equally reinforced. Separate groups of rats trained in these tasks and receiving post-training intra-BLA injections of an anxiogenic dose of RS 79948–197 displayed *enhanced* acquisition of the response learning task and *impaired* acquisition of the place learning task (Wingard and Packard, 2008). This behavioral profile is consistent with the hypothesis that the facilitation of response learning produced by the drug results from an impairing effect on hippocampus-dependent place learning. Indeed, we have previously observed that post-training neural inactivation of the dorsal hippocampus also enhances response learning and impairs place learning. An interfering competitive action of the hippocampus during training in the single-solution response task presumably occurs because the spatial location of the escape platform varies across trials (Schroeder et al., 2002; Chang and Gold, 2003; for a review on competition between multiple memory systems see Poldrack and Packard, 2003).

In a final recent set of experiments, we examined whether the BLA is critical for the ability of RS 79948–197 to both enhance response learning and impair place learning when the drug is administered peripherally. Separate groups of rats trained in either the single-solution response or place tasks received post-training peripheral injection of an anxiogenic dose of RS 79948–197 and *concurrent* intra-BLA injections of the local anesthetic bupivacaine. In this study, both the enhancing *and* the impairing effect of peripheral administration of RS 79948–197 on response and place learning, respectively, were blocked by neural inactivation of the BLA (Packard and Gabriele, 2009). These findings provide compelling evidence for a critical role for the BLA in mediating the influence of emotional arousal on different types of memory.

In summary, lower animal studies indicate that peripheral or intra-BLA administration of an anxiogenic drug(s) can bias rats toward the use of dorsal-striatal habit memory and that the influence of the BLA on the relative use of multiple memory systems appears to modulate the degree of interference between cognitive and habit memory. In the remaining discussion, we consider the extent to which stress may affect hippocampal and dorsal striatal morphology, whether emotional arousal may also influence the relative use of multiple memory systems in humans, and briefly describe possible implications of this hypothesis for understanding the role of learning and memory processes in various psychopathologies.

THE HIPPOCAMPUS, DORSAL STRIATUM, AND STRESS

When an organism senses a threat, stress hormones are released via the HPA axis and bear a significant and unequal impact upon various brain structures related to learning and memory (for review see McGaugh, 2002). Among these brain structures, the hippocampus and dorsal striatum appear to be differentially affected by stress. In rats, chronic stress causes atrophy of hippocampal neurons of the CA3 region (Watanabe et al., 1992; Magariños and McEwen, 1995) and hypertrophy in the dorsal striatum (Dias-Ferreira et al., 2009). Also, in a longitudinal MRI study, rats subjected to 21 days of chronic restraint stress displayed a 3% reduction in hippocampal gray matter volume, an effect that was not observed in non-stressed controls (Lee et al., 2009). fMRI studies reveal potentially similar results in human subjects with anxiety disorders. Numerous studies have shown that people who have been exposed to trauma and developed post-traumatic stress disorder (PTSD) generally have smaller hippocampi than those who did not develop PTSD (Gilbertson et al., 2002; Bremner et al., 2003; Lindauer et al., 2004; Carrion et al., 2007). In addition, there is evidence that people with PTSD or obsessive-compulsive disorder (OCD) have enlarged caudate nuclei (Looi et al., 2009; Radua et al., 2010). It is unclear whether chronic stress affects the relative size of these brain structures or if smaller hippocampi and larger caudate nuclei precede the development of these anxiety disorders. Indeed, the nature of the relationship between hippocampal gray matter volume and PTSD has attracted considerable debate (Bremner, 2001; Pitman, 2001). In favor of a causal relationship, there is evidence that stressful life events can negatively affect hippocampal morphology in humans. Using a longitudinal MRI paradigm, researchers measured hippocampal gray matter volume at two time points, separated by a three month interval. The number of stressful life events experienced during the three-month interval was positively correlated with a reduction in gray matter volume of the right hippocampus (Papagni et al., 2011), suggesting that the relationship between PTSD and hippocampal volume may be causal.

Interestingly, a single stressful experience may be sufficient to affect the morphology of the hippocampal formation. Several studies have shown that acute stress suppresses neurogenesis of progenitor cells in the dentate gyrus of rodents (Galea et al., 1996; Gould et al., 1997; Tanaput et al., 2001) and non-human primates (Gould et al., 1998). Moreover, in humans hydrocortisone administration decreased activation of the hippocampus in the retrieval phase of a declarative memory task (Oei et al., 2007).

It is less clear whether acute or chronic stress affects the function of the dorsal striatum. However, evidence from human neuroimaging studies suggests that the dorsal striatum may play a role in the processing of negative stimuli. In healthy subjects, the dorsal striatum responds intensely when viewing unpleasant pictures, relative to positive or neutral pictures (Carretie et al., 2009). In addition, in anxious subjects, dorsal striatal activation increases when reading negative words as opposed to positive or neutral ones (Roiser et al., 2008). Lastly, subjects with Huntington's

disease (a disease associated with deterioration of the dorsal striatum) are impaired in their ability to recognize negative facial expressions (Gray et al., 1997; Johnson et al., 2007).

THE AFFECT OF STRESS ON THE RELATIVE USE OF MULTIPLE MEMORY SYSTEMS IN HUMANS

As described earlier, numerous studies in rats suggest a dynamic impact of emotional arousal on hippocampus-dependent and dorsal striatal-dependent memory systems. Specifically, acute stress and/or anxiety appears to bias rats to solve dual solution tasks by employing an S-R habit learning strategy, at the expense of the competing cognitive memory system (Packard and Wingard, 2004; Wingard and Packard, 2008). To the extent that the influence of emotional arousal on the hippocampus and dorsal striatum is similar in rodents and humans, it is possible that the effect of stress on the *relative* use of memory systems observed in rodents may also be observed in humans.

Indeed, recent studies building on the earlier research in lower animals indicate that both acute and chronic stress may also bias human subjects to implement an S-R habit learning strategy to solve a dual solution task. For example, Schwabe et al. (2007) trained subjects to locate a "win-card" in a 3D model of a room. Over 12 trials, subjects could locate the win-card by using a spatial strategy (i.e., the card is always in the same spatial location) or a stimulus-response strategy (i.e., the card is always next to the plant). On the 13th trial, the plant was moved to a different location which allowed the experimenters to assess the type of learning strategy used. Prior to training, subjects were exposed to an acute stressor consisting of giving a speech and performing mental math in front of an audience. Subjects in this stressed condition implemented an S-R strategy to locate the win-card significantly more often than controls. Interestingly, high salivary cortisol at the time of learning predicted habit behavior in stressed and non-stressed conditions. In a subsequent study, subjects with higher scores on a chronic stress questionnaire implemented an S-R strategy in a 2-D dual solution task significantly more often than subjects with lower scores (Schwabe et al., 2008a). Therefore, similar to the effects of acute stress, chronic stress also appears to favor habit learning, at the expense of spatial learning, in humans.

Consistent with these findings, another study assessed the effect of emotional arousal on retention of the striatal-dependent weather prediction task (Steidl et al., 2011). For each trial in this task, subjects are asked to predict the weather based on a random set of cards depicting different abstract shapes. Each possible combination of cards has a predetermined probability of signifying rain or sunshine, and after each prediction subjects are given feedback as to whether their prediction was correct or incorrect. In this particular study, in order to manipulate the level of emotional arousal, subjects were presented with either "arousing" or "neutral" pictures during acquisition of the task. In a retention test given 1.5 months after training, subjects who had viewed the arousing pictures exhibited sustained memory for the task, whereas subjects who had viewed the neutral pictures exhibited considerable memory decay. Previous studies using fMRI or enlisting subjects with selective damage to the basal ganglia have indicated that the striatum has a central role in the initial acquisition of the weather prediction task (Knowlton et al., 1996; Poldrack et al., 1999). Therefore, it could be interpreted that heightened emotional arousal may have further enhanced the role of the striatum during training, thus strengthening the memory and improving performance in the retention test. However, it should be noted that the hippocampus is implicated in later performance of the weather prediction task (Knowlton et al., 1994, 1996), suggesting that a hippocampus-dependent learning system may have also had a role in the enhanced retention (Steidl et al., 2006).

Interestingly, some research has shown that stress promotes habit behavior in instrumental learning tasks as well. In one study (Schwabe and Wolf, 2009), human subjects were exposed to the socially-evaluated cold pressor test or a non-stressed control condition and then trained on two instrumental tasks, each associated with a distinct food outcome. After training, one of the food outcomes was devalued by feeding the subject with the food until satiation. In a subsequent extinction test, subjects exposed to pre-training stress continued performing the same instrumental response despite it being associated with the devalued food outcome (i.e., pre-training stress prompted habitual behavior). Subjects unexposed to stress decreased the instrumental behavior associated with the devalued food outcome, suggesting the use of a more cognitive, goal-directed learning system. In a separate fMRI study, it was observed that habit behavior in the food devaluation paradigm was associated with increased activation of the dorsal striatum, while goal-directed behavior was associated with increased activation of the ventromedial prefrontal cortex (Tricomi et al., 2009). Therefore, stress-induced habit behavior in this task may also represent a shift to a dorsal striatal-dominant activation pattern.

While behavioral stressors appear to bias humans toward the use of a habit memory system at the expense of the competing cognitive system, studies investigating the role of the human stress hormone cortisol seem to yield opposite results. For example, one study observed that low basal cortisol levels were associated with the use of an S-R habit strategy, whereas higher levels were associated with the use of a spatial strategy in a dual solution virtual maze task (Bohbot et al., 2011). However, subjects' cortisol levels did not correlate with their scores on the Perceived Stress Questionnaire, suggesting that sample cortisol levels in this study may not have reflected actual feelings of stress. The effect of stress on the hippocampus is typically described as following an inverted U-shape, with high and low levels of stress leading to impairments and a "middle" level being optimal for hippocampus function. Considering that no subjects reported high stress, the authors suggest that the higher cortisol readings in this study may actually represent the middle of this inverted-U, thus favoring the use of a hippocampus-dependent memory system. Another study investigating the effect of cortisol showed that orally administered hydrocortisone biased women to solve a dual solution task using a spatial strategy, at the expense of the habit system (Schwabe et al., 2008b). Interestingly, exogenous cortisol treatment was also associated with poorer performance in both spatial and response learners. To explain these results in the context of earlier work, the authors hypothesize that under low cortisol levels the hippocampus controls behavioral output. Under moderate levels, hippocampus function declines and the dorsal striatum

seizes control, and under high levels hippocampus and dorsal striatum function decline, but the balance between systems is restored and the hippocampus regains control. It is interesting to note a contrast between this explanation and the one proposed by Bohbot et al. (2011). Whereas Schwabe et al. (2008b) suggest that the hippocampus gains control at low and high cortisol levels, Bohbot et al. (2011) propose that the hippocampus controls behavioral output at medium levels. The different methods used in these studies (e.g., behavioral tasks; monitoring endogenous cortisol vs. manipulating exogenous cortisol) may in part account for this discrepancy. In this context, it is worth noting that human fMRI studies have established a negative correlation between cortisol levels and hippocampus activity (Oei et al., 2007).

Aside from a potential U-effect, there may be another explanation for the seemingly opposite effects of cortisol. Using the instrumental food-devaluation paradigm discussed earlier, researchers found that only concurrent administration of the α_2-noradrenergic receptor antagonist yohimbine and hydrocortisone promoted habit behavior in humans, whereas administration of hydrocortisone alone resulted in goal-directed, cognitive behavior (Schwabe et al., 2010). Therefore, it appears that increases in both cortisol and norepinephrine may be required to induce a habit bias in dual solution tasks. This finding may explain why a behavioral stressor like the socially-evaluated cold pressor test, which increases plasma norepinephrine (Blandini et al., 1992) and salivary cortisol (Schwabe et al., 2008), can induce a habit bias (Schwabe and Wolf, 2009), whereas a pharmacological increase in cortisol alone does not (Schwabe et al., 2008b).

In summary, both chronic and acute stress appears to bias humans to solve dual solution tasks with a habit memory system, consistent with the research in lower animals. However, when manipulating and monitoring cortisol levels, a more complex picture emerges, and the effect of stress on the relative use of memory systems may follow a U-shaped curve or depend on an interaction between both cortisol and norepinephrine.

POTENTIAL MECHANISMS UNDERLYING THE STRESS-MEDIATED HABIT BIAS IN HUMANS

Extensive research indicates that in some learning situations the hippocampus and dorsal striatum vie for control of behavioral output (for review see Poldrack and Packard, 2003). For example, in rats, lesions, or neural inactivation of the hippocampus can lead to enhanced acquisition of striatal-dependent habit tasks (e.g., Packard et al., 1989; Packard and McGaugh, 1992; Schroeder et al., 2002). In view of evidence that high levels of stress can impair hippocampus-dependent learning in rats, it has been suggested that the stress or anxiety-induced shift to habit learning may result from the hippocampus relinquishing control and releasing the habit memory system from competition (Wingard and Packard, 2008). Consistent with this idea, numerous human studies have shown that high levels of stress at the time of encoding or retrieval impair performance in hippocampus-dependent memory tasks (Schwabe et al., 2009; Merz et al., 2010; Schwabe and Wolf, 2010; Thomas et al., 2010). Therefore, in dual solution tasks, it is possible that stressed individuals are more proficient in solving the task with their unimpaired habit system and thus, in order to preserve performance levels, implement an S-R strategy as opposed to a cognitive strategy. Consistent with this interpretation, subjects with lower scores in episodic memory tasks were more likely to be response learners in a dual solution virtual maze task (Bohbot et al., 2011). It is important to note that stressed human subjects may be generally unaware of alternative strategy options (e.g., spatial) for solving a given dual solution task (Schwabe et al., 2007; Schwabe and Wolf, 2009). Therefore, it is unlikely that stressed individuals make a *conscious* decision to abstain from cognitive solutions and opt for a habit learning strategy. Rather, stressed human subjects may rely on their habit system, simply because the available cognitive solutions go unnoticed.

As mentioned earlier, stressful life events are associated with reduced gray matter volume of the right hippocampus in humans (Papagni et al., 2011). This finding may be relevant for understanding the effect of stress on memory systems, particularly as the relative size of the hippocampus and dorsal striatum may predict the learning strategy used. In one study (Bohbot et al., 2007), researchers utilized a virtual eight-arm radial maze that could be solved by associating distal cues (e.g., mountains, trees, etc.) with the location of the correct maze arms (i.e., a spatial strategy) or by memorizing the sequence of left and right arrow presses on the keyboard that lead to the correct maze arms (i.e., an S-R strategy). To determine which strategy a subject used, the distal cues were blocked in the last trial of the experiment. MRI scans revealed that greater density in the hippocampus was positively correlated with the number of errors in the final probe trial (suggesting the use of a spatial strategy) and that greater density in the dorsal striatum was negatively correlated with the number of errors in the probe trial (suggesting the use of an S-R strategy). Chronic stress may potentially exert its influence on multiple memory systems by affecting the relative volume of the hippocampus and dorsal striatum. Whether the more modest morphological changes induced by acute stress could underlie the habit bias remains to be determined.

As previously described, several studies in lower animals indicate that the effects of emotional arousal on memory depend on the integrity of the BLA (for review see McGaugh, 2004) and also implicate this brain region in orchestrating the use of multiple memory systems during periods of high emotional arousal (e.g., Packard and Wingard, 2004; Wingard and Packard, 2008; Packard and Gabriele, 2009). Interestingly, human fMRI studies reveal that the degree of amygdala activation during encoding positively correlates with the recall of emotion-laden memories (Hamann et al., 1999; Canli et al., 2000). However, to our knowledge, no studies have investigated the relationship between amygdala activation and the *relative use* of memory systems in humans.

Finally, human case studies reveal that acute or chronic anxiety may underlie the development and persistence of several psychopathologies with "habit-like" behavioral features, including for example OCD, post-traumatic stress disorder, and drug addiction. For instance, in OCD, the exaggerated fear of germs or infection may cause a person to "solve the problem" habitually, thus leading to excessive hand washing (Jones and Menzies, 1998). In post-traumatic stress, a significantly traumatic experience can lead to the development of non-context-specific cued recall of the

memory. In this way, some aspects of PTSD may be analogous to the previously described studies showing a stress-induced facilitation of S-R habit (or, cued) learning and concomitant disregard for the spatial context of the learning environment (Schwabe et al., 2007, 2009). In addition, several studies have evidenced a relationship between acute stressors and relapse into habit-like drug seeking behavior in lower animals (Shaham and Stewart, 1995; Shepard et al., 2004; Buffalari and See, 2009) and humans (Kosten et al., 1986; Sinha et al., 1999, 2009). Moreover, there is increasing evidence that the dorsal striatum plays an important role in the expression of drug-seeking behaviors in animals (Ito et al., 2002; Fuchs et al., 2006; See et al., 2007) and humans (Garavan et al., 2000; Volkow et al., 2006). Thus, one might speculate that anxiety and/or stress may influence relapse in drug addiction by favoring the use of habit memory to guide the expression of maladaptive behaviors. Further research examining the relationship between the neural bases of emotional arousal and the relative use of multiple memory systems may prove useful for understanding various human psychopathologies.

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