EMBODYING THE SELF: NEUROPHYSIOLOGICAL PERSPECTIVES ON THE PSYCHOPATHOLOGY OF ANOMALOUS BODILY EXPERIENCES

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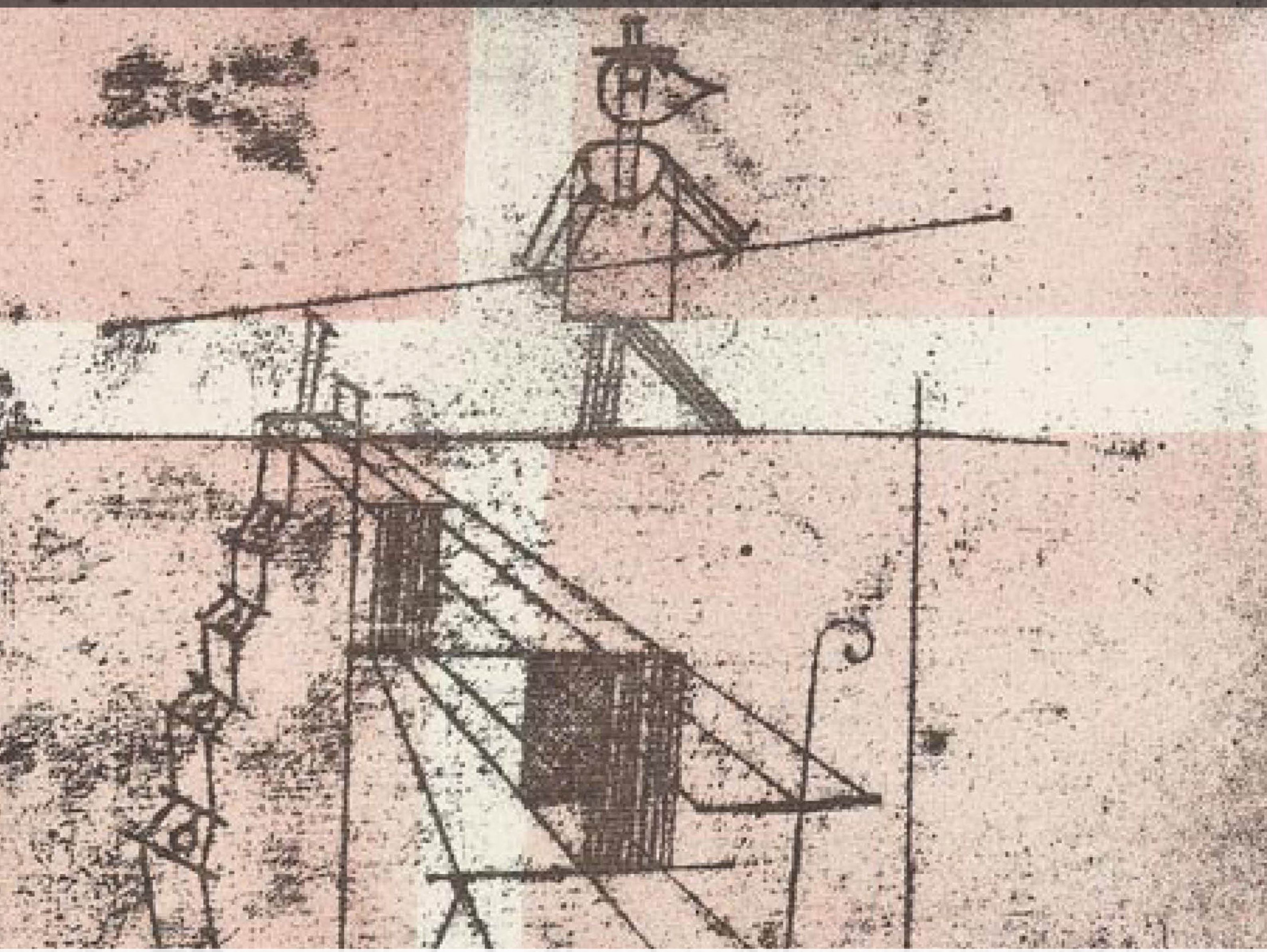

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EMBODYING THE SELF: NEUROPHYSIOLOGICAL PERSPECTIVES ON THE PSYCHOPATHOLOGY OF ANOMALOUS BODILY EXPERIENCES

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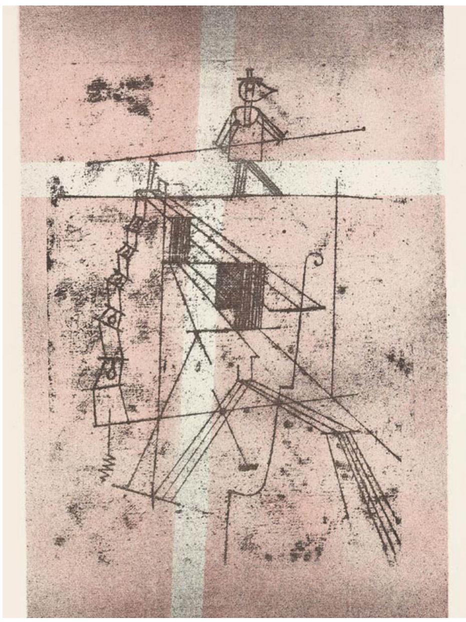

Tightrope Walker (Seiltänzer) from the portfolio Art of the Present (Die Kunst der Gegenwart) by Paul Klee (1923). Art in the Public Domain.

Since the beginning of the 20th Century, phenomenology has developed a distinction between lived body (Leib) and physical body (Koerper), a distinction well known as body-subject vs. body-object (Hanna and Thompson 2007). The lived body is the body experienced from within - my own direct experience of my body lived in the first-person perspective, myself as a spatiotemporal embodied agent in the world. The physical body on the other hand, is the body thematically investigated from a third person perspective by natural sciences as anatomy and physiology.

An active topic affecting the understanding of several psychopathological disorders is the relatively unknown dynamic existing between aspects related to the body-object (that comprises the neurobiological substrate of the disease) and the body-subject (the experiences reported by patients) (Nelson and Sass 2017). A clue testifying the need to better explore this dynamic in the psychopathological context is the marked gap that still exists between patients' clinical reports (generally entailing disturbing experiences) and etiopathogenetic theories and therapeutic practices, that are mainly postulated at a bodily/brain level of description and analysis. The phenomenological exploration typically targets descriptions of persons' lived experience. For instance, patients suffering from schizophrenia may describe their thoughts as alien ("thoughts are intruding into my head") and the world surrounding them as fragmented ("the world is a series of snapshots") (Stanghellini et al., 2015). The result is a rich and detailed collection of the patients' qualitative self-descriptions (Stanghellini and Rossi, 2014), that reveal fundamental changes in the structure of experiencing and can be captured by using specific assessment tools (Parnas et al. 2005; Sass et al. 2017; Stanghellini et al., 2014).

The practice of considering the objective and the subjective levels of analysis as separated in the research studies design has many unintended consequences. Primarily, it has the effect of limiting actionable neuroscientific progress within clinical practice. This holds true both in terms of availability of evidence-based treatments for the disorders, as well as for early diagnosis purposes. In response to this need, this collection of articles aims to promote an interdisciplinary endeavor to better connect the bodily, objective level of analysis with its experiential corollary. This is accomplished by focusing on the convergence between (neuro) physiological evidence and the phenomenological manifestations of anomalous bodily experiences present in different disorders.

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EDITORIAL
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Editorial: Embodying the Self: Neurophysiological Perspectives on the Psychopathology of Anomalous Bodily Experiences

Mariateresa Sestito [1,2]*, *Andrea Raballo* [3], *Giovanni Stanghellini* [4,5] *and Vittorio Gallese* [2,6]

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Keywords: anomalous experiences, body-object, body-subject, embodiment, mirror neurons system, neurophysiology, phenomenology, psychopathology

Editorial on the Research Topic

Embodying the Self: Neurophysiological Perspectives on the Psychopathology of Anomalous Bodily Experiences

Since the beginning of the twentieth Century, phenomenology has developed a distinction between lived body (*leib*) and physical body (*koerper*), a distinction well known as body-subject vs. body-object (Hanna and Thompson, 2003). The lived body is the body experienced from within—my own direct experience of my body lived in the first-person perspective, myself as a spatiotemporal embodied agent in the world. The physical body on the other hand, is the body thematically investigated from a third person perspective by natural sciences such as anatomy and physiology.

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The practice of considering the objective and the subjective levels of analysis as separated in the research studies design has many unintended consequences. Primarily, it has the effect of limiting actionable neuroscientific progress within clinical practice. This holds true both in terms of availability of evidence-based treatments for the disorders, as well as for early diagnosis purposes. In response to this need, this collection of articles aims to promote an interdisciplinary endeavor to better connect the bodily, objective level of analysis with its experiential corollary. This

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is accomplished by focusing on the convergence between (neuro) physiological evidence and the phenomenological manifestations of anomalous bodily experiences present in different disorders. Still indeed, little effort has been channeled in order to plan comprehensive research protocols that include aspects derived from the lived world of patients.

The idea of addressing the human body going beyond the simple Hippocratic idea is revitalized in the concept of *Embodied Medicine* proposed by Riva et al. Body representation is a complex aspect, as it involves the encoding and integration of a wide range of multisensory—somatosensory, visual, auditory, vestibular, visceral—and motor signals (Blanke, 2012). Specifically for self-bodily recognition, behavioral and anatomical data suggest that implicit and explicit routes for self-body knowledge are dissociated and mediated by different cerebral networks at a brain level (Candini et al.). The concept of *Embodied Medicine* takes advantage from the multisensory nature of the body and promote the use of advanced technologies for altering the experience of being in a body, with the goal of improving health and well-being. In particular, the technology proposed by Riva et al. works as a means to modify the inner body for treating different neurological and psychiatric diseases and their phenotypical manifestations. The commentary of Pistoia et al. in this respect, illustrates other potential applications of this technology specifically in the context of neurological disorders like the Locked-in Syndrome.

The contribution from Northoff and Stanghellini outlines an experimentally testable hypothesis meant to provide converging evidence from psychopathological facts (phenomenology, see Stanghellini et al., 2014) and neurophysiological measures in schizophrenia. This is accomplished by combining temporal measures of the brain's spontaneous activity of interoceptive stimuli and temporal measures for the subjective experience of the body. Along similar lines, the work of Ebisch et al. supports the existence of a brain network processing the integration of information derived from multiple sources during social perception. Authors here hypothesize that such integrative processing of social information occurring at a brain level might be mediated by the linking of external stimuli with self-experience.

An empirical attempt to find a common structure that integrates intero- and exteroceptive stimuli processing can be found in other articles included in this collection. In their study, Ardizzi et al. consider the individual sensitivity to detect the visceral sensations originating inside of the body (i.e., interoception accuracy) as a facet of self-integrity in schizophrenia. The results report a reduced sensitivity in patients to their inner bodily signals, that correlates with positive symptoms severity.

Numerous studies show that interoception is altered in different psychiatric disorders. For example, low interoceptive accuracy was established in anorexia nervosa (Pollatos et al., 2008; Stanghellini et al., 2012, 2015b; Gaudio et al., 2014), major depression (Furman et al., 2013; Harshaw, 2015) and depersonalization- derealization disorders (Sedeño et al., 2014). Ambrosecchia et al. report how interoception and autonomic regulation are modulated during social interactions in a population of restrictive anorexia nervosa patients. Authors suggest that an autonomic imbalance and its altered relationship with interoception might have a key role in emotional and social disposition manifestations of the disorder. In their article, Pollatos et al. report how anorexia patients show a significant decrease of interoceptive accuracy during self-focus sessions, a therapeutic practice aimed at increasing attention to patients' own bodily features. This study provides insights into phenomenological aspects related to body-avoidance feelings that characterize anorexia, and draws attention to possible implications for treatment.

Anomalous bodily experiences may also accompany a number of chronic pain conditions. The work from Tajadura-Jiménez et al. describes how acoustic sensory feedback can alter humans' body perception and the pain experienced, suggesting potential practical applications in the clinical setting. In their study, Valenzuela-Moguillansky et al. highlight possible interactions between exteroceptive and interoceptive self-body awareness aspects in patients suffering from fibromyalgia. Authors then relate these aspects to pain, suggesting suitable therapeutic practices tapping into this interaction.

Specifically in the context of schizophrenia, however, genetics still remain a crucial risk factor. The work of Henriksen et al. reviews the state of the art of the complex genetic architecture of schizophrenia and related phenotypes evident in clinical practice. Empirical research on anomalous self-experiences reported by patients with schizophrenia (Parnas and Handest, 2003) indeed, considers this aspect to be an intermediate phenotype of the disorder. Investigating the neurophysiological correlates of anomalous self-experience became a topic of intense research. Some studies for example, point toward a disturbance of emotional motor resonance and multisensory integration as body-level correlates of anomalous self-experience in schizophrenia (Sestito et al., 2013, 2015a,b; Gallese and Ferri, 2014; Ebisch and Gallese, 2015). In this respect, the explorative study conducted by Sestito et al. provide support for a complex interaction between anomalous self-experiences and psychotic symptoms in the context of neutral stimuli misperception in schizophrenia. These preliminary findings outline some testable perspectives on the connection between molecular neurochemistry of delusions formation at a brain level and their psychopathological corollary. Gallager and Trigg illustrate the relevance of phenomenological accounts of schizophrenia and agoraphobia, highlighting the importance of considering the interdependent nature of neural aspects, subjective experience, and social environment. In the work of Haug et al., results describe how anomalous self-experiences might be a useful target in other psychopathological conditions like depression, to assist the clinician in understanding patients' experience of self-esteem to prevent suicidality. Taken together, these studies show the potential of applying anomalous self-experiences as a target phenotype for neurobiological and genetic research in the context of schizophrenia and other psychopathological diseases.

Further theoretical efforts directed at exploring the connections between anomalous self-experiences and the brain substrate are presented in the works of Kuang and Jalal and Ramachandran. The paper of Kuang proposes a unified social motor cognition theory in order to conceal the neural and the mental levels of cognitive processing in the context of the mirror-touch synaesthesia manifestations. The neural level is herein considered the physical process regarding basic sensory-motor aspects of the action, which supports motor imitation and goal understanding (i.e., the Mirror Neuron System, MNS) whereas, the mental level concerns the attribution of mental states, which supports inferring others' minds and self-other distinctions. In the work of Jalal and Ramachandran for example, the MNS substrate is suggested to play a role in giving rise to a particular sort of out of body experiences occurring during the REM sleep. Such experiences include sensing and seeing the presence of threatening intruders in one's bedroom—the so called "ghostly bedroom intruder" experience. According to these authors, in this condition the activation of the MNS would enable to see the world from an allocentric perspective, without leaving one's own body.

Further efforts are needed to indentify comprehensive protocols capitalizing upon the integration between the phenomenological and the (neuro) physiological levels of analysis. In this respect, the embodied cognition approach—considering the MNS as a neural substrate—offers an insightful perspective to inspire future research protocols aimed at bridging the body-object and the body-subject. To pursue this endeavor, it will be critical to unravel the (neuro) physiological mechanisms enabling the integration between inner body signals and exteroceptive inputs. The topic "Embodying the self: neurophysiological perspectives on the psychopathology of anomalous bodily experiences" is a very active research topic that has a major importance in providing advances for intervention approaches and for the understanding of vulnerability markers to enhance early identification of psychopathological diseases.

AUTHOR CONTRIBUTIONS

MS: Intellectual conceptualization, literature review, and manuscript drafting. AR: Intellectual conceptualization and literature review. GS: Literature review. VG: Intellectual conceptualization, literature review, and manuscript drafting supervision. All the authors contributed to the final revision of the manuscript.

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REFERENCES

Blanke, O. (2012). Multisensory brain mechanisms of bodily self consciousness. *Nat. Rev. Neurosci.* 13, 556–571. doi: 10.1038/nrn3292

Ebisch, S. J. H., and Gallese, V. (2015). A neuroscientific perspective on the nature of altered self-other relationships in schizophrenia. *J. Conscious. Stud.* 22, 220–240.

Furman, D. J., Waugh, C. E., Bhattacharjee, K., Thompson, R. J., and Gotlib, I. H. (2013). Interoceptive awareness, positive affect, and decision making in major depressive disorder. *J. Affect. Disord.* 151, 780–785. doi: 10.1016/j.jad.2013.06.044

Gallese, V., and Ferri, F. (2014). Psychopathology and the bodily self. The case of schizophrenia. *Psychopathology* 47, 357–364. doi: 10.1159/000365638

Gaudio, S., Brooks, S. J., and Riva, G. (2014). Non visual multisensory impairment of body perception in anorexia nervosa: a systematic review of neuropsychological studies. *PLoS ONE* 9:e110087. doi: 10.1371/journal.pone.0110087

Hanna, R., and Thompson, E. (2003). The mind-body-body problem. *Theor. Hist. Sci. Int. J. Interdiscipl. Stud.* 7, 23–42. doi: 10.12775/ths.2003.002

Harshaw, C. (2015). Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychol. Bull.* 141, 311–363. doi: 10.1037/a0038101

Nelson, B., and Sass, L. A. (2017). Towards integrating phenomenology and neurocognition: possible neurocognitive correlates of basic self-disturbance in schizophrenia. *Curr. Prob. Psychiatry* 18 184–200. doi: 10.1515/cpp-2017-0015

Parnas, J., and Handest, P. (2003). Phenomenology of anomalous self-experience in early schizophrenia. *Compr. Psychiatry* 44, 121–134. doi: 10.1053/comp.2003.50017

Parnas, J., Møller, P., Kircher, T., Thalbitzer, J., Jansson, L., Handest, P., et al. (2005). EASE: examination of anomalous self-experience. *Psychopathology* 38 236–258. doi: 10.1159/000088441

Pollatos, O., Kurz, A. L., Albrecht, J., Schreder, T., Kleemann, A. M., Schopf, V., et al. (2008). Reduced perception of bodily signals in anorexia nervosa. *Eat. Behav.* 9, 381–388.doi: 10.1016/j.eatbeh.2008.02.001

Sass, L., Pienkos, E., Skodlar, B., Stanghellini, G., Fuchs, T., Parnas, J., et al. (2017). EAWE: examination of anomalous world experience. *Psychopathology* 50 10–54. doi: 10.1159/000454928

Sedeño, L., Couto, B., Melloni, M., Canales-Johnson, A., Yoris, A., Baez, S., et al. (2014). How do you feel when you can't feel your body? Interoception, functional connectivity and emotional processing in depersonalization-derealization disorder. *PLoS ONE* 9:e98769. doi: 10.1371/journal.pone.0098769

Sestito, M., Raballo, A., Umiltà, M. A., Amore, M., Maggini, C., and Gallese, V. (2015a). Anomalous echo: exploring abnormal experience correlates of emotional motor resonance in Schizophrenia Spectrum. *Psychol. Res.* 229, 559–564. doi: 10.1016/j.psychres.2015.05.038

Sestito, M., Raballo, A., Umiltà, M. A., Leuci, E., Tonna, M., Fortunati, R., et al. (2015b). Mirroring the self: testing neurophysiological correlates of disturbed self-experience in schizophrenia spectrum. *Psychopathology* 48, 184–191. doi: 10.1159/000380884

Sestito, M., Umiltà, M. A., De Paola, G., Fortunati, R., Raballo, A., Leuci, E., et al. (2013). Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front. Hum. Neurosci.* 7:368. doi: 10.3389/fnhum.2013.00368

Stanghellini, G., Ballerini, M., Blasi, S., Mancini, M., Presenza, S., Raballo, A., et al. (2014). The bodily self: a qualitative study of abnormal bodily phenomena in persons with schizophrenia. *Compr. Psychol.* 55, 1703–1711. doi: 10.1016/j.comppsych.2014.06.013

Stanghellini, G., Ballerini, M., Presenza, S., Mancini, M., Raballo, A., Blasi, S., et al. (2015a). Psychopathology of lived time: abnormal time experience in persons with schizophrenia. *Schizophr. Bull.* 42, 45–55. doi: 10.1093/schbul/sbv052

Stanghellini, G., Castellini, G., Brogna, P., Faravelli, C., and Ricca, V. (2012). Identity and eating disorders (IDEA): a questionnaire evaluating identity and embodiment in eating disorder patients. *Psychopathology* 45, 147–158. doi: 10.1159/000330258

Stanghellini, G., and Rossi, R. (2014). Pheno-phenotypes: a holistic approach to the psychopathology of schizophrenia. *Curr. Opin. Psychiatry* 27, 236–241. doi: 10.1097/YCO.0000000000000059

Stanghellini, G., Trisolini, F., Castellini, G., Ambrosini, A., Faravelli, C., and Ricca, V. (2015b). Is feeling extraneous from one's own body a core vulnerability feature in eating disorders?. *Psychopathology* 48, 18–24. doi: 10.1159/000364882

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PERSPECTIVE
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Embodied Medicine: Mens Sana in Corpore Virtuale Sano

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Progress in medical science and technology drastically improved physicians' ability to interact with patient's physical body. Nevertheless, medicine still addresses the human body from a Hippocratic point of view, considering the organism and its processes just as a matter of mechanics and fluids. However, the interaction between the cognitive neuroscience of bodily self-consciousness (BSC), fundamentally rooted in the integration of multisensory bodily inputs, with virtual reality (VR), haptic technologies and robotics is giving a new meaning to the classic Juvenal's latin dictum "*Mens sana in corpore sano*" (a healthy mind in a healthy body). This vision provides the basis for a new research field, "Embodied Medicine": the use of advanced technologies for altering the experience of being in a body with the goal of improving health and well-being. Up to now, most of the research efforts in the field have been focused upon how external bodily information is processed and integrated. Despite the important results, we believe that existing bodily illusions still need to be improved to enhance their capability to effectively correct pathological dysfunctions. First, they do not follow the suggestions provided by the free-energy and predictive coding approaches. More, they lacked to consider a peculiar feature of the human body, the multisensory integration of internal inputs (interoceptive, proprioceptive and vestibular) that constitute our inner body dimension. So, a future challenge is the integration of simulation/stimulation technologies also able to measure and modulate this internal/inner experience of the body. Finally, we also proposed the concept of "Sonoception" as an extension of this approach. The core idea is to exploit recent technological advances in the acoustic field to use sound and vibrations to modify the internal/inner body experience.

Keywords: embodied medicine, bodily self-consciousness, body matrix, predictive coding, interoception, proprioception, virtual reality, sonoception

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INTRODUCTION: GOING BEYOND THE PHYSICAL BODY AND CONVENTIONAL MEDICAL APPROACH

According to Hippocratic physicians, the main goal of medicine was to counter diseases by aiding the natural resistance of the body to overcome the metabolic imbalance (Riva, 2016a). Since then, research in pharmacology and technology has drastically improved physicians' ability to interact with the body. However, medicine still addresses the human body as Hippocratic physicians did thousands of years ago, i.e., as just a physical body. The interaction between the cognitive neuroscience of bodily self-consciousness (BSC) and multisensory integration (Aspell et al., 2012) with virtual reality (VR), robotics and haptics is giving a new meaning to the classic Juvenal's latin dictum "*Mens sana in corpore sano*" (a healthy mind in a healthy body). Specifically, recent advances in VR, haptic technologies, bio/neuro-feedback and brain/body stimulation technologies provide the tools for altering the human experience of being in a body (BSC) with the goal of improving health and well-being, thereby going beyond the (mentioned) conventional medical approach of only altering our physical body (Riva, 2016a).

THE MULTISENSORY NATURE OF THE BODY

The most basic foundations of the self are arguably housed in those brain systems that represent the body (Aspell et al., 2012). Body representation is complex and involves the encoding and integration of a wide range of multisensory (somatosensory, visual, auditory, vestibular, visceral) and motor signals (Blanke, 2012). Importantly, while external objects of perception come and go, multisensory bodily inputs are continuously present and proposed as the basis for BSC (Blanke, 2012). This multisensory representation is thought to be controlled by the "Body Matrix"—a complex network of multisensory and homeostatic brain areas whose role is to protect the body by activating perceptual and behavioral programs (effectors) when something (e.g., sensation, an injury, or a pathology) alters the body and the space around it (Moseley et al., 2012b; Gallace and Spence, 2014; Wallwork et al., 2016). According to several scholars, the body matrix sustains a multisensory representation (Blanke et al., 2015) of the space around the body (peripersonal space) that not only extends beyond the body surface to integrate both somatotopic and peripersonal sensory data (Makin et al., 2008; Serino et al., 2015) but also integrates body-centered spatial sensory data (Petkova et al., 2011; Pfeiffer et al., 2013) with an object-centered body image from vision and memory (Tsakiris, 2010; Maselli, 2015) and signals from the internal organs, such as the heart and lungs (Park et al., 2016; Tsakiris and Critchley, 2016; Tsakiris, 2017). Moreover, its contents are argued to be shaped by predictive multisensory integration (Seth et al., 2012; Suzuki et al., 2013; Talsma, 2015)—higher-order networks generate bottom-up and top-down predictions about the expected sensory inputs that are used to coordinate its contents into a coherent mental representation (Bayesian principle). Specifically, according to the recent "free-energy self" model (Apps and Tsakiris, 2014; Tsakiris, 2017), individuals process their body in a probabilistic manner as the most likely to be "me". In this view, the experience of the body is the result of a probabilistic process associating the different unimodal properties of the body from several sensory systems: *exteroception* (the body perceived through the senses, e.g., vision and touch), *proprioception* (the sense of the position of the body/body segments originating through input of muscles and joints), *vestibular input* (the sense of motion and position of the body originating through vestibular system coding for the head position and movements) and interoception (the sense of the physiological condition of the body originating through muscular and visceral sensations or vasomotor activity).

THE BODY MATRIX

What is the evolutionary role of the body matrix? Apparently, the body matrix serves to maintain the integrity of the boundaries of the body at both homeostatic and psychophysiological levels (Moseley et al., 2012b). This neural network might coordinate/supervise the distribution of cognitive and physiological resources necessary to protect the body (and the space around it) and adapt it to changes in structure and orientation, as recent VR-based experimental work revealed (Llobera et al., 2013). An important effect of this control is the top-down modulation induced by multisensory conflicts (e.g., visuo-tactile) over the interoceptive homeostatic systems (Blanke et al., 2016). Besides the role of body matrix in high-end cognitive processes such as social cognition (Tajadura-Jiménez et al., 2012) it exerts a top-down modulation over basic physiological mechanisms such as thermoregulatory control (Moseley et al., 2012a). In addition to supporting this vision, a recent review by Blanke et al. (2016) underlying how experimental alterations of BSC are associated with changes at the physiological level (i.e., skin conductance response to a threat directed towards the virtual body), body temperature and pain thresholds, also indicates that "changes in BSC induced by multisensory conflicts (e.g., visuo-tactile) interact with the interoceptive homeostatic systems" (p. 330). A recent study by Finotti and Costantini (2016) further expands this vision, highlighting the existence of biochemical mechanisms accounting for the dependency of multisensory body integration and BSC on the immune system, which may have important "implications for a range of neurological, psychiatric and immunological conditions where alterations of multisensory integration, body representation and dysfunction of the immune system co-exist" (p. 1).

Gallace and Spence (2014) explained that the body matrix control over physiological functions is achieved by the connections that exist between the posterior cingulate cortex and the insula. In fact, there are a number of inhibitory connections between the insula and autonomic brain stem structures (Fechir et al., 2010). Importantly, Guterstam et al. (2015b) recently demonstrated that the posterior cingulate cortex plays a key role in integrating the neural representations of self-location and body ownership—a fundamental component of BSC.

In this view, damage, malfunctioning or altered feedback from and toward the body matrix may be involved in the etiology of different clinical conditions (Riva, 2016a), from neurological disorders like neglect (Lenggenhager et al., 2012; Bolognini et al., 2016) and chronic pain (Tsay et al., 2015; Di Lernia et al., 2016b) to psychiatric disorders like schizophrenia (Ferri et al., 2014; Postmes et al., 2014), depression (Wheatley et al., 2007; Barrett et al., 2016), depersonalization/derealization disorder (Simeon et al., 2000; Jáuregui Renaud, 2015) and eating disorders (Riva et al., 2013; Riva, 2014, 2016b; Dakanalis et al., 2016; Serino et al., 2016a).

THE EMERGENCE OF EMBODIED MEDICINE

After some seminal attempts at using a rubber hand illusion (RHI; Botvinick and Cohen, 1998) and VR to modify the experience of the body (Riva, 1998a,b; Perpiña et al., 2003), in 2007, two European teams of cognitive neuroscientists independently reported in Science (Ehrsson, 2007; Lenggenhager et al., 2007) how VR technology could be used to alter BSC (producing an out-of-body experience). Since then, different researchers have used the class of bodily illusions—having the aforementioned RHI as the prototypical paradigm (Serino and Dakanalis, 2016) to study the mechanisms behind body experience and its link with higher cognitive processes. Although this perspective article does not focus on an in-depth discussion of body illusion studies, which have recently been reviewed and summarized elsewhere (Costantini, 2014; Dieguez and Lopez, 2016; Serino and Dakanalis, 2016), it is worth noting some of these studies whose results are relevant for the topic of this article. First, it has been demonstrated that illusory ownership over an invisible body reduces social anxiety responses (Guterstam et al., 2015a). Moreover, the ownership over a dark-skinned rubber hand reduces implicit racial bias (Maister et al., 2013) while the illusory embodiment of a virtual child's body causes implicit attitude changes (Banakou et al., 2013). Finally, and beside the view of body illusions as potential non-invasive approaches for rehabilitation with neurological and psychiatric (Costantini, 2014), it has been shown that efficient episodic-memory encoding requires perception of the world from the perspective of one's own body (Bergouignan et al., 2014).

The approach used in the aforementioned studies creates a multisensory conflict using the exteroceptive signals of the body (touch and vision). Specifically, the experience of "being" in a different synthetic/surrogate body is achieved through the cross-modal congruence between what people feel via the somatosensory pathways and what they see in VR (Normand et al., 2011; Preston et al., 2015). To reach this goal, the required technology includes a high-end immersive VR system, a real-time motion capture and a simple haptic system integrated in a platform also able to provide physiological and brain electrical activity recordings (Spanlang et al., 2014; Castelvecchi, 2016). Currently, this set-up is still expensive, costing up to $114,000 (Castelvecchi, 2016). Moreover, the field is dominated by academic research and development with almost no technology companies translating this research into true clinical VR applications. However, as VR technology is advancing quickly, this picture is expected to change due to more user-friendly (Oculus Rift and HTC) devices, available to consumers this year, which showcase high-quality VR experiences at reasonable price points—less than $3000 for a fully configured system (Castelvecchi, 2016).

But how can we use technology to modify the contents of the body matrix? As underlined by the free-energy principle (Friston, 2010; Friston et al., 2010; Limanowski and Blankenburg, 2013), our brain tries to minimize the amount of free-energy (or "surprise") associated with the current experience by making predictions about the sensorial consequences produced by the experienced events in the environment. In this view, the contents of the body matrix are adjusted on the basis of the (dis)agreement between the actual sensory activity and the expected inputs generated through predictive multisensory integration (Allen et al., 2016). In principle, this can be done in two ways (Limanowski and Blankenburg, 2013; O'Reilly et al., 2013):

- by changing *what is predicted* by selecting only the sensory activity that confirms the model's predictions (as happens in the RHI). This is achieved by reallocating resources to a previously deprioritized region of space and/or re-planning a motor response to an unexpected stimulus;
- by changing the *predictions of the model* through the dynamic optimization of its parameters. However, this happens only when the level of estimation of uncertainty (Courville et al., 2006), which reflects the agent's knowledge of the environment and can be reduced when the agent has the opportunity to make further observations of the environment, is high.

In other words, *significant prediction errors* (high surprise), which can reduce the level of estimation uncertainty, will result in strong adjustments in the internal representation to predict future events effectively (O'Reilly et al., 2013). In line with this view, a possible way of correcting a dysfunctional representation of the body and improving the old model is the use of technologies to induce a controlled mismatch between the predicted/dysfunctional model and actual sensory input (Riva, 2008, 2011; Di Lernia et al., 2016a). Some recent studies have provided scientific support to this approach. For instance, driven by the evidence that body and pain representations in the brain are multisensory and partially overlap, a recent study using VR to induce changes in BSC with the goal of modulating pain, showed that embodiment over a virtual/surrogate body can impact physiological automatic responses to noxious stimuli (Romano et al., 2016). In a more recent study, Falconer et al. (2016) used a VR body-swapping illusion protocol with a sample of depressed patients to improve their self-compassion. After three repetitions of the body swapping experience, patients achieved a significant reduction in depression severity and self-criticism. While these studies highlight embodied virtual bodies as a promising technique for future pain treatments and depression, other research provides evidence that a body-swap illusion (i.e., an illusion of body ownership over a body different from the current one) can change body perception (Normand et al., 2011), memory (Serino et al., 2016b) and affect (Preston and Ehrsson, 2014), and motivate initiation and maintenance of healthy eating behaviors even in eating disorders (Keizer et al., 2016; Serino and Dakanalis, 2016) and non-operable extremely obese patients (i.e., with body mass index (BMI) >60 kg/m^2; Serino et al., 2016c).

THE OPEN CHALLENGE: ALTERING THE BODY MATRIX

Despite the aforementioned (relevant) results, we believe that the existing bodily illusions still need to be improved to enhance their capability to alter/correct pathological dysfunctions effectively in

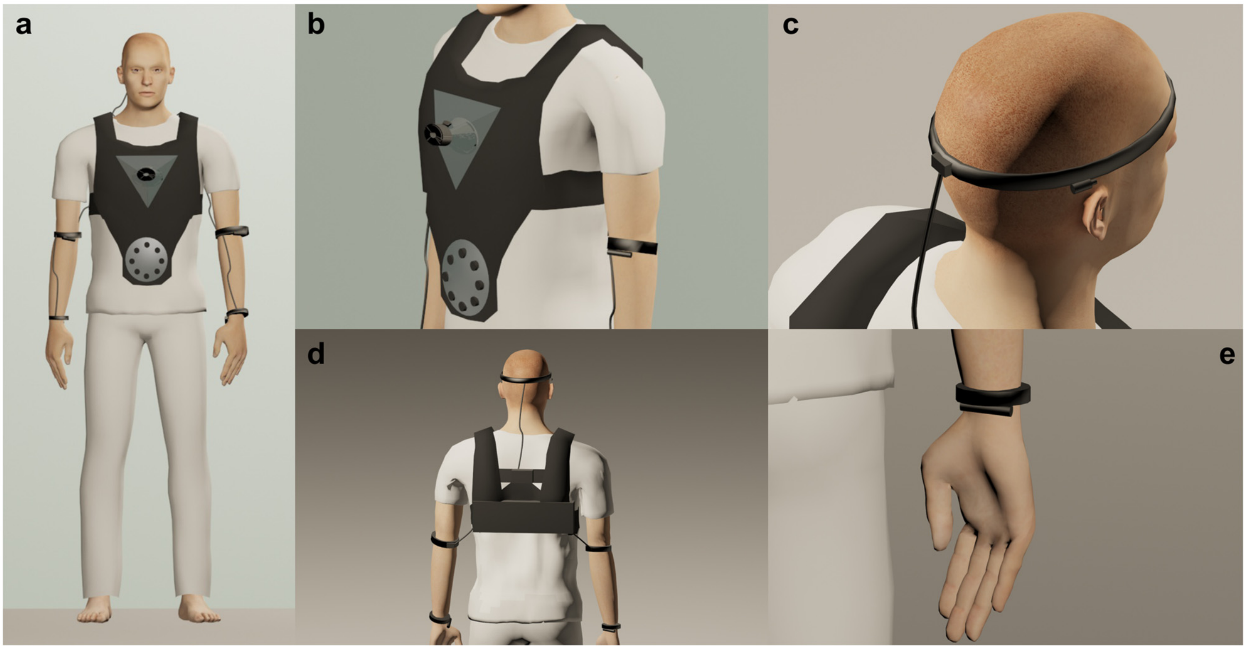

FIGURE 1 | The technology used by Sonoception. (A) A novel non-invasive technological paradigm using wearable acoustic and vibrotactile transducers. This approach is able to modulate the inner body through the perception of movements in specific body parts. **(B)** Low Bass Frequency and Ultrasounds contactless transducers are embedded in a jacket akin to a life-vest, inducing the illusion of the perception of movements from the heart and the stomach. **(C)** A detail of a wearable linear actuator that conduces bone-vibration evoking vestibular myogenic potentials originating from selective activation of the otolithic organs. **(D)** Battery pack and electronics are hidden on the back of jacket. This system will be easy to wear and to integrate with other interfaces such as bio-signal recording and stimulation systems. **(E)** A detail of the spindle actuator applied to a wrist produces a sensation of hand displacement.

the contents of the body matrix. For example, bodily illusions are hypothesized to influence pain through "substituting" the painful body part with a virtual one (Li et al., 2011). However, a recent systematic review assessing the effects of bodily illusions on clinical pain (Boesch et al., 2016) clearly showed that exteroceptive embodiment illusions, including full body ones, do not decrease pain. This gap will be overcome by bridging existing technological advances with the cognitive neuroscience of body experience and clinical research in neurology and psychiatry. The final goal is to achieve what we propose to call "Embodied Medicine" (Riva, 2016a), i.e., the use of advanced technologies to modify our experience of being in a body to improve health and well-being.

A first issue that is not addressed in the existing body illusion protocols is the assessment of the level of surprise induced by the virtual embodiment. As already noted, if the body illusion does not produce a *significant prediction error* (high surprise), reducing the level of estimation uncertainty, it is not able to update the predictive internal models of the body matrix (O'Reilly et al., 2013). However, while some of the available studies on bodily illusions used galvanic skin response to assess the level of arousal induced by stimuli threatening the body (for example Ehrsson et al., 2008; Senna et al., 2014), none of them explicitly assessed the level of surprise in their protocols. How can we measure it? The use of eye tracking assesses pupil dilation (increased pupil diameter), a relevant marker of uncertainty and surprise (Lavin et al., 2014).

A second relevant issue is the link between surprise and updating. Even if surprise and updating are usually strongly correlated, they are distinct processes (O'Reilly et al., 2013). As underlined by O'Reilly et al. (2013), "the relationship between surprise and updating depends, among other things, on the learning rate, the degree of expected stochasticity in the environment, and the expected frequency or rate of change in the underlying environment" (p. E3661). In this view, bodily illusions have to be developed to maximize the probability of updating the predictive model by assessing and tuning these variables. Moreover, both pupil dilation (increased pupil diameter) and the activity of the anterior cingulate cortex (ACC) can be used to assess the updating of the predictive model (Behrens et al., 2007; O'Reilly et al., 2013). Preliminary results of a local brain activity (LBA) neurofeedback training of the ACC revealed more local ACC-activity after successful training. This also suggests the possibility of integrating bodily illusions with a LBA-feedback protocol targeting this area to further improve the updating process (Radke et al., 2014).

Finally, to date, most of the research effort, also from the technological point of view, has addressed how external information from the body is processed and integrated and contributes to our sense of self. Notwithstanding the success

TABLE 1 | Sonoception: rationale and technology.

Inner body sensory system	Body site	Technology	Proposed approach
Interoception	Stomach	Ultrasound	Ultrasound waves (>20 KHz)—frequencies higher than the upper audible limit of human hearing—are often used in medicine (i.e., sonography of fetus) as totally free from side effects for human health. The ultrasonic technological devices developed for medical applications are basically used for imaging visceral anatomy. However, in recent research (Marzo et al., 2015), usage of ultrasonic transducers has been suggested as a new methodology that "can exert radiation forces and form acoustic traps at points where these forces converge permitting the levitation of particles of a wide range of materials and sizes through air, water or biological tissues" (p. 2). In this vein, holographic acoustic elements could be employed to translate the particles of food eaten with consequent motion of the stomach walls (Kang and Yeh, 2010; Hong et al., 2011).
Interoception	Heart	Low bass frequency	Bass sounds (50–120 Hz) are also prevalent in living and working environments and, despite its low audibility, low frequency noise often causes a person to experience a vibratory sensation. One of the most prominent effects of high-level low frequency sound is the so-called "chest slam", i.e., the sensation that the chest is resonating. Studies report that pure tones with sound pressure levels of 100 dB enable the perception of chest vibration (Schust, 2004; Takahashi, 2011).
Proprioception	Muscles	Vibrotactile transducers	Cutaneous receptors in the skin around fingers, elbows, ankles and knee joints provide exteroceptive and proprioceptive information. Similar to muscle spindles, these receptors encode both movement kinematics and show directional sensitivity (Lee et al., 2013). When a vibration of approximately 70–100 Hz is applied to a tendon of the biceps or triceps muscle of a physically immobile limb obstructed from view, a sensation of arm displacement is generated (Naito et al., 1999). Notably, increasing the vibration frequency increases the velocity of the perceived illusory movement (Roll and Vedel, 1982). When the vibratory stimulation is interrupted, the spindle discharge decreases, inducing the perception that the limb is returning towards its original position.
Vestibular input	Otolith organs	Vibrotactile trasnducers	The otoliths (the utricular and saccular maculae) are the gravity sensing organs of the inner ears. Air-conducted sounds and bone-conducted vibration have been proposed as two effective methods to evoke vestibular myogenic potentials originating from selective activation of the otolithic end organs (Manzari et al., 2010). Bone-conduced vibration at frequency of 500 Hz produces consistent craniocentric whole-body responses in standing subjects (Welgampola and Day, 2006; Curthoys and Grant, 2015). The characteristics of the response are compatible with mediation by vestibular input, although the sway direction is different from that evoked by galvanic vestibular stimulation. This suggests that different patterns of input are produced by the two types of stimulation, possibly involving different proportions of afferents from the otoliths and semicircular canals. If so, bone-conducted sound, used either in isolation or combination with galvanic vestibular stimulation, may enable investigation of hitherto unexplored aspects of vestibular function in intact freely behaving human subjects.

of such advances, what makes our body so special is that, unlike other physical objects, not only do we perceive it through external senses (exteroception) but we also have an internal access to it through inner (interoceptive, proprioceptive and vestibular) signals. So, a future challenge is to bridge VR with bio/neuro-feedback and brain/body stimulation technologies also able to measure and modulate the internal/inner body experience. For example, Suzuki et al. (2013) created a "cardiac RHI" in which a computer-generated augmented-reality with feedback of interoceptive (cardiac) information facilitated the online integration of exteroceptive and interoceptive signals.

At present, different companies are also working in this direction. For instance, Doppel[1], a UK SME, developed a wearable technology able to alter the heart rhythm by providing a customized haptic feedback to the wrist. The device is based on the concept of "entrainment"—a process by which people innately respond to external rhythms by auto-adjusting their heart rate to synchronize with the beat. Here, we propose the concept of "Sonoception" as a possible extension of this non-invasive approach. The core idea is to exploit recent technological advances in the acoustic field to use sound and vibrations to modify the internal/inner body experience.

[1] http://www.doppel.london/

SONOCEPTION: USING SOUND AND VIBRATION TO MODIFY THE INNER BODY

Although academic and professional institutions have been slow to recognize the emergence of acoustics as a technological science (Doak, 1964), there have been advances and dissemination of knowledge of sound and vibration in recent years (Brouet et al., 2016; Mitrou et al., 2017). Sound and vibration are two, highly interrelated physical phenomena; sound is a form of energy generated by vibrations and, in turn, vibration is an oscillatory motion. Sound and vibration can affect the human body and its well-being through mechanoreceptors (receptors specialized in sensing mechanical forces) which translate the sensory input into specific somatosensory experiences due to their different threshold sensitivity to vibration (Guignard, 1971). For example, although it is well-known that the heart is sensitive to both external and internal mechanical forces, only recently have several scholars explored the subtle effects of force on cardiac function and its relevance for pathology by linking cardiovascular mechanotransduction to the arterial myogenic response (Sharif-Naeini et al., 2010; Zamir et al., 2012). Moreover, it is well known that both sound and vibration cause fluid pressure waves in the inner ear that can induce vertigo and vestibular disorders

(Dix and Hallpike, 1952). Finally, the stimulation of different esophageal mechanoreceptors mediate different sets of reflexes through the activation of different sets of medullary vagal nuclei (Lang et al., 2011). Again, esophageal sensory nerves play a key role in esophageal functional disorders, chronic unexplained symptoms that have no detectable structural, inflammatory, or metabolic disease (Sengupta, 2006). These examples suggest a direct link between sound and vibration, somatosensory experiences and different diseases through the mediation of mechanoreceptors.

Based on this knowledge, and with the aim of s(t)imulating all the components of the inner body, the technology used by Sonoception would make use of the technology displayed in **Figure 1**. Specifically, (for a detailed description of the technology and rationale, see **Table 1**):

- For *Interoception* we will employ contactless acoustic transducers to stimulate mechanoreceptors from chest and abdomen, inducing respectively the perception of movements in the heart in the stomach. A different strategy will be employed for the two organs; while ultrasounds will be used for the stomach, we plan to use low bass frequencies for the heart.
- For *Proprioception* and the *Vestibular Input*, we will use vibrotactile transducers to stimulate mechanoreceptors placed on muscles and on otolith organs within the vestibular system.

By exploiting the technology based on the concept of Sonoception, it will be possible to modulate the inner body (including interoception, proprioception and vestibular input), to explore how these changes may affect the internal/inner subjective experience and, more importantly, to understand how variations of inner (interoceptive, proprioceptive and vestibular) signals are related to BSC. We are aware of the explorative nature of this approach but we believe that Sonoception could open novel scientific questions on the relationship between the self and inner subjective experience.

CONCLUDING REMARKS

With these probable/proposed changes, a possible long-term goal is the reverse engineering of the psychosomatic processes. While the inter-disciplinary medical field of psychosomatic medicine explores the relationship between psychosocial and behavioral factors on bodily processes (Kiecolt-Glaser et al., 2002), embodied medicine could do the opposite, i.e., altering bodily processes to influence psychosocial and behavioral factors (Riva, 2016a).

We suggest a software module working in a closed loop (e.g., a classifier like the technologies used in the Brain-Computer Interfaces) to facilitate the integration of the external (exteroceptive) and internal/inner (interoceptive, proprioceptive and vestibular) inputs originating from the body and the environment. This software will process and classify the psychophysiological signals, which will be translated as vibratory signals and sent back to the body by the contactless acoustic transducers in real time. This approach will allow the development of a hardware/software platform bridging VR with bio/neuro-feedback and brain/body stimulation technologies and offer an integrated tool able to address all the components of our bodily experience. Nevertheless, future clinical studies are needed to identify the best protocols and combination of technological tools to transform the dictum "*Mens Sana in Corpore Virtuale Sano*" into reality. Specifically, future research should aim at exploring the psycho-physiological and neural mechanisms enabling integration between inner body signals and exteroceptive inputs in (healthy and) clinical conditions characterized by alterations of body representation and multisensory integration of bodily information, and an altered body matrix.

AUTHOR CONTRIBUTIONS

Professor GR conceived and developed the initial draft. SS, DDL, EFP and AD worked with Professor GR to enhance the original draft and develop it into the final draft. All authors have reviewed and approved the final manuscript as submitted.

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REFERENCES

Allen, M., Fardo, F., Dietz, M. J., Hillebrandt, H., Friston, K. J., Rees, G., et al. (2016). Anterior insula coordinates hierarchical processing of tactile mismatch responses. *Neuroimage* 127, 34–43. doi: 10.1016/j.neuroimage.2015.11.030

Apps, M. A., and Tsakiris, M. (2014). The free-energy self: a predictive coding account of self-recognition. *Neurosci. Biobehav. Rev.* 41, 85–97. doi: 10.1016/j.neubiorev.2013.01.029

Aspell, J. E., Lenggenhager, B., and Blanke, O. (2012). "Multisensory perception and bodily self-consciousness: from out-of-body to inside-body experience," in *The Neural Bases of Multisensory Processes*, eds M. M. Murray and M. T. Wallace (Boca Raton, FL: CRC Press), 467–481.

Banakou, D., Groten, R., and Slater, M. (2013). Illusory ownership of a virtual child body causes overestimation of object sizes and implicit attitude changes. *Proc. Natl. Acad. Sci. U S A* 110, 12846–12851. doi: 10.1073/pnas.1306779110

Barrett, L. F., Quigley, K. S., and Hamilton, P. (2016). An active inference theory of allostasis and interoception in depression. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 371:20160011. doi: 10.1098/rstb.2016.0011

Behrens, T. E., Woolrich, M. W., Walton, M. E., and Rushworth, M. F. (2007). Learning the value of information in an uncertain world. *Nat. Neurosci.* 10, 1214–1221. doi: 10.1038/nn1954

Bergouignan, L., Nyberg, L., and Ehrsson, H. H. (2014). Out-of-body-induced hippocampal amnesia. *Proc. Natl. Acad. Sci. U S A* 111, 4421–4426. doi: 10.1073/pnas.1318801111

Blanke, O. (2012). Multisensory brain mechanisms of bodily self-consciousness. *Nat. Rev. Neurosci.* 13, 556–571. doi: 10.1038/nrn3292

Blanke, O., Faivre, N., and Dieguez, S. (2016). "Chapter 20—Leaving body and life behind: out-of-body and near-death experience," in *The Neurology of Conciousness*, 2nd Edn. eds S. Laureys, O. Gosseries and G. Tononi (New York, NY: Academic Press), 323–347.

Blanke, O., Slater, M., and Serino, A. (2015). Behavioral, neural, and computational principles of bodily self-consciousness. *Neuron* 88, 145–166. doi: 10.1016/j.neuron.2015.09.029

Boesch, E., Bellan, V., Moseley, G. L., and Stanton, T. R. (2016). The effect of bodily illusions on clinical pain: a systematic review and meta-analysis. *Pain* 157, 516–529. doi: 10.1097/j.pain.0000000000000423

Bolognini, N., Convento, S., Casati, C., Mancini, F., Brighina, F., and Vallar, G. (2016). Multisensory integration in hemianopia and unilateral spatial neglect: evidence from the sound induced flash illusion. *Neuropsychologia* 87, 134–143. doi: 10.1016/j.neuropsychologia.2016.05.015

Botvinick, M., and Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature* 391:756. doi: 10.1038/35784

Brouet, F., Twiefel, J., and Wallaschek, J. (2016). Modal interaction in ultrasonic welding block sonotrodes induced by the mistuning of the material properties. *J. Sound Vib.* 381, 1–13. doi: 10.1016/j.jsv.2016.06.021

Castelvecchi, D. (2016). Low-cost headsets boost virtual reality's lab appeal. *Nature* 533, 153–154. doi: 10.1038/533153a

Costantini, M. (2014). Body perception, awareness, and illusions. *Wiley Interdiscip. Rev. Cogn. Sci.* 5, 551–560. doi: 10.1002/wcs.1309

Courville, A. C., Daw, N. D., and Touretzky, D. S. (2006). Bayesian theories of conditioning in a changing world. *Trends Cogn. Sci.* 10, 294–300. doi: 10.1016/j.tics.2006.05.004

Curthoys, I. S., and Grant, J. W. (2015). How does high-frequency sound or vibration activate vestibular receptors? *Exp. Brain Res.* 233, 691–699. doi: 10.1007/s00221-014-4192-6

Dakanalis, A., Gaudio, S., Serino, S., Clerici, M., Carrà, G., and Riva, G. (2016). Body-image distortion in anorexia nervosa. *Nat. Rev. Dis. Primers* 2:16026. doi: 10.1038/nrdp.2016.26

Dieguez, S., and Lopez, C. (2016). The bodily self: insights from clinical and experimental research. *Ann. Phys. Rehabil. Med.* doi: 10.1016/j.rehab.2016.04.007 [Epub ahead of print].

Di Lernia, D., Serino, S., Cipresso, P., and Riva, G. (2016a). Ghosts in the Machine. Interoceptive modeling for chronic pain treatment. *Front. Neurosci.* 10:314. doi: 10.3389/fnins.2016.00314

Di Lernia, D., Serino, S., and Riva, G. (2016b). Pain in the body. altered interoception in chronic pain conditions: a systematic review. *Neurosci. Biobehav. Rev.* 71, 328–341. doi: 10.1016/j.neubiorev.2016.09.015

Dix, M., and Hallpike, C. (1952). *The Pathology, Symptomatology and Diagnosis of Certain Common Disorders of the Vestibular System.* Thousand Oaks, CA: SAGE Publications.

Doak, P. E. (1964). Preface. *J. Sound Vib.* 1, i–iii. doi: 10.1016/0022-460X(64)90002-1

Ehrsson, H. H. (2007). The experimental induction of out-of-body experiences. *Science* 317:1048. doi: 10.1126/science.1142175

Ehrsson, H. H., Rosén, B., Stockselius, A., Ragnö, C., Köhler, P., and Lundborg, G. (2008). Upper limb amputees can be induced to experience a rubber hand as their own. *Brain* 131, 3443–3452. doi: 10.1093/brain/awn297

Falconer, C. J., Rovira, A., King, J. A., Gilbert, P., Antley, A., Fearon, P., et al. (2016). Embodying self-compassion within virtual reality and its effects on patients with depression. *BJPsych Open* 2, 74–80. doi: 10.1192/bjpo.bp.115.002147

Fechir, M., Klega, A., Buchholz, H. G., Pfeifer, N., Balon, S., Schlereth, T., et al. (2010). Cortical control of thermoregulatory sympathetic activation. *Eur. J. Neurosci.* 31, 2101–2111. doi: 10.1111/j.1460-9568.2010.07243.x

Ferri, F., Costantini, M., Salone, A., Di Iorio, G., Martinotti, G., Chiarelli, A., et al. (2014). Upcoming tactile events and body ownership in schizophrenia. *Schizophr. Res.* 152, 51–57. doi: 10.1016/j.schres.2013.06.026

Finotti, G., and Costantini, M. (2016). Multisensory body representation in autoimmune diseases. *Sci. Rep.* 6:21074. doi: 10.1038/srep21074

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* 11, 127–138. doi: 10.1038/nrn2787

Friston, K. J., Daunizeau, J., Kilner, J., and Kiebel, S. J. (2010). Action and behavior: a free-energy formulation. *Biol. Cybern.* 102, 227–260. doi: 10.1007/s00422-010-0364-z

Gallace, A., and Spence, C. (2014). *In Touch With the Future: The Sense of Touch From Cognitive Neuroscience To Virtual Reality.* Oxford: Oxford University Press.

Guignard, J. C. (1971). Human sensitivity to vibration. *J. Sound Vib.* 15, 11–16. doi: 10.1016/0022-460x(71)90354-3

Guterstam, A., Abdulkarim, Z., and Ehrsson, H. H. (2015a). Illusory ownership of an invisible body reduces autonomic and subjective social anxiety responses. *Sci. Rep.* 5:9831. doi: 10.1038/srep09831

Guterstam, A., Björnsdotter, M., Gentile, G., and Ehrsson, H. H. (2015b). Posterior cingulate cortex integrates the senses of self-location and body ownership. *Curr. Biol.* 25, 1416–1425. doi: 10.1016/j.cub.2015.03.059

Hong, Z. Y., Xie, W. J., and Wei, B. (2011). Acoustic levitation with self-adaptive flexible reflectors. *Rev. Sci. Instrum.* 82:074904. doi: 10.1063/1.3610652

Jáuregui Renaud, K. (2015). Vestibular function and depersonalization/derealization symptoms. *Multisens. Res.* 28, 637–651. doi: 10.1163/22134808-00002480

Kang, S. T., and Yeh, C. K. (2010). Potential-well model in acoustic tweezers. *IEEE Trans. Ultrason. Ferroelectr. Freq. Control.* 57, 1451–1459. doi: 10.1109/TUFFC.2010.1564

Keizer, A., Van Elburg, A., Helms, R., and Dijkerman, H. C. (2016). A virtual reality full body illusion improves body image disturbance in anorexia nervosa. *PLoS One* 11:e0163921. doi: 10.1371/journal.pone.0163921

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., and Glaser, R. (2002). Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom. Med.* 64, 15–28. doi: 10.1097/00006842-200201000-00004

Lang, I. M., Medda, B. K., and Shaker, R. (2011). Differential activation of medullary vagal nuclei caused by stimulation of different esophageal mechanoreceptors. *Brain Res.* 1368, 119–133. doi: 10.1016/j.brainres.2010.10.061

Lavin, C., San Martin, R., and Rosales Jubal, E. (2014). Pupil dilation signals uncertainty and surprise in a learning gambling task. *Front. Behav. Neurosci.* 7:218. doi: 10.3389/fnbeh.2013.00218

Lee, B. C., Martin, B. J., and Sienko, K. H. (2013). The effects of actuator selection on non-volitional postural responses to torso-based vibrotactile stimulation. *J. Neuroeng. Rehabil.* 10:21. doi: 10.1186/1743-0003-10-21

Lenggenhager, B., Loetscher, T., Kavan, N., Pallich, G., Brodtmann, A., Nicholls, M. E., et al. (2012). Paradoxical extension into the contralesional hemispace in spatial neglect. *Cortex* 48, 1320–1328. doi: 10.1016/j.cortex.2011.10.003

Lenggenhager, B., Tadi, T., Metzinger, T., and Blanke, O. (2007). Video ergo sum: manipulating bodily self-consciousness. *Science* 317, 1096–1099. doi: 10.1126/science.1143439

Li, A., Montano, Z., Chen, V. J., and Gold, J. I. (2011). Virtual reality and pain management: current trends and future directions. *Pain Manag.* 1, 147–157. doi: 10.2217/pmt.10.15

Limanowski, J., and Blankenburg, F. (2013). Minimal self-models and the free energy principle. *Front. Hum. Neurosci.* 7:547. doi: 10.3389/fnhum.2013.00547

Llobera, J., Sanchez-Vives, M. V., and Slater, M. (2013). The relationship between virtual body ownership and temperature sensitivity. *J. R. Soc. Interface* 10:20130300. doi: 10.1098/rsif.2013.0300

Maister, L., Sebanz, N., Knoblich, G., and Tsakiris, M. (2013). Experiencing ownership over a dark-skinned body reduces implicit racial bias. *Cognition* 128, 170–178. doi: 10.1016/j.cognition.2013.04.002

Makin, T. R., Holmes, N. P., and Ehrsson, H. H. (2008). On the other hand: dummy hands and peripersonal space. *Behav. Brain Res.* 191, 1–10. doi: 10.1016/j.bbr.2008.02.041

Manzari, L., Burgess, A. M., and Curthoys, I. S. (2010). Effect of bone-conducted vibration of the midline forehead (Fz) in unilateral vestibular loss (uVL). Evidence for a new indicator of unilateral otolithic function. *Acta Otorhinolaryngol. Ital.* 30:175. doi: 10.1016/s1388-2457(11)60029-1

Marzo, A., Seah, S. A., Drinkwater, B. W., Sahoo, D. R., Long, B., and Subramanian, S. (2015). Holographic acoustic elements for manipulation of levitated objects. *Nat. Commun.* 6:8661. doi: 10.1038/ncomms9661

Maselli, A. (2015). Allocentric and egocentric manipulations of the sense of self-location in full-body illusions and their relation with the sense of body ownership. *Cogn. Process.* 16, 309–312. doi: 10.1007/s10339-015-0667-z

Mitrou, G., Ferguson, N., and Renno, J. (2017). Wave transmission through two-dimensional structures by the hybrid FE/WFE approach. *J. Sound Vib.* 389, 484–501. doi: 10.1016/j.jsv.2016.09.032

Moseley, G. L., Gallace, A., and Iannetti, G. D. (2012a). Spatially defined modulation of skin temperature and hand ownership of both hands in patients with unilateral complex regional pain syndrome. *Brain* 135, 3676–3686. doi: 10.1093/brain/aws297

Moseley, G. L., Gallace, A., and Spence, C. (2012b). Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'. *Neurosci. Biobehav. Rev.* 36, 34–46. doi: 10.1016/j.neubiorev.2011.03.013

Naito, E., Ehrsson, H. H., Geyer, S., Zilles, K., and Roland, P. E. (1999). Illusory arm movements activate cortical motor areas: a positron emission tomography study. *J. Neurosci.* 19, 6134–6144.

Normand, J. M., Giannopoulos, E., Spanlang, B., and Slater, M. (2011). Multisensory stimulation can induce an illusion of larger belly size in immersive virtual reality. *PLoS One* 6:e16128. doi: 10.1371/journal.pone.0016128

O'Reilly, J. X., Schuffelgen, U., Cuell, S. F., Behrens, T. E., Mars, R. B., and Rushworth, M. F. (2013). Dissociable effects of surprise and model update in parietal and anterior cingulate cortex. *Proc. Natl. Acad. Sci. U S A* 110, E3660–E3669. doi: 10.1073/pnas.1305373110

Park, H. D., Bernasconi, F., Bello-Ruiz, J., Pfeiffer, C., Salomon, R., and Blanke, O. (2016). Transient modulations of neural responses to heartbeats covary with bodily self-consciousness. *J. Neurosci.* 36, 8453–8460. doi: 10.1523/JNEUROSCI.0311-16.2016

Perpiña, C., Botella, C., and Baños, R. M. (2003). Virtual reality in eating disorders. *Eur. Eat. Disord. Rev.* 11, 261–278. doi: 10.1002/erv.520

Petkova, V. I., Khoshnevis, M., and Ehrsson, H. H. (2011). The perspective matters! Multisensory integration in ego-centric reference frames determines full-body ownership. *Front. Psychol.* 2:35. doi: 10.3389/fpsyg.2011.00035

Pfeiffer, C., Lopez, C., Schmutz, V., Duenas, J. A., Martuzzi, R., and Blanke, O. (2013). Multisensory origin of the subjective first-person perspective: visual, tactile and vestibular mechanisms. *PLoS One* 8:e61751. doi: 10.1371/journal.pone.0061751

Postmes, L., Sno, H. N., Goedhart, S., van der Stel, J., Heering, H. D., and de Haand, L. (2014). Schizophrenia as a self-disorder due to perceptual incoherence. *Schizophr. Res.* 152, 41–50. doi: 10.1016/j.schres.2013.07.027

Preston, C., and Ehrsson, H. H. (2014). Illusory changes in body size modulate body satisfaction in a way that is related to non-clinical eating disorder psychopathology. *PloS One* 9:e85773. doi: 10.1371/journal.pone.0085773

Preston, C., Kuper-Smith, B. J., and Ehrsson, H. H. (2015). Owning the body in the mirror: the effect of visual perspective and mirror view on the full-body illusion. *Sci. Rep.* 5:18345. doi: 10.1038/srep18345

Radke, S., Kellermann, T., Kogler, L., Schuch, S., Bauer, H., and Derntl, B. (2014). "Training the ACC with localized EEG-neurofeedback—a pioneer study," in *2nd Conference of the European Society for Cognitive and Affective Neuroscience (ESCAN)* (Dortmund).

Riva, G. (1998a). Modifications of body image induced by virtual reality. *Percept. Motor Skills* 86, 163–170. doi: 10.2466/pms.1998.86.1.163

Riva, G. (1998b). Virtual Reality vs. Virtual Body: the use of virtual environments in the treatment of body experience disturbances. *Cyberpsychol. Behav.* 1, 129–138. doi: 10.1089/cpb.1998.1.129

Riva, G. (2008). From virtual to real body: virtual reality as embodied technology. *J. Cyberther. Rehabil.* 1, 7–22.

Riva, G. (2011). The key to unlocking the virtual body: virtual reality in the treatment of obesity and eating disorders. *J. Diabetes Sci. Technol.* 5, 283–292. doi: 10.1177/193229681100500213

Riva, G. (2014). Out of my real body: cognitive neuroscience meets eating disorders. *Front. Hum. Neurosci.* 8:236. doi: 10.3389/fnhum.2014.00236

Riva, G. (2016a). "Embodied medicine: what human-computer confluence can offer to health care," in *Human Computer Confluence: Transforming Human Experience Through Symbiotic Technologies*, eds A. Gaggioli, A. Ferscha, G. Riva, S. Dunne and I. Viaud-Delmon (Warsaw: De Gruyter Open), 55–79.

Riva, G. (2016b). Neurobiology of anorexia nervosa: serotonin dysfunctions link self-starvation with body image disturbances through an impaired body memory. *Front. Hum. Neurosci.* 10:600. doi: 10.3389/fnhum.2016.00600

Riva, G., Gaggioli, A., and Dakanalis, A. (2013). From body dissatisfaction to obesity: how virtual reality may improve obesity prevention and treatment in adolescents. *Stud. Health Technol. Inform.* 184, 356–362. doi: 10.3233/978-1-61499-209-7-356

Roll, J. P., and Vedel, J. P. (1982). Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Exp. Brain Res.* 47, 177–190. doi: 10.1007/bf00239377

Romano, D., Llobera, J., and Blanke, O. (2016). Size and viewpoint of an embodied virtual body impact the processing of painful stimuli. *J. Pain* 17, 350–358. doi: 10.1016/j.jpain.2015.11.005

Schust, M. (2004). Effects of low frequency noise up to 100 Hz. *Noise Health* 6, 73–85.

Sengupta, J. N. (2006). Esophageal sensory physiology. *GI Motility Online* doi: 10.1038/gimo16

Senna, I., Maravita, A., Bolognini, N., and Parise, C. V. (2014). The marble-hand illusion. *PLoS One* 9:e91688. doi: 10.1371/journal.pone.0091688

Serino, S., and Dakanalis, A. (2016). Bodily illusions and weight-related disorders: clinical insights from experimental research. *Ann. Phys. Rehabil. Med.* doi: 10.1016/j.rehab.2016.10.002 [Epub ahead of print].

Serino, S., Dakanalis, A., Santino, G., Carrà, G., Cipresso, P., Clerici, M., et al. (2016a). Out of body, out of space: impaired reference frame processing in eating disorders. *Psychiatry Res.* 230, 732–734. doi: 10.1016/j.psychres.2015.10.025

Serino, S., Pedroli, E., Keizer, A., Triberti, S., Dakanalis, A., Pallavicini, F., et al. (2016b). Virtual reality body swapping: a tool for modifying the allocentric memory of the body. *Cyberpsychol. Behav. Soc. Netw.* 19, 127–133. doi: 10.1089/cyber.2015.0229

Serino, S., Scarpina, F., Keizer, A., Pedroli, E., Dakanalis, A., Castelnuovo, G., et al. (2016c). A novel technique for improving bodily experience in a non-operable super–super obesity case. *Front. Psychol.* 7:837. doi: 10.3389/fpsyg.2016.00837

Serino, A., Noel, J.-P., Galli, G., Canzoneri, E., Marmaroli, P., Lissek, H., et al. (2015). Body part-centered and full body-centered peripersonal space representations. *Sci. Rep.* 5:18603. doi: 10.1038/srep18603

Seth, A. K., Suzuki, K., and Critchley, H. D. (2012). An interoceptive predictive coding model of conscious presence. *Front. Psychol.* 3:395. doi: 10.3389/fpsyg.2011.00395

Sharif-Naeini, R., Folgering, J. H. A., Bichet, D., Duprat, F., Delmas, P., Patel, A., et al. (2010). Sensing pressure in the cardiovascular system: Gq-coupled mechanoreceptors and TRP channels. *J. Mol. Cell. Cardiol.* 48, 83–89. doi: 10.1016/j.yjmcc.2009.03.020

Simeon, D., Guralnik, O., Hazlett, E. A., Spiegel-Cohen, J., Hollander, E., and Buchsbaum, M. S. (2000). Feeling unreal: a PET study of depersonalization disorder. *Am. J. Psychiatry* 157, 1782–1788. doi: 10.1176/appi.ajp.157.11.1782

Spanlang, B., Normand, J.-M., Borland, D., Kilteni, K., Giannopoulos, E., Pomes, A., et al. (2014). How to build an embodiment lab: achieving body representation illusions in virtual reality. *Front. Robot. Ai* 1:9. doi: 10.3389/frobt.2014.00009

Suzuki, K., Garfinkel, S. N., Critchley, H. D., and Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia* 51, 2909–2917. doi: 10.1016/j.neuropsychologia.2013.08.014

Tajadura-Jiménez, A., Grehl, S., and Tsakiris, M. (2012). The other in me: interpersonal multisensory stimulation changes the mental representation of the self. *PLoS One* 7:e40682. doi: 10.1371/journal.pone.0040682

Takahashi, Y. (2011). A study on the contribution of body vibrations to the vibratory sensation induced by high-level, complex low-frequency noise. *Noise Health* 13, 2–8. doi: 10.4103/1463-1741.73993

Talsma, D. (2015). Predictive coding and multisensory integration: an attentional account of the multisensory mind. *Front. Integr. Neurosci.* 9:19. doi: 10.3389/fnint.2015.00019

Tsakiris, M. (2010). My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia* 48, 703–712. doi: 10.1016/j.neuropsychologia.2009.09.034

Tsakiris, M. (2017). The multisensory basis of the self: from body to identity to others. *Q. J. Exp. Psychol. (Hove)* 70, 597–609. doi: 10.1080/17470218.2016.1181768

Tsakiris, M., and Critchley, H. (2016). Interoception beyond homeostasis: affect, cognition and mental health. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 371:20160002. doi: 10.1098/rstb.2016.0002

Tsay, A., Allen, T. J., Proske, U., and Giummarra, M. J. (2015). Sensing the body in chronic pain: a review of psychophysical studies implicating altered body representation. *Neurosci. Biobehav. Rev.* 52, 221–232. doi: 10.1016/j.neubiorev.2015.03.004

Wallwork, S. B., Bellan, V., Catley, M. J., and Moseley, G. L. (2016). Neural representations and the cortical body matrix: implications for sports medicine and future directions. *Br. J. Sports Med.* 50, 990–996. doi: 10.1136/bjsports-2015-095356

Welgampola, M. S., and Day, B. L. (2006). Craniocentric body-sway responses to 500 Hz bone-conducted tones in man. *J. Physiol.* 577, 81–95. doi: 10.1113/jphysiol.2006.115204

Wheatley, J., Brewin, C. R., Patel, T., Hackmann, A., Wells, A., Fisher, P., et al. (2007). I'll believe it when I can see it: imagery rescripting of intrusive sensory memories in depression. *J. Behav. Ther. Exp. Psychiatry* 38, 371–385. doi: 10.1016/j.jbtep.2007.08.005

Zamir, M., Kimmerly, D. S., and Shoemaker, J. K. (2012). Cardiac mechanoreceptor function implicated during premature ventricular contraction. *Auton. Neurosci.* 167, 50–55. doi: 10.1016/j.autneu.2011.12.003

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frontiers in Human Neuroscience

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Implicit and Explicit Routes to Recognize the Own Body: Evidence from Brain Damaged Patients

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Much research suggested that recognizing our own body-parts and attributing a body-part to our physical self-likely involve distinct processes. Accordingly, facilitation for self-body-parts was found when an implicit, but not an explicit, self-recognition was required. Here, we assess whether implicit and explicit bodily self-recognition is mediated by different cerebral networks and can be selectively impaired after brain lesion. To this aim, right- (RBD) and left- (LBD) brain damaged patients and age-matched controls were presented with rotated pictures of either self- or other-people hands. In the Implicit task participants were submitted to hand laterality judgments. In the Explicit task they had to judge whether the hand belonged, or not, to them. In the Implicit task, controls and LBD patients, but not RBD patients, showed an advantage for self-body stimuli. In the Explicit task a disadvantage emerged for self-compared to others' body stimuli in controls as well as in patients. Moreover, when we directly compared the performance of patients and controls, we found RBD, but not LBD, patients to be impaired in both the implicit and explicit recognition of self-body-part stimuli. Conversely, no differences were found for others' body-part stimuli. Crucially, 40% RBD patients showed a selective deficit for implicit processing of self-body-part stimuli, whereas 27% of them showed a selective deficit in the explicit recognition of their own body. Additionally, we provide anatomical evidence revealing the neural basis of this dissociation. Based on both behavioral and anatomical data, we suggest that different areas of the right hemisphere underpin implicit and explicit self-body knowledge.

Keywords: implicit and explicit dissociation, mental rotation, body-part, self-other recognition, brain damaged patient

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INTRODUCTION

The body, including its various parts, is an important component of our self and its identity, as well as one of its most distinctive physical features. Previous studies showed that the recognition of a body (or body-parts) as one's own depends on a multitude of information. These studies suggest that bodily self-recognition results from the simultaneous processing of visual components (Sugiura et al., 2005; Devue et al., 2007), somatosensory and proprioceptive signals (for a review see Blanke, 2012), and motor information (Sugiura et al., 2006; Frassinetti et al., 2009). Starting from this evidence here we focus on the contribution of visual and motor information to bodily self-processing. A relevant distinction has been recently made in the field between implicit and explicit body knowledge. In this respect, Frassinetti et al. (2008, 2009, 2010) investigated the implicit recognition of self-body-parts by using a visual matching-to-sample task. Participants were required to decide which of two vertically aligned images (high or low) matched the central target stimulus (i.e., an Implicit task). Stimuli could depict participants' or other people's body-parts (hand, foot, arm, leg). Results showed that participants were more accurate with self rather than others' body-parts. This facilitation was called *self-advantage effect*. Interestingly, the self-advantage effect was not found when participants were explicitly required to judge whether the upper or the lower stimulus corresponded to their own body-parts (Frassinetti et al., 2011). This suggests possible dissociation between implicit and explicit bodily self-processing. However, neither such implicit-explicit dissociation in the self-advantage effect nor its underlying neural correlates have been demonstrated so far in brain damaged patients.

To better investigate the mechanisms of the implicit and explicit bodily self-processing, in a following study the authors adopted a laterality judgment task (Ferri et al., 2011). In a first experiment (implicit), participants were requested to report the laterality of images depicting self or other's hands presented at different angular orientations, whereas in the second experiment (explicit), participants were asked to recognize their own hand (Ferri et al., 2011). In order to perform the former but not the latter task, participants simulated a motor rotation of their own body-parts so as to match that of the observed stimulus (Ionta et al., 2007, 2012). In the laterality judgment task, a facilitatory effect (i.e., faster response times) was found in response to hand stimuli belonging to the participants (self-stimuli), suggesting that the body self-advantage is based on a sensorimotor representation. This facilitatory effect was not observed in the second task, that is, during the explicit discrimination between self and others' stimuli. Indeed, participants performed worst with self-compared to others' stimuli. The authors hypothesize that to successfully recognize a stimulus as own body-part, participants compare the displayed picture with the mental representation of one's own body, using visual cue and information arise from memory. However, this representation may be affected by perceptual distortions, such as an overestimation of the body size or distorted body shape. Thus, when participants match the image of their own body-part with the displayed hand, the judgment of ownership is more vulnerable to errors than the implicit one. Overall, these results raise the possibility that bodily self-recognition is based on, at least, two different mechanisms for the implicit and explicit self-body processing, subtended by two different cerebral networks. As a consequence, different brain lesions might selectively impair either the implicit or the explicit self-body processing.

To test these hypotheses, patients with focal cerebral lesion (15 RBD and 15 LBD patients) and a group of healthy subjects were recruited and asked to perform two experiments.

In the first experiment participants were submitted to a laterality judgment task of rotated hands with different angular orientation (Implicit task). In the second experiment they were asked to explicitly recognize their own hand (Explicit task; see Ferri et al., 2011 for the experimental paradigms). In both experiments, the displayed hand was the participants' hand (self-condition) in half of the trials, whereas it depicted other people's hand (other condition) in the rest of the trials.

We expected to find one of the following alternative outcomes. If implicit and explicit body processing are mediated by different neural networks, then at least some of the patients showing poor performance in the Implicit task should perform similarly to controls in the Explicit task, or the opposite. This does not hold, indeed, in cases where the lesion includes brain regions involved in both tasks. If, in contrast, implicit and explicit self-body-parts recognition is mediated by the same network, all patients should perform worse than controls in both the implicit and the explicit tasks.

MATERIALS AND METHODS

Participants and Neuropsychological Assessment

Fifteen RBD patients (9 males, age = 59.3.4 ± 7 years; education = 10.9 ± 4.7 years) and 15 LBD patients (10 males, age = 63.1 ± 7 years; education = 8.9 ± 2.7 years) participated in the study. All patients were right handed by their own verbal report and were assessed for the presence of a general cognitive impairment through the Mini-Mental State Examination (Folstein et al., 1975). Thirty healthy volunteers were recruited through a recreational center as controls: half of them were matched with the RBD patients, whereas the other half were matched with the LBD patients. Three one-way ANOVAs confirmed that the four groups were not significantly different for age [$F_{(3,\ 60)} = 4.46, p = 0.13$], education [$F_{(3,\ 60)} = 5.63, p = 0.17$] and MMSE score [$F_{(3,\ 54)} = 2.07, p = 0.17$]. Finally, no significant difference was found for the variable sex across the four groups, as a chi-square test confirmed [$\chi^2_{(1)} = 1.07, p = 0.30$].

The presence and severity of extrapersonal neglect (Bell's Cancellation test; Gauthier et al., 1989), personal neglect (Fluff Test; Cocchini et al., 2001) and anosognosia for hemiplegia and hemianestesia (Spinazzola et al., 2008) were also assessed (for details see **Table 1**).

Patients were recruited at the Fondazione Maugeri Hospital (Castel Goffredo, Italy) and at the Villa Bellombra Rehabilitation Hospital (Bologna, Italy).

All participants, naive to the purpose of the study, gave their informed consent to participate to the study. The study was approved by the local ethics committee (Villa Bellombra Hospital and Department of Psychology of Bologna), and all procedures were in agreement with the 2008 Helsinki Declaration.

Patients' Lesion

Brain lesions of 12 RBD and 12 LBD were identified by Computerized Tomography and Magnetic Resonance digitalized images (CT/MRI). For each patient, the location and extent

TABLE 1 | Clinical and neuropsychological data of right brain damaged (a) and left brain damaged patients (b).

A

Patient	AGE	TPL	AETIOLOGY	MMSE*	Bells**	Fluff	AHP***	AHE***
RBD 1	79	60	I	30	**5**	2	0	0
RBD 2	73	39	I	30	0	0	0	0
RBD 3	48	19	I	–	**5**	1	0	0
RBD 4	39	228	I	–	2	1	0	0
RBD 5	57	650	I	–	3	0	0	0
RBD 6	59	50	I	–	0	0	0	0
RBD 7	62	30	I	28	0	0	0	0
RBD 8	54	392	H	28	2	1	0	0
RBD 9	71	39	I	22	**15**	0	0	0
RBD 10	65	73	H	24	**14**	**10**	**1**	**1**
RBD 11	61	37	I	–	0	0	0	**1**
RBD 12	64	79	H	23	**12**	**5**	0	**2**
RBD 13	68	16	I	28	0	1	0	0
RBD 14	34	50	H	30	0	1	0	0
RBD 15	55	96	I	30	3	0	0	0

B

Patient	AGE	TPL	AETIOLOGY	MMSE*	Token Test
LBD 1	65	70	H	–	–
LBD 2	44	93	H	27	26
LBD 3	57	25	I	22	33
LBD 4	77	43	I	28	–
LBD 5	67	52	I	22	26
LBD 6	51	34	H	27	32
LBD 7	47	51	I	24	30
LBD 8	61	47	H	30	34
LBD 9	52	35	H	25	30
LBD 10	63	31	I	28	32
LBD 11	64	52	I	28	31
LBD 12	72	28	I	20	22
LBD 13	75	39	I	26	34
LBD 14	82	60	I	25	30
LBD 15	70	95	I	28	32

*TPL, Time post lesion (days); I, ischemic stroke, H, hemorrhagic stroke; *MMSE, Mini Mental State Examination (scores are corrected for years of education and age); **Bells Test, left omissions; Fluff test, omissions; ***AHP, anosognosia for hemiplegia; ***AHE, anosognosia for hemianestesia (scoring 0 = no anosognosia, 1 = moderate anosognosia, 2 = severe anosognosia, each value refers to the left upper limb). Bold characters indicated pathological performance.*

of brain damage was delineated and manually mapped in the stereotactic space of the MNI by using the free software MRIcro (Rorden and Brett, 2000).

As first step, MNI template was rotated (pitch only) to approximate the slice plane of the patient's scan. A trained rater (MC), using anatomically landmarks, manually mapped the lesion onto each correspondent template slice. After that, drawn lesions were inspected by a second trained rater (FF) and in case of disagreement, an intersection lesion map was used. Finally, lesions maps were rotated back into the standard space applying the inverse of the transformation parameters used on the stage of adaptation to the brain scan.

To compare lesions' extension we conducted a Mann Whitney U-test on the mean number of voxels involved by the lesion for each patients in the RBD patients' group and LBD patients' group. Results confirmed that the two groups were not significantly different regarding the 'total lesion volume' [$U = 47.00$; $z = -1.68$; $p = 0.09$].

The maximum lesion overlap of RBD patients' lesions was mainly located along two different regions: one encompassing frontal subcortical region (putamen, paraventricular area, internal and external capsule) and one involving temporo-parietal regions such as the insular cortex, the superior temporal and postcentral gyri and the inferior parietal lobe

(BA 40) (for a graphical representation, see **Figure 1A**). The maximum lesion overlap of LBD patients' lesions involved a frontal subcortical region (paraventricular area, internal and external capsule), the postcentral gyrus and the inferior parietal lobe (BA 40) (for a graphical representation, see **Figure 1B**).

Behavioral Studies

Stimuli and Procedure

Gray-scale pictures of the dorsal view of right and left hands (see **Figure 2**) were used as experimental stimuli. We adopted only the dorsal view of hand to compare the present findings with the previous ones of our group (Ferri et al., 2011). The hands of each participant were photographed with a digital camera in a session prior to the experiments. Hands were always photographed with constant artificial light, in the same position and at a fixed distance from the camera (40 cm).

Pictures were modified with Adobe Photoshop® CS4 software: each hand was cut from the original picture, centered and then pasted on a white background. Finally, each photograph was clockwise rotated to obtain six predefined orientation (0°, 60°, 120°, 180°, 240°, 300°), in which fingers pointing upwards defined the upright orientation. Half of the trials ($n = 144$) depicted the participant's own left or right hand ("self" trials), whereas the other half depicted the right or left hand of three other people ("other" trials). As far as the latter one, three stimuli were selected from a database of hands pictures as the best match with each participant's hand for size, age, skin color and gender. The luminosity of the gray-scale picture was adjusted taking into account the individually skin shades.

Participants sat in front of a PC screen, at a viewing distance of about 40 cm. A central fixation cross (500 ms duration) was presented at the beginning of each trial followed by a display containing hand's picture on a white background. Stimuli presentation was controlled by E-Prime 2.0 (Psychology Software Tools Inc.) and each trial was timed-out by the participant's response (up to 4000 ms).

In Experiment 1 participants had to judge the laterality (left or right) of displayed hand by pressing as accurately as possible and within the allowed time interval, a left or a right response key ("R" or "P" on keyboard). In Experiment 2, participants had to explicitly judge whether the displayed hand corresponded or not to their own hand by pressing as accurately as possible and within the allowed time interval, a left or a right previously assigned response key ("R" or "P" on keyboard). In both Experiments the response keys were counterbalanced between subjects. Since patients responded by using their not affected hand, that's the left for RBD and the right for LBD, healthy subjects were accordingly divided in two groups: 15 who responded by using the index finger of the right hand, and 15 who using their left hand.

Patients with neglect and/or left hemianopia were submitted to an adapted version of Implicit and Explicit Task in which all stimuli were displayed on the right side of the screen. Analogously, an adapted version of both experiments to patients showing right hemianopia was designed by shifting all stimuli to the left side of the screen.

Both experiments were always preceded by 8 trials as practice. Then, each experiment comprised 288 trials, 72 trials for each of the four conditions: self-right hand, self-left hand, other-right hand, and other-left hand. Furthermore, each orientation was randomly presented 12 times per condition. Since Experiment 1 investigated the implicit and Experiment 2 the explicit bodily self-recognition, Experiment 1 was always conducted before Experiment 2. All participants performed both experiments in one single session lasting up to 1 h.

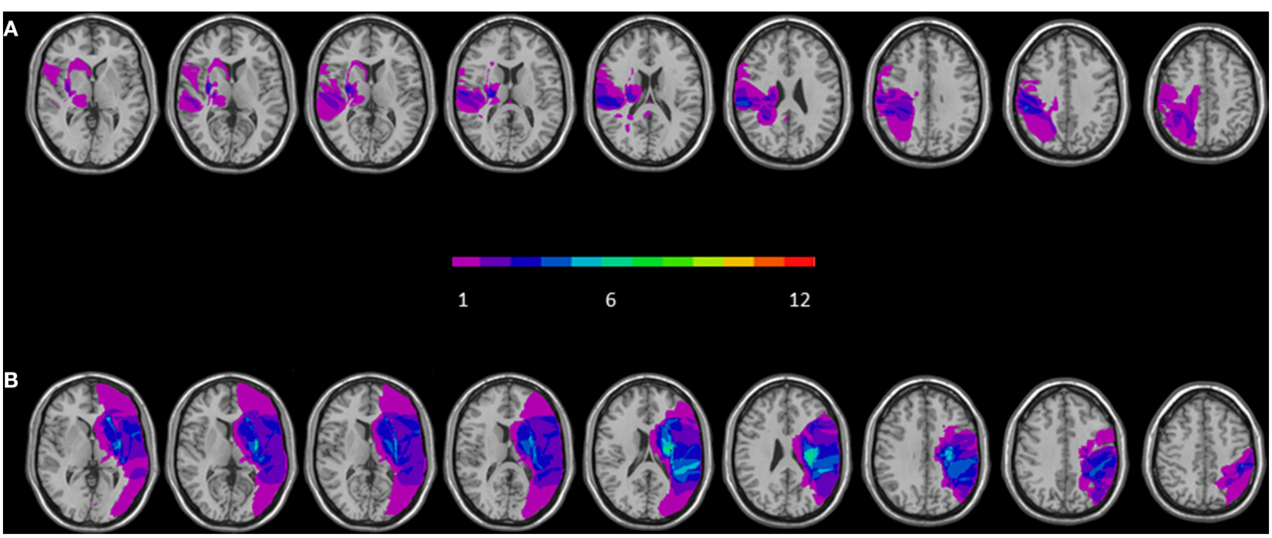

FIGURE 1 | Overlay of reconstructed lesion plots of LBD (A) and RBD patients (B) superimposed onto MNI template. The number of overlapping lesions is illustrated by different colors coding from violet ($n = 1$) to green ($n = 7$).

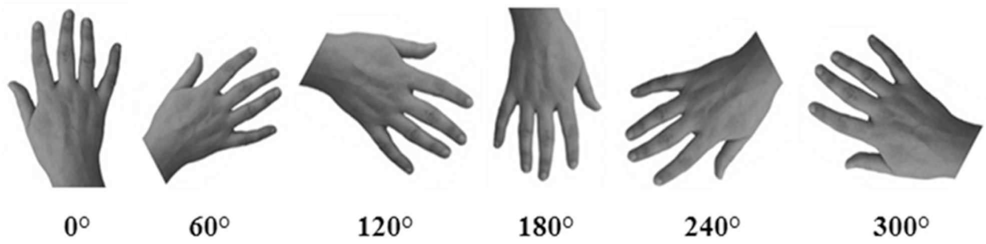

FIGURE 2 | An example of stimuli representing hands at different orientations. In the Implicit task, participants were required to judge the laterality of each stimulus. In the Explicit task, participants were required to judge if the hand was or was not their own.

Statistical Analyses

Data from Experiment 1 (Implicit task) and Experiment 2 (Explicit task) were analyzed separately on mean response times (RTs) for correct trials and on the percentage of correct responses (accuracy). First of all, the presence of the self-advantage effect and the strategy to solve the task (i.e., the mental rotation) were separately tested in healthy subjects and in RBD and LBD patients (Analysis on each group). For healthy subjects, an ANOVA was conducted with Owner (self and other), Laterality (left and right displayed hand) and Orientation (0°, 60°, 120°, 180°, 240°, 300°) as within-subjects factors and Group (H-R = healthy subjects responding with the right finger and H-L = healthy subjects responding with the left finger) as between-subjects factor. For patients, separate ANOVAs were conducted for RBD and LBD patients with Owner (self and other), Laterality (left and right displayed hand) and Orientation (0°, 60°, 120°, 180°, 240°, 300°) as within-subjects factors.

Subsequently, we directly compared patients' performance with the healthy subjects group using the same hand in performing the task. For this reason, separate ANOVAs were conducted (Patients and healthy subjects comparison), with Owner, Laterality, as within-subjects factors: the first, between RBD patients and healthy subjects responding with the right finger (H-R) and the second, between LBD patients and healthy subjects responding with the left finger (H-L). Since these analyses were conducted to compare patients' and controls' performance, only the variable Group and its interaction with other variables will be reported.

Finally, we compared the performance of the four groups on a self-advantage index (i.e., self-minus other). Accordingly, we conducted two One-Way ANOVAs on RTs and on percentage of correct responses, separately for Implicit and Explicit task considering the Group factor (H-R, H-L, LBD, and RBD patients). Where necessary, post-hoc analyses were conducted by using Bonferroni's correction. The magnitude of effect size was expressed by $\eta^2{}_p$.

RESULTS

Within-Group Results of Experiment 1 (Implicit Task)

Analysis on Healthy Subjects

The main effect of **Owner** was significant [$F_{(1,\ 28)} = 6.14$; $p < 0.02$; $\eta^2{}_p = 0.18$]: participants responded faster to self than to other people's hand (self = 1370 ms vs. other = 1421 ms). The main effect of **Orientation** was significant [$F_{(5,\ 140)} = 54.74$ $p < 0.0001$; $\eta_p^2 = 0.66$], since RTs to stimuli at 180° (1696 ms) were longer than all other orientations (0° = 1189 ms, 60° = 1291 ms, 120° = 1481 ms, 240° = 1438 ms, 300° = 1279 ms, $p < 0.0001$ in all cases; see **Figure 3A**). Moreover, longer RTs were observed at 120° and 240° compared to RTs at 0°, 60°, and 300°, $p < 0.005$ for all comparisons). These results show that participants used mental rotation strategy to solve the Implicit task, both for right and left stimuli.

The variable Group and its interaction with other variables were not significant suggesting that the responding hand did not influence the described effects.

As far as the percentage of correct responses, similar results were found: the main effect of **Owner** was significant [$F_{(1,\ 28)} = 11.95$; $p < 0.002$; $\eta_p^2 = 0.30$]: participants were more accurate with self than with other people's hand (self = 88% vs. other = 86%; see **Figure 4A**). The main effect of **Orientation** was significant [$F_{(5,\ 140)} = 20.72$; $p < 0.0001$; $\eta_p^2 = 0.43$], since participants were less accurate at 180° (73%) than all other orientations (0° = 93%, 60° = 93%, 120° = 86%, 240° = 86%, 300° = 92%, $p < 0.03$ in all cases). Crucially, the interaction **Owner × Laterality** was significant [$F_{(1,\ 28)} = 4.40$; $p < 0.05$; $\eta_p^2 = 0.14$]: when the right hand is displayed, participants were more accurate with self (89%) compared to other people's hand (85%; $p < 0.01$). No significant difference was found for the left hand instead. The variable Group and its interaction with other variables were not significant suggesting that the responding hand did not influence the described effects.

RBD Patients

The variable **Orientation** was significant [$F_{(1,\ 14)} = 50.22$; $p < 0.0001$; $\eta_p^2 = 0.78$]: since RTs to stimuli at 180° (2107 ms) were longer than all other orientations (0° = 1551 ms, 60° = 1657 ms, 120° = 2107 ms, 240° = 1742 ms, 300° = 1623 ms, $p < 0.001$ in all cases; see **Figure 3B**).

The interaction **Laterality × Orientation** was significant [$F_{(5,\ 70)} = 5.72$; $p < 0.001$; $\eta_p^2 = 0.29$]: participants responded faster when the right (ipsilesional) hand is rotated at 0° (1428 ms) compared to the left (contralesional hand) hand (1674 ms) but these variables did not interact with Owner.

Analysis on the percentage of correct responses, put in evidence a significant effect of **Owner** [$F_{(1,\ 14)} = 4.59$; $p < 0.05$; $\eta_p^2 = 0.25$] since RBD patients were *less* accurate with self

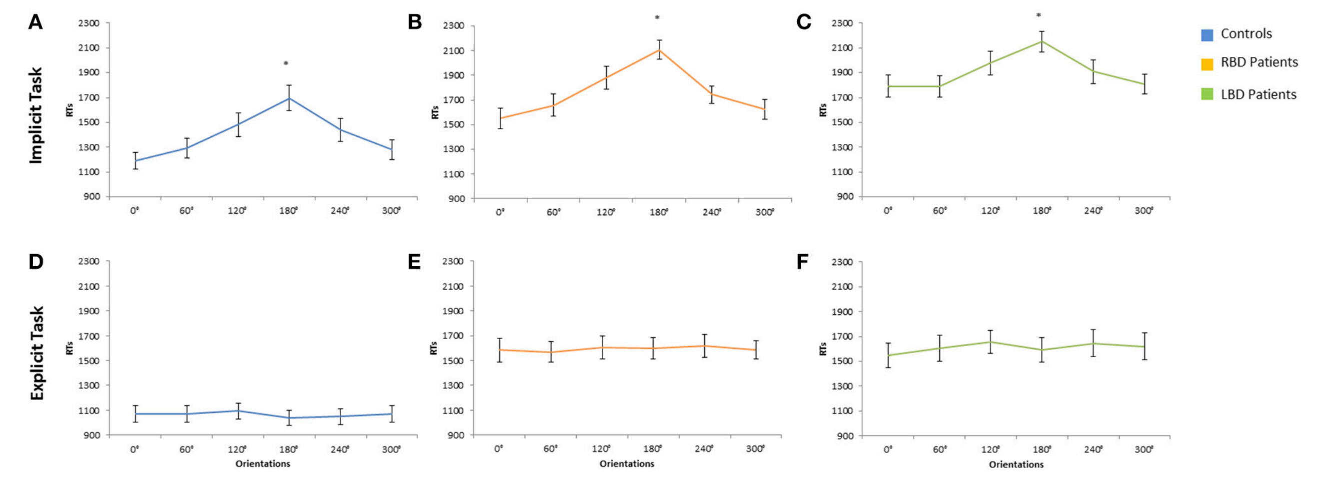

FIGURE 3 | Mean response times of controls, right brain damaged (RBD) and left brain damaged (LBD) patients in Implicit (A–C) and Explicit (D–F) task, respectively. Results are displayed as a function of displayed hand Orientation. The significant difference between 180° and all other orientations is starred. Error bars depict SEMs. The "*"indicate the significant difference.

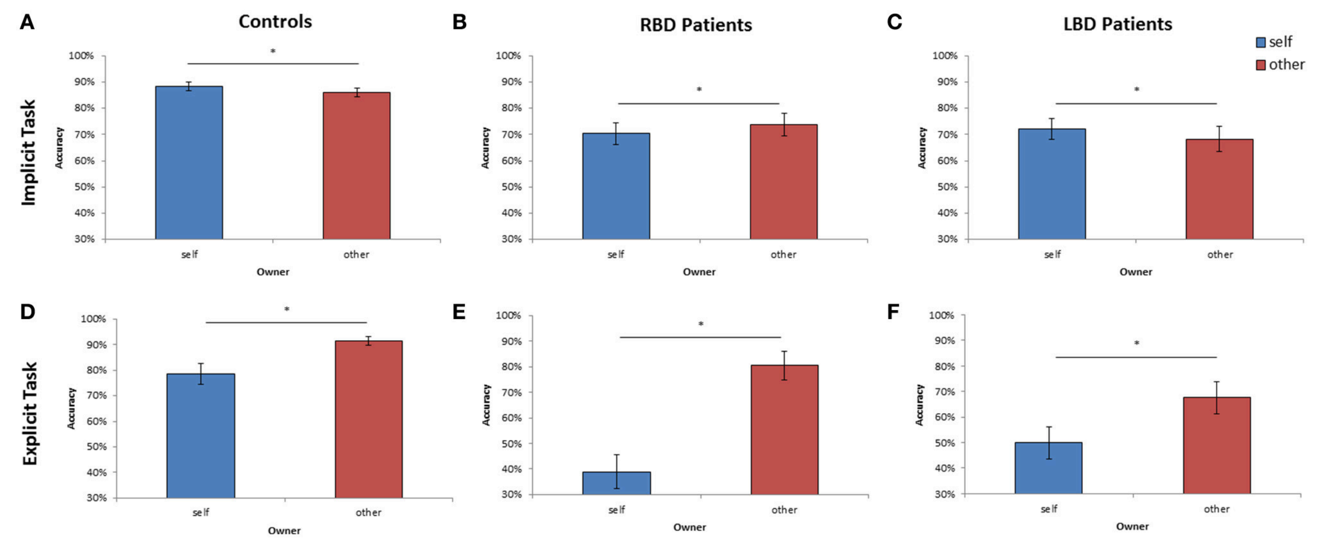

FIGURE 4 | Mean of correct response of controls, right brain damaged (RBD) and left brain damaged (LBD) patients in Implicit (A–C) and Explicit (D–F) task, respectively. The significant difference between self and other stimuli is starred. Error bars depict SEMs. The "*"indicate the significant difference.

than with other people's hand (self = 70% vs. other = 74%; see **Figure 4B**). Furthermore, the variable **Orientation** was significant [$F_{(1, 14)} = 12.95$; $p < 0.0001$; $\eta_p^2 = 0.48$]: participants were less accurate at 180° (52%) than all other orientations (0° = 81%, 60° = 77%, 120° = 67%, 240° = 76%, 300° = 80%, $p < 0.03$ in all cases).

LBD Patients

The main effect of **Owner** was significant [$F_{(1, 14)} = 7.57$; $p < 0.02$; $\eta_p^2 = 0.35$]: participants responded faster with self than with other people's hand (self = 1869 ms vs. other=1938 ms).

The variable **Orientation** was significant [$F_{(1, 14)} = 9.77$; $p < 0.0001$; $\eta_p^2 = 0.41$]: since RTs to stimuli at 180° (2150 ms) were longer than all other orientations (0° = 1791 ms, 60° = 1790 ms, 120° = 1977 ms, 240° = 1907 ms, 300° = 1808 ms, $p < 0.05$ in all cases; see **Figure 3C**).

Analysis on the percentage of correct responses, confirmed a significant effect of **Owner** [$F_{(1, 14)} = 4.41$; $p < 0.05$; $\eta_p^2 = 0.24$], being the LBD patients more accurate with self than with other people's hand (self = 72% vs. other = 68%; see **Figure 4C**). Furthermore, the variable **Orientation** was significant [$F_{(1, 14)} = 7.73$; $p < 0.0001$; $\eta_p^2 = 0.35$]: since participants were less accurate at 180° (58%) than all other orientations (0° = 75%, 60° = 75%, 120° = 69%, 240° = 71%, 300° = 74%, $p < 0.02$ in all cases).

Within-Group Results of Experiment 2 (Explicit Task)

Analysis on Healthy Subjects

The main effect of **Owner** was significant [$F_{(1, 28)} = 13.62$; $p < 0.001$; $\eta_p^2 = 0.32$]: RTs were longer for self (1200 ms) than for other people's stimuli (930 ms) showing the so called self-disadvantage effect.

The variable Orientation was not significant [$F_{(5, 140)} = 1.20$; $p > 0.05$], suggesting that participants did not use mental rotation strategy to solve the Explicit task (0° = 1068 ms, 60° = 1069 ms, 120° = 1092 ms, 180° = 1040 ms, 240° = 1050 ms, 300° = 1070 ms; see **Figure 3D**).

As far as the percentage of correct responses, the following results were found: the main effect of **Owner** was significant [$F_{(1, 28)} = 12.09$; $p < 0.001$; $\eta_p^2 = 0.30$]: healthy participants were *less* accurate with self (79%) than with others' stimuli (91%; see **Figure 4D**) showing the so called self-disadvantage effect.

The variable Orientation was not significant [$F_{(5, 140)} = 0.92$; $p = 0.47$], suggesting that participants did not use mental rotation strategy to solve the Explicit task (0° = 83%, 60° = 87%, 120° = 85%, 180° = 85%, 240° = 85%, 300° = 85%).

RBD Patients

The main effect of **Owner** was significant [$F_{(1, 14)} = 37.28$; $p < 0.001$; $\eta_p^2 = 0.73$]: RTs were longer for self (1975 ms) than for other people's stimuli (1212 ms) showing the so called self-disadvantage effect.

The variable Orientation was not significant [$F_{(5, 140)} = 1.20$; $p > 0.05$], suggesting that RBD patients did not use mental rotation strategy to solve the Explicit task (0° = 1583 ms, 60° = 1569 ms, 120° = 1607 ms, 180° = 1600 ms, 240° = 1617 ms, 300° = 1586 ms, see **Figure 3E**).

Concerning the percentage of correct responses, RBD patients were *less* accurate with self than with other people's hand [39% vs. 80%, $F_{(1, 14)} = 20.47$; $p < 0.005$; $\eta_p^2 = 0.44$; see **Figure 4E**] and were *less* accurate with left than with right hand [54% vs. 65%, $F_{(1, 14)} = 10.78$; $p < 0.0001$; $\eta_p^2 = 0.59$]. The interaction **Owner** × **Laterality** was significant [$F_{(1, 14)} = 8.17$; $p < 0.01$; $\eta_p^2 = 0.37$]: when the displayed stimulus belonged to participants, they were less accurate with the left contralesional hand (29%) compared to the right ipsilesional responding hand (49%; $p < 0.003$), conversely this effect was not found with others' stimuli (left = 79% vs. right = 81%; $p = 0.99$).

LBD Patients

The main effect of **Owner** was significant [$F_{(1, 14)} = 17.81$; $p < 0.001$; $\eta_p^2 = 0.60$]: RTs were longer for self (1740 ms) than for other people's stimuli (1483 ms) showing the so called self-disadvantage effect.

The variable Orientation was not significant [$F_{(5, 140)} = 1.20$; $p > 0.05$], suggesting that LBD patients did not use mental rotation strategy to solve the Explicit task (0° = 1549 ms, 60° = 1605 ms, 120° = 1656 ms, 180° = 1593 ms, 240° = 1645 ms, 300° = 1619 ms, see **Figure 3F**).

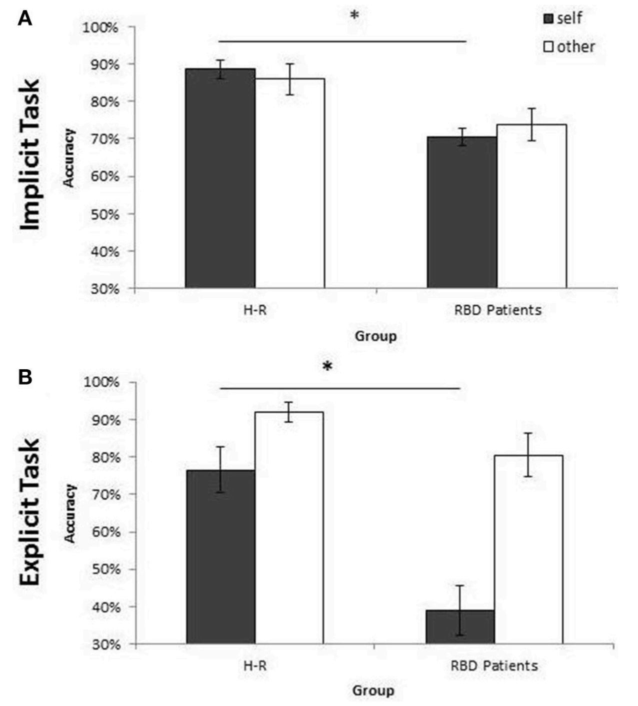

FIGURE 5 | Mean of correct response of Controls and RBD in the Implicit (A) and Explicit (B) task. Results are displayed as a function of ownership (self/other). Between-group significant difference are starred. Error bars depict SEMs. The "*"indicate the significant difference.

Again, analysis on the percentage of correct responses, put in evidence that LBD patients were *less* accurate with self than with other people's hand [50% vs. 68%, $F_{(1, 14)} = 12.89$; $p < 0.003$; $\eta_p^2 = 0.48$, see **Figure 4F**].

Between-Group Results of Experiment 1 (Implicit Task)

RBD Patients and Healthy Subjects Responding with the Right Finger (H-R)

The variable **Group** was significant [$F_{(1, 28)} = 9.66$; $p < 0.004$; $\eta_p^2 = 0.26$], which was mainly due to longer response time in RBD patients (1760 ms) compared to controls (1358 ms).

The interaction **Owner** × **Group** was significant [$F_{(1, 28)} = 5.89$, $p < 0.02$; $\eta_p^2 = 0.17$]: RBD patients responded slower than controls when the displayed hand belonged to them (1804 ms vs. 1326 ms; $p < 0.007$) but not with other people's hand (1716 ms vs. 1390 ms; $p = 0.12$).

Similar results were obtained when the percentage of correct responses were analyzed: RBD patients were less accurate than controls [72% vs. 87%; $F_{(1, 28)} = 10.37$; $p < 0.003$; $\eta_p^2 = 0.27$]. Moreover, the interaction **Owner** × **Group** [$F_{(1, 28)} = 11.33$; $p < 0.002$; $\eta_p^2 = 0.29$] showed a selective deficit of RBD patients compared to controls with self (70% vs. 89%; $p < 0.004$) but not with other people's stimuli (74% vs. 86%; $p = 0.10$; see **Figure 5A**).

LBD Patients and Healthy Subjects Responding with the Left Finger (H-L)

The variable **Group** was significant considering both RTs, since LBD patients were slower than controls [1904 ms vs. 1433 ms; $F_{(1,\ 28)} = 9.12$; $p < 0.005$; $\eta_p^2 = 0.25$] and accuracy, because LBD patients were less accurate than controls [70% vs. 87%; $F_{(1,\ 28)} = 12.34$, $p < 0.001$; $\eta_p^2 = 0.31$]. The interaction Owner × Group was not significant, neither for RTs [$F_{(1,\ 28)} = 0.62$, $p = 0.44$] nor for accuracy [$F_{(1,\ 28)} = 0.83$, $p = 0.37$].

RBD, LBD Patients, and Healthy Subjects (H-L and H-R)

The ANOVA conducted on the self-advantage index (self-minus other) showed a significant effect of the variable **Group** considering both RTs [$F_{(3,\ 56)} = 3.92$; $p < 0.01$; $\eta^2{}_p = 0.17$] and accuracy [$F_{(3,\ 56)} = 3.10$; $p < 0.03$; $\eta^2{}_p = 0.14$], since RBD patients performed worse compared to three groups (all ps < 0.005).

Between-Group Results of Experiment 2 (Explicit Task)

RBD Patients and Healthy Subjects Responding with the Right Finger (H-R)

The variable **Group** was significant [$F_{(1,\ 28)} = 12.17$, $p < 0.001$; $\eta^2{}_p = 0.30$]: RBD patients responded slower (1594 ms) than controls (1119 ms). The interaction **Owner** × **Group** was significant [$F_{(1,\ 28)} = 5.92$; $p < 0.02$; $\eta_p^2 = 0.17$] since with self-stimuli, RBD patients performed worse than controls (1293 ms; $p < 0.001$) whereas no such effect was found with other people's stimuli (945 ms; $p = 0.61$).

Analysis conducted on the percentage of correct responses put in evidence a similar pattern of results. Again, RBD patients were less accurate than controls [60% vs. 84%; $F_{(1,\ 28)} = 18.74$; $p < 0.001$; $\eta_p^2 = 0.40$]. The interaction **Owner** × **Group** [$F_{(1,\ 28)} = 5.94$; $p < 0.02$; $\eta_p^2 = 0.17$] confirmed that the impairment of RBD patients compared with controls was selective for self-hand (39% vs. 76%; $p < 0.001$) and not for other people's hand (80% vs. 92%; $p = 0.89$; see **Figure 5B**).

LBD Patients and Healthy Subjects Responding with the Left Finger (H-L)

The variable **Group** was significant both for RTs, being LBD patients slower than controls [1611 ms vs. 1010 ms; $F_{(1,\ 28)} = 24.8$; $p < 0.0001$; $\eta_p^2 = 0.47$] and accuracy, since LBD patients were less accurate than controls [59% vs. 86%; $F_{(1,\ 28)} = 14.97$; $p < 0.001$; $\eta_p^2 = 0.35$]. The interaction **Owner** × **Group** was not significant, neither for RTs [$F_{(1,\ 28)} = 0.37$, $p = 0.55$] nor for accuracy [$F_{(1,\ 28)} = 1.07$, $p = 0.31$].

RBD, LBD Patients, and Healthy Subjects (H-L and H-R)

The ANOVA conducted on the self-advantage index (self-minus other) showed a significant effect of the variable **Group** considering both RTs [$F_{(3,\ 56)} = 6.45$; $p < 0.01$; $\eta_p^2 = 0.26$] and accuracy [$F_{(3,\ 56)} = 4.54$; $p < 0.001$; $\eta_p^2 = 0.26$], since RBD patients performed worse compared to three groups (all ps < 0.007).

DISSOCIATIONS BETWEEN IMPLICIT AND EXPLICIT SELF-BODY KNOWLEDGE

To sum up, previous analysis on RTs and accuracy showed that all participants adopted the mental rotation strategy to solve the laterality task (Implicit task), but not to perform the owner recognition task (Explicit task). Furthermore, in the Implicit Task a self-advantage emerged in controls and LBD patients, whereas a lack of this facilitation was found in RBD patients. Specifically, RBD patients were selectively impaired compared to controls in implicit processing self-body-parts. In the Explicit task, a self-disadvantage emerged in all groups of participants, and again RBD patients were selectively impaired compared to controls in self-body-parts processing.

Thus, in line with the aim of the present study, it is crucial to investigate possible dissociation in the implicit or in the explicit processing of self-body-parts in RBD patients and its neural correlates.

Behavioral Data on Implicit and Explicit Dissociation in RBD Patients

Since in the group analysis possible dissociations may have gone unobserved because of the well-known averaging artifact (Shallice, 1988), we compared the performance of each patient with the performance of the control group for self body-parts (mean percentage of accuracy obtained for self-trials collapsing the variables Orientation and Laterality), separately in the Implicit and in the Explicit task, by using a modified t-test which takes into account the size of the control group (Crawford et al., 2010). This comparison revealed that 10 out of 15 RBD patients were selectively impaired in the implicit or in the explicit self-body processing compared to controls: 6/15 (40%) were selectively impaired in the implicit and 4/15 (27%) in the explicit self-body processing (for statistical details see Supplemental Material).

Lesion Study on Implicit and Explicit Dissociation in RBD Patients

Since two distinct deficits were observed within the RBD patients group, we separately overlaid lesions of patients with impaired implicit and explicit self-body-parts recognition.

The RBD patients who showed a selective impairment in the Implicit task when self-body-parts was presented were affected by lesion involving a subcortical frontal region (caudate, putamen, internal, and external capsule and paraventricular area) and the temporal gyrus (for a graphical representation, see **Figure 6A**). Conversely, RBD patients selectively impaired in explicit self-body-parts recognition were affected by lesion involving the insular cortex and the cingulate gyrus (for a graphical representation, see **Figure 6B**). To exclude the dissociations observed within the RBD patients group were simply due to difference in the lesions extension, the Mann Whitney U-test ($U = 4.00$; $z = 0.70$; $p = 0.50$) was conducted to compare the average of voxels involved by the lesion. The lack of significance confirmed that the lesion extension did not differ across the two groups.

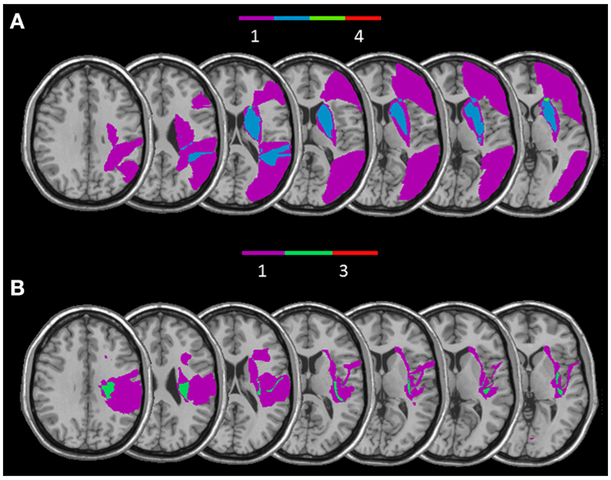

FIGURE 6 | Overlay of reconstructed lesion plots of RBD patients impaired with self-body processing in the Implicit (A) and in the Explicit task (B) superimposed onto MNI template.

DISCUSSION

The main focus of the current study was to explore whether implicit and explicit recognition of self-body-parts could be selectively impaired after brain lesions. To this aim, thirty patients (15 RBD and 15 LBD) and thirty age-matched neurologically healthy subjects were submitted to two different tasks designed for testing implicit and explicit body-parts recognition.

In the Implicit task (Experiment 1), healthy subjects' performance was better when the displayed hand was their own hand compared to other people's hand, showing the so called self-advantage effect. In contrast, such self-advantage effect could no longer be observed in the Explicit task (Experiment 2). Indeed, when participants were required to judge if the displayed hand was their own hand, they were slower and less accurate with their own hand compared to others' hand.

Another critical difference between the Implicit and the Explicit task performance in healthy subjects is that different strategies were used to perform the two tasks. Mental motor rotation of body-parts is required to solve the laterality judgment task (Experiment 1; Parsons, 1987, 1994; Parsons and Fox, 1998; Ionta et al., 2007) while it is not necessary to explicitly recognize one's own hand (Experiment 2). The difference in task requirements is reflected in the classical bell-shaped function observed for response times only in Experiment 1 but not in Experiment 2 (see **Figure 2**). In order to perform the hand laterality judgment task (Implicit task) participants were required to recall the visuomotor representation of one's own body (Parsons, 1987, 1994). Thus, the self-advantage effect found in the Implicit task is likely to be closely related to the involvement of motor function. Taken together, data of Experiment 1 and Experiment 2 suggest that there are two ways to access to bodily self-knowledge: one way leading to an implicit, but not to an explicit knowledge, and the other way leading to an explicit knowledge.

Results on patients with a focal brain lesion confirmed the existence of these different ways. Indeed, different pattern of results were found in RBD and LBD patients. In the laterality judgment task, LBD patients were faster (and more accurate) when the displayed stimulus depicted their own hand compared with other peoples' hand, suggesting that they have implicitly recognized their own hand and a facilitation emerged in this condition. This facilitation for self-stimuli was not found in RBD patients. Moreover, when patients and controls' performance was compared only RBD patients, and not LBD patients, where selectively impaired in self-related stimuli.

As far as for the Explicit task, a worse performance in recognizing self than others' stimuli was found in controls as well as in brain damaged patients, independently from the left or right side of the lesion. Comparing patients' and healthy subjects' performance, again only patients with a right brain lesion were selectively impaired in recognize their own hand.

Since RBD patients, compared to the healthy subjects, were selectively impaired in processing of self but not others' body parts, and in agreement with our previous findings (Frassinetti et al., 2008), we speculate that, viewing a body-part and viewing one's own body-parts represent two functionally different processes involving distinct brain areas. Converging evidence have demonstrated that posterior regions, such as EBA and FBA, are activated en pictures of body and body-parts are presented (Downing and Peelen, 2016). On the other hand brain lesion mapping studies suggest that, in the right hemisphere, a fronto-parietal network as well as subcortical frontal regions are key for self-body processing (Frassinetti et al., 2008, 2009, 2012).

In addition to our previous knowledge, here behavioral and anatomical data put in evidence two, at least partially, distinct networks in the same right hemisphere involved in processing self-body stimuli when an explicit recognition is or it is not required. From a behavioral point of view, 40% RBD patients showed a selective deficit for implicit processing of self-body stimuli, whereas 27% of them showed a selective deficit in the explicit recognition of their own body. The overlap of RBD patients' lesions, who showed a selective impairment in implicit self-body-parts processing, mainly involved subcortical structures, such as the basal ganglia (caudate nucleus, putamen) and internal capsule, that are implicated in motor functions. Coherently, several neuroimaging studies showed that the ability to physically distinguish self from non-self-stimuli, such as one's own body from another's body and one's own action from another's action, primarily involved somatosensory and motor cortices (Uddin et al., 2005; Sugiura et al., 2006; Devue et al., 2007; Ferri et al., 2012). Further evidence derives from a recent study that applied single-pulse TMS to the right motor cortex and observed an increase in cortical excitability for self-specific stimuli when compared to non-self-specific stimuli (Salerno et al., 2012). Thus, both behavioral and anatomical data support the role of an integrated cortical–subcortical motor network in the right hemisphere in building the implicit knowledge of bodily self.

RBD patients selectively impaired in explicit self-body-parts recognition were affected by lesion involving the insular cortex and the cingulate gyrus. Noticeably, during the Explicit task participants had to give a judgment about the ownership of the observed hand. From this perspective, our results are consistent with earlier neuroimaging (Tsakiris et al., 2007) and neuropsychological (Karnath and Baier, 2010) studies showing that the right insula is involved in the explicit (or active) sense of body ownership (Tsakiris et al., 2010). Also, earlier studies suggested that both the insula and the cingulate cortex play a crucial role in the integration of body ownership and interoceptive awareness (Ehrsson, 2007). These studies used the rubber hand illusion, an experimental manipulation adopted to temporary altered the sense of body ownership. They demonstrated that threat to the rubber hand induce a correlation between the strength of the illusion and the cerebral activity evoked in the cingulate and insular cortices (Ehrsson, 2007).

Our findings are also in agreement with the dissociation between implicit and explicit forms of awareness in disorders concerning bodily recognition and sense of body ownership. Moro et al. (2011) investigated the neural correlates of implicit and emergent motor awareness in patients with anosognosia for hemiplegia. Analogous to our results here, they observed that deficits in implicit and emergent awareness are associated with damage to subcortical motor structures and insular regions, respectively (see also Moro, 2013). As far as the anosognosia for hemianestesia (AHE), in our sample, 2 out of 3 RBD patients affected by AHE showed a selective impairment in the explicit bodily self-recognition. Furthermore, one of them was also affected by corporeal neglect. We may suggest that we observed a co-occurrence of altered bodily self-awareness and altered ability to explicitly recognize the own one body. However, further studies will better clarify the relationship between the clinical deficit and the occurrence of bodily self-recognition impairment.

Patients with somatoparaphrenia and anosognosia do not show an explicit knowledge but can have spared implicit awareness of their body and of its motor potentialities (for a review see Vallar and Ronchi, 2006, 2009; Moro et al., 2008). However, to our knowledge, this is the first time that the opposite dissociation (an impaired implicit and a spared explicit knowledge) is described. This suggests, in line with our results in RBD patients, that within the self-body representation, the implicit and explicit knowledge, involved at least partially different brain regions, and thus may be selectively damaged following a brain lesion. Our patients did not show signs and did not report symptoms of somatoparaphrenia. Somatoparaphrenia has been reported, with a few exceptions, in right brain-damaged patients, with motor and somatosensory deficits, and it is most often characterized by a delusion of disownership of left-sided body parts (Vallar and Ronchi, 2009; Gandola et al., 2012). It is important to note that the conditions in which somatoparaphrenia emerges are very different from the experimental setting used in the present study. Indeed, here patients were asked to judge whether the pictures displayed on a computer screen depicted or not their own hand. By contrast, somatoparaphrenia is characterized by spontaneous limb disownership and confabulations concerning their affected limb. None of the RBD patients impaired in explicit self-hand recognition spontaneously confabulated about their affected limbs. Two, not alternative, hypothesis can be put forward in this respect. The first one is that the two deficits (somatoparaphrenia and the deficit here mentioned) refer to different body representations. The second one is that additional cognitive components are impaired in somatoparaphrenia. To verify this hypothesis a further study should be conducted comparing patients with and without somatoparaphrenia in the Implicit and Explicit task.

In sum, the present findings lead to consider that different brain lesions may cause specific deficits in bodily self-processing. Indeed, our results suggested the existence of two of distinct networks within the right hemisphere underlying implicit and explicit self-body recognition.

This could be particularly relevant for the diagnosis and rehabilitation of these disorders. Thus, the evaluation of implicit and explicit impairment in self-body processing should be included in the post-lesion neuropsychological assessment performed in the rehabilitative clinical practice. Furthermore, specific attention to the bodily self-processing should be carried out especially during the early phases following brain damage. Indeed, in these stages, plastic phenomena concerning both the brain and self-processing reorganization can occur. Thus, appropriate therapeutic strategies integrating sensorimotor, emotional and cognitive components may be introduced to support structure and functions of bodily reorganization of the self, including implicit aspects of the subjective experience.

AUTHOR CONTRIBUTIONS

MC and FFr designed the study, analyzed the data and drafted the manuscript. MC performed data collection. FFe, MF, SA, GN, and VG critically revised the manuscript. All authors approved the final version of the manuscript.

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REFERENCES

Blanke, O. (2012). Multisensory brain mechanisms of bodily self-consciousness. *Nat. Rev.* 13, 556–571. doi: 10.1038/nrn3292

Cocchini, G., Beschin, N., and Jehkonen, M. (2001). The fluff test: a simple task to assess body representation neglect. *Neuropsychol. Rehabil.* 11, 17–31. doi: 10.1080/09602010042000132

Crawford, J. R., Garthwaite, P. H., and Porter, S. (2010). Point and interval estimates of effect sizes for the case-controls design in neuropsychology: rationale, methods, implementations, and proposed reporting standards. *Cogn. Neuropsychol.* 27, 245–260. doi: 10.1080/09602010042000132

Devue, C., Collette, F., Balteau, E., Degueldre, C., Luxen, A., Maquet, P., et al. (2007). Here I am: the cortical correlates of visual self-recognition. *Brain Res.* 1143, 169–182. doi: 10.1016/j.brainres.2007.01.055

Downing, P. E., and Peelen, M. V. (2016). Body selectivity in occipitotemporal cortex: causal evidence. *Neuropsychologia* 83, 138–148. doi: 10.1016/j.neuropsychologia.2015.05.033

Ehrsson, H. H. (2007). The experimental induction of out-of-body experiences. *Science* 317, 1048. doi: 10.1126/science.1142175

Ferri, F., Frassinetti, F., Ardizzi, M., Costantini, M., and Gallese, V. (2012). A sensorimotor network for the bodily self. *J. Cogn. Neurosci.* 24, 1584–1595. doi: 10.1162/jocn_a_00230

Ferri, F., Frassinetti, F., Costantini, M., and Gallese, V. (2011). Motor simulation and the bodily self *PLoS ONE* 6:e17927. doi: 10.1371/journal.pone.0017927

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Frassinetti, F., Ferri, F., Maini, M., Benassi, M. G., and Gallese, V. (2011). Bodily self: an implicit knowledge of what is explicitly unknown. *Exp. Brain Res.* 212, 153–160. doi: 10.1007/s00221-011-2708-x

Frassinetti, F., Fiori, S., D'Angelo, V., Magnani, B., Guzzetta, A., Brizzolara, D., et al. (2012). Body knowledge in brain-damaged children: a double-dissociation in self and other's body processing. *Neuropsychologia* 50, 181–188. doi: 10.1016/j.neuropsychologia.2011.11.016

Frassinetti, F., Maini, M., Benassi, M., Avanzi, S., Cantagallo, A., and Farnè, A. (2010). Selective impairment of self-body-parts processing in right brain-damaged patients. *Cortex* 46, 322–328. doi: 10.1016/j.cortex.2009.03.015

Frassinetti, F., Maini, M., Romualdi, S., Galante, E., and Avanzi, S. (2008). Is it mine? Hemispheric asymmetries in corporeal self recognition. *J. Cogn. Neurosci.* 20, 1507–1516. doi: 10.1162/jocn.2008.20067

Frassinetti, F., Pavani, F., Zamagni, E., Fusaroli, G., Vescovi, M., Benassi, M., et al. (2009). Visual processing of moving and static self-body-parts. *Neuropsychologia* 47, 1988–1993. doi: 10.1016/j.neuropsychologia.2009.03.012

Gandola, M., Invernizzi, P., Sedda, A., Ferrè, E. R., Sterzi, R., Sberna, M., et al. (2012). An anatomical account of somatoparaphrenia. *Cortex* 48, 1165–1178. doi: 10.1016/j.cortex.2011.06.012

Gauthier, L., Dehaut, F., and Joanette, Y. (1989). The bells' test: a quantitative and qualitative test for visual neglect. *Int. J. Clin. Neuropsychol.* 11, 49–54.

Ionta, S., Fourkas, A. D., Fiorio, M., and Aglioti, S. M. (2007). The influence of hands posture on mental rotation of hands and feet. *Exp. Brain Res.* 183, 1–7. doi: 10.1007/s00221-007-1020-2

Ionta, S., Perruchoud, D., Draganski, B., and Blanke, O. (2012). Body context and posture affect mental imagery of hands. *PLoS ONE* 7:e34382. doi: 10.1371/journal.pone.0034382

Karnath, H. O., and Baier, B. (2010). Right insula for our sense of limb ownership and self-awareness of actions. *Brain Struct. Funct.* 214, 411–417. doi: 10.1007/s00429-010-0250-4

Moro, V. (2013). The interaction between implicit and explicit awareness in anosognosia: emergent awareness. *Cogn. Neurosci.* 4, 199–200. doi: 10.1080/17588928.2013.853656

Moro, V., Berlucchi, G., Lerch, J., Tomaiuolo, F., and Aglioti, S. M. (2008). Selective deficit of mental visual imagery with intact primary visual cortex and visual perception. *Cortex* 44, 109–118. doi: 10.1016/j.cortex.2006.06.004

Moro, V., Pernigo, S., Zapparoli, P., Cordioli, Z., and Aglioti, S. M. (2011). Phenomenology and neural correlates of implicit and emergent motor awareness in patients with anosognosia for hemiplegia. *Behav. Brain Res.* 225, 259–269. doi: 10.1016/j.bbr.2011.07.010

Parsons, L. M. (1987). Imagined spatial transformations of one's hands and feet. *Cogn. Psychol.* 19, 178–241. doi: 10.1016/0010-0285(87)90011-9

Parsons, L. M. (1994). Temporal and kinematic properties of motor behavior reflected in mentally simulated action. *J. Exp. Psychol. Hum. Percept. Perform.* 20, 709–730. doi: 10.1037/0096-1523.20.4.709

Parsons, L. M., and Fox, P. T. (1998). The neural basis of implicit movements used in recognizing hand shape. *Cogn. Neuropsychol.* 15, 583–615.

Rorden, C., and Brett, M. (2000). Stereotaxic display of brain lesions. *Behav. Neurol.* 12, 191–120. doi: 10.1155/2000/421719

Salerno, S., Zamagni, E., Urquizar, C., Salemme, R., Farnè, A., and Frassinetti, F. (2012). Increases of corticospinal excitability in self-related processing. *Eur. J. Neurosci.* 36, 2716–2721. doi: 10.1111/j.1460-9568.2012.08176.x

Shallice, T. (1988). From Neuropsychology to Mental Structure. *Cambridge, UK: Cambridge University Press.*

Spinazzola, L., Pia, L., Folegatti, A., Marchetti, C., and Berti, A. (2008). Modular structure of awareness for sensorymotor disorders: evidence from anosognosia for emiplegia and anosognosia for hemiaenesthesia. *Neuropsychologia* 46, 915–926. doi: 10.1016/j.neuropsychologia.2007.12.015

Sugiura, M., Sassa, Y., Jeong, H., Miura, N., Akitsuki, Y., and Horie, K. (2006). Multiple brain networks for visual self-recognition with different sensitivity for motion and body part. *Neuroimage* 32, 1905–1917. doi: 10.1016/j.neuroimage.2006.05.026

Sugiura, M., Watanabe, J., Maeda, Y., Matsue, Y., Fukuda, H., and Kawashima, R. (2005). Cortical mechanisms of visual self-recognition. *Neuroimage* 24, 143–149. doi: 10.1016/j.neuroimage.2004.07.063

Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P., and Fink, G. R. (2007). Neural signatures of body ownership: a sensory network for bodily self-consciousness. *Cereb. Cortex* 17, 2235–2244. doi: 10.1093/cercor/bhl131

Tsakiris, M., Longo, M. R., and Haggard, P. (2010). Having a body versus moving your body: neural signatures of agency and body-ownership. *Neuropsychologia* 48, 2740–2749. doi: 10.1016/j.neuropsychologia.2010.05.021

Uddin, L. Q., Kaplan, J. T., Molnar-Szakacs, I., Zaidel, E., and Iacoboni, M. (2005). Self-face recognition activates a frontoparietal "mirror" network in the right hemisphere: an event-related fMRI study. *Neuroimage* 25, 926–935. doi: 10.1016/j.neuroimage.2004.12.018

Vallar, G., and Ronchi, R. (2006). Anosognosia for motor and sensory deficits after unilateral brain damage: a review. *Restor. Neurol. Neurosci.* 24, 247–257.

Vallar, G., and Ronchi, R. (2009). Somatoparaphrenia: a body delusion. A review of the neuropsychological literature. *Exp. Brain Res.* 192, 533–551. doi: 10.1007/s00221-008-1562-y

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GENERAL COMMENTARY
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Commentary: Embodied Medicine: Mens Sana in Corpore Virtuale Sano

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A commentary on

Embodied Medicine: Mens Sana in Corpore Virtuale Sano
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We read with interest the recently published paper about the potential role of "*embodied medicine*" (Riva et al., 2017). Authors suggest the use of advanced technologies for altering the experience of being in a body, with the goal of improving the well-being of patients. This paradigm is intriguingly summarized through the key message "*Mens Sana in Corpore Virtuale Sano*" and is recommended for patients with different neurological and psychiatric disorders including neglect, chronic pain, schizophrenia, depression and eating disorders. Here we report about a neurological syndrome which, in our opinion, might greatly benefit from the proposed approach and from simulation/stimulation technologies able to modulate the inner body dimension. This is the *Locked-in Syndrome* (LIS) characterized by a condition of severe motor entrapment due to the interruption of corticospinal, corticobulbar and cortico-cerebellar pathways as a result of a ventral brainstem lesion (**Figures 1A,B**). Patients are completely entrapped within their body because of quadriplegia, anarthria and lower cranial nerve paralysis, and communicate with the environment only through vertical eye movements and blinking which are the only motor outputs preserved. Despite this, consciousness and sensory pathways (exteroception, proprioception, vestibular inputs, and interoception) are completely conserved. Although cognition is also traditionally considered unaffected, due to the preservation of supratentorial structures, we recently described some non-motor symptoms in these patients, including motor imagery defects, selective emotional dysfunctions and pathological laughter and crying, and interpreted them as a consequence of a body representation disorder (Conson et al., 2008; Sacco et al., 2008; Pistoia et al., 2010). This fits with later volumetric data obtained in these patients, revealing the presence of an unexpected cortical loss involving areas typically associated with the mirror neuron system and the body matrix (Pistoia et al., 2016). As reminded by the authors, an accurate body representation is the result of the effective integration of multisensory (somatosensory, visual, auditory, vestibular, visceral) and motor signals, which provides an evolutionary advantage by maintaining a homeostatic protective *milieu* for human beings. This system, subserved by cortico-ponto-cerebellar pathways, matches bodily sensations and motor intentions in order to protect the body by triggering perceptual and behavioral programs (effectors) when something alters the body and the space around it (Riva et al., 2017). In patients with LIS, the lack of functioning efferent pathways, both at corticospinal and cortico-cerebellar level, may interfere with the body representation system, weaken the boundaries of the body and lead to unexpected symptoms in cognitive domains. Specifically patients are

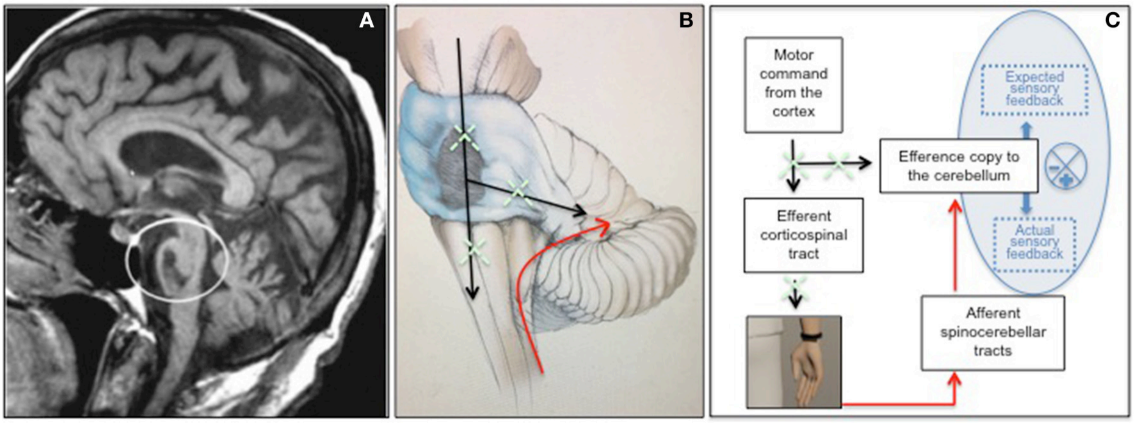

FIGURE 1 | Ventral brainstem lesion in the locked-in syndrome as shown by MRI **(A)**; graphical representation of interrupted efferent corticospinal and corticocerebellar tracts (in black) and preserved afferent spinocerebellar tracts (in red) in LIS patients **(B)**; hypothesized mechanism by which Sonoception technology may contribute to reduce the mismatch between the efferent (defective) and the afferent (healthy) pathways in LIS and to restore properly working forward programs **(C)**.

less accurate than healthy control subjects in recognizing others' negative facial expressions, thus confirming that voluntary activation of mimicry is a high-level simulation mechanism crucially involved in explicit attribution of emotions (Pistoia et al., 2010). Similarly, patients with LIS show motor imagery defects including difficulties in mentally manipulating the hands thus endorsing the view that motor imagery is subserved by activation of motor information (Conson et al., 2008). Finally, they can suffer from a pathological laughter and crying syndrome, as a result of a continuous disagreement between preserved centripetal bodily sensations and affected centrifugal motor outputs (Sacco et al., 2008). All these symptoms may be interpreted as the result of a body matrix disorder (Conson et al., 2009, 2010; Babiloni et al., 2010; Pistoia et al., 2016).

To date, when reasoning about embodiment, much consideration has been given to the integration of various sensory modalities (somatosensory, visual, auditory, vestibular, visceral) while less attention has been paid to the role that efferent pathways play in shaping the body's inner dimension and representation (Ehrsson, 2007; Lenggenhager et al., 2007; Petkova and Ehrsson, 2008; Guterstam et al., 2015). Patients with LIS may represent an experimental model to better investigate the role of efferent pathways in embodied simulation mechanisms and become a target population for innovative rehabilitative approaches aimed at reducing the percentage of disagreement within the body matrix computational processes. These approaches can include virtual reality and haptic technologies, bio/neuro-feedback strategies and brain/body stimulation paradigms. In patients with LIS, the technology used by Sonoception may be used in the attempt to reduce the mismatch between the efferent (defective) and the afferent (healthy) pathways. For instance, as shown in **Figure 1C**, vibrotactile transducers may be applied to a physically immobile limb of patients, in order to generate a sensation of arm displacement and to train the self-monitoring of patients. In fact, in healthy subjects, self-monitoring is based on the proper working of an internal forward model: every time that a motor command arises in the motor cortex, this information also reaches the cerebellum where a copy about the command is registered (Wolpert et al., 1995; Ito, 2008). The information transfer is subserved by the corticocerebellar pathways. In this way the cerebellum is able to predict the sensorial consequences of the action resulting from the command and to compare these sensory predictions to the actual sensory feedback received through the spinocebellar tracts (Wolpert et al., 1995; Ito, 2008). If the mismatch between sensory predictions and sensory feedback is little, this confirms that the action is self-generated and leads to an attenuation of the intensity of the sensation associated with the action itself. On the other hand, if the discrepancy between sensory predictions and sensory feedback is high, it is likely that the action is not self-generated and this leads to a relative increase in the intensity of the sensation associated with the stimulus. In patients with LIS the interruption of both corticospinal and corticocerebellar pathways, against the preservation of spinocerebellar pathways, interferes with the proper working of the forward model by producing a continuous mismatch between sensory predictions and sensory feedback. Providing a sensation of arm displacement in these patients may contribute to reduce this mismatch and to restore the functional coupling between motor intentions and sensory feedback. A specific training based on this approach may, in the long term, promote a partial motor recovery, especially when a small proportion of corticospinal fibers had survived the initial injury. This might contribute to improving the well-being of a population of patients whose chances of recovery have always been considered exceedingly small.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

Babiloni, C., Pistoia, F., Sarà, M., Vecchio, F., Buffo, P., Conson, M., et al. (2010). Resting state eyes-closed cortical rhythms in patients with locked-in syndrome: an EEG study. *Clin. Neurophysiol*. 121, 1816–1824. doi: 10.1016/j.clinph.2010.04.027

Conson, M., Pistoia, F., Sarà, M., Grossi, D., and Trojano, L. (2010). Recognition and mental manipulation of body parts dissociate in locked-in syndrome. *Brain Cogn*. 73, 189–193. doi: 10.1016/j.bandc.2010.05.001

Conson, M., Sacco, S., Sarà, M., Pistoia, F., Grossi, D., and Trojano, L. (2008). Selective motor imagery defect in patients with locked-in syndrome. *Neuropsychologia* 46, 2622–2628. doi: 10.1016/j.neuropsychologia.2008.04.015

Conson, M., Sarà, M., Pistoia, F., and Trojano, L. (2009). Action observation improves motor imagery: specific interactions between simulative processes. *Exp. Brain Res*. 199, 71–81. doi: 10.1007/s00221-009-1974-3

Ehrsson, H. H. (2007). The experimental induction of out-of-body experiences. *Science* 317:1048. doi: 10.1126/science.1142175

Guterstam, A., Björnsdotter, M., Gentile, G., and Ehrsson, H. H. (2015). Posterior cingulate cortex integrates the senses of self-location and body ownership. *Curr. Biol.* 25, 1416–1425. doi: 10.1016/j.cub.2015.03.059

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci.* 9, 304–313. doi: 10.1038/nrn2332

Lenggenhager, B., Tadi, T., Metzinger, T., and Blanke, O. (2007). Video ergo sum: manipulating bodily self-consciousness. *Science* 317, 1096–1099. doi: 10.1126/science.1143439

Petkova, V. I., and Ehrsson, H. H. (2008). If i were you: perceptual illusion of body swapping. *PLoS ONE* 3:e3832. doi: 10.1371/journal.pone.0003832

Pistoia, F., Conson, M., Trojano, L., Grossi, D., Ponari, M., Colonnese, C., et al. (2010). Impaired conscious recognition of negative facial expressions in patients with locked-in syndrome. *J. Neurosci.* 30, 7838–7844. doi: 10.1523/JNEUROSCI.6300-09.2010

Pistoia, F., Cornia, R., Conson, M., Gosseries, O., Carolei, A., Sacco, S., et al. (2016). Disembodied mind: cortical changes following brainstem injury in patients with locked-in syndrome. *Open Neuroimag. J.* 10, 32–40. doi: 10.2174/1874440001610010032

Riva, G., Serino, S., Di Lernia, D., Pavone, E. F., and Dakanalis, A. (2017). Embodied medicine: mens sana in corpore virtuale sano. *Front. Hum. Neurosci.* 11:120. doi: 10.3389/fnhum.2017.00120

Sacco, S., Sarà, M., Pistoia, F., Conson, M., Albertini, G., and Carolei, A. (2008). Management of pathologic laughter and crying in patients with locked-in syndrome: a report of 4 cases. *Arch. Phys. Med. Rehabil.* 89, 775–778. doi: 10.1016/j.apmr.2007.09.032

Wolpert, D. M., Ghahramani, Z., and Jordan, M. I. (1995). An internal model for sensorimotor integration. *Science* 269, 1880–1882. doi: 10.1126/science.7569931

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HYPOTHESIS AND THEORY
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How to Link Brain and Experience? Spatiotemporal Psychopathology of the Lived Body

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The focus of the present article is on sketching a psychopathology of the body in schizophrenia and linking it to brain activity. This is done providing converging data from psychopathological evidence (phenomenal), phenomenological contructs (trans-phenomenal) and neuroscientific measures (pre-phenomenal). The phenomenal level is the detailed documentation of the patients' subjective anomalous experiences. These phenomena are explicit contents in the patients' field of consciousness. The trans-phenomenal level targets the implicit yet operative matrix that underlies these anomalous subjective experiences. Abnormal phenomena are viewed as expressions of a modification of trans-phenomenal matrix, that is, in terms of an abnormal synthesis or integration through time of intero-, proprio- and extero-ceptive stimuli. Finally, we link the abnormalities of the trans-phenomenal matrix to pre-phenomenal alterations of the brain resting state and of its spatio-temporal organization, as documented by neurobiological methods providing spatial and temporal resolution of intrinsic brain activity (with many features of the resting state remaining yet unclear though). Based on phenomenological research, the body in schizophrenia is typically experienced in an itemized way as an object external to one's self and unrelated to events in the external world. Based on neurobiological data, we tentatively hypothesize that such anomalies of the lived body are related to decreased integration between intero-, extero- and proprioceptive experiences by the brain's spontaneous activity and its temporal structure. Taken all together, this suggests that we view abnormalities of bodily experience in terms of their underlying abnormal spatiotemporal features which, as we suppose, can be traced back to the spatiotemporal features of the brain's spontaneous activity.

Keywords: abnormal bodily phenomena, brain resting state, phenomenology, schizophrenia, spatio-temporal psychopathology

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INTRODUCTION

Psychopathological disorders are complex disturbances showing a wide variety of symptoms that cover most brain functions, including sensorimotor, affective, cognitive, and social functions. For instance, schizophrenic patients suffer from cognitive dysfunction (e.g., formal thought disorders), affective changes (e.g., inadequate or diminished affective modulation), social withdrawal (e.g., lack of attunement, inability of immersion in the world), and sensorimotor symptoms (e.g., catatonia).

Neuroimaging using techniques like functional magnetic resonance imaging (fMRI) and Electroencephalogram (EEG) have focused on extrinsic activity that concerns the brain's response to sensorimotor, cognitive, affective or social stimuli or tasks, i.e., stimulus-induced or task-evoked activity. For all the progress in investigating the brain's extrinsic activity and its various functions, diagnostic or therapeutic markers still remain elusive. In its search for these specific markers, recent neuroimaging in psychiatry has shifted to the brain's *intrinsic* activity, its so-called resting state activity.

Roughly, the brain's intrinsic or resting state activity describes the brain's neural activity in the absence of any specific tasks or stimuli (Logothetis et al., 2009). However, the term "resting state" must be considered relative (rather than absolute) since even in the absence of specific stimuli or tasks, there is still plenty of processing going on. For instance, the interoceptive stimuli from the own body like the heart or the respiration continue to enter into the resting state (Duncan and Northoff, 2013; Weinberger and Radulescu, 2016); these are usually filtered out in subsequent resting state analyses but may nevertheless modify its ongoing dynamics (Duncan and Northoff, 2013; Northoff, 2014a). Moreover, there are plenty of cognitions in the form of task-unrelated thoughts or mind wandering, going on in the resting state (Smallwood and Schooler, 2015). Taken into account these (Weinberger and Radulescu, 2016, and others) different lines of processing, the resting state cannot really be conceived a proper rest in the literal form of the term. It may instead be rather conceived a state where the neural processing is directed more towards internal contents as related to the own body and cognitions rather than the external contents of the environment as when applying specific stimuli or tasks (Vanhaudenhuyse et al., 2011; Northoff, 2014a). When we speak of "resting state" in the following, we presuppose such more internally-directed state (as distinguished from a more externally-directed state) rather than a "true" resting state.

The brain's resting state activity can spatially be characterized by various neural networks consisting of regions showing close "functional connectivity" yielding a particular spatial structure (see below for details; methodological issues like global signal regression in especially fMRI need to be considered though; Weinberger and Radulescu, 2016; Duncan and Northoff, 2013). The same applies to the temporal domain, where fluctuations in different frequency ranges are coupled with each other, providing "neural synchrony" (Engel et al., 2013). Neuroimaging reports a variety of changes in both functional connectivity and neural synchrony in various psychiatric disorders (that show low degrees of specificity and large heterogeneity though; see Weinberger and Radulescu, 2016). The exact meaning of these spatial and temporal abnormalities in the resting state, if real and based on alterations in physiological mechanisms, for psychiatric symptoms remains unclear though.

Based on the spatiotemporal features of the resting state and their alterations in psychiatric disorders, one of us (Northoff, 2015a,b) suggested a novel approach to psychopathology, called "*patiotemporal psychopathology*". In a nutshell, such spatiotemporal psychopathology conceives psychopathological symptoms in spatiotemporal terms (of the resting state) rather than in sensorimotor, affective, or cognitive terms (as related to abnormal task-evoked or stimulus-induced activity). Among others, such spatiotemporal approach to psychopathological abnormal phenomena claims that the spatiotemporal alterations of the resting state and its internally-directed processing are manifest in abnormal experience of time and space as well as of self, other and body (Stanghellini, 2009; Stanghellini et al., 2014a, 2016).

The aim of this article is to apply this approach to psychopathological abnormalities of the body in schizophrenia. We conceive psychopathological symptoms of the body neither in cognitive nor in sensorimotor (or affective) terms, but trace them to abnormal spatial and temporal features of the resting state and its internally-directed processing. The first part of the article will briefly explain and sketch our methodological approach namely how to link the brain's resting state to abnormal subjective experiences and psychopathological symptoms. The second and third part will shed some detailed light on the brain's resting state activity and how its internally-directed processing are related to time in general (second part) and self/body in particular (third part). That provides the ground for conceiving psychopathological abnormalities of the body in schizophrenia in spatiotemporal terms (fourth part of this article). Finally, a fifth part shall sketch some implications of such approach. It shall be mentioned that, due to space constraints, we will not be able to discuss other approaches like the neurophenomenological approach (Thompson, 2007; Fazelpour and Thompson, 2015) that also aims to link brain and experience (in a slightly different way though than the way we aim to do; see Appendix 1 in Northoff (2014b) for discussing the neurophenomenological approach as distinguished from a neurophenomenal approach as also suggested here).

METHOD—SPATIOTEMPORAL APPROACH TO BRAIN AND EXPERIENCE

Bottom-Up Approach: From the Brain's Spontaneous Activity Over its Pre-phenomenal Features to the Phenomenal Features of Experience

Methodologically, spatiotemporal psychopathology includes two central features: first, the investigation of the patients' brain and its spontaneous or resting state activity in terms of the spatiotemporal features of its internally-directed processing, and secondly, the investigation of the patients' subjective experience of themselves and the world in predominantly spatiotemporal terms such that it can be linked directly to the former. While the first is done in neuroscience (Northoff, 2014a,b, 2015a,b), the second requires a phenomenological approach (Stanghellini and Rossi, 2014). At first glance one may be puzzled to combine phenomenological investigation of subjective experience with neuroscientific characterization of the resting state since both cover different and seemingly mutually exclusive domains: neuronal activity, e.g., brain, and subjective experience, e.g., selfhood and personhood. In order to make direct link between the subjective experiences' phenomenal features and the resting state's internally-directed processing possible, we need to reveal some features that commonly underlie both, are shared, and can therefore provide the hitherto missing link. We assume that these commonly shared and underlying features are spatiotemporal features that structure and organize both the brain's resting state and the person's subjective experience.

The investigation of spatiotemporal features in the brain's resting state can be done in more or less a direct way by investigating spatial variables like functional connectivity within and between regions/networks and temporal measures as frequency fluctuations and variability (Fox et al., 2005; Deco et al., 2013; Cabral et al., 2014; Northoff, 2014a,b, 2015a,b; Smallwood and Schooler, 2015; we need to take into account several not yet fully resolved methodological issues like heart and respiration rate control and global signal regression; Duncan and Northoff, 2013; Weinberger and Radulescu, 2016). We assume that the resting state's internally-directed processing and its spatiotemporal features predispose the various features of subjective experiences of self, body and taken in this sense, the resting state's internally-directed processing and its spatiotemporal features are not merely neuronal but rather "pre-phenomenal" with the prefix "pre" indicating that they predispose the transformation of the brain's merely neuronal activity into the phenomenal features of subjective experience. Without getting into detail here, we characterize "phenomenal" in terms of various features that are supposed to signify experience or consciousness; these include intentionality, self-perspectival organization, unity, temporal continuity, and qualia (among others; for details, see Van Gluick (2014) in Stanford Encyclopedia as well as Northoff (2014b) for details).

This can be referred to as "bottom up approach": from the brain's spontaneous activity (bottom) to experience, i.e., consciousness (top). The brain's spontaneous activity and the spatiotemporal structure of its internally-directed processing predispose experience and can therefore be methodologically described as being pre-phenomenal. That though raises the questions: how does exactly the spatiotemporal structure characterize phenomenal experience, and which spatiotemporal structure surfaces in experience?

Top-Down Approach: From Experience Over its Trans-Phenomenal Features to the Brain's Spontaneous Activity

In order to address this question, we methodologically need first to investigate experience itself and reveal its underlying spatiotemporal structure. Methodologically, this requires the opposite approach: rather than moving bottom-up from the brain's spontaneous activity to spatiotemporal structure (and from there to experience), we now need to move top-down from to its (underlying) spatiotemporal structure. Starting from experience, the top-down approach may then conjoint with the bottom-up approach in the spatiotemporal structure as shared and converging point between experience and brain.

This raises the following question: how do we investigate and reveal the spatiotemporal features of a person's subjective experience? In a nutshell, this method, namely phenomenological investigation, entails a two-step procedure that reveals the phenomenal and trans-phenomenal features of experience.

The first—called *phenomenal* exploration—is the gathering of qualitative descriptions of a person's lived experiences. For instance, a patient may describe his thoughts as alien ("Thoughts are intruding into my head") and the world surrounding him as fragmented ("The world is a series of snapshots"). The result is a rich and detailed collection of the patients' self-descriptions (Stanghellini and Rossi, 2014). In this way, we detect the critical points where the constitution of experience is vulnerable and open to derailments reflecting the "phenomenal features" of patients' subjective experiences of specific contents, e.g., objects and events in themselves and the world. In short, phenomenal exploration as first step focuses on *contents*; experience is considered here in a content-based way.

The second step aims to shift to phenomenology proper in that it seeks the underlying or basic structures or existential dimensions of the life-worlds patients live in. Abnormal phenomena are here viewed as the outcome of a profound modification of human subjectivity within the world. Phenomenology is committed to attempting to discover the common source that ties the seemingly heterogeneous individual experiences or phenomena related to contents together thus targeting its underlying constitutive structures, namely spatiotemporal structures. These structures are not directly experienced by the person. We call these features *trans*-phenomenal, rather than merely "phenomenal".

Historically, the prefix "trans" in "trans-phenomenal" alludes to the concept of "transcendental" as originating in philosophy. Kant used this concept to denote those conditions that are necessary for making something possible without being sufficient for its actual realization and manifestation.

The concept of "trans-phenomenal" targets those features that underlie and even more important, *constitute* subjective experience prior to and independent of the contents, e.g., events and objects. Taken in this way, the "trans-phenomenal features" concern those spatial and temporal features that structure and constitute the subject's experience of self, body and objects and events in the world. This second step of phenomenological analysis, then, aims to recover the underlying spatiotemporal structures, the trans-phenomenal features that usually recede into the background and remain implicit yet operative in our subjective self- and world-experience.

Any phenomenon is viewed as the expression of a given form of trans-phenomenal matrix. Abnormal phenomena are the outcome of a profound modification of this matrix—that is, the transcendental (non experienced) structure that gives form to experience. For example, in schizophrenia, the person may lose its anchoring in the lived body as a Gestalt of organs and functions delimited from the external environment (Narayanan et al., 2014), or in temporal continuity (Sun et al., 2013a), or in anisotropic space, meaning space that is imbued with a point of view (Uhlhaas et al., 2006), or in intersubjective attunement and common sense (Uhlhaas and Singer, 2012), or in selfhood (Ranlund et al., 2014; for review, see Moran and Hong, 2011; Sass and Pienkos, 2013; Mancini et al., 2014).

We postulate that the trans-phenomenal features refer to spatiotemporal features since they constitute and construct the background of the contents of experience and of the life-world. Thereby the spatiotemporal features remain most often tacitly or implicitly in the background of our experience that is dominated by its contents where they nevertheless structure and organize the latter (see below for details). Our top-down approach thus proceeds from the contents of phenomenal experience to its underlying tacit or implicit trans-phenomenal background which is constitutive of experience itself. The trans-phenomenal background itself is outside of what Markovà and Berrios (2015) consider a "psychiatric object" amenable to direct psychopathological analyses. None the less, its characteristics can be deduced from careful assessement and measures conducted on the phenomenal level (for details, see Stanghellini and Ballerini, 2008).

Convergence Between Bottom-Up and Top-Down Approaches: Correspondence or Convergence Between Pre- and Trans-Phenomenal Features

Can we link and converge the "trans-phenomenal features" of experience to the "pre-phenomenal features" of the brain's spontaneous activity? As indicated both "pre-phenomenal" and "trans-phenomenal" features both concern spatiotemporal features: the "pre-phenomenal features" are those spatiotemporal features of the brain's resting state that are investigated via biological methods, whereas the "trans-phenomenal" features are the same events investigated via phenomenological methods. We may assume that they are (or refer to) the same event detected and thus described in different terms (neurobiological vs. phenomenological). We suggest that whenever we find a given form of spatiotemporal pattern on the pre-phenomenal level (the brain's spontaneous activity) this will consistently converge and match with a corresponding spatiotemporal pattern on the trans-phenomenal level. The pre- and trans-phenomenal underpin phenomenal features and thus experience, and predispose and constitute subjective experience of ourselves and the world. Due to their predisposing character, alterations in the resting state's pre-phenomenal internally-directed processing with its spatiotemporal features may translate (in a more or less direct way) into corresponding changes in the subjective experience of space, time, body, self, others, etc.

Let us put our hypothesis into a more succinct philosophical way. The "trans-phenomenal" and the "pre-phenomenal" are *not* two distinct levels of the living organism. They are just *methodologically* distinct. This means that to access, measure and describe these two levels we need distinct methods, e.g., bottom-up neuro-biological and top-down phenomenological approaches as described above. Note also that our claim is more empirical than ontological and taken within the empirical domain when we postulate (empirical) convergence or correspondence between the spatiotemporal features on the trans-phenomenal and the neuro-biological level. Such claim for empirical correspondence or convergence between trans-phenomenal and neuronal (or better neuro-spatiotemporal) levels does not necessarily imply their ontological identity we "pre-phenomenal" level of the brain and its spontaneous activity (with its internally-directed processing) and the "trans-phenomenal" level underlying experience by using distinct measures (see **Figure 1**).

Let us rephrase such spatiotemporal approach to psychopathological symptoms with regard to the concepts of the pre- and trans-phenomenal features. We suggest that these spatiotemporal abnormalities are manifest in the patients' abnormal subjective self- and world-experience and in their respectively underlying spatiotemporal structure, the trans-phenomenal features. The latter in turn may be predisposed in the brain's resting state and its spatiotemporal features, the pre-phenomenal features. Accordingly, we assume direct linkage from the resting state and its internally-directed processing's pre-phenomenal spatiotemporal features over the trans-phenomenal

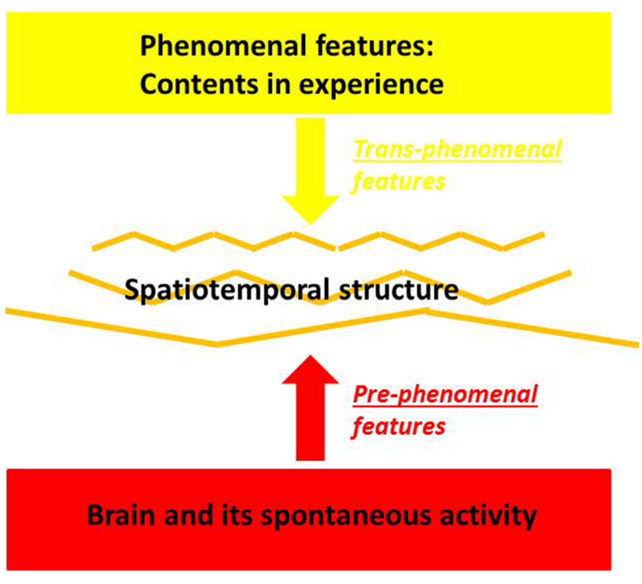

FIGURE 1 | Pre- and Trans-phenomenal features in brain and experience.

spatiotemporal features, to abnormal spatiotemporal structuring of cognitive, affective social and sensorimotor functions as these are manifest on the phenomenal level in the various psychopathological symptoms. This shall be illustrated, specified and exemplified in the following by the example of bodily symptoms in schizophrenia.

It is important to note once more that our approach is not confined to the contents of experience. It considers abnormal contents as endpoints while focusing on their underlying construction and constitution: the contents are supposed to emerge from an abnormal underlying spatiotemporal structure, e.g., the trans-phenomenal features, which in turn are constituted in this way by abnormalities in the spontaneous activity's pre-phenomenal features, i.e., its spatiotemporal structure. The focus on structure rather than the contents of experience distinguishes our approach from alternative hypotheseis like standard cognitive approaches (Halligan and David, 2001). There the focus on contents, and on the way these contents are associated (e.g., integration of information) by means of cognitive functions, predominates.

BRAIN, TIME AND EXPERIENCE OF THE LIVED BODY

From Brain to Time: Operational Measures and the Spatiotemporal Structure of the Brain's Spontaneous Activity

One should be aware that the concept of the brain's intrinsic or resting state activity is a rather heterogeneous one and raises several methodological questions (see also Morcom and Fletcher, 2007a,b; Deco et al., 2013; Duncan and Northoff, 2013; Ganzetti and Mantini, 2013; Northoff, 2014a; Weinberger and Radulescu, 2016). Besides resting state activity, other terms like baseline, spontaneous activity or intrinsic activity are also used to describe the internally generated activity in the brain (see Deco et al., 2013; Ganzetti and Mantini, 2013; Northoff, 2014a). Even more important, the exact relationship between resting state activity and stimulus-induced or task-evoked activity remains unclear with some authors assuming mere additive interaction (Fox et al., 2005) while others presume non-linear interaction (He, 2013 Huang et al. 2015). This makes the distinction between resting state and stimulus-induced activity rather blurry so that we conceive both in relative rather than absolute terms. The terms resting state and stimulus-induced activity index extremes on a balance between internally- and externally-directed processing with a mixture of both being the "normal" case.

Resting state activity can be measured in different ways: metabolic investigations using positron emission tomography (PET) focus on measuring quantitatively the brain's energetic metabolism indicating the resting state's utilization and distribution of for instance glucose (Shulman et al., 2014). In contrast, fMRI as relying on the blood-oxygen-level dependent (BOLD) effects as a neuro-vascular (rather than metabolic) signal targets different resting state's neural networks as based on statistical, i.e., correlative relationships between different regions' voxel signifying functional connectivity (Raichle et al., 2001; Menon, 2011; Cabral et al., 2014; which may also depend on some methodological specifics such as global signal regression Saad et al., 2012; Gotts et al., 2013). Resting state activity can also concern electrophysiological or magnetic activity as measured with EEG or magnetoencephalography (MEG; Deco et al., 2013; Ganzetti and Mantini, 2013) that targets neural activity changes in different frequency ranges. Finally, one may also measure the resting state activity in psychological terms as for instance by the degree of mind wandering or spontaneous/random thoughts (Kam et al., 2013).

The different measures of resting state activity may be characterized as spatial, temporal or spatiotemporal. PET, for instance provides spatial resolution while basically showing no temporal resolution. The focus is on spatial resolution in fMRI too though functional connectivity is based on calculating time series of voxel thus introducing a temporal component. EEG/MEG show excellent temporal resolution but low spatial resolution. This makes clear-cut segregation of spatial and temporal features in resting state activity impossible entailing its integrated spatiotemporal nature.

One may want to contest that the resting state's integrated spatiotemporal nature makes the assumption that its abnormalities are spatiotemporal almost trivially true. Resting state abnormalities are by the very nature of brain activity which is by default spatiotemporal. That is certainly true. However, the various investigations demonstrated that the resting state's internally directed processing and its spatiotemporal features are rather dynamic and thus subject to continuous change. The resting state's internally-directed processing continuously construct spatiotemporal features which differ from moment to moment dynamically over time. When speaking of the term "spatiotemporal" we mean such ongoing and continuous dynamic changes in internally-directed processing with the continuous construction of novel spatiotemporal features at each moment in time. Briefly, the term "spatiotemporal" is meant in a dynamic rather than static way.

Even more important, the central point in this article is not about the resting state itself and its internally-directed processing but rather about how its continuous dynamic construction of spatiotemporal features is altered in psychiatric disorders and translates into psychopathological symptoms: the abnormal spatiotemporal nature of the brain's resting state and its internally-directed processing is supposed to directly translate into corresponding spatiotemporal abnormalities that underlie and account for psychopathological symptoms. Distinct spatiotemporal alterations in the resting state's internally-directed processing may then be assumed to lead to distinct psychopathological symptoms.

Generally, this provides a novel perspective on psychopathological symptoms, i.e., an internally-directed resting state-based spatiotemporal perspective that complements current more externally-directed task-evoked-based sensorimotor, affective, cognitive, or social approaches (Northoff, 2015a,b). This means that psychopathological symptoms can be accounted for in terms of the spatial and temporal features of the brain's resting state and its continuous internally-directed processing.

From Brain Over Time to the Body: Integration of the Body's Intero- and Proprioceptive Input within the Resting State's Spatiotemporal Structure

The resting state is determined as the *spontaneous activity* of the brain and its internally-directed processing that *remains independent* of specific externally-directed processing and the respective external stimulus input. That though implies that there is still plenty of unspecific stimulus input from outside the brain into its resting state. This concerns exteroceptive stimuli from at least four senses which even during sleep provide continuous and unspecific input. The same applies to the body. The body is always there and provides continuous intero- and proprioceptive input into the brain and its resting state (see **Figure 2**).

How can we empirically support the assumption of the continuous intero- and proprioceptive input into our brain's resting state? One would for instance expect direct correlation between the interoceptive input from the heart and resting state activity in corresponding regions. This has indeed been shown in a recent study. Chang et al. (2013) demonstrated the degree of heart rate variability directly impacted the degree of functional connectivity, i.e., its variability in the brain's resting state activity. Especially the functional connectivity of the dorsal anterior cingulate cortex and the amygdala with subcortical regions in the brain stem, the thalamus and putamen was modulated by the degree of heart variability.

Accordingly, heart rate variability, exerts direct impact on the brain's resting state, i.e., the variability or dynamics of its functional connectivity in those regions, i.e., subcortical and their relation to cortical ones, that show strong interoceptive input. One may even want to go further and postulate that the temporal structure of the heart's interoceptive input may

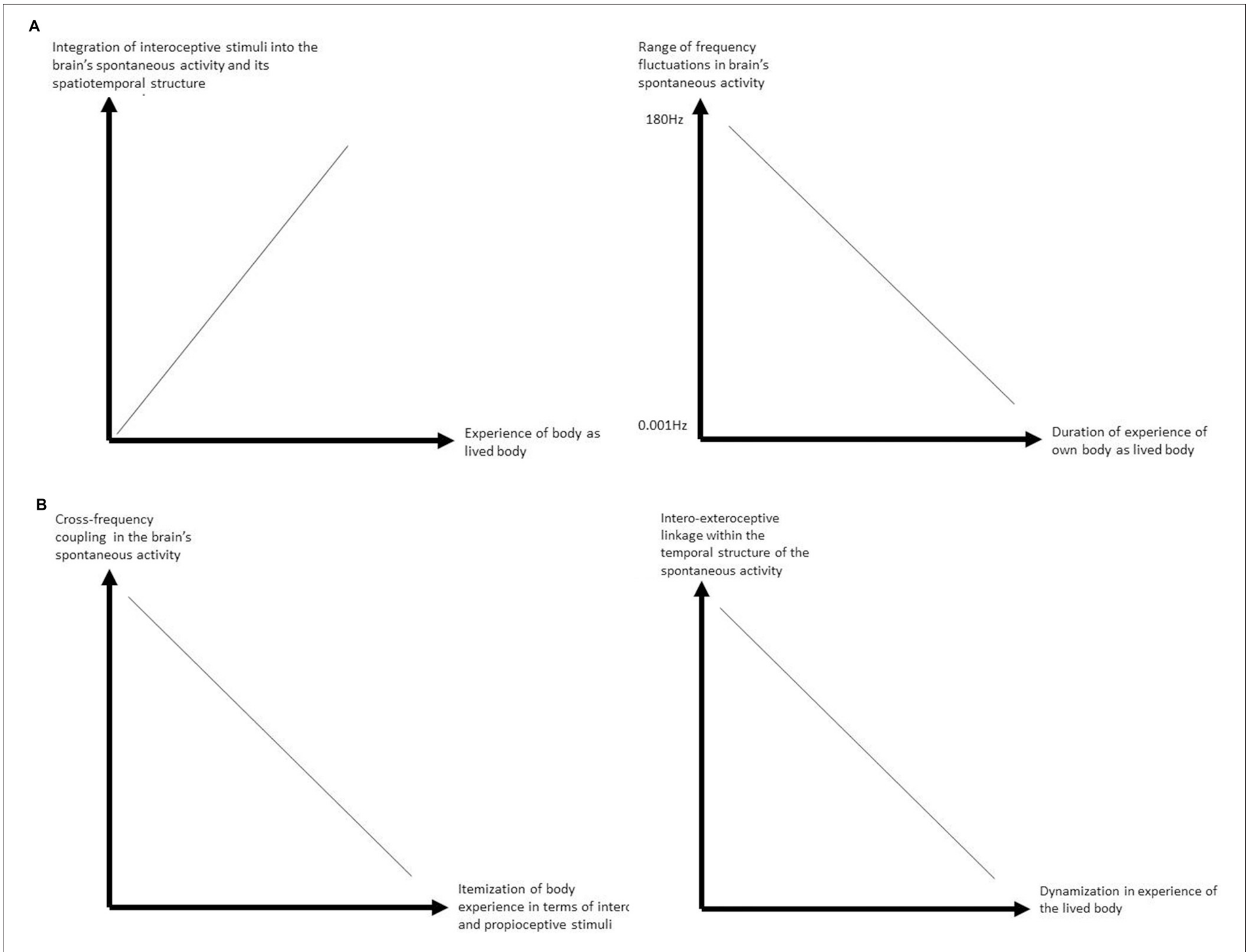

FIGURE 2 | (A) Relationship between interoceptive stimulus processing and experience of lived body. **(B)** Relationship between interoceptive stimulus processing and itemization and dynamization of the (lived) body in experience.

be related to and be encoded into the temporal structure of the brain's intrinsic activity and its internally-directed processing (see for instance (Northoff, 2014a) for further details of such encoding of what can be called "vegetative statistics"). That though remains to be shown in future studies.

How do these findings and suggestions stand in relation to experience and psychopathology of the body? The interaction of the intero- and proprioceptive input from the body into the brain's resting state activity entails that these inputs are set and integrated within the ongoing spatial and temporal dynamics, i.e., structure of the resting state. They are integrated and encoded within the resting state's internally-directed processing and its functional connectivity (as shown above) and possibly also into its ongoing frequency fluctuations (as it remains to be demonstrated). More generally, this means that the incoming input from the body, intero- and proprioceptive, becomes integrated within a larger spatiotemporal framework of the resting state's internally-directed processing.

How can we further support the assumption of such spatiotemporalization of the body's intero- and proprioceptive input? This can indeed be supported on phenomenological grounds.

From Experience to Time: "Trans-Phenomenal Temporality"

We assume that the resting-state brain activity predisposes in a pre-phenomenal way what we will call in the following transcendental temporality (TT) as specific "trans-phenomenal feature".

The general hypothesis is that the integrity of TT is the background and condition of possibility for the integrity of the experience of time, space, body, self, and all the other dimensions of the life world. In this paragraph, we provide some introductory remarks about the concepts of lived time and TT.

We must distinguish two levels of analysis of temporality: the phenomenal and the trans-phenomenal one. On the first level we find the abnormalities of time experience. We refer to this feature of temporality with the term "phenomenal" or "lived" time. We may experience lived time as fast or slow, continuous or discontinuous, future- or past-directed, etc. The second level of temporality is *pre-thematic*, in the sense that we are not directed to it and as such it remains in the background of our phenomenal experience. It is *pre-reflectively* present. It "*functions*" implicitly and automatically. It is *passive* in the sense that it produces associative connections prior to any active engagement and is *involuntary* since it does not involve "higher" voluntary level. We refer to it with the term TT. TT underlies and constitutes any given phenomenal experience for which reason we speak of "transcendental" temporality. It is the temporal infrastructure of all experience. It has its lawful, fundamental regularity as a mode of genesis and constitution of experience.

The integrity of TT is the condition of possibility of the identity through time of an object of perception as well as of the person who perceives it. Our experience of the permanence in time of a given object whose aspects cannot exist simultaneously but only appear across time (e.g., a melody, or a tridimensional object seen from different perspectives) would be impossible if our consciousness were only aware of what is given in a punctual "now". We can perceive an object as a unitary and identical object because our consciousness is not caught in the "now", but the now-moment has a "width" that extends toward the recollection of past and the expectation of the future.

Time consciousness has a threefold intentional structure: primal impressions are articulated with the retention of the just-elapsed and the protention or anticipation of the just-about-to-occur. Also, the feel we have of ourselves as unitary subjects of experience remaining permanent through time is due to the integrity of TT. If we have the feel of our mental life as a streaming self-awareness this is a consequence of the continuity of inner time consciousness as the innermost structure of our acts of perception. Thanks to the unified, pre-reflexive (that is, implicit and tacit), operation of primal impression, protention and retention underlying our experience of the present our consciousness is internally related to itself and self-affecting.

Such temporal structure characterized by primal impression, protention and retention is not phenomenal since it is not experienced as such. Instead, distinguishing it from the merely phenomenal "lived time" (that is, time as it is experienced by the subject), such temporal structure, i.e., TT, is rather a "trans-phenomenal feature" that underlies and constitutes any given phenomenal experience. TT is *per se* unexperienced, thus lies on the trans-phenomenal level rather than the phenomenal as lived time. The characteristics of time experience, i.e., lived time, are simply one of the phenomenal consequences of the integrity or of the disruption of the TT. A fundamental consequence of the temporal structure provided by the integrity of TT is that we do not have partial views of ourselves and of the world, or mere isolated snapshots, or two-dimensional figures or representations, because each item of our experience is constantly integrated into a continuum which connects the present moment's "adumbration" with retention (what we already know or have just perceived of that, or a similar, object) and protention (what we expect or imagine it to be). An "intentional arc" in consciousness bridges the retained past with the anticipated future, and thus makes possible our "milieu humain" (Merleau-Ponty, 1962, p. 158).

Conscious experience at any moment stretches from the here-and-now backwards to the past and towards the future. This function provides consciousness of the temporal horizon of the present object. No experience and no coherence of consciousness is possible without the temporal constitution of "primal presentational, retentional and protentional intentions [*urimpressionalen, retentionalen und protentionalen Intentionen*]" (Husserl, 2001, p. 233). As we have seen, there are, at least, two levels in the temporal structure of our experience: the phenomenal level, that is, the thematic articulations in the form of our active recollection and expectation, memory and imagination. And the trans-phenomenal one, that is, the implicit, pre-conceptual structuring in the form of the passive synthesis of retention and protention that we called TT. In Husserl's terms, the constitution or construction of the structure of time is the outcome of a *passive synthesis*. Taken within our framework, "passive synthesis" may then refer to those features which we described as "trans-temporal features". In the first place, passive synthesis occurs in the constitution of the basic temporal field in which all experience occurs. According to Husserl (2001), the basic temporal unit is not a "knife-edge" present, but a "duration-block". It is a "constitutive flux" that that has a threefold structure. As we have seen, this temporal field is a dynamic structure that comprises the primal presentation of the now-phase articulated with the retention of the just-elapsed and the protention or anticipation of the just-about-to-occur. The structure of TT is the integration of protention-primal presentation-retention. The temporal flow of consciousness retains and protends itself and is in this way is self-unifying or, so to say, "self-synthesizing".

We associate the term "passive synthesis" with the constitution of experience. This is in accordance with the fact that we postulate passive synthesis to constitute the trans-phenomenal features of experience. We argue that the trans-phenomenal features of experience correspond the pre-phenomenal features of the brain's spontaneous activity. This means that the concept of passive synthesis may then also be considered within the context of the brain and thus within a neuronal rather than exclusively phenomenological context. We therefore distinguish a narrow and wide meaning of the term "passive synthesis": the narrow meaning uses this term in an exclusively phenomenological context. The wide meaning, in contrast, extends and enlarges the concept of passive synthesis to indicate the constitution and construction of spatiotemporal features on the middle level between brain and experience, where the brain's pre-phenomenal features converge with the experience's trans-phenomenal features.

Synthesis' means that something is put and linked together. We saw above that interoceptive stimuli from the body and exteroceptive stimuli from the world are linked and (knitted together in the brain's resting state). Most importantly, this also means that the different time scales of the respective stimuli (including both internal, (or interoceptive) and external (or exteroceptive) are linked together. For instance, the 1 s scale of the interoceptive stimuli from the heart (as reflecting the delta frequency range) are integrated with the longer time scales of for instance our view of an elephant moving by (which may last around 10–20 s thus covering the infraslow range like slow four). These different time scales of intero- and exterocepetive stimuli are now linked and integrated within the brain's resting state activity which leads to the construction or synthesis of a particular temporal structure. One may consequently want to characterize the brain's resting state by synthesis of different time scales. Based on empirical data, we assume that such construction of different time scales by the brain's resting state and its different frequency fluctuations predisposes the synthesis of the threefold temporal structure as described by Husserl (2001; for details, see Northoff, 2014b).

The synthesis is not subject to active construction and determination by the person himself. In other terms, the synthesis is not voluntary (and non-automatic) but involuntary (and automatic) occurring by default. This is exactly the case in the brain's resting state and its continuous construction of time during internally-directed processing: it occurs in an automatic way by default and therefore does not underlie our active and voluntary (usually cognitive) control. Hence, the resting state's continuous construction of time and temporal structure during its internally-directed processing can indeed by described as passive and synthetic (see chapters 13–15 and Appendix 2 in Northoff, 2014b for details as well as Northoff, 2015a). Taken in this sense, the notion of passive indicates that such synthesis occurs by default, e.g., in automatic way.

Passive Synthesis and Body: From Passive Synthesis of Time to the Experience of Lived Body

We so far tried to demonstrate how the brain's spontaneous activity and its internally-directed processing constructs a specific temporal structure within which the intero- and proprioceptive stimuli from the body are passively synthesized. We then went on to show the transcendental structure of experience and characterized its underlying construction processes by the concept of "passive synthesis". This leaves now open the final step how such passive construction or synthesis of a temporal structure in both spontaneous activity and experience leads to the experience of the body as lived body. This is the focus in this section.

Since the beginning of the 20th Century, phenomenology has developed a distinction between lived body (*Leib*) and physical body (*Koerper*), or body-subject and body-object. The first is the body experienced from within, my own direct experience of my body in the first-person perspective, myself as a spatiotemporal embodied agent in the world, the second is the body thematically investigated from without, as for example by natural sciences as anatomy and physiology, a third person perspective. Phenomenology conceives of the lived body as the center of the experience of my self, and especially of the most primitive form of self-awareness, as the perspectival origin of my experiences (i.e., perceptions or emotions), actions and thoughts. The lived body has also the power of organizing experience.

Husserl (1912–1915) showed that a modification in one's lived body implies a modification in the perception of the external world: "The shape of material things as aistheta, just as they stand in front of me in an intuitive way, depends on my configuration, on the configuration of the experiencing subject, refers to my own body". By means of the integrity of kinaesthesia—the sense of the position and movement of voluntary muscles—my own body is the constant reference of my orientation in the perceptive field. The perceived object gives itself through the integration of a series of prospective appearances.

The lived body is not only the perspectival origin of my perceptions and the locus of their integration, it is the means by which I own the world, insomuch as it structures and organizes the chances of participating in the field of experience. The living body perceives worldly objects as parts of a situation in which it is engaged, of a project to which it is committed, so that its actions are responses to situations rather than reactions to stimuli. Last but not least, the lived body is also at the center of intersubjectivity if we understand intersubjectivity as intercorporeality, i.e., the immediate, pre-reflexive perceptual linkage between my own and the other's body through which I recognize another being as an alter ego and make sense of her actions (Stanghellini, 2009).

How now can we link the experience of the body as lived body to the brain and its spatiotemporal structure during internally-directed processing? Based on the above sections, this leads to postulate what can be described as the "temporal hypothesis of the lived body". We tentatively postulate that the difference between objective vs. lived body in experience is closely related to the resting state's spatiotemporal features during internally-directed processing: the better the body's intero- and proprioceptive input is integrated into the resting state's ongoing temporal structure during its internally-directed processing, the higher the degree of subjective experience of the body as "lived body" as distinguished from the experience of a merely "objective body". Though awaiting empirical support, this can be well tested experimentally in the future by combining temporal measures of the neuronal processing of interoceptive stimuli (like measuring variability in different frequency fluctuations of the brain's spontaneous activity and how that relates to the timing of the interoceptive stimuli from for instance heart beat or respiration rate) and temporal measures for the subjective experience of the body.

Specifically, we hypothesize that the temporal dimensions in our experience of the lived body as for instance the subjectively experienced durations of the experience of the body in first-person perspective (as distinguished from the objective observation of the body in third-person perspective) may correspond to the duration of the predominant frequency fluctuations into which the body's intero- and proprioceptive input is integrated during specifically the resting state and its internally-directed activity: the lower and stronger the brain's frequency fluctuations that primarily integrates the body's proprio- and interoceptive input, the longer the periods of first-person perspectival experience of the own body as lived body.

In the following, we will focus on the temporal underpinnings of our experience of the lived body. This is to neglect many other relevant dimensions like the spatial and subjective dimensions: the body as lived body is not only about time but also space. Moreover, we leave out the question: "how and why is it possible for us to experience our body as lived body at all?" Finally, we did not touch upon the subjective character of the body as our *own body* and thus in a self-related way. The discussion of these issues is beyond the scope of this article though and has been detailed elsewhere (Northoff, 2014b).

ABNORMALITIES IN EXPERIENCE OF TIME AND LIVED BODY IN SCHIZOPHRENIA

How about psychopathological abnormalities in the experience of the lived body? Our "temporal hypothesis of the lived body" points out that alterations can occur at different levels. Either the changes can occur primarily at the level of the body which then sends abnormal intero- and proprioceptive input to the brain and its spontaneous activity; this may be the case in various medical disorders like heart disease that often go along with strong psychological symptoms like anxiety. Or, alternatively, the primary abnormality may lie in the brain itself whose spontaneous activity may construct an abnormal temporal structure which renders the subsequent integration of the body's intero- and proprioceptive stimuli also abnormal. This, as we will demonstrate in the following, seems to be the case in schizophrenia.

For that purpose, we first pursue a top-down approach of the experiential abnormalities in schizophrenia with regard to the lived body. We first sketch abnormal experience of the lived body in schizophrenia which will be accompanied by discussing abnormal experience of time in these patients. That in turn serves to account for the abnormal experience of the lived body in terms of an abnormal underlying temporal structure reflecting what we described above as trans-temporal features. Such temporal top-down approach to the experience of the lived body will then be complemented by a bottom-up approach from the brain's spontaneous activity and its pre-phenomenal abnormalities.

Abnormal Experience of the Lived Body

In general, persons with schizophrenia experience throughout the course of their illness that the body loses its ambivalent status of being both an anonymous, physical object (a body as an object among other objects) and an integral part of our subjective experience (a personal body or lived body). The "vital" or "organic" part of embodiment becomes objectified: "I am provided with an anal expeller", "arms are just prostheses", "hands disjointed from arms", "[I am] a bionic creature", "a second body growing inside me", "eyes are videocameras", "instincts directed by electrodes".

As the body transforms into a deanimated object, the self loses its otherwise inescapable connection to the body, it becomes a purely spiritual person, that is, a person with only mental, intellectual dimensions who considers herself as having (not being) a body, possessing it, and accordingly having complete voluntary control over this animal part of her being: "like a cybernaut in my body", "push button to activate brain", "supervisor of my animal body", "all these hairs ... animal body", "[in my body] like an emperor in his pyramid", "supernatural powers".

There are two main properties of abnormal bodily experiences in schizophrenia: dynamization of bodily boundaries and construction, and morbid objectivization/devitalization (Stanghellini et al., 2012, 2014a,b; Madeira et al., 2016).

Dynamization

Patients complain about their body being violated by entities or forces coming from without their own bodily boundaries, e.g., about the intrusion or incorporation of extrapersonal things, forces, and events. This is a perplexing metamorphosis in one's corporeal borders and *Gestalt*. Violation typically entails dynamism in the sense of experiencing something moving into oneself, not merely the static presence in oneself of something that should occupy a position external to the self. Patients also experience a dynamization of bodily construction. This is an experience of body disintegration which involves a shifting around of the usual spatial relationships between body parts, or a dynamic distortion of body *Gestalt*, i.e., of one's body as a unitary and integrated structure. Parts of the body are felt as moving away from their usual position. Their body structure is being disintegrated and bodily parts are itemized (i.e., disaggregation of bodily parts or dissolution/loss of coherence of bodily structure).

A third aspect of bodily dynamization is the experience of externalization, that is, feeling one's body or parts of it projected beyond one's ego boundaries into the outer space. As is the case with violation and distortion of body construction, also externalization is not a static experience but it implies movement. Ego and corporeal boundaries, so to say, are violated from within by parts of the body that are felt as expelled into the outer space. In this type of experience as well, parts of one's body are experienced as thing-like entities in an outer space.

Thingness/Mechanization

The other characterizing feature of anomalous bodily experiences is an uncanny morbid objectivization and devitalization of the body or its parts. In morbid objectivization, parts of one's body that are usually silently and implicitly present and at work become explicitly experienced. Typically, morbid objectivization goes together with the experience of devitalization, that is, parts of one's body are felt as devoid of life and/or substituted by some kind of mechanism. In general, the body or its parts are experienced as mere things or, thing-like entities, rather than as living flesh. Parts of oneself are spatialized—experienced as if they were dis-integrated from the living totality of one's body. Persons with schizophrenia typically describe their condition as that of a deanimated body ("Heart no more there", "Brain into ashes", "Nerves as strings pulling me up"), or a disembodied mind ("I am like fog on quagmire", "Just ethereal, no body").

On the other hand, one may feel like a scanner or disincarnated mind which lives as a mere spectator of one's own perceptions, actions, and thoughts. Acts of perception themselves are no more experienced from within, but from without, becoming objects of noetic awareness ("It was as if I could see my eyes watching the scene", "I was like a receptor of stimuli"). The self breaks down into an experiencing I-subject contemplating an experienced I-object while the latter is acting or perceiving ("[My] eyes watching TV", "[My] hand masturbating"). The phenomenality of this experience is no longer implicitly embedded in itself, that is, characterized by a pre-reflective self-awareness. In other words, the act of experiencing turns out to be an explicitly intelligible object.

The intimate, pre-reflective (that is, implicit and operative) awareness of my perceptions, actions, and thinking as *my own* is replaced by a second-order noetic (that is, explicit and conscious) awareness of something which perceives that I am perceiving, acting or thinking: "I am the spectator of my body split from the world", "One part of the brain talks to the other", "The world is an illusion because it is seen through a brain". Persons with schizophrenia often describe their condition as that of a deanimated body ("Heart no more there", "Brain into ashes", "Nerves like strings pulling me up"), or a disembodied mind ("[I am] like fog on quagmire", "Just ethereal, no body"). On the face of it, such self-descriptions may seem metaphorical, but they contain a bodily "organic echo" which reveals how these persons are actually feeling and experiencing. On the one hand, one's existence feels like that of a cyborg or a lifeless, purely mechanical body ("[I felt] like a puppet", "No emotions, just impulses", "[the body] a mechanical engine", "I didn"t move it [the body] . . . it moved me").

Abnormal Experience of Lived Time

Schizophrenic persons typically describe their sense of temporal reality as: "things to a standstill", "immobility, but not calm", "time going back to same moment over and over", "people like statues", "frozen moment", "out of time", "marmoreal", "unreal stillness". Time is fragmented, there is a breakdown in time Gestalt, and an itemization of now-moments. The mere succession of conscious moments as such cannot establish the experience of continuity. Another typical phenomenon is that a revelation is on the verge to happen, the world is on the verge of ending, a new world is coming, one's own life is on the point of undergoing a radical change. Time is "a state of suspense", "pregnant now", "being is hanging", "something imminent", "something . . . I didn't know what . . . was going to happen . . . between inspiration and expiration" (Stanghellini and Rosfort, 2013).

The main feature of abnormal time experience in schizophrenia is Disarticulation—a breakdown of the synthesis of past, present and future. Disarticulation of time experience includes four subcategories.

Disruption of Time Flowing

Patients live time as fragmented. Past, present and future are experienced as disarticulated. The intentional unification of consciousness is disrupted. The present moment has no reference to either past or future. The external world appears as a series of snapshots. Typical sentence: "World like a series of photographs".

Déjà vu/Vecu

Patients experience places, people and situations as already seen and the news as already heard. This abnormal time experience entails a disarticulation of time structure as the past is no more distinguishable from the present moment. The already-happened prevails. Typical sentence: "When I heard news I felt I had heard it before".

Premonitions About Oneself

Patients feel that something is going to happen to them or that they are going to do something. This abnormal time experience entails a disarticulation of time structure as the immediate future intrudes into the present moment. The about-to-happen prevails. Typical sentence: "I felt something good was going happen to me".

Premonitions About the External World

Patients feel that something is going to happen in the external world. As the previous one, this abnormal time experience entails a disarticulation of time structure as the immediate future intrudes into the present moment. The about-to-happen prevails. Typical sentence: "Something is going on, as if some drama unfolding" (Stanghellini et al., 2016).

Disintegration of TT as Core Disorder

We assume that the disintegration of time experience on the phenomenal level reflects the disarticulation of TT on the trans-phenomenal level. The manifold of the phenomenal anomalies that we found in the life-world of persons with schizophrenia—including anomalies of phenomenal consciousness (e.g., disintegration of the appearance of external objects and itemization of external world experience), selfhood (e.g., disruption of the implicit sense of being a unified, bounded and incarnated entity), and sociality (e.g., breakdown of one's sense of being naturally immersed in a meaningful flow of social interactions with others; Stanghellini et al., 2016)—can be traced back to a fundamental trans-phenomenal abnormality, namely the disintegration of TT. We thus pursue the second step of our top-down approach in schizophrenia, stepping down from the contents of experience, e.g., body and time, to the underlying temporal features, the trans-temporal features, that structure and organize the contents and thus the background within which the latter can be experienced.

We argue that the fragmentation of bodily experience taking place on the phenomenal level is originated by a fragmentation of TT—that is, of the pre-reflexive synthesis of impression-retention-protention. The latter takes place on the trans-phenomenal, non-experienced level and is closely related to anomalies of the resting state, which in their own turn take place on the pre-phenomenal level.

There are two features of bodily experience related to a breakdown of TT. The first is that if TT breaks down, increased heart rate, bodily tension, to impulse to flee away, blurred vision due to midriasis will appear in one's field of consciousness as single items disconnected form each other, unrelated to one's own self. The second one is that they will also appear as unrelated from their source in the outside world. TT is the condition of possibility for coordinating intero- and proprioceptive feelings between themselves, and with exteroceptive ones. This means that TT is needed for experiencing these phenomena as belonging to my own embodied and situated self as a spatiotemporal entity.

Bodily feelings that are no longer embedded in one's global awareness of one's own body (coenesthesia) are experienced as, e.g., uncanny bodily sensations (coenesthopathies), automatic movements, made impulses and actions, motor blockages, etc. Coenesthesia (*koiné aesthesis* literally means the faculty that brings together different senses) is the name for the integration of the manifold of impressions coming from one's own body, including phenomena related intero- and exteroceptive functions, like neurovegetative functions (e.g., increase in heart rate), emotions (e.g., bodily feelings of tension), voluntary movements (e.g., fleeing), involuntary movements (e.g., midriasis), etc.

The origin of these symptoms could be searched for at the basic level where the temporal coherence of conscious awareness is constituted. A failure of the constitutive temporal synthesis may create micro-gaps of conscious experience. Feelings or sensations that are no longer embedded in the continuity of basic self-experience may appear in consciousness as "erratic blocks" and experienced as being inserted, or externalized. This is known in the clinic of schizophrenia as permeability of Ego boundaries. This coheres with the hypothesis that a breakdown of temporality may be bound up with the breakdown of pre-reflexive self-awareness.

As to the second phenomenal feature, the disruption of TT will make intero- and proprioceptive phenomena appear with no connection with events and situations in the surrounding world. For instance, disesthesic paroxisms when in stressful situation will not recognized as the manifestations of a stress reaction o an emotion elicited by the situation itself. The coupling between bodily sensations and life situation needs the integrity of TT as these are two moments in the spatiotemporal self-world relation. If the continuity of temporal experience disintegrates, overarching meaningful unification of world- (e.g., threatening situation) and self-experience (e.g., anxiety) is no longer available. The outcome is that I may feel oppressed by uncanny and incomprehensible bodily sensations evoked by interpersonal contact without me being aware that they evoked by interpersonal contacts. All this may lead to typical schizophrenic phenomena as full-blown psychotic symptoms as for instance so-called bizarre delusions.

Abnormal Temporal Structure of Brain's Spontaneous Activity and the Experience of the Lived Body

Can we link these phenomenal features to the brain and its spontaneous activity? Without going into detail, the empirical findings show evidence for what we describe as "temporal dysbalance" and "temporal fragmentation" in the spontaneous activity during internally-directed processing (for details, see Northoff, 2014b, 2015b). Briefly, EEG and fMRI findings indicate an abnormally shift towards slower and infraslow frequency fluctuations in schizophrenia at the expense of higher frequencies like gamma amounting to "temporal dysbalance" (Uhlhaas et al., 2006; Kikuchi et al., 2011; Moran and Hong, 2011; Spencer, 2012; Ford et al., 2012; Uhlhaas and Singer, 2012, 2013, 2015; Hanslmayr et al., 2013; Sun et al., 2013a; Narayanan et al., 2014; Ranlund et al., 2014). In addition to such temporal dysbalance between higher and lower frequencies, one can also observe decreased coupling or linkage between different frequencies, e.g., cross-frequency cocupling, between lower and higher frequencies, in schizophrenia (Allen et al., 2013; Sun et al., 2013a,b). This amount to what can be described as "temporal fragmentation" in spontaneous activity.

How now are the above described trans-temporal features of the abnormal lived body experience in schizophrenia related to the abnormal temporal structure in the brain's spontaneous activity? We described temporal fragmentation as related to decreased cross-frequency coupling. Decreased cross-frequency coupling means that the continuous interoceptive body like the heart at every second is no longer linked to and integrated with other stimuli from the body (and also the environment) that do not fall within exactly the same time range. In the healthy brain, even stimuli that occur before or after the heartbeat can be linked and integrated due to the coupling of different frequency, e.g., those related to the heart and the ones related to other stimuli. This is no longer possible once the different frequencies are no longer coupled to each other. Both heart and other vegetative stimuli are processed in a segregated way and no longer integrated and linked to each other by the spontaneous activity's (lacking) temporal structure during its internally-directed processing. They are consequently experienced in an isolated way.

In addition to the various vegetative or interoceptive stimuli among each other, they are also no longer properly integrated and linked to exteroceptive stimuli from the environment and proprioceptive stimuli. That in turn leads to segregation between the different stimuli, extero- and interoceptive and proprioceptive. On the experiential level this means that they and their respective objects, world and body become segregated or "itemized", as we say above. One consequently want to hypothesize that the degree of itemization as subjectively experienced is directly proportional to the degree of (lacking) cross-frequency coupling (in exactly those frequencies that allow for integrating the various interoceptive stimuli among each other and with the extero- and proprioceptive stimuli): the low the degree of cross-frequency coupling among the relevant frequencies, the higher the degree of itemization of the body as subjectively experienced.

Such segregated processing may then also lead to the dynamization of body boundaries as described above. If the various intero- and proprioceptive stimuli can no longer be integrated anymore, the body boundaries can no longer be clearly demarcated and distinguished from the environment. Due to lack of intero- and proprioceptive integration, the body is no longer determined as whole with clear-cut boundaries which thereby become fragile and volatile, e.g., dynamic (see **Figures 3A,B**).

Finally, the above described temporal dysbalance with a relative shift towards low frequencies at the expense of higher frequencies may abnormally impair the processing of stimuli in faster frequencies while stimuli in the lower range may be processed abnormally strong. This means that low- and high-frequency stimuli are processed in a dysbalanced way by the brain's spontaneous activity: high frequency stimuli are no longer processed as strongly while low-frequency stimuli are abnormally reinforced in their neural processing by the spontaneous activity's temporal dysbalance. In other terms low- and high-frequency stimuli from the body (and the environment) are somewhat segregated from each other. This further reinforces the split or segregation of experience into time-based units of experience, "experiential moments"

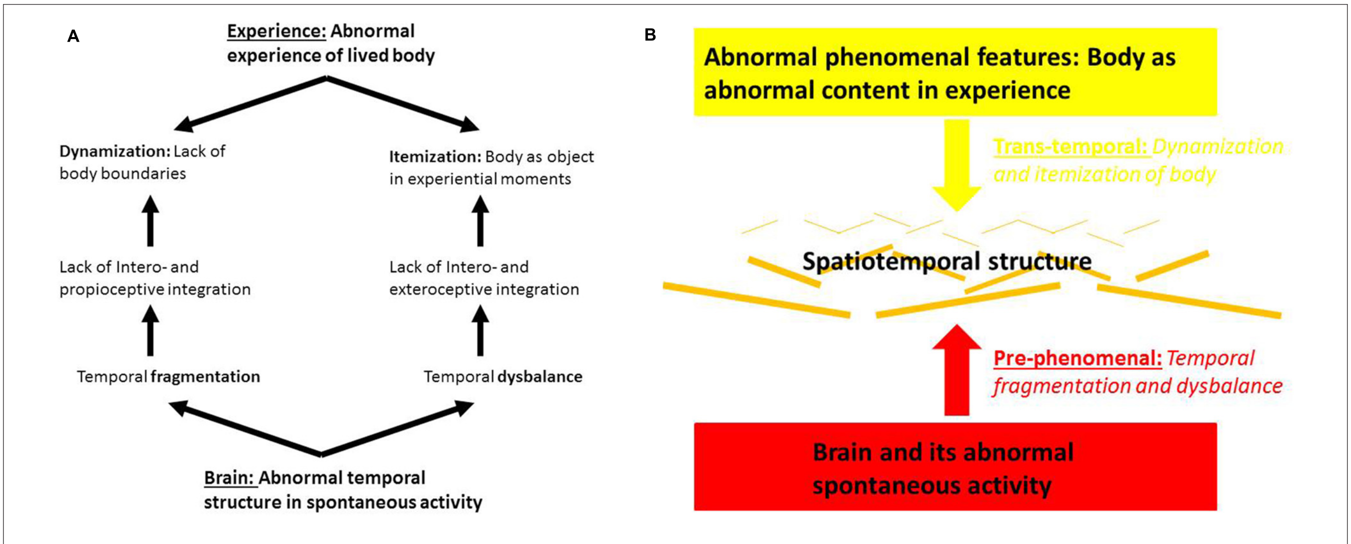

FIGURE 3 | (A) Brain and body experience in schizophrenia. **(B)** Abnormal pre- and trans-phenomenal features in brain and body experience in schizophrenia.

that are detached from each other without any global awareness.

CONCLUSION: A SPATIOTEMPORAL APPROACH TO BRAIN, EXPERIENCE AND PSYCHOPATHOLOGY

Our article focused on the question how to link brain and experience as in the title. The purpose was not to transform a hypothesis into a law of nature with the alibi of neuroimaging techniques (Markovà and Berrios, 2015). Rather, we wanted to test a hypothesis providing converging data from psychopathological evidence (phenomenal), phenomenological contructs (trans-phenomenal) and neuroscientific measures (pre-phenomenal). Rather than laws, we here target the resting state's capacities or predispositions (Northoff, 2013, 2015a, Northoff and Heiss, 2015) to construct a spatiotemporal structure with these capacities being abnormally altered in schizophrenia. Hence, our hypothesis is about the resting state's capacity to construct a spatiotemporal structure for both intero- and exteroceptive stimulus processing and integration rather than to claim for imaging-based empirical generalizations, e.g., laws. The difference between laws and capacities lies mainly in the fact that the realization of capacities is strongly context-dependent with, more specifically, the brain's spontaenous activity being dependent upon its respective environmental, e.g., socio-cultural and experiential, context (for instance, see Nakao et al., 2013; Northoff, 2014b; Duncan et al., 2015). This contrasts with the concept of laws whose instantiaton and realization remains context-independent. For the reasons of brevity, we could not go into detail about such socio-cultural and experiential context-dependence of the brain's spontaneous activity and its spatiotemporal structure in this article. However, as it is clear, it is highly relevant for especilly psychosis and schizoprhenia where such socio-cultural and experiential context-dependence has often been observed.

We first attempted to sketched an appropriate methodological approach, a spatiotemporal approach that combines and integrates both bottom-up approaches from brain to experience and top-down approaches from experience to brain. Specifically, the bottom-up approach focuses on the brain and its spontaneous activity's internally-directed processing and how the latter is characterized by spatiotemporal structure and their pre-phenomenal nature as predisposing certain experiential, e.g., phenomenal features. In contrast, the top-down approach starts with an analysis of subjective experience and reveals its underlying spatiotemporal features, the trans-phenomenal feature of temporality as we described it. In our tentative model, bottom-up and top-down approach converge in spatiotemporal features that allow for convergence the brain's spontaneous activity's pre-phenomenal features and the experience's trans-phenomenal features.

Based on phenomenological research, the body in schizophrenia is typically experienced in an itemized way as an object external to one's self. Based on neurobiological data, we hypothesize that such itemization of the lived body is related to decreased integration between intero-, extero- and proprioceptive stimuli by the brain's spontaneous activity and its temporal structure during internally-directed processing. Taken all together, this suggests that we view abnormalities of bodily experience in terms of their underlying abnormal spatiotemporal features which, as we suppose, can be traced back to the spatiotemporal features of the brain's spontaneous activity. Such "Spatiotemporal Psychopathology" (see also Northoff, 2015a,b) of the "lived body" may be developed further in the future as well as applied to other phenomenal features like experience of self, time, and space in schizophrenia and other psychiatric disorders like depression.

AUTHOR CONTRIBUTIONS

GN and GS contributed equally to this work.

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REFERENCES

Allen, M., Smallwood, J., Christensen, J., Gramm, D., Rasmussen, B., Jensen, C. G., et al. (2013). The balanced mind: the variability of task-unrelated thoughts predicts error monitoring. *Front. Hum. Neurosci.* 7:743. doi: 10.3389/fnhum.2013.00743

Cabral, J., Kringelbach, M. L., and Deco, G. (2014). Exploring the network dynamics underlying brain activity during rest. *Prog. Neurobiol.* 114, 102–131. doi: 10.1016/j.pneurobio.2013.12.005

Chang, C., Metzger, C. D., Glover, G. H., Duyn, J. H., Heinze, H. J., and Walter, M. (2013). Association between heart rate variability and fluctuations in resting-state functional connectivity. *Neuroimage* 68, 93–104. doi: 10.1016/j.neuroimage.2012.11.038

Deco, G., Jirsa, V. K., and McIntosh, A. R. (2013). Resting brains never rest: computational insights into potential cognitive architectures. *Trends Neurosci.* 36, 268–274. doi: 10.1016/j.tins.2013.03.001

Duncan, N. W., Hayes, D. J., Wiebking, C., Tiret, B., Pietruska, K., Chen, D. Q., et al. (2015). Negative childhood experiences alter a prefrontal-insular-motor cortical network in healthy adults: a preliminary multimodal rsfMRI-fMRI-MRS-dMRI study. *Hum. Brain Mapp.* 36, 4622–4637. doi: 10.1002/hbm.22941

Duncan, N. W., and Northoff, G. (2013). Overview of potential procedural and participant-related confounds for neuroimaging of the resting state. *J. Psychiatry. Neurosci.* 38, 84–96. doi: 10.1503/jpn.120059

Engel, A. K., Gerloff, C., Hilgetag, C. C., and Nolte, G. (2013). Intrinsic coupling modes: multiscale interactions in ongoing brain activity. *Neuron* 80, 867–886. doi: 10.1016/j.neuron.2013.09.038

Fazelpour, S., and Thompson, E. (2015). The Kantian brain: brain dynamics from a neurophenomenological perspective. *Curr. Opin. Neurobiol.* 31, 223–229. doi: 10.1016/j.conb.2014.12.006

Ford, J. M., Dierks, T., Fisher, D. J., Herrmann, C. S., Hubl, D., Kindler, J., et al. (2012). Neurophysiological studies of auditory verbal hallucinations. *Schizophr. Bull.* 38, 715–723. doi: 10.1093/schbul/sbs009

Fox, M. D., Snyder, A. Z., Zacks, J. M., and Raichle, M. E. (2005). Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat. Neurosci.* 9, 23–25. doi: 10.1038/nn1616

Ganzetti, M., and Mantini, D. (2013). Functional connectivity and oscillatory neuronal activity in the resting human brain. *Neuroscience* 240, 297–309. doi: 10.1016/j.neuroscience.2013.02.032

Gotts, S. J., Saad, Z. S., Jo, H. J., Wallace, G. L., Cox, R. W., and Martin, A. (2013). The perils of global signal regression for group comparisons: a case study of autism spectrum disorders. *Front. Hum. Neurosci.* 7:356. doi: 10.3389/fnhum.2013.00356

Halligan, P. W., and David, A. S. (2001). Cognitive neuropsychiatry: towards a scientific psychopathology. *Nat. Rev. Neurosci.* 2, 209–215. doi: 10.1038/35058586

Hanslmayr, S., Backes, H., Straub, S., Popov, T., Langguth, B., Hajak, G., et al. (2013). Enhanced resting-state oscillations in schizophrenia are associated with decreased synchronization during inattentional blindness. *Hum. Brain Mapp.* 34, 2266–2275. doi: 10.1002/hbm.22064

He, B. J. (2013). Spontaneous and task-evoked brain activity negatively interact. *J. Neurosci.* 33, 4672–4682. doi: 10.1523/JNEUROSCI.2922-12.2013

Husserl, E. (1912–1915). *Ideen zu einer Reinen Phaenomenologie und Phaenomenologische Philosophie. II. Phaenomenologische Untersuchungen zur Konstitution.* Den Haag: Nijhoff.

Husserl, E. (2001). *Analyses Concerning Passive and Active Synthesis: Lectures on Transcendental Logic.* Vol. 9, Netherlands: Springer Science + Business Media.

Kam, J. W., Bolbecker, A. R., O'Donnell, B. F., Hetrick, W. P., and Brenner, C. A. (2013). Resting state EEG power and coherence abnormalities in bipolar disorder and schizophrenia. *J. Psychiatr. Res.* 47, 1893–1901. doi: 10.1016/j.jpsychires.2013.09.009

Kikuchi, M., Hashimoto, T., Nagasawa, T., Hirosawa, T., Minabe, Y., Yoshimura, M., et al. (2011). Frontal areas contribute to reduced global coordination of resting-state gamma activities in drug-naive patients with schizophrenia. *Schizophr. Res.* 130, 187–194. doi: 10.1016/j.schres.2011.06.003

Logothetis, N. K., Murayama, Y., Augath, M., Steffen, T., Werner, J., and Oeltermann, A. (2009). How not to study spontaneous activity. *Neuroimage* 45, 1080–1089. doi: 10.1016/j.neuroimage.2009.01.010

Madeira, L., Bonoldi, I., Rocchetti, M., Samson, C., Azis, M., Queen, B., et al. (2016). An initial investigation of abnormal bodily phenomena in subjects at ultra high clinical risk for psychosis: their prevalence and clinical implications. *Compr. Psychiatry* 66, 39–45. doi: 10.1016/j.comppsych.2015.12.005

Mancini, M., Presenza, S., Bernardo, D. L., Lardo, P. P., Totaro, S., Trisolini, F., et al. (2014). The life-world of persons with schizophrenia. A panoramic view. *J. Psychopathol.* 20, 423–434.

Markovà, I . S., and Berrios, G. E. (2015). "Neuroimaging in psychiatry: epistemological considerations," in *Alternative Perspectives on Psychiatric Validation*, eds P. Zachar, D. St. Stoyanov, M. Aragona, and A. Jablensky (Oxford: Oxford University Press), 112–127.

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn. Sci.* 15, 483–506. doi: 10.1016/j.tics.2011.08.003

Merleau-Ponty, M. (1962). *Phenomenology of Perception*, Vol. 10, London: Routledge.

Moran, L. V., and Hong, L. E. (2011). High vs. low frequency neural oscillations in schizophrenia. *Schizophr. Bull.* 37, 659–663. doi: 10.1093/schbul/sbr056

Morcom, A. M., and Fletcher, P. C. (2007a). Cognitive neuroscience: the case for design rather than default. *Neuroimage* 37, 1097–1099. doi: 10.1016/j.neuroimage.2007.07.018

Morcom, A. M., and Fletcher, P. C. (2007b). Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage* 37, 1073–1082. doi: 10.1016/j.neuroimage.2006.09.013

Nakao, T., Bai, Y., Nashiwa, H., and Northoff, G. (2013). Resting-state EEG power predicts conflict-related brain activity in internally guided but not in externally guided decision-making. *Neuroimage* 66, 9–21. doi: 10.1016/j.neuroimage.2012.10.034

Narayanan, M., Huynh, J. L., Wang, K., Yang, X., Yoo, S., McElwee, J., et al. (2014). Common dysregulation network in the human prefrontal cortex underlies two neurodegenerative diseases. *Mol. Syst. Biol.* 10:743. doi: 10.15252/msb.20145304

Northoff, G. (2013). Brain and self - a neurophilosophical account. *Child Adolesc. Psychiatry Ment. Health* 7:28. doi: 10.1186/1753-2000-7-28

Northoff, G. (2014a). *Unlocking the Brain: Volume 1: Coding*, Vol. 1. Oxford: Oxford University Press.

Northoff, G. (2014b). *Unlocking the Brain. Volume II: Consciousness.* Oxford: Oxford University Press.

Northoff, G. (2015a). Resting state activity and the stream of consciousness in schizophrenia-neurophenomenal hypotheses. *Schizophr. Bull.* 41, 280–290. doi: 10.1093/schbul/sbu116

Northoff, G. (2015b). Spatiotemporal psychopathology I: is depression a spatiotemporal disorder of the brain's resting state? *J. Affect. Disord.*

Northoff, G., and Heiss, W. D. (2015). Why is the distinction between neural predispositions, prerequisites, and correlates of the level of consciousness clinically relevant? Functional brain imaging in coma and vegetative state. *Stroke* 46, 1147–1151. doi: 10.1161/strokeaha.114.007969

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U S A* 98, 676–682. doi: 10.1073/pnas.98.2.676

Ranlund, S., Nottage, J., Shaikh, M., Dutt, A., Constante, M., Walshe, M., et al. (2014). Resting EEG in psychosis and at-risk populations—a possible endophenotype? *Schizophr. Res.* 153, 96–102. doi: 10.1016/j.schres.2013.12.017

Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., et al. (2012). Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain Connect.* 2, 25–32. doi: 10.1089/brain.2012.0080

Sass, L. A., and Pienkos, E. (2013). Space, time and atmosphere. A comparative phenomenology of melancholia, mania and schizophrenia, part II. *J. Conscious. Stud.* 20, 131–152.

Shulman, R. G., Hyder, F., and Rothman, D. L. (2014). Insights from neuroenergetics into the interpretation of functional neuroimaging: an alternative empirical model for studying the brain's support of behavior. *J. Cereb. Blood Flow Metab.* 34, 1721–1735. doi: 10.1038/jcbfm.2014.145

Smallwood, J., and Schooler, J. W. (2015). The science of mind wandering: empirically navigating the stream of consciousness. *Annu. Rev. Psychol.* 66, 487–518. doi: 10.1146/annurev-psych-010814-015331

Spencer, K. M. (2012). Baseline gamma power during auditory steady-state stimulation in schizophrenia. *Front. Hum. Neurosci.* 5:190. doi: 10.3389/fnhum.2011.00190

Stanghellini, G. (2009). Embodiment and schizophrenia. *World Psychiatry* 8, 56–59. doi: 10.1002/j.2051-5545.2009.tb00212.x

Stanghellini, G., and Ballerini, M. (2008). Qualitative analysis. Its use in psychopathological research. *Acta Psychiatr. Scand.* 117, 161–163. doi: 10.1111/j.1600-0447.2007.01139.x

Stanghellini, G., Ballerini, M., Blasi, S., Mancini, M., Presenza, S., Raballo, A., et al. (2014a). The bodily self: a qualitative study of abnormal bodily phenomena in persons with schizophrenia. *Compr. Psychiatry* 55, 1703–1711. doi: 10.1016/j.comppsych.2014.06.013

Stanghellini, G., Ballerini, M., and Cutting, J. (2014b). Abnormal bodily phenomena questionnaire. *J. Psychopathol.* 20, 36–41.

Stanghellini, G., Ballerini, M., Fusar Poli, P., and Cutting, J. (2012). Abnormal bodily experiences may be a marker of early schizophrenia? *Curr. Pharm. Des.* 18, 392–398. doi: 10.2174/138161212799316181

Stanghellini, G., Ballerini, M., Presenzsa, S., Macini, M., Raballo, A., Blasi, S., et al. (2016). Psychopathology of lived time: abnormal: time experience in persons with Schizophrenia. *Schizophr. Bull.* 42, 45–55. doi: 10.1093/schbul/sbv052

Stanghellini, G., and Rosfort, R. (2013). *Emotions and Personhood: Exploring Fragility-Making Sense of Vulnerability.* Oxford: Oxford University Press.

Stanghellini, G., and Rossi, R. (2014). Pheno-phenotypes: a holistic approach to the psychopathology of schizophrenia. *Curr. Opin. Psychiatry* 27, 236–241. doi: 10.1097/YCO.0000000000000059

Sun, L., Castellanos, N., Grützner, C., Koethe, D., Rivolta, D., Wibral, M., et al. (2013a). Evidence for dysregulated high- frequency oscillations during sensory processing in medication-naive, first episode schizophrenia. *Schizophr. Res.* 150, 519–525. doi: 10.1016/j.schres.2013.08.023

Sun, M., Holter, S. M., Stepan, J., Garrett, L., Genius, J., Kremmer, E., et al. (2013b). Crybb2 coding for β2-crystallin affects sensorimotor gating and hippocampal function. *Mamm. Genome* 24, 333–348. doi: 10.1007/s00335-013-9478-7

Thompson, E. (2007). *Mind in Life: Biology, Phenomenology, and the Sciences of Mind.* Cambridge, MA: Harvard University Press.

Uhlhaas, P. J., Linden, D. E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., et al. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J. Neurosci.* 26, 8168–8175. doi: 10.1523/jneurosci.2002-06.2006

Uhlhaas, P. J., and Singer, W. (2012). Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. *Neuron* 75, 963–980. doi: 10.1016/j.neuron.2012.09.004

Uhlhaas, P. J., and Singer, W. (2013). High-frequency oscillations and the neurobiology of schizophrenia. *Dialogues Clin. Neurosci.* 15, 301–313.

Uhlhaas, P. J., and Singer, W. (2015). Oscillations and neuronal dynamics in schizophrenia: the search for basic symptoms and translational opportunities. *Biol. Psychiatry* 77, 1001–1009. doi: 10.1016/j.biopsych.2014.11.019

Van Gluick, R. (2014). "Consciousness," in *Stanford Encyclopedia of Philosophy*, ed. E. N. Zalta (Stanford, CA: Stanford University).

Vanhaudenhuyse, A., Demertzi, A., Schabus, M., Noirhomme, Q., Bredart, S., Ohmura, Y., et al. (2011). Two distinct neuronal networks mediate the awareness of environment and of self. *J. Cogn. Neurosci.* 23, 570–578. doi: 10.1162/jocn.2010.21488

Weinberger, D. R., and Radulescu, E. (2016). Finding the elusive psychiatric "Lesion" with 21st-century neuroanatomy: a note of caution. *Am. J. Psychiatry.*, 173, 27–33. doi: 10.1176/appi.ajp.2015.15060753

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Integrative Processing of Touch and Affect in Social Perception: An fMRI Study

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Social perception commonly employs multiple sources of information. The present study aimed at investigating the integrative processing of affective social signals. Task-related and task-free functional magnetic resonance imaging was performed in 26 healthy adult participants during a social perception task concerning dynamic visual stimuli simultaneously depicting facial expressions of emotion and tactile sensations that could be either congruent or incongruent. Confounding effects due to affective valence, inhibitory top–down influences, cross-modal integration, and conflict processing were minimized. The results showed that the perception of congruent, compared to incongruent stimuli, elicited enhanced neural activity in a set of brain regions including left amygdala, bilateral posterior cingulate cortex (PCC), and left superior parietal cortex. These congruency effects did not differ as a function of emotion or sensation. A complementary task-related functional interaction analysis preliminarily suggested that amygdala activity depended on previous processing stages in fusiform gyrus and PCC. The findings provide support for the integrative processing of social information about others' feelings from manifold bodily sources (sensory-affective information) in amygdala and PCC. Given that the congruent stimuli were also judged as being more self-related and more familiar in terms of personal experience in an independent sample of participants, we speculate that such integrative processing might be mediated by the linking of external stimuli with self-experience. Finally, the prediction of task-related responses in amygdala by intrinsic functional connectivity between amygdala and PCC during a task-free state implies a neuro-functional basis for an individual predisposition for the integrative processing of social stimulus content.

Keywords: social perception, emotion, somatosensory, fMRI, facial expression, tactile sensation

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INTRODUCTION

The recognition of others' emotions and bodily feelings offers primary information to predict and attribute meaning to the intentional behavior of others. One important and outstanding question concerns the integrative processing of such signals from our social world in order to give sense to complex social perceptions. Social perception commonly employs multiple sources of information regarding others' experiences. For example, at a primary non-verbal level, a strong link exists between emotional expressions and bodily sensations as well as motor behavior, while the latter two are often used to infer others' affective states (Gallese et al., 2004; Bastiaansen et al., 2009). How is the integration of manifold bodily signals accomplished in the human brain?

An impressing amount of neuroscientific and meta-analytic data suggests that these different types of information recruit partially distinct functional networks, including sensorimotor, affective and mentalizing circuits (Gallese, 2003; Van Overwalle and Baetens, 2009; Keysers et al., 2010; Bernhardt and Singer, 2012; Bickart et al., 2014; Schurz et al., 2014). However, also overlap has been reported in sensorimotor and affective circuits supporting the social perception of both others' sensorimotor and others' affective experiences (Molenberghs et al., 2012) as well as between pre-reflective and inferential forms of social cognition (Fan et al., 2011). Except for affective regions (e.g., anterior insula, anterior cingulate cortex, and amygdala), also sensorimotor structures contributing to the recognition of others' bodily sensations (e.g., somatosensory cortex, frontal operculum, and premotor cortex; Keysers et al., 2010; Gallese and Ebisch, 2013) are involved in recognizing others' affective states (Adolphs et al., 2000; Pitcher et al., 2008; Hillis, 2014). Brain regions more generally involved in different types of social information processing could be hypothesized to have integrative functions, like conflict resolution or affective responses based on coherence of information from multiple sources (Etkin et al., 2006; de Lange et al., 2008; Muller et al., 2011).

Some studies provided insight into the neural mechanisms that may contribute to the integrative processing of social information from multiple sources. For instance, supramodal representations of crossmodal information (visual and auditory information) about others' emotional states have been linked with left amygdala and posterior cingulate cortex (PCC), whereas ambiguous crossmodal information elicited stronger neural activity in a network comprising frontoparietal sensorimotor and cingulo-insular affective circuits (Klasen et al., 2011). Furthermore, by studying contextual framing of social signals, stronger activity was found in bilateral amygdala, anterior insula, temporal pole, and fusiform gyrus for facial expressions of emotion in affective contexts compared with neutral contexts (Mobbs et al., 2006). However, it remains poorly understood whether these circuits could be involved more specifically in the integrative processing of social information about others' feelings from manifold bodily sources (e.g., "direct" affective information from facial expressions and "indirect" affective information from sensorimotor experiences). Modulating the coherence of social stimulus content (e.g., directly comparing congruent and incongruent information) within a single domain (e.g., unimodal, visual, information) could offer the possibility to study brain integrative functioning at the basis of making sense of the content of our social perceptions.

Interestingly, amygdala and fusiform gyrus are involved together in face perception (Adolphs, 2002; Herrington et al., 2011). Amygdala has been associated particularly with encoding relevance and impact of socio-emotional stimuli including faces (Ewbank et al., 2009; Adolphs, 2010; Bickart et al., 2014), and subjective judgments of facial expressions of emotions (Adolphs et al., 2002; Wang et al., 2014). In addition, PCC supports self-related processing by integrating external stimuli in one's own personal context through the interaction between memory and emotion (Northoff and Bermpohl, 2004; Vogt et al., 2006; van der Meer et al., 2010), whereas anterior insula associates self-related processing with the organisms transient physiological bodily states (Craig, 2009). Hence, these brain structures could contribute to the integrative processing of social information underlying the awareness of others' affective experiences in complex social perceptions. This possibly is mediated by the self-relatedness of content (Vogt et al., 2006; Northoff et al., 2009; Bickart et al., 2014). In particular, congruent content or social perceptions likely is more familiar to the observer in terms of own personal experiences, leading to a higher self-relatedness or relevance.

The present functional magnetic resonance imaging (fMRI) study aimed at elucidating the integrative processing of multiple signals during social perception in the visual domain, focusing on facial expressions of emotion of other individuals that are either congruent or incongruent with the tactile sensations of those individuals. Both are frequently employed bodily sources to understand another one's inner state, but are rarely investigated simultaneously. Moreover, the relationship between task-evoked neural responses and ongoing brain activity during a task-free state will be investigated. The latter could clarify how neural responses to complex social stimuli depend on intrinsic brain function which is proposed to constitute a neural predisposition characterizing individual reactions to external stimuli (Northoff, 2013, 2014).

It was hypothesized that the encoding of social stimulus congruence depends on brain circuits underlying affective and self-related processing, like amygdala, fusiform gyrus, anterior insula, and PCC. Increased neural responses in these structures imply enhanced integrative processing of others' affective experiences due to coherence of content. Alternatively, but not mutually exclusive, conflicting information could claim higher neural processing capacity in sensorimotor and affective circuits or in the mentalizing network associated with inferential/effortful social cognition. Finally, it was expected that enhanced neural responses to congruent stimuli could be associated with task-free brain activity as measured by intrinsic functional connectivity patterns of the implied brain structures, especially regions associated with high metabolism during task-free states and self-related processing, like PCC.

MATERIALS AND METHODS

Participants

Twenty-six participants were included in the present fMRI study (five females, age range: 20–42 years). All participants were healthy, right handed and had normal vision capabilities (correction < 0.75). Written informed consent was obtained from all participants after full explanation of the procedure of the study, in line with the Declaration of Helsinki. The experimental protocol was approved by the local institutional ethics committee. The participants were given a recompense for participating in the fMRI experiment.

Stimuli

Four types of video stimuli were created for the experiment. To control for effects due to the integrative processing of information from different perceptual modalities rather than content, participants in the fMRI experiment were presented social information only in the visual domain: short video clips depicting others' sensory-affective experiences.

The duration of each video clip was 2400 ms. Video clips were in color and depicted an actor sitting on a chair and being caressed or hit on their left hand by another actor. While being caressed or hit, the actor facially expressed an emotion, pleasure or pain, that could be either congruent or incongruent with the sensation induced by the touch. In half of the clips, a woman expressed an emotion, while being caressed or hit by a man. In the other half a man expressed an emotion, while being caressed or hit by a woman. Of the touching actor only the hand and arm were visible. These video clips can be categorized in four experimental conditions based on the combination of tactile sensation and facial expression: (1) caress-pleasure, (2) hit-pain, (3) caress-pain, and (4) hit-pleasure. Videos stills are visualized in **Figure 1**.

To evaluate whether the congruent and incongruent video stimuli used for the fMRI experiment differed with respect to the perceived self-relatedness and familiarity with the content, an independent sample of 42 participants (31 males, 11 females; 20–37 years) was included in the study (after concluding the fMRI experiments) and asked to judge these aspects of the stimuli. Chi-square tests showed that there was no significant difference in gender distribution between the sample included in the fMRI experiment and the stimulus judgments ($\chi^2 = 0.43$, $p > 0.5$). Since different participants were included in the fMRI task and the stimulus ratings, the results obtained by both procedures cannot be explained by an interaction between them, possibly altering stimulus interpretation: the fMRI results (stimulus congruence coding) could not be influenced by the self-relatedness/familiarity judgments, and the self-relatedness/familiarity judgments could not be influenced by the fMRI task (stimulus congruence coding).

Firstly, self-relatedness was assessed by asking participants "How much do you personally associate with or relate to this picture?" (translated from Italian). It was further explained that they needed to rate the personal association with the video content based on the strength of their subjective or personal experience of themselves while viewing the videos (see also Schneider et al., 2008). Secondly, to assess participants' familiarity with the video content, all videos were shown again and participants were asked "How much are you familiar with the experience depicted by the video" (translated from Italian). To indicate the degree of self-relatedness or familiarity, participants' responses were obtained by a drawing a horizontal line on a Visual Analog Scale (vertical line of 10 cm) ranging from "low personal association" to "high personal association" or from "low familiarity" to "high familiarity," respectively. Ratings were quantified by measuring the distance in mm between the lower point of the line and the sign of the participant on the scale.

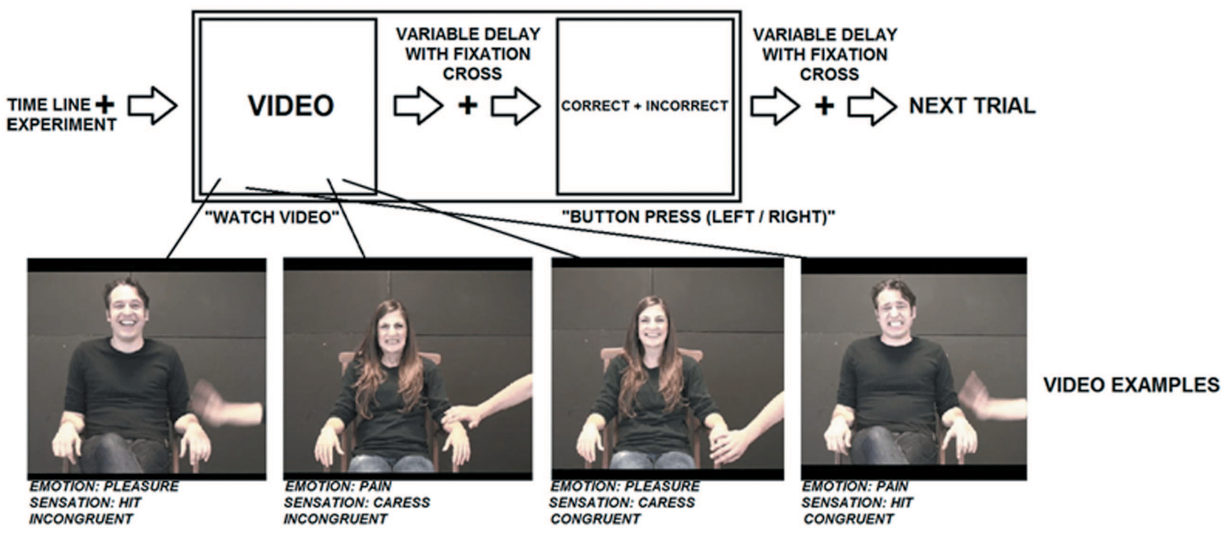

FIGURE 1 | Visualization of the experimental stimuli and procedure.

Self-relatedness judgments yielded the following ratings: caress-pleasure = 56.59 ± 25.38; hit-pain = 40.25 ± 28.22; caress-pain = 23.35 ± 20.41; hit-pleasure = 38.72 ± 22.55. Analysis of variance (ANOVA) concerning the self-relatedness judgments of the video stimuli showed a significant interaction between facial expression and tactile sensation ($F_{1,41} = 17.149$, $p < 0.001$), indicating an effect of stimulus congruence. *Post hoc* analysis showed that the caress-pleasure condition (congruent) was characterized by a stronger self-relatedness than the hit-pleasure condition (incongruent; $p < 0.001$) and the caress-pain condition (incongruent; $p < 0.005$). The hit-pain condition (congruent) was characterized by a stronger self-relatedness than the caress-pain condition (incongruent; $p < 0.005$), while there was no difference between the hit-pain condition (congruent) and hit-pleasure condition (incongruent; $p > 0.5$). In addition to the interaction effect, a main effect of facial expression was found due to a stronger self-relatedness of the expression of pleasure, compared to pain ($F_{1,41} = 19.614$, $p < 0.001$). No significant effect of tactile sensation was found on self-relatedness ($p > 0.5$).

Familiarity judgments yielded the following ratings: caress-pleasure = 63.73 ± 25.13; hit-pain = 34.72 ± 28.51; caress-pain = 24.02 ± 17.99; hit-pleasure = 38.71 ± 25.06. ANOVA concerning the familiarity judgments of the video stimuli showed a significant interaction between facial expression and tactile sensation ($F_{1,41} = 25.740$, $p < 0.001$), indicating an effect of stimulus congruence. *Post hoc* analysis showed that the caress-pleasure condition (congruent) was characterized by a stronger familiarity than the hit-pleasure (incongruent; $p < 0.005$) and the caress-pain condition (incongruent; $p < 0.001$). The hit-pain condition (congruent) was characterized by a stronger familiarity than the caress-pain condition (incongruent; $p < 0.005$), while there was no difference between the hit-pain condition (congruent) and the hit-pleasure condition (incongruent; $p > 0.5$). In addition to the interaction effect, a main effect of facial expression was found due to a stronger self-relatedness of the expression of pleasure, compared to pain ($F_{1,41} = 35.436$, $p < 0.001$), and a main effect of tactile sensation was found due to a stronger familiarity of caress, compared to hit ($F_{1,41} = 4.716$, $p < 0.05$).

Experimental Procedure

The participant was in a supine position in the MRI scanner and completed two task-free fMRI blocks (2 min × 5.2 min; eyes open with fixation cross) and four task fMRI runs (4 min × 7.7 min). During task fMRI, participants were shown a series of brief video clips as described above. The conditions were presented in randomized order and each condition (type of stimulus) was repeated 48 times.

The experimental conditions allowed investigating the independent effects of tactile sensation, facial expression and their interaction (i.e., effect of congruence between tactile sensation and facial expression). Importantly, regarding the sensation × expression interaction effect, the content of the videos was exactly the same between the congruent and incongruent conditions (conditions 1 and 2 *versus* conditions 3 and 4).

Each video clip was followed by a fixation cross with a random duration of 2400, 4800, or 7200 ms. In 23% of the cases ($N = 48$) and in casual order, the fixation cross was followed by the question: "Please indicate by means of a button press whether you find that the emotional expression (pleasure, pain) in the last video was correct (i.e., congruent) or incorrect (i.e., incongruent) with respect to the tactile sensation (caress, hit)." This task made it possible to direct and monitor the attention of the participant to both the facial expression and the tactile sensation depicted by the video clips. Furthermore, although this task required an explicit judgment of the tactile sensation and facial expression, and their congruency, it avoided forced choices based on conflicting information, because participants were not asked to make decisions about the actor's experience. For instance, it was not asked to decide "how does the actor depicted in the video feel considering the sensation and expression together," since this may enhance conflict processing when the expression is incongruent with the sensation.

Since it was not predictable when the questions would appear, participants needed to attend both aspects in all videos to be able to respond correctly when required. Specifically, when participants were required to respond, the words "correct" and "incorrect" appeared on the left and right side of the screen for 2400 ms. Participants were asked to press either the left or right button with the index or medium finger of their right hand. In order to avoid that participants could predict and prepare an eventual motor response with a particular finger, the words "correct" and "incorrect" were presented randomly in left–right or right–left order. For example, if the last seen video was congruent and "correct" was written on the left side, while "incorrect" appeared on the right side, participants responded with a left button press with their index finger. Differently, if the last seen video was congruent and "correct" appeared on the right side, participants responded with a right button press with their medium finger.

The time course of the experiment is visualized in **Figure 1**. Prior to scanning, participants underwent a practicing session outside the scanner to assure that they understood the task.

fMRI Data Acquisition

For each participant, blood-oxygen-level-dependent (BOLD) contrast functional imaging was performed with a Philips Achieva scanner at 3 Tesla at the Institute of Advanced Biomedical Technologies (ITAB), Chieti, Italy. A T1-weighted anatomical (3D MPRAGE pulse sequence; 1 mm isotropic voxels) and T2*-weighted functional data were collected with an eight channel phased array head coil. Two task-free, eyes-open (fixation cross) scanning blocks were performed consisting of 160 functional volumes each. Four task-fMRI scanning blocks were performed consisting of 193 functional volumes each. EPI data (gradient echo pulse sequence) were acquired from 33 slices (in-plane voxel size 2.396 mm × 2.396 mm, slice thickness 3.5 mm), TR = 2400 ms, TE = 72 ms, flip angle = 80°, Field of View = 230 mm). Slices were oriented parallel to the AC–PC axis of the observer's brain.

fMRI Data Preprocessing and Analysis

Raw fMRI data were analyzed with Brain Voyager QX 2.3 software (Brain Innovation, Maastricht, The Netherlands). Due to T1 saturation effects, the first five scans of each run were discarded from the analysis. Preprocessing of functional data included slice scan time correction, motion correction and removal of linear trends from voxel time series. A three-dimensional motion correction was performed with a rigid-body transformation to match each functional volume to the reference volume estimating three translation and three rotation parameters. Preprocessed functional volumes of a participant were co-registered with the corresponding structural data set. As the 2D functional and 3D structural measurements were acquired in the same session, the coregistration transformation was determined using the slice position parameters of the functional images and the position parameters of the structural volume. Structural and functional volumes were transformed into the Talairach space (Talairach and Tournoux, 1988) using a piecewise affine and continuous transformation. Functional volumes were re-sampled at a voxel size of 3 mm × 3 mm × 3 mm and spatially smoothed with a Gaussian kernel of 6 mm full-width half maximum to account for intersubject variability.

The task-fMRI time series were modeled by means of a two gamma hemodynamic response function using predictors (videos differentiated by experimental condition and question/response). The intertrial interval was used as a baseline period and was not modeled. Prior to statistical analysis, a percent signal change normalization of the time series from the different runs was performed. The parameters (beta values) estimated in individual subject analysis were entered in a second level voxel-wise random effect group analysis.

The following effects were tested by an ANOVA: (1) within-subject factor "facial expression (pain, pleasure)" [(caress-pleasure + hit-pleasure) *versus* (caress-pain + hit-pain)]; (2) within-subject factor "tactile sensation (hit, caress)" [(caress-pleasure + caress-pain) *versus* (hit-pain + hit-pleasure)]; (3) interaction effect "facial expression × tactile sensation" [(caress-pleasure + hit-pain) *versus* (caress-pain + hit-pleasure)]. Note that the interaction effect is equivalent to the contrast between the congruent and the incongruent conditions and, thus, indicating the congruence effect. The p-value (<0.001 uncorrected) of the group statistical maps and an estimate of the spatial correlation of voxels were used as input in a Monte Carlo simulation (1000 simulations) to access the overall significance level and to determine a cluster size threshold (k) in order to obtain a significance level that was cluster level corrected for multiple comparisons ($p < 0.05$ corrected; $k > 10$, $F > 13.88$, and $p < 0.001$ at the voxel level; Forman et al., 1995; Cox, 1996).

Covariance Structural Equation Modeling (SEM)

Complementary to the principal analysis of task-evoked BOLD responses, structural equation modeling (SEM) was applied as a confirmatory method to infer task-related functional interactions between brain regions from task-related activations within brain regions. In particular, it allows to test specific hypotheses about functional dependence of activity patterns between brain regions, in our case during the social perception of congruent *versus* incongruent social stimuli across participants.

Structural equation modeling conveys assumptions about the relationships between activity in brain regions in terms of uni- or bi-directional interaction effects by combining anatomical connectivity information and functional data of covariance across participants. Different from PsychoPhysical Interactions (Friston et al., 1997), it is model-based and allows more complex models that consider multiple brain regions and interactions. Different from Dynamic Causal Modeling (DCM; Penny et al., 2004), SEM is a static model, and is not directly influenced by variations and shape of hemodynamic responses (Handwerker et al., 2012). Although, the same analysis on a larger number of subjects is recommended to draw final conclusions on the nature of amygdala interactions suggested by SEM, satisfying reliability of SEM results has been demonstrated for a sample size typical for fMRI studies (Protzner and McIntosh, 2006). Differential beta-values for the contrast between the congruent and the incongruent conditions were used as extracted from the regions of interest (ROIs) characterized by a significant tactile sensation × facial expression interaction effect.

Prior to SEM, an exploratory factor analysis [Principal Axis Factoring (PAF)] was performed on the differential beta-values (congruent minus incongruent conditions) from the interaction ROIs obtained by the voxel-wise ANOVA. PAF allows to select a set of ROIs offering a good compromise between model complexity and interpretability for further SEM. Specifically, relying on the same statistical information (i.e., covariance) as SEM, PAF identifies a latent component: a "hidden" variable inferred from the correlations between the observed activation patterns in the ROIs through a mathematical model. As such, a factor obtained by PAF highlights a discrete network of selected ROIs characterized by common activation patterns suggesting functional interaction among them, though not providing any information about directionality. According to the scree test (Cattell, 1966), one factor could be extracted if explaining 49.61% of the variance, whereas absolute loadings can be required for each ROI greater than 0.30 (Kline, 1994). PAF yielded a satisfying one-factor solution including five ROIs with above threshold loadings exclusively on the first factor: left fusiform gyrus (FFG), left dorsal PCC, bilateral ventral PCC and left amygdala (**Table 1**).

Subsequently, SEM was performed based on a Path Analysis Model with only observed variables (see for examples of a similar approach in neuroimaging research McIntosh, 1998; Horwitz et al., 1999; Ingvar and Petersson, 2000; Addis et al., 2007) by using the LISREL 8.7 statistical package (Joreskog and Sorbom, 2006). Path analysis allows to solve a set of simultaneous regression equations that theoretically establish the relationship among multiple variables (i.e., regional activation patterns) in a specified model (Anderson and Gerbing, 1988; MacCallum and Austin, 2000). Each ROI in the model defines a regression equation relating its pattern of neural response to the responses in the ROIs connected to it. The simultaneous system of equations is solved via least squares or maximum likelihood for the

TABLE 1 | Pattern matrix of the PAF analysis.

	Factor		
	1	**2**	**3**
Left fusiform gyrus*	**0.91**	−0.11	0.20
Left dorsal posterior cingulate cortex*	**0.84**	0.50	−0.10
Right ventral posterior cingulate cortex*	**0.83**	−0.15	0.09
Left ventral posterior cingulate cortex*	**0.83**	0.10	0.09
Left amygdala*	**0.79**	0.18	−0.23
LH_aSPC	**0.66**	−0.12	**0.33**
RH_SFS	0.05	**0.86**	0.21
LH_SFS	−0.20	**0.83**	0.17
RH_vACC	0.11	**0.52**	−0.42
LH_STG	0.13	0.24	**0.68**
Eigenvalue	4.96	1.64	1.19
% of variance	49.61	16.4	11.91

Loadings above the cut-off threshold are indicated in bold. Regions uniquely comprised in the first factor (but not in the other factors) are indicated by an asterisk.

strengths of the interactions (the path coefficients) joining the regions. The standardized path coefficients can be interpreted as partial correlation or regression coefficients that convey assumptions about the directionality of ROI interactions for task performance.

Based on the literature on anatomical as well as functional connections between amygdala and FFG, and between FFG and PCC (but not between amygdala and PCC; Freese and Amaral, 2006; Vogt et al., 2006; Hagmann et al., 2008; Adolphs, 2010; Pessoa and Adolphs, 2010; Bzdok et al., 2013; Bickart et al., 2014), we tested four competitive models: (1) [PCC → left FFG → left amygdala]; (2) [amygdala → FFG → PCC]; (3) [PCC → FFG ↔ amygdala]; (4) [PCC ↔ FFG ← amygdala]. Thus, in specifying the models it was considered that the direction of functional interactions between the regions remains to be explored. The models can be considered equally complex, because characterized by the same number of parameters, while only differing in the directionality of the connections. Moreover, neither specific constraints were applied on the models nor parameters were released. It was not possible to test other possibilities of interactions between these regions due to the absence of an independent variable in those cases.

We tested these four models concerning the effects on BOLD response (i.e., average differential beta values from participants) due to stimulus congruence (congruent *versus* incongruent). As a further control analyses, the same models were also tested for the effects due to facial expression (pain *versus* pleasure) and tactile sensation (hit *versus* caress).

Task-Free fMRI Data Preprocessing and Analysis

To investigate whether differential brain responses to congruent and incongruent stimuli (tactile sensation × facial expression interaction effect) could be explained by brain intrinsic functional organization, the relationship was tested between task-evoked neural responses (differences between beta values of the congruent and the incongruent conditions) in left amygdala, representing a final processing stage according to the SEM results, and intrinsic functional connectivity during task-free fMRI scanning with the other ROIs composing the model, representing previous processing stages. Intrinsic functional connectivity is operationally defined as the statistical dependence between low-frequency (0.009–0.08 Hz), task-independent BOLD fluctuations in distant brain regions and is considered to represent an index of intrinsic long-range communication across the brain (Van Dijk et al., 2010).

For intrinsic functional connectivity analysis of the task-free fMRI sessions, in addition to the fMRI preprocessing steps described for task-fMRI data, a second step of data preprocessing (Ebisch et al., 2011; Power et al., 2014) was performed on the task-free fMRI time series by using self-devised MATLAB (The Mathworks, Inc., Natick, MA) scripts. These included: (1) bandpass filtering between 0.009 and 0.08 Hz; (2) regression of global, white matter, and ventricle signals, and their first derivatives; (3) regression of three dimensional motion parameters, and their first derivatives; (4) scrubbing of motion affected functional volumes including frame-wise displacement (FD; threshold = 0.5%) and differential spatial variance (DVARS; threshold = 4.6%).

Since intrinsic functional connectivity analysis was performed on a separate task-free data set, more general and independent ROIs were created, that is, a priory voxel clusters defined as spheres with a 6 mm radius and functionally based on the peak coordinates of the activation clusters (showing a tactile sensation × facial expression interaction effect) included in the SEM analysis.

Connectivity indices were calculated (and transformed by Fisher r-to-z transformation) for each subject by correlating the average ROI time-courses from left amygdala with the average ROI time-courses from FFG, dorsal PCC and bilateral ventral PCC. Both individual task-evoked neural responses in amygdala and functional connectivity indices (z-scores based on the correlations) were transformed in natural log values in order to account for non-linear relationships. Finally, Pearson correlation coefficients were calculated between task-evoked neural responses in left amygdala and its functional connectivity indices during task-free fMRI with the other ROIs of the network (FFG, left/right vPCC, left dPCC).

RESULTS

Behavioral Results of the fMRI Experiment

Analysis of task performance during the fMRI experiment showed that participants made on average 1.5 errors (standard deviation = 1.7; range: 0–5) when responding to the correct/incorrect questions throughout the experiment corresponding to an error rate of 3%. This suggests that the task was easy, that agreement among participants about stimulus congruence was high, and that participants attentively watched the relevant aspects of video content.

Task fMRI Results: Stimulus Congruence

The tactile sensation × facial expression interaction [(caress-pleasure + hit-pain) *versus* (caress-pain + hit-pleasure)] was of principal interest for the study, because it indicates an effect of stimulus congruency. This statistical interaction based on ANOVA yielded significant clusters ($F_{1,25} > 13.88$; $p < 0.001$) in bilateral ventral PCC (vPCC), superior/lateral prefrontal cortex, left (ventrolateral) amygdala, dorsal PCC (dPCC), posterior superior temporal gyrus, anterior superior parietal cortex (aSPC) and anterior FFG, and right ventral anterior cingulate cortex (**Table 2**; **Figure 2**).

For *post hoc* analysis, for each participant the beta values of the clusters obtained by the interaction contrast were calculated from the average signal time course of the voxels included in each cluster. Average beta values showed that activation in all these interaction ROIs was stronger during the congruent conditions, compared to the incongruent conditions (**Table 2**; **Figure 3**). No brain regions were characterized by increased activity for the

TABLE 2 | Statistical and anatomical details about the voxel clusters characterized by a significant tactile sensation × facial expression interaction effect.

Brain region	Talairach coordinates (x/y/z) peak	Peak *F*-value	Uncorrected *p*-value of peak voxel	Cluster size	Experimental condition	Peak ß-value (± standard error)
Right PFC (BA8)	20/25/48	25.15	<0.00005	378	Caress-pleasure	−0.02 (± 0.04)
					Hit-pain	−0.05 (± 0.05)
					Caress-pain	−0.18 (± 0.04)
					Hit-pleasure	−0.11 (± 0.05)
Left PFC (BA8)	−16/13/54	28.22	<0.00005	1242	Caress-pleasure	−0.03 (± 0.03)
					Hit-pain	0.01 (± 0.03)
					Caress-pain	−0.11 (± 0.03)
					Hit-pleasure	−0.10 (± 0.02)
Left aSPC (BA 7)	−28/−44/48	24.37	<0.00005	243	Caress-pleasure	0.54 (± 0.08)
					Hit-pain	0.63 (± 0.07)
					Caress-pain	0.50 (± 0.08)
					Hit-pleasure	0.52 (± 0.07)
Left dPCC (BA 31)	−16/−32/39	27.96	<0.00005	837	Caress-pleasure	0.06 (± 0.03)
					Hit-pain	0.10 (± 0.03)
					Caress-pain	−0.03 (± 0.03)
					Hit-pleasure	0.00 (± 0.03)
Left vPCC (BA 17/18/19/23/30)	−7/−50/3	24.92	<0.00005	7749	Caress-pleasure	0.43 (± 0.15)
					Hit-pain	0.38 (± 0.15)
					Caress-pain	0.24 (± 0.15)
					Hit-pleasure	0.23 (± 0.14)
Right vPCC (BA 17/18/19/23/30)	11/−62/6	31.03	<0.00001	4860	Caress-pleasure	1.12 (± 0.19)
					Hit-pain	1.10 (± 0.18)
					Caress-pain	1.03 (± 0.18)
					Hit-pleasure	0.92 (± 0.18)
Right vACC (BA 24/32)	2/34/12	19.64	<0.0005	351	Caress-pleasure	−0.23 (± 0.05)
					Hit-pain	−0.18 (± 0.05)
					Caress-pain	−0.29 (± 0.05)
					Hit-pleasure	−0.40 (± 0.05)
Left amygdala	−34/−8/−15	39.13	<0.000005	837	Caress-pleasure	0.12 (± 0.03)
					Hit-pain	0.14 (± 0.02)
					Caress-pain	0.05 (± 0.03)
					Hit-pleasure	0.02 (± 0.02)
Left FFG (BA 36/37)	−28/−38/−9	19.00	<0.0005	405	Caress-pleasure	0.04 (± 0.04)
					Hit-pain	−0.03 (± 0.04)
					Caress-pain	−0.06 (± 0.05)
					Hit-pleasure	−0.12 (± 0.04)
Left STG (BA 19/39)	−40/−53/18	26.58	<0.00005	1755	Caress-pleasure	0.13 (± 0.06)
					Hit-pain	0.18 (± 0.07)
					Caress-pain	0.04 (± 0.07)
					Hit-pleasure	0.09 (± 0.07)

BA, Brodmann area; PFC, prefrontal cortex; aSPC, anterior superior parietal cortex; d/vPCC, dorsal/ventral posterior cingulate cortex; vACC, ventral anterior cingulate cortex; FFG, fusiform gyrus; STG, superior temporal gyrus.

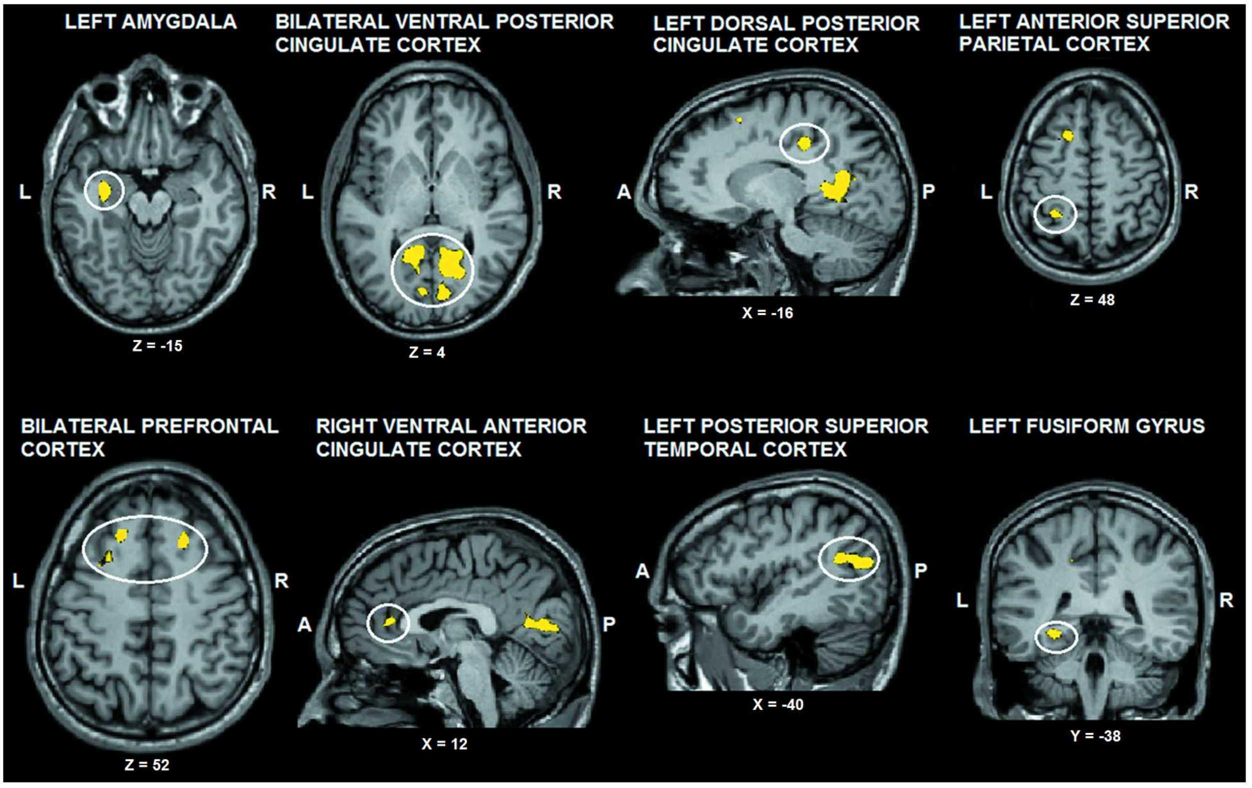

FIGURE 2 | Voxel clusters (thresholded at $p < 0.05$ corrected; $k > 10$) characterized by a significant interaction effect "facial expression × tactile sensation." BOLD responses in these clusters were stronger during the congruent conditions, compared to the incongruent conditions. L: left; R: right; A: anterior; P: posterior.

incongruent conditions, compared to the congruent conditions, even when using a threshold of $p < 0.01$ uncorrected.

An additional control analysis using paired-sample t-tests was performed to rule out the possibility that increased BOLD responses to the congruent stimuli could be attributed to a cumulative processing of information from different sources regarding specific emotional content (e.g., expression and sensation of pain or expression and sensation of pleasure). The brain regions that were exclusively characterized by an interaction effect (congruent > incongruent) in the absence of a tactile sensation or facial expression effect (neither significant nor trend; $p > 0.1$) were left (ventrolateral) amygdala, left dPCC, left vPCC, and left aSPC (**Figure 3**).

Task fMRI Results: Main Effects of Tactile Sensation and Facial Expression

Group statistical fMRI maps (ANOVA: $F_{1,25} > 13.88$; $p < 0.001$) showed a significant main effect of the facial expression factor in bilateral dorsal anterior cingulate/supplementary motor cortex, ventral and dorsal premotor cortex, lateral prefrontal cortex, inferior frontal gyrus, anterior insula, nucleus caudatus, inferior parietal lobule/supramarginal gyrus, extrastriate cortex, fusiform gyrus, inferior temporal cortex, PCC, and right superior temporal sulcus. Except for PCC (pleasure > pain), BOLD response in these regions was stronger for the expression of pain, compared to the expression of pleasure (**Figure 4**).

A significant main effect (ANOVA: $F_{1,25} > 13.88$; $p < 0.001$) of the tactile sensation factor was detected in bilateral lateral post-central gyrus (caress > hit), anterior temporal-parietal junction (hit > caress), left dorsal precentral gyrus (hit > caress), inferior parietal lobule/supramarginal gyrus (hit > caress), superior temporal gyrus (hit > caress), posterior parietal cortex (caress > hit), left occipital cortex/fusiform gyrus, and right occipital cortex/fusiform gyrus (caress > hit; **Figure 5**).

Task fMRI Results: Overlap between Main Effects of Tactile Sensation and Facial Expression

Conjunction analysis was performed to test whether voxel clusters existed that were modulated both by the tactile sensation factor and by the facial expression factor. Such a characteristic could provide a neural substrate allowing the convergence of these types of information. Conjunction analysis was based on the minimum statistic for the conjunction null (Nichols et al., 2005) and concerned the contrast [(caress-pleasure + caress-pain) *versus* (hit-pleasure + hit-pain)] ∩ [(caress-pleasure + hit-pleasure) *versus* (caress-pain + hit-pain)]. This analysis yielded

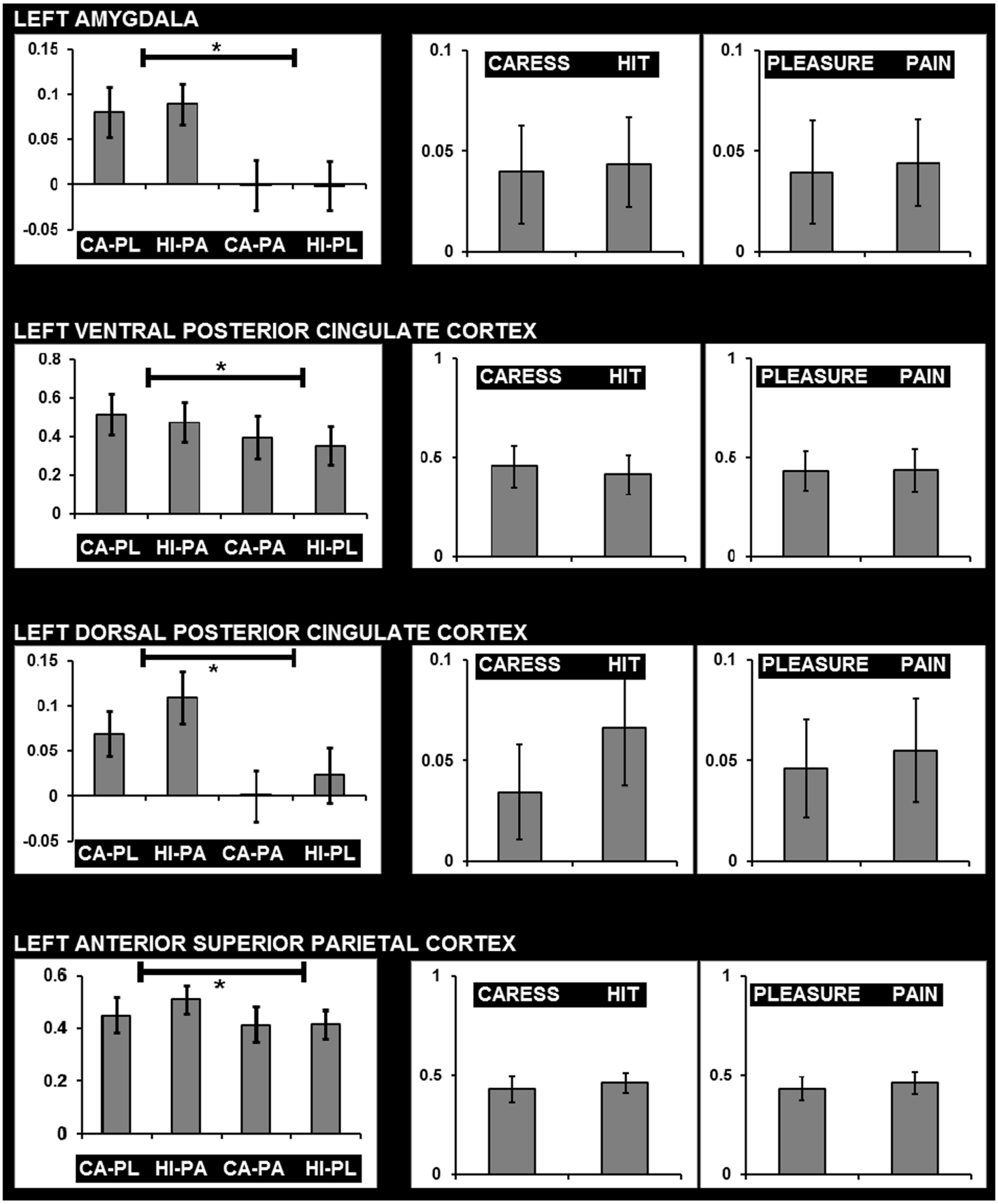

FIGURE 3 | Graphs showing average beta values and standard errors for the experimental conditions regarding voxels clusters characterized by a significant facial expression × tactile sensation interaction effect, *and* the absence of significant effects due tactile sensation or facial expression separately. Graphs on the left show beta values for the four conditions (CA-PL: caress-pleasure; HI-PA: hit-pain; CA-PA: caress-pain; HI-PL: hit-pleasure) indicating stronger responses for congruent compared to incongruent stimuli. Graphs on the right show average beta values for caress *versus* hit stimuli, and pleasure *versus* pain stimuli, illustrating the absence of differences between the observation of distinct tactile sensations or distinct facial expressions in these regions. *, statistically significant difference $p < 0.05$.

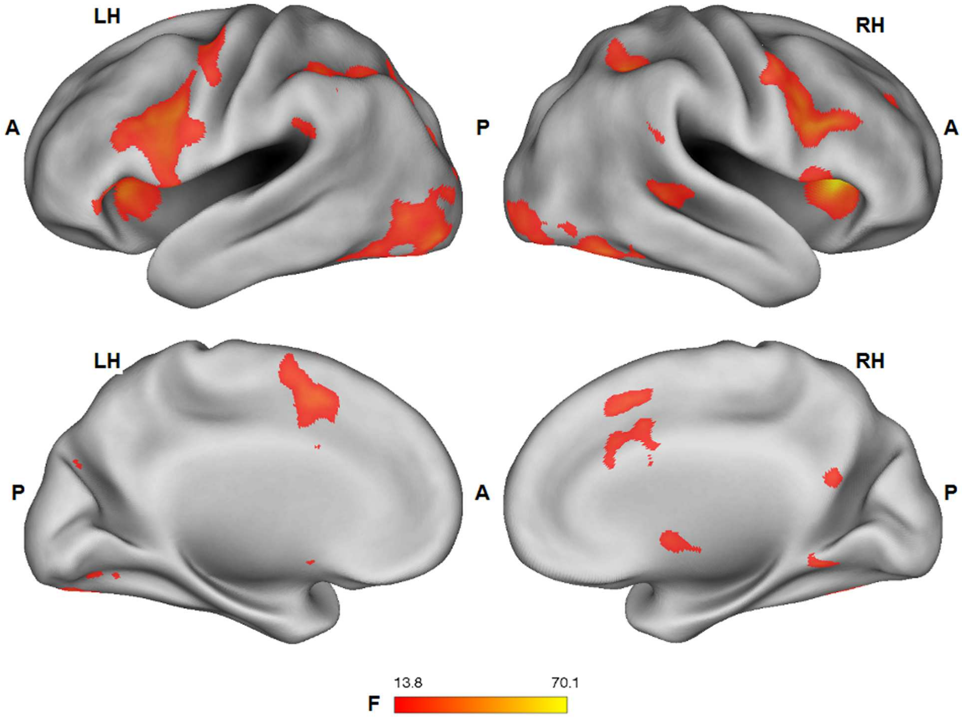

FIGURE 4 | Group statistical maps (*F*-statistics) showing voxels characterized by a significant effect of the facial expression factor (thresholded at $p < 0.05$ corrected; $k > 10$). L: left; R: right; A: anterior; P: posterior.

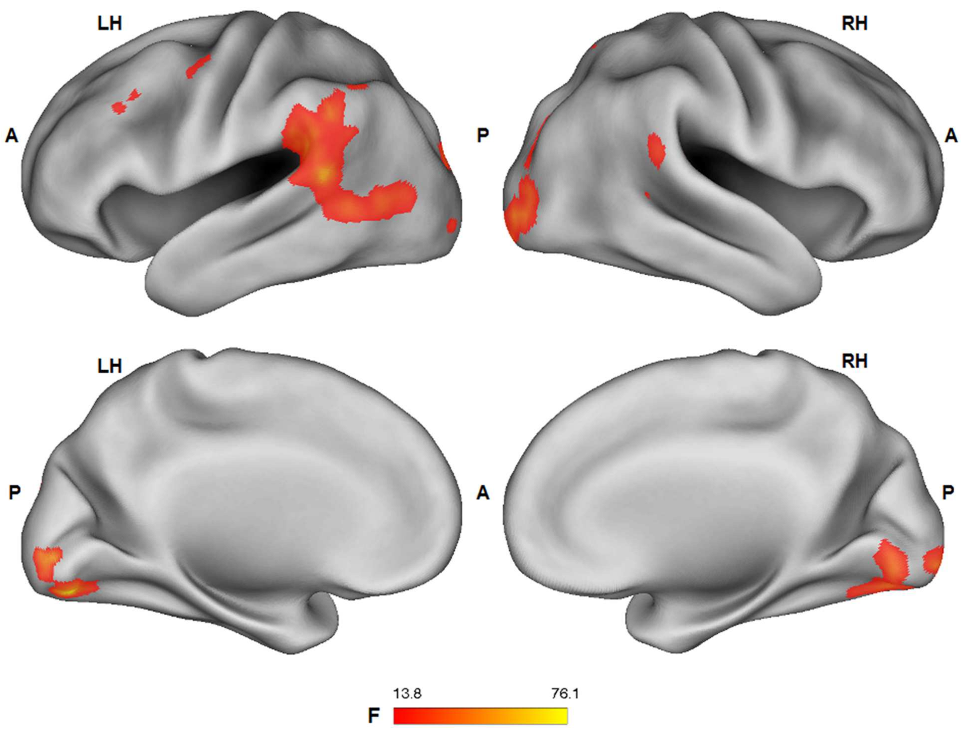

FIGURE 5 | Group statistical maps (*F*-statistics) showing voxels characterized by a significant effect of the tactile sensation expression factor (thresholded at $p < 0.05$ corrected; $k > 10$). L: left; R: right; A: anterior; P: posterior.

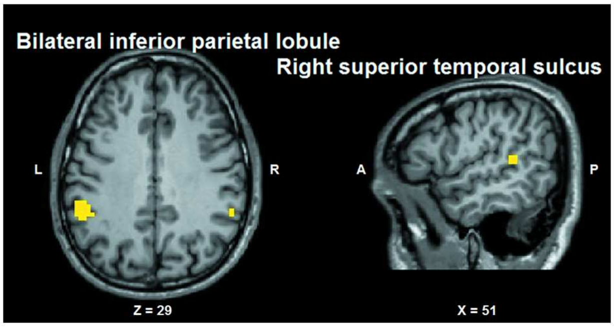

FIGURE 6 | Group statistical maps (conjunction thresholded at $p < 0.05$ corrected; $k > 10$) showing overlapping modulation by the observation of different tactile sensations as well as by different facial expressions. L: left; R: right; A: anterior; P: posterior.

overlapping voxel clusters ($t_{25} > 3.72$; $p < 0.001$) for the tactile sensation and the facial expression factors in bilateral anterior inferior parietal lobule (aIPL)/supramarginal gyrus and right superior temporal gyrus (STS; **Figure 6**).

Task fMRI Results: SEM

Regarding SEM, the fit of each model was assessed by means of the following goodness of fit indices: (1) the chi-square (χ^2) statistic and its degrees of freedom; (2) the root mean square error of approximation (RMSEA) and its 90% confidence interval (90% CI); (3) the Non-Normed Fit Index (NNFI), 4) the Comparative Fit Index (CFI); and (5) the standardized root mean square residuals (SRMRs). Furthermore, to compare the alternative models, the Expected Cross-Validation Index (ECVI) was used. A model was considered to the data when: $\chi^2/\mathrm{df} \leq 2$, CFI and NNFI ≥ 0.97, SRMR ≤ 0.05, and RMSEA ≤ 0.05 (90% CI: the lower boundary of the CI should contain zero for exact fit and be <0.05 for close fit). A model with an ECVI smaller than the ECVI-for-comparison model should be preferred. Based on the fit values, the models can be categorized in (1) under/not-identified models if one or more parameters may not be uniquely determined, because there is not enough information; (2) just-identified models when all of the parameters are uniquely determined, and (3) over-identified models if there is more than one way of estimating a parameter and therefore are not exhaustive (Hooper et al., 2008; Kline, 2015). Thus, a just-identified model provides the best solution to describe the data.

Structural equation modeling confirmed the model based on directional effects from left vPCC and dPCC to left fusiform gyrus, and from left fusiform gyrus to left amygdala, while strong bidirectional interactions were found between bilateral vPCC and left dPCC (model 1 visualized in **Figure 7**). The other models were characterized by an over-fit (model 3; not satisfying the goal of parsimony by adding unnecessary parameters resulting in a too complex model which is impossible to falsify) or yielded inadequate fit indices (models 2 and 4). Moreover, when testing the models in the control contexts of effects due to tactile sensations and facial expressions, inadequate fit indices were obtained in all cases. Statistical data of the different models in the different contexts are presented in **Table 3**.

Task-Free fMRI Results: Intrinsic Functional Connectivity

Analysis of the statistical dependency between differential beta values in left amygdala (congruent *minus* incongruent; obtained from the task-fMRI data set) and functional connectivity indices (obtained from the task-free fMRI data set) yielded a significant correlation ($r = -0.58$; $p < 0.008$ Bonferroni corrected for multiple comparisons) between the congruency effects in left amygdala during task-performance and its connectivity with left dPCC, but not with the others ROIs (FFG: $r = -0.05$; left vPCC: -0.08; right vPCC: -0.17, all $p > 0.5$ Bonferroni corrected for multiple comparisons), during the task-free fMRI blocks (**Figure 8**).

When looking at the intrinsic functional connectivity indices during the task-free state at the group level, an average correlation between BOLD low-frequency fluctuations in left amygdala and left dPCC of $r = -0.01$ is detected ($SD = 0.29$; minimum $r = -0.42$; maximum $r = 0.67$; $t = -0.0617$; $p = 0.5$). Therefore, these data imply that a stronger differentiation between the congruent and incongruent stimuli is accompanied by an absence or even antagonistic relationship (i.e., a negative correlation coefficient) between intrinsic activity in left amygdala and left dPCC. Vice versa, the more left amygdala and dPCC co-vary during a task-free state, the lesser the differentiation between congruent and incongruent stimuli in amygdala during task-performance.

DISCUSSION

This study aimed at investigating the integrative processing of information from multiple sources during social perception, in particular others' tactile sensations and facial expressions of emotion. Integrative processing as represented by an effect of stimulus congruence was detected in left ventrolateral amygdala, left dPCC, left vPCC, and left aSPC. In all cases, neural activity was stronger when the facial expression was congruent with the tactile sensation regarding valence. Furthermore, no additional effects due to tactile sensation or facial expression was observed in these brain regions, that is, the congruency effects did not differ as a function of emotion or sensation. These findings show that congruent, unimodal social stimuli with emotional content can naturally induce stronger responses of affective networks, especially amygdala and PCC.

Amygdala has been proposed as a key structure in the human brain facilitating social life (Adolphs, 2010; Bickart et al., 2014). Its functions are strongly related to encoding emotional relevance as well as salience or impact of stimuli (Ewbank et al., 2009; Pessoa and Adolphs, 2010) independent of stimulus valence (Fitzgerald et al., 2006; van der Gaag et al., 2007). Particularly relevant for social perception, amygdala supports the recognition of facial expressions of emotion (Adolphs, 2002) and amygdala neurons were found to encode subjective judgments of emotional faces (Wang et al., 2014). In addition, the location of the amygdala

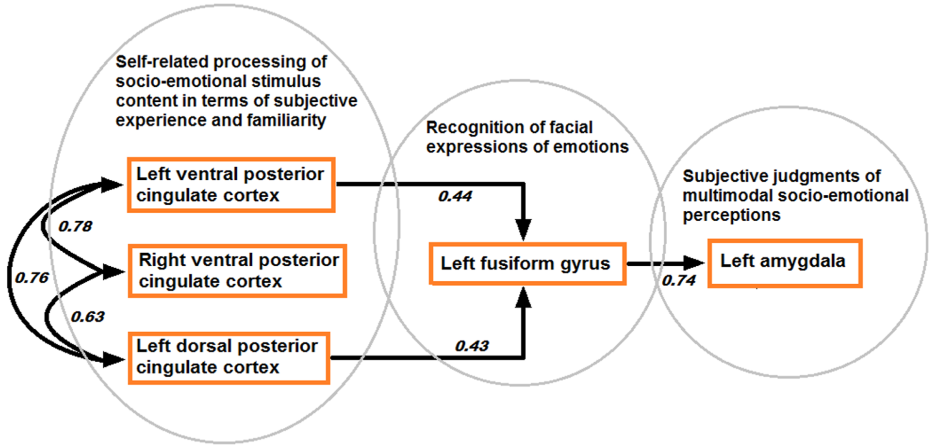

FIGURE 7 | Model of directional effects (indicating standardized path coefficients) between posterior cingulate cortex, fusiform gyrus, and amygdala obtained by SEM for the differentiation between congruent and incongruent stimuli, and a recapitulation of the task-related fMRI results concerning the encoding of socio-emotional stimulus congruence within the network.

cluster in the present study corresponds most closely to the ventrolateral amygdala (Ball et al., 2009; Saygin et al., 2011; Bzdok et al., 2013) embedded in a network supporting the integration of multisensory information from the environment with self-relevant cognition (Adolphs, 2010; Saygin et al., 2011; Bickart et al., 2014) and awareness of others' emotions (Bickart et al., 2014).

A parsimonious interpretation of BOLD modulations due to stimulus congruence in ventrolateral amygdala would thus be that they reflect an augmented self-relevance or impact of congruent socio-emotional stimuli. Alternatively, facial expressions of emotion that correspond to what one would expect from the context in which they occur, would facilitate subjective judgments of the depicted emotional experiences in amygdala. Such expectations could be based on one's personal experiences with a certain situation. For instance, when witnessing someone expressing pain while being hit by someone, it is likely easier to judge the other's affective experience as one is familiar with the experience of expressing pain while being hit. The latter interpretation seems to be favored when considering the full picture of results.

TABLE 3 | Structural equation modeling (SEM) fit values for the four alternative models applied to the three experimental factors (tactile sensation, facial expression, tactile sensation × facial expression).

Factors/models	χ^2	df	χ^2/df	NNFI	CFI	RMSEA	90% CI	SRMR	ECVI
Expression × sensation (congruence)									
Model 1**	3.69	4	0.92	0.99	0.99	0.00	0.00–0.31	0.06	1.41
Model 2	12.87	5	2.57	0.80	0.90	0.26	0.08–0.83	0.35	179
Model 3	0.66	3	0.22	1.07	1.00	0.00	0.00–0.17	0.02	1.36
Model 4	15.55	3	5.18	0.64	0.89	0.40	0.21–0.61	0.140	2.02
Expression									
Model 1	14.15	4	3.54	0.65	0.86	0.34	0.10–1.16	0.11	2.10
Model 2	21.00	5	4.2	0.41	0.70	0.37	0.21–0.53	0.35	2.12
Model 3	11.83	3	3.94	0.53	0.86	0.37	0.16–0.70	0.12	2.08
Model 4	4.54	3	1.51	0.93	0.98	0.15	0.00–0.40	0.073	1.61
Sensation									
Model 1	4.97	4	1.24	0.94	0.98	0.10	0.00–0.35	0.06	1.68
Model 2	11.77	5	2.35	0.65	0.82	0.25	0.01–0.87	0.25	1.74
Model 3	4.93	3	1.64	0.87	0.96	0.17	0.00–0.56	0.06	1.77
Model 4	13.01	3	4.34	0.22	0.77	0.37	0.18–0.59	0.160	1.96

*NNFI, Non-Normed Fit index; CFI, Comparative Fit Index; RMSEA, root mean square error of approximation; 90% CI, RMSEA 90% confidence interval; SRMR, standardized root mean square residual; ECVI, Expected Cross-Validation Index; ** model characterized by adequate fit indices.*
Model 1: PCC → FFG → amygdala;
Model 2: PCC → FFG ↔ amygdala;
Model 3: amygdala → FFG → PCC;
Model 4: PCC ↔ FFG ← amygdala.

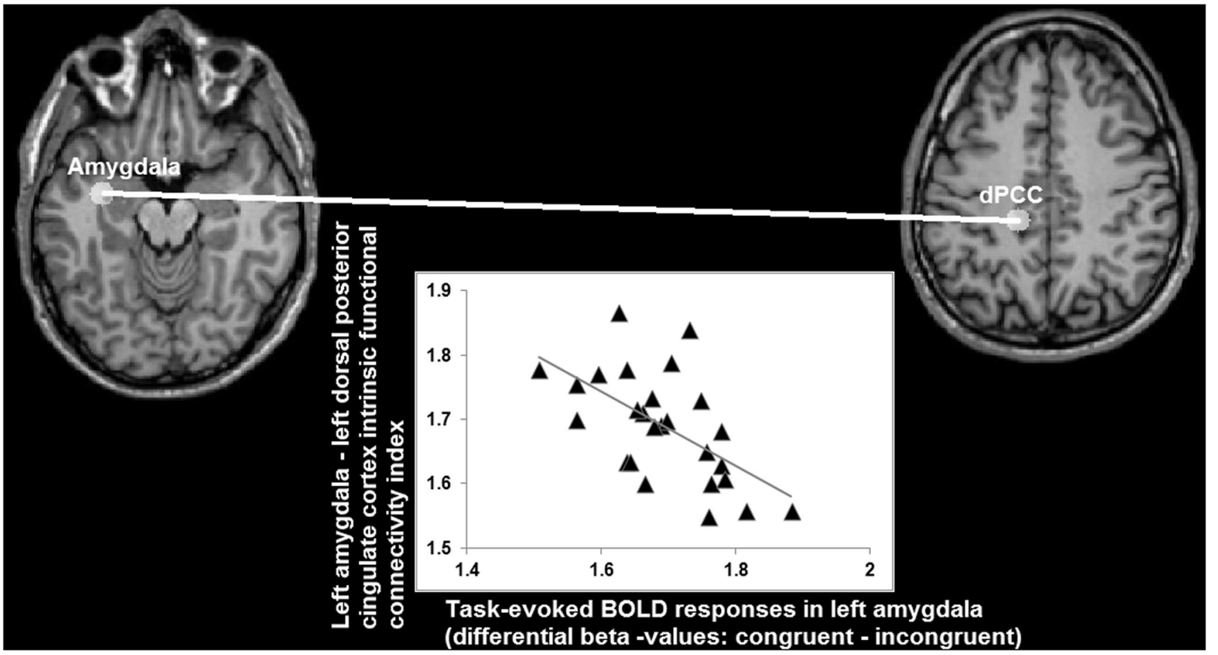

FIGURE 8 | Relationship ($r = -0.58$) between differential BOLD responses in left amygdala for congruent and incongruent stimuli, and its intrinsic functional connectivity with left dorsal posterior cingulate cortex (axes indicating natural log values).

Several other brain regions showed activation patterns similar to those detected in amygdala, including FFG and v/dPCC. FFG is a main structure sending afferent information to amygdala with a principal role in the perception of faces and emotional expressions (Kanwisher et al., 1997; McCarthy et al., 1997; Fairhall and Ishai, 2007; Herrington et al., 2011; Saygin et al., 2012). PCC, instead, contributes to self-reflection and the integration of self-referential stimuli in one's own personal context (Northoff and Bermpohl, 2004; van der Meer et al., 2010), functions that can be extended to social cognition, too (Schilbach et al., 2008). These functions are also supported by the involvement of PCC in autobiographical memory (Svoboda et al., 2006; Spreng and Grady, 2010) and in the interaction between memory and emotion (Maddock et al., 2003; van der Meer et al., 2010).

To investigate the mutual relationships among amygdala, FFG and PCC, SEM was performed on the fMRI data as an exploratory analysis. SEM results preliminary confirmed a model presuming that amygdala activity depended on earlier processing stages in left FFG, whereas individual FFG activity in turn could be predicted by activity patterns in left vPCC and dPCC. Left vPCC and dPCC also interacted with each other and right vPCC. Although, some studies suggested early processing of emotional faces in amygdala (Vuilleumier et al., 2004; Vuilleumier and Pourtois, 2007) influencing FFG activity, others showed amygdala activity being mediated by visual and fusiform cortices (Haxby et al., 2002). Amygdala is possibly involved in multiple processing stages of complex socio-emotional stimuli (Adolphs et al., 2002; Pourtois et al., 2010).

The present results indicating a late, higher-level involvement of amygdala can be argued to be in line with the experimental context implying the explicit comprehension and integration of multimodal aspects of social stimuli, like emotional expressions and bodily sensations. In particular, the task may have put the participants in a cognitive perspective by requiring the explicit differentiation between congruent and incongruent stimuli. Accordingly, relatively long response latencies of amygdala neurons were also reported during the subjective, explicit recognition of facial expressions of emotion (Wang et al., 2014). Furthermore, whereas effects were found to be mainly left lateralized, socio-emotional functions of the amygdala, including the subjective recognition of emotion, may be bilateral (Baas et al., 2004; Mobbs et al., 2006; Wang et al., 2014). However, literature remains somewhat inconclusive about functional differences between left and right amygdala (Adolphs, 2010), and some models suggest that left amygdala more specifically contributes to cognitive perceptual processing of emotional information in contrast to more fast and automatic responses in right amygdala (Gläscher and Adolphs, 2003).

In addition to amygdala, PCC might add subjective information about self-relatedness or familiarity of socio-emotional stimuli to further stimulus encoding in FFG and amygdala (Northoff and Bermpohl, 2004; Schilbach et al., 2008). In support of a possible link between the coding of stimulus congruence and self-relatedness of stimulus content or stimulus familiarity, stimulus evaluations in an independent sample of participants showed that the congruent videos were perceived as significantly more self-related in terms of subjective experiences as well as more familiar based on personal past experiences.

One exception to these rating results was the *post hoc* contrasts between the hit-pain (congruent) and the hit-pleasure (incongruent) condition, given that no significant difference was detected concerning self-relatedness and familiarity. This possibly could be attributed to the fact that on average facial expressions of pleasure also were judged as being more self-related as well as more familiar than facial expressions of pain. Moreover, while the fMRI task (judging stimulus congruence) explicitly required participants to consider both the tactile sensation and the facial expression, this was not the case for the judgments of self-relatedness and familiarity. Thus, participants also may have focused more on the facial expression than the tactile sensation during the self-relatedness/familiarity judgments. Further experiments are warranted to disentangle these aspects.

However, because self-relatedness/familiarity judgments and fMRI data were obtained in different samples of participants, the link between self-relatedness/familiarity judgments and stimulus congruence coding remains speculative, and these rating results cannot be related directly to the fMRI data. Directly relating stimulus judgments and neural activity patterns would be necessary to test the hypothesized link between integrative processing of social stimulus content and self-processing in subsequent studies by correlating such variables within the same sample.

Notably, the results obtained by intrinsic functional connectivity analysis on a separate task-free dataset from the same participants further showed that differentiation between congruent and incongruent social stimuli in left amygdala inversely depended on its intrinsic functional connectivity with left dPCC: a weaker or more negative relationship between amygdala and dPCC during a task-free state (i.e., a state of intrinsic or spontaneous activity patterns without being involved in a specific task) was associated with an increased differentiation between congruent and incongruent social stimuli during task-performance. In line with previous studies (Roy et al., 2009; Leech et al., 2012), the absence of a significant positive functional connectivity as observed in the present study suggested that amygdala and PCC belong to distinct networks that are functionally independent when not performing a specific task. Whereas the relationship between task-evoked activity and intrinsic functional connectivity has been investigated by relatively few studies (e.g., Fox et al., 2006; Mennes et al., 2010; Touroutoglou et al., 2014), a negative relationship also has been reported by a previous study (He, 2013).

The relationship between task-evoked activity in amygdala and intrinsic functional connectivity between amygdala and dPCC might reflect neural predisposition explaining inter-individual variability in the integrative processing of social stimulus content (Northoff, 2013, 2014). An increased independence of spontaneous activity in amygdala from dPCC in an individual may allow amygdala to respond more dynamically to certain environmental stimuli. Relevantly, PCC has been identified as a central brain hub characterized by a topology that allows switching and integration of processing in different networks involved in internally and externally guided information processing (Leech et al., 2012; de Pasquale et al., 2015). Alterations in the interaction between internally (e.g., self-related processing) and externally guided (e.g., social stimuli) information processing may be especially relevant as a putative mechanism explaining certain psychopathological phenomena typically observed in psychosis, such as disturbances in self-other relationship (Ebisch and Aleman, 2016).

Some other issues need to be mentioned. As detected by a conjunction analysis investigating the overlap between the main effects of facial expression and tactile sensation, the only brain regions modulated by both factors were left IPL/supramarginal gyrus and right STS. The aIPL activation cluster likely is located in the putative human homolog of macaque area PF/PFG (Caspers et al., 2006), a multisensory region with motor, somatosensory, visual and mirror properties (Fogassi et al., 2005; Rozzi et al., 2008). In humans, it was found to be involved in action observation and imitation (Caspers et al., 2010), and the observation of others' tactile experiences (Ebisch et al., 2008; Morrison et al., 2013). Based on this information, we propose that information about others' tactile experiences can converge with the motor aspects of others' facial expressions of emotion based on multimodal integration and mirror properties of aIPL.

Secondly, although both facial expressions and tactile sensations depicted affective experiences, no statistical interactions between these aspects were found in brain regions commonly implicated in the understanding of others' affective experiences, like anterior insula, supplementary motor cortex, or orbitofrontal cortex (Bastiaansen et al., 2009; Fan et al., 2011; Bernhardt and Singer, 2012; Hillis, 2014; Lamm et al., 2015). However, a possible explanation is provided by an fMRI study (Di Dio et al., 2007) illustrating a subjective encoding of external stimuli in amygdala (i.e., beauty judgments of artworks), in contrast to objective processing in insula (i.e., watching canonical masterpieces, compared to modified versions of these pictures). Similarly, in the present study congruency of information provided by facial expressions and bodily experiences can be considered a mere subjective judgment associated with amygdala. Because in the present study a large consensus existed across participants regarding stimulus (in)congruence (>95%), this interpretation could not be tested directly. Further studies are warranted to elucidate the effects of stimulus congruence in interaction with inter-individual variability in previous subjective experiences of this congruence within the same participants (e.g., familiarity or personal relevance).

Finally, in the present study the incongruent stimuli did not induce any increase of neural activity, compared to the congruent stimuli. Incongruent stimuli could be expected to recruit mentalizing networks (de Lange et al., 2008; Van Overwalle and Baetens, 2009; Schurz et al., 2014), while higher cognitive demands can suppress affect processing (Okon-Singer et al., 2013), and incongruent conditions could lead to higher conflict processing (Etkin et al., 2006; Klasen et al., 2011; Muller et al., 2011). However, although the congruence judgment task likely provided an explicit context, it must be noted that, in contrast to previous studies, we did not require participants to make forced choices or decisions about the experiences of the actors in the videos in case of contradictory information. These characteristics of the paradigm kept cognitive demands and conflict processing minimal. Therefore, the present findings suggest that social situations that are less intuitive to understand (e.g., incongruent stimuli) are not automatically associated with higher demands on social reasoning or conflict processes, though it also must be mentioned that the experimental paradigm may not have excluded conflict processing completely.

CONCLUSION

The present findings suggest that a network including PCC, FFG, and amygdala is involved in the integrative processing of social information from manifold bodily sources about others' feelings. In particular, these results imply that the natural perception of coherent social situations has a higher socio-emotional impact or self relevance than ambiguous perceptions involving a network related to emotion and self-related processing. Directly investigating the hypothesized link between integrative processing during social perception and self-related processing within the same sample may represent an important topic for subsequent studies.

AUTHOR CONTRIBUTIONS

Study conception and design: SE, VG, Anatolia Salone, MG, GLR; acquisition of data and participant recruitment: SE, Anatolia Salone, GM, MP; data processing: SE, Anatolia Salone; data analysis: SE, DM, GN, LC, Aristide Saggino; writing the manuscript: SE, Anatolia Salone, GM, LC, DM, MP, Aristide Saggino, GLR, MG, GN, VG.

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REFERENCES

Addis, D. R., Moscovitch, M., and McAndrews, M. P. (2007). Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. *Brain* 130, 2327–2342. doi: 10.1093/brain/awm166

Adolphs, R. (2002). Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behav. Cogn. Neurosci. Rev.* 1, 21–62. doi: 10.1177/1534582302001001003

Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Ann. N. Y. Acad. Sci.* 1191, 42–61. doi: 10.1111/j.1749-6632.2010.05445.x

Adolphs, R., Baron-Cohen, S., and Tranel, D. (2002). Impaired recognition of social emotions following amygdala damage. *J. Cogn. Neurosci.* 14, 1264–1274. doi: 10.1162/089892902760807258

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., and Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *J. Neurosci.* 20, 2683–2690.

Anderson, J. C., and Gerbing, D. W. (1988). Structural equation modeling in practice: a review and recommended two-step approach. *Psychol. Bull.* 103, 411–423. doi: 10.1037/0033-2909.103.3.411

Baas, D., Aleman, A., and Kahn, R. S. (2004). Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. *Brain Res.* 45, 96–103. doi: 10.1016/j.brainresrev.2004.02.004

Ball, T., Derix, J., Wentlandt, J., Wieckhorst, B., Speck, O., Schulze-Bonhage, A., et al. (2009). Anatomical specificity of functional amygdala imaging of responses to stimuli with positive and negative emotional valence. *J. Neurosci. Methods* 180, 57–70. doi: 10.1016/j.jneumeth.2009.02.022

Bastiaansen, J. A., Thioux, M., and Keysers, C. (2009). Evidence for mirror systems in emotions. *Philos. Trans. R. Soc. B* 364, 2391–2404. doi: 10.1098/rstb.2009.0058

Bernhardt, B. C., and Singer, T. (2012). The neural basis of empathy. *Ann. Rev. Neurosci.* 35, 1–23. doi: 10.1146/annurev-neuro-062111-150536

Bickart, K. C., Dickerson, B. C., and Barrett, L. F. (2014). The amygdala as a hub in brain networks that support social life. *Neuropsychologia* 63, 235–248. doi: 10.1016/j.neuropsychologia.2014.08.013

Bzdok, D., Laird, A. R., Zilles, K., Fox, P. T., and Eickhoff, S. B. (2013). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Hum. Brain Mapp.* 34, 3247–3266. doi: 10.1002/hbm.22138

Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., and Zilles, K. (2006). The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. *Neuroimage* 33, 430–448. doi: 10.1016/j.neuroimage.2006.06.054

Caspers, S., Zilles, K., Laird, A. R., and Eickhoff, S. B. (2010). ALE meta-analysis of action observation and imitation in the human brain. *Neuroimage* 50, 1148–1167. doi: 10.1016/j.neuroimage.2009.12.112

Cattell, R. B. (1966). The scree test for the number of factors. *Multivar. Behav. Res.* 1, 245–276. doi: 10.1207/s15327906mbr0102_10

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173. doi: 10.1006/cbmr.1996.0014

Craig, A. D. (2009). How do you feel–now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. doi: 10.1038/nrn2555

de Lange, F. P., Spronk, M., Willems, R. M., Toni, I., and Bekkering, H. (2008). Complementary systems for understanding action intentions. *Curr. Biol.* 18, 454–457. doi: 10.1016/j.cub.2008.02.057

de Pasquale, F., Della Penna, S., Sporns, O., Romani, G. L., and Corbetta, M. (2015). A dynamic core network and global efficiency in the resting human brain. *Cereb. Cortex* doi: 10.1093/cercor/bhv185

Di Dio, C., Macaluso, E., and Rizzolatti, G. (2007). The golden beauty: brain response to classical and renaissance sculptures. *PLoS ONE* 2:e1201. doi: 10.1371/journal.pone.0001201

Ebisch, S. J., and Aleman, A. (2016). The fragmented self: imbalance between intrinsic, and extrinsic self-networks in psychotic disorders. *Lancet Psychiatry*

Ebisch, S. J., Gallese, V., Willems, R. M., Mantini, D., Groen, W. B., Romani, G. L., et al. (2011). Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum. Brain Mapp.* 32, 1013–1028. doi: 10.1002/hbm.21085

Ebisch, S. J., Perrucci, M. G., Ferretti, A., Del Gratta, C., Romani, G. L., and Gallese, V. (2008). The sense of touch: embodied simulation in a visuotactile mirroring mechanism for observed animate or inanimate touch. *J. Cogn. Neurosci.* 20, 1611–1623. doi: 10.1162/jocn.2008.20111

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., and Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 51, 871–882. doi: 10.1016/j.neuron.2006.07.029

Ewbank, M. P., Barnard, P. J., Croucher, C. J., Ramponi, C., and Calder, A. J. (2009). The amygdala response to images with impact. *Soc. Cogn. Affect. Neurosci.* 4, 127–133. doi: 10.1093/scan/nsn048

Fairhall, S. L., and Ishai, A. (2007). Effective connectivity within the distributed cortical network for face perception. *Cereb. Cortex* 17, 2400–2406. doi: 10.1093/cercor/bhl148

Fan, Y., Duncan, N. W., de Greck, M., and Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neurosci. Biobehav. Rev.* 35, 903–911. doi: 10.1016/j.neubiorev.2010.10.009

Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., Nathan, P. J., and Phan, K. L. (2006). Beyond threat: amygdala reactivity across multiple expressions of facial affect. *Neuroimage* 30, 1441–1448. doi: 10.1016/j.neuroimage.2005.11.003

Fogassi, L., Ferrari, P. F., Gesierich, B., Rozzi, S., Chersi, F., and Rizzolatti, G. (2005). Parietal lobe: from action organization to intention understanding. *Science* 308, 662–667. doi: 10.1126/science.1106138

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., and Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn. Reson. Med.* 33, 636–647. doi: 10.1002/mrm.1910330508

Fox, M. D., Snyder, A. Z., Zacks, J. M., and Raichle, M. E. (2006). Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. *Nat. Neurosci.* 9, 23–25. doi: 10.1038/nn1616

Freese, J. L., and Amaral, D. G. (2006). Synaptic organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J. Comput. Neurol.* 496, 655–667. doi: 10.1002/cne.20945

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., and Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6, 218–229. doi: 10.1006/nimg.1997.0291

Gallese, V. (2003). The roots of empathy: the shared manifold hypothesis and the neural basis of intersubjectivity. *Psychopathology* 36, 171–180. doi: 10.1159/000072786

Gallese, V., and Ebisch, S. (2013). Embodied simulation and touch: the sense of touch in social cognition. *Phenomenol. Mind.* 4, 269–291.

Gallese, V., Keysers, C., and Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends Cogn. Sci.* 8, 396–403. doi: 10.1016/j.tics.2004.07.002

Gläscher, J., and Adolphs, R. (2003). Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. *J. Neurosci.* 23, 10274–10282.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., et al. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol.* 6:e159. doi: 10.1371/journal.pbio.0060159

Handwerker, D. A., Gonzalez-Castillo, J., D'Esposito, M., and Bandettini, P. A. (2012). The continuing challenge of understanding and modeling hemodynamic variation in fMRI. *Neuroimage* 62, 1017–1023. doi: 10.1016/j.neuroimage.2012.02.015

Haxby, J. V., Hoffman, E. A., and Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. *Biol. Psychiatry* 51, 59–67. doi: 10.1016/S0006-3223(01)01330-0

He, B. J. (2013). Spontaneous and task-evoked brain activity negatively interact. *J. Neurosci.* 33, 4672–4682. doi: 10.1523/JNEUROSCI.2922-12.2013

Herrington, J. D., Taylor, J. M., Grupe, D. W., Curby, K. M., and Schultz, R. T. (2011). Bidirectional communication between amygdala and fusiform gyrus during facial recognition. *Neuroimage* 56, 2348–2355. doi: 10.1016/j.neuroimage.2011.03.072

Hillis, A. E. (2014). Inability to empathize: brain lesions that disrupt sharing and understanding another's emotions. *Brain* 137, 981–997. doi: 10.1093/brain/awt317

Hooper, D., Coughlan, J., and Mullen, M. R. (2008). Structural equation modeling: guidelines for determining model fit. *Electron. J. Bus. Res. Methods* 6, 53–60.

Horwitz, B., Tagamets, M. A., and McIntosh, A. R. (1999). Neural modeling, functional brain imaging, and cognition. *Trends Cogn. Sci.* 3, 91–98. doi: 10.1016/S1364-6613(99)01282-6

Ingvar, M., and Petersson, K. M. (2000). *Functional Maps and Brain Networks, Brain Mapping: The Systems*. (Cambridge: Academic Press), 111–140.

Joreskog, K. G., and Sorbom, D. (2006). *LISREL for Windows*. Lincolnwood, IL: Scientific Software International.

Kanwisher, N., McDermott, J., and Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J. Neurosci.* 17, 4302–4311.

Keysers, C., Kaas, J. H., and Gazzola, V. (2010). Somatosensation in social perception. *Nat. Rev. Neurosci.* 11, 417–428. doi: 10.1038/nrn2833

Klasen, M., Kenworthy, C. A., Mathiak, K. A., Kircher, T. T., and Mathiak, K. (2011). Supramodal representation of emotions. *J. Neurosci.* 31, 13635–13643. doi: 10.1523/JNEUROSCI.2833-11.2011

Kline, P. (1994). *An Easy Guide to Factor Analysis*. London: Routledge.

Kline, R. B. (2015). *Principles and Practice of Structural Equation Modeling*. New York City: Guilford publications.

Lamm, C., Silani, G., and Singer, T. (2015). Distinct neural networks underlying empathy for pleasant and unpleasant touch. *Cortex* 70, 79–89. doi: 10.1016/j.cortex.2015.01.021

Leech, R., Braga, R., and Sharp, D. J. (2012). Echoes of the brain within the posterior cingulate cortex. *J. Neurosci.* 32, 215–222. doi: 10.1523/JNEUROSCI.3689-11.2012

MacCallum, R. C., and Austin, J. T. (2000). Applications of structural equation modeling in psychological research. *Ann. Rev. Psychol.* 51, 201–226. doi: 10.1146/annurev.psych.51.1.201

Maddock, R. J., Garrett, A. S., and Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum. Brain Mapp.* 18, 30–41. doi: 10.1002/hbm.10075

McCarthy, G., Puce, A., Gore, J. C., and Allison, T. (1997). Face-specific processing in the human fusiform gyrus. *J. Cogn. Neurosci.* 9, 605–610. doi: 10.1162/jocn.1997.9.5.605

McIntosh, A. R. (1998). Understanding neural interactions in learning and memory using functional neuroimaging. *Ann. N. Y. Acad. Sci.* 855, 556–571. doi: 10.1111/j.1749-6632.1998.tb10625.x

Mennes, M., Kelly, C., Zuo, X. N., Di Martino, A., Biswal, B. B., Castellanos, F. X., et al. (2010). Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity. *Neuroimage* 50, 1690–1701. doi: 10.1016/j.neuroimage.2010.01.002

Mobbs, D., Weiskopf, N., Lau, H. C., Featherstone, E., Dolan, R. J., and Frith, C. D. (2006). The Kuleshov Effect: the influence of contextual framing on emotional attributions. *Soc. Cogn. Affect. Neurosci.* 1, 95–106. doi: 10.1093/scan/nsl014

Molenberghs, P., Cunnington, R., and Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci. Biobehav. Rev.* 36, 341–349. doi: 10.1016/j.neubiorev.2011.07.004

Morrison, I., Tipper, S. P., Fenton-Adams, W. L., and Bach, P. (2013). "Feeling" others' painful actions: the sensorimotor integration of pain and action information. *Hum. Brain Mapp.* 34, 1982–1998. doi: 10.1002/hbm.22040

Muller, V. I., Habel, U., Derntl, B., Schneider, F., Zilles, K., Turetsky, B. I., et al. (2011). Incongruence effects in crossmodal emotional integration. *Neuroimage* 54, 2257–2266. doi: 10.1016/j.neuroimage.2010.10.047

Nichols, T., Brett, M., Andersson, J., Wager, T., and Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage* 25, 653–660. doi: 10.1016/j.neuroimage.2004.12.005

Northoff, G. (2013). What the brain's intrinsic activity can tell us about consciousness? A tri-dimensional view. *Neurosci. Biobehav. Rev.* 37, 726–738. doi: 10.1016/j.neubiorev.2012.12.004

Northoff, G. (2014). *Unlocking the Brain*. New York: Oxford University Press.

Northoff, G., and Bermpohl, F. (2004). Cortical midline structures and the self. *Trends Cogn. Sci.* 8, 102–107. doi: 10.1016/j.tics.2004.01.004

Northoff, G., Schneider, F., Rotte, M., Matthiae, C., Tempelmann, C., Wiebking, C., et al. (2009). Differential parametric modulation of self-relatedness and emotions in different brain regions. *Hum. Brain Mapp.* 30, 369–382. doi: 10.1002/hbm.20510

Okon-Singer, H., Lichtenstein-Vidne, L., and Cohen, N. (2013). Dynamic modulation of emotional processing. *Biol. Psychol.* 92, 480–491. doi: 10.1016/j.biopsycho.2012.05.010

Penny, W. D., Stephan, K. E., Mechelli, A., and Friston, K. J. (2004). Modelling functional integration: a comparison of structural equation and dynamic causal models. *Neuroimage* 23, S264–S274. doi: 10.1016/j.neuroimage.2004.07.041

Pessoa, L., and Adolphs, R. (2010). Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. *Nat. Rev. Neurosci.* 11, 773–783. doi: 10.1038/nrn2920

Pitcher, D., Garrido, L., Walsh, V., and Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *J. Neurosci.* 28, 8929–8933. doi: 10.1523/JNEUROSCI.1450-08.2008

Pourtois, G., Spinelli, L., Seeck, M., and Vuilleumier, P. (2010). Temporal precedence of emotion over attention modulations in the lateral amygdala: Intracranial ERP evidence from a patient with temporal lobe epilepsy. *Cogn. Affect. Behav. Neurosci.* 10, 83–93. doi: 10.3758/CABN.10.1.83

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., and Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84, 320–341. doi: 10.1016/j.neuroimage.2013.08.048

Protzner, A. B., and McIntosh, A. R. (2006). Testing effective connectivity changes with structural equation modeling: what does a bad model tell us? *Hum. Brain Mapp.* 27, 935–947. doi: 10.1002/hbm.20233

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M., Uddin, L. Q., Gotimer, K., et al. (2009). Functional connectivity of the human amygdala using resting state fMRI. *Neuroimage* 45, 614–626. doi: 10.1016/j.neuroimage.2008.11.030

Rozzi, S., Ferrari, P. F., Bonini, L., Rizzolatti, G., and Fogassi, L. (2008). Functional organization of inferior parietal lobule convexity in the macaque monkey: electrophysiological characterization of motor, sensory and mirror responses and their correlation with cytoarchitectonic areas. *Europ. J. Neurosci.* 28, 1569–1588. doi: 10.1111/j.1460-9568.2008.06395.x

Saygin, Z. M., Osher, D. E., Augustinack, J., Fischl, B., and Gabrieli, J. D. (2011). Connectivity-based segmentation of human amygdala nuclei using probabilistic tractography. *Neuroimage* 56, 1353–1361. doi: 10.1016/j.neuroimage.2011.03.006

Saygin, Z. M., Osher, D. E., Koldewyn, K., Reynolds, G., Gabrieli, J. D., and Saxe, R. R. (2012). Anatomical connectivity patterns predict face selectivity in the fusiform gyrus. *Nat. Neurosci.* 15, 321–327. doi: 10.1038/nn.3001

Schilbach, L., Eickhoff, S. B., Rotarska-Jagiela, A., Fink, G. R., and Vogeley, K. (2008). Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. *Consciousn. Cogn.* 17, 457–467. doi: 10.1016/j.concog.2008.03.013

Schneider, F., Bermpohl, F., Heinzel, A., Rotte, M., Walter, M., Tempelmann, C., et al. (2008). The resting brain and our self: self-relatedness modulates resting state neural activity in cortical midline structures. *Neurosci.* 157, 120–131. doi: 10.1016/j.neuroscience.2008.08.014

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., and Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neurosci. Biobehav. Rev.* 42, 9–34. doi: 10.1016/j.neubiorev.2014.01.009

Spreng, R. N., and Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *J. Cogn. Neurosci.* 22, 1112–1123. doi: 10.1162/jocn.2009.21282

Svoboda, E., McKinnon, M. C., and Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 44, 2189–2208. doi: 10.1016/j.neuropsychologia.2006.05.023

Talairach, J., and Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging.* 1st Edn, Stuttgart: Thieme.

Touroutoglou, A., Bickart, K. C., Barrett, L. F., and Dickerson, B. C. (2014). Amygdala task-evoked activity and task-free connectivity independently contribute to feelings of arousal. *Hum. Brain Mapp.* 35, 5316–5327. doi: 10.1002/hbm.22552

van der Gaag, C., Minderaa, R. B., and Keysers, C. (2007). The BOLD signal in the amygdala does not differentiate between dynamic facial expressions. *Soc. Cogn. Affect. Neurosci.* 2, 93–103. doi: 10.1093/scan/nsm002

van der Meer, L., Costafreda, S., Aleman, A., and David, A. S. (2010). Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neurosci. Biobehav. Rev.* 34, 935–946. doi: 10.1016/j.neubiorev.2009.12.004

Van Dijk, K. R., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., and Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *J. Neurophysiol.* 103, 297–321. doi: 10.1152/jn.00783.2009

Van Overwalle, F., and Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage* 48, 564–584. doi: 10.1016/j.neuroimage.2009.06.009

Vogt, B. A., Vogt, L., and Laureys, S. (2006). Cytology and functionally correlated circuits of human posterior cingulate areas. *Neuroimage* 29, 452–466. doi: 10.1016/j.neuroimage.2005.07.048

Vuilleumier, P., and Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia* 45, 174–194. doi: 10.1016/j.neuropsychologia.2006.06.003

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., and Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat. Neurosci.* 7, 1271–1278. doi: 10.1038/nn1341

Wang, S., Tudusciuc, O., Mamelak, A. N., Ross, I. B., Adolphs, R., and Rutishauser, U. (2014). Neurons in the human amygdala selective for perceived emotion. *Proc. Nat. Acad. Sci. U.S.A.* 111, E3110–E3119. doi: 10.1073/pnas.1323342111

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Interoception and Positive Symptoms in Schizophrenia

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The present study focuses on the multifaceted concept of self-disturbance in schizophrenia, adding knowledge about a not yet investigated aspect, which is the interoceptive accuracy. Starting from the assumption that interoceptive accuracy requires an intact sense of self, which otherwise was proved to be altered in schizophrenia, the aim of the present study was to explore interoceptive accuracy in a group of schizophrenia patients, compared to healthy controls. Furthermore, the possible association between interoceptive accuracy and patients' positive and negative symptomatology was assessed. To pursue these goals, a group of 23 schizophrenia patients and a group of 23 healthy controls performed a heartbeat perception task. Patients' symptomatology was assessed by means of the Positive and Negative Syndrome Scale (PANSS). Results demonstrated significantly lower interoceptive accuracy in schizophrenia patients compared to healthy controls. This difference was not accounted for participants' age, BMI, anxiety levels, and heart rate. Furthermore, patients' illness severity, attention and pharmacological treatment did not influence their interoceptive accuracy levels. Interestingly, a strong positive relation between interoceptive accuracy and positive symptoms severity, especially Grandiosity, was found. The present results demonstrate for the first time that interoceptive accuracy is altered in schizophrenia. Furthermore, they prove a specific association between interoceptive accuracy and positive symptomatology, suggesting that the symptom Grandiosity might be protective against an altered basic sense of self in patients characterized by higher sensibility to their inner bodily sensations.

Keywords: basic self, bodily self, grandiosity, interoception, interoceptive accuracy, positive symptoms, schizophrenia, selfhood

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INTRODUCTION

> *"A circle is the only geometric shape defined by its centre. No chicken and egg about it, the centre came first, the circumference follows. The earth, by definition, has a centre. And only the fool that knows it can go wherever he pleases, knowing the centre will hold him down, stop him flying out of orbit. But when your sense of centre shifts, comes whizzing to the surface, the balance has gone. The balance has gone. The balance my baby has gone."*
>
> [Sarah Kane, Crave]

These words allow to grasp the core subjective experience of schizophrenia, the loss of the most fundamental selfhood, which is interchangeably named as "minimal self", "basic self", "proto-self", or "ipseity" (Hur et al., 2014). Assuming selfhood as a multi-layered concept, its most primitive, pre-reflective, and immediate layer, which remains when all other levels are stripped away, can be considered as the basic experience of the self (Sass and Parnas, 2003; Fuchs, 2005). In schizophrenia it principally refers to the loss of the basic sense of ownership and agency of one's own experiences, thoughts, or actions (Jaspers, 1923). Robust empirical evidence indicates that both full-blown psychosis (Peled et al., 2000, 2003; Thakkar et al., 2011; Ferri et al., 2013) and psychosis proneness among non-clinical samples (Morgan et al., 2011; Germine et al., 2013) are associated with a blurred and extremely flexible sense of body ownership, measured by the Rubber Hand Illusion paradigm (RHI, Botvinick and Cohen, 1998). Further studies, although not consistently (for a review see Hur et al., 2014), demonstrated the presence of an altered sense of agency in people suffering from schizophrenia. Indeed, among schizophrenia patients both abnormal over-estimations (Haggard et al., 2003; Voss et al., 2010; Maeda et al., 2012) and under-estimations (Synofzik et al., 2010; Renes et al., 2013) of the causality between one's own actions and the subsequent external events were found.

Interestingly, specific relations between deficits in basic self experiences and schizophrenia symptomatology have been extensively demonstrated. For instance, Schneiderian first rank symptoms (i.e., thought insertion, thought-broadcasting, somatic passivity, delusional perception) are associated to altered sense of ownership and agency (Fourneret et al., 2001; Jeannerod, 2009; Waters and Badcock, 2010); while weak body ownership is associated to positive schizophrenia symptoms (Peled et al., 2000; Thakkar et al., 2011) and anhedonia negative symptom (Ferri et al., 2014). Furthermore, abnormal over-estimation of individual sense of agency strongly correlates with positive psychotic symptoms severity (Voss et al., 2010) and prevalence (Maeda et al., 2013). Consistently, a significant under-estimation of individual sense of agency appeared to be related with the prevalence of negative psychotic symptoms (Maeda et al., 2013).

Another intriguing aspect of the self experience, which recently gained a lot of attention, is interoception. It is defined as the individual sensitivity to physiological stimuli originating inside of the body (Craig, 2002). Interoception, far from being considered as an unitary concept, can be quantified along the three dimensions of: interoceptive accuracy (i.e., objective performance at behavioral task requiring the detection of visceral sensations); interoceptive sensibility (i.e., explicit self-assessment of subjective interoception abilities by questionnaires) and interoceptive awareness (i.e., metacognitive awareness obtained by confidence-accuracy correspondence) (Garfinkel et al., 2014). The most studied dimension is the interoceptive accuracy, which assumes a fundamental self experience related to the implicit and pre-reflective notion of the self. In fact, the attribution of feelings and sensations to one's own body presupposes an intact basic sense of self. "*No chicken and egg about it, the centre came first, the circumference follows*": necessarily, first I implicitly feel myself, then I can attribute internal body sensations to myself. In more empirical terms, a link between interoceptive accuracy and basic self experiences has to be expected. Coherently, low interoceptive accuracy resulted associated to a greater malleability of body sense of ownership among healthy participants (Tsakiris et al., 2011; Tajadura-Jiménez et al., 2012; Suzuki et al., 2013). The strict relation between interoceptive accuracy and basic self experiences finds neuroscientific support in the fact that the most salient inner bodily feelings, contributing to a "cinemascopic representation of the entire body from within", require the Insular cortex (Craig, 2003) the brain structure also involved in interoceptive processes (Pollatos et al., 2007b; Jarrahi et al., 2015).

The recent growing interest in interoception is justified by two reasons. First, interoceptive accuracy has been demonstrated to play a crucial role in the modulation of numerous aspects of cognitive and affective human life. It influences decision making processes (Werner et al., 2009) as well as the perception and evaluation of emotional stimuli (Pollatos et al., 2007a; Dunn et al., 2010a). Furthermore, it also appears to be involved in the autonomic regulation during social interactions (Ferri et al., 2013) and in individual resilience ability (Haase et al., 2016). Second, interoceptive accuracy appeared to be compromised in several psychiatric disorders, such as anorexia nervosa, major depression, depersonalization-derealization disorders, and anxiety disorders (Pollatos et al., 2008; Furman et al., 2013; Gaudio et al., 2014; Sedeño et al., 2014; Harshaw, 2015).

Remarkably, studies regarding the abilities to perceive one's own internal bodily signals in schizophrenia are still lacking. This lacuna is particularly important for several reasons. As described above, schizophrenia is characterized by altered experience of the basic sense of self (i.e., body ownership and sense of agency), which has been proved to be related to interoception in healthy participants. Furthermore, the unusual bodily and visceral sensations included in the "coenaesthesic" schizophrenia symptoms (Parnas et al., 2005b; Vollmer-Larsen et al., 2007) (e.g., migrating inner sensations wandering through the body, electric, or thermal feelings, abnormal sense of pulling/pressure or heaviness/emptiness inside of the body, and dysesthetic crises involving the vegetative system) suggest a severe impairment in the patients' sensitivity to internal bodily signals. Finally, schizophrenia patients show anatomical and functional alterations in the Insular cortex (Kasai et al., 2003; Wylie and Tregellas, 2010; Ebisch et al., 2011, 2013, 2014), which possibly accounts for a large variety of symptoms encompassing affect and pain processing, hallucination (especially visceral hallucinations) (Kathirvel and Mortimer, 2013), self-perception and also visceral abnormal sensations.

All this evidence taken together, in addition to the huge impact of interoceptive accuracy on fundamental cognitive and affective aspects of human life, makes the investigation of interoceptive accuracy in schizophrenia and its potential influence on symptomatology of crucial relevance.

In the present study, interoceptive accuracy was estimated in a group of schizophrenia patients compared to healthy controls. Furthermore, the possible relation between individual interoceptive accuracy and positive and negative symptomatology was assessed. To these goals, all the participants performed a heartbeat perception task (Schandry, 1981). Furthermore, schizophrenia patients completed a clinical evaluation of their symptomatology by means of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The heartbeat perception task was chosen instead of the heartbeat discrimination task – a different technique to assess individual interoceptive accuracy (Brener and Kluvitse, 1988) – because, whereas in the execution of the heartbeat perception task attention is directly focused only on inner bodily signals (i.e., heartbeats), in the heartbeat discrimination task participants are required to integrate internal and external signals (i.e., heartbeats and sounds) to give a synchrony judgment. Given the multisensory integration deficits frequently described in schizophrenia patients (for a review see Tseng et al., 2015), we wanted to rule out any possible confounding effect of these deficits on the assessment of participants' interoceptive abilities.

Drawing from the prior studies, here briefly revised, we expected to find significantly lower interoceptive accuracy in schizophrenia patients, with respect to healthy controls. Moreover, due to the novelty of the issue a specific relation between interoceptive accuracy and patients' symptomatology was assessed in an explorative way.

TABLE 1 | Demographic information about Schizophrenia patients (SCZ) and healthy controls (HC).

	SCZ	HC
n.	23	23
Age (mean ± *SD*)	33.78 ± 6.33	31.91 ± 9.18
Male sex, (*n*° – %)	17–73.91	20–86.96
Right handedness, (n° – %)	20–86.96	21–91.30
Body Mass Index (BMI), Kg/m^2 (mean ± *SD*)	24.31 ± 2.31	23.27 ± 2.54
Heart Rate (HR), bpm (mean ± *SD*)	86.48 ± 16.21	76.72 ± 15.59
Diagnosis		
Schizophrenia paranoid subtype, (n° – %)	20–86.95	n.a.
Schizoaffective disorder, (n° – %)	3–13	n.a.
Illness duration, year (mean ± *SD*)	9.22 ± 3.61	n.a.
Structured Clinical Interview for DSM-IV Axis II disorders (SCID-II)		
Cluster A, (n° – %)	2–8.69	n.a.
Cluster B, (n° – %)	2–8.69	n.a.
Cluster C, (n° – %)	2–8.69	n.a.
Global Assessment of Functioning Scale (GAF) (mean ± *SD*)	46.70 ± 7.60	n.a.
Symptom Checklist-90-Revised (SCL-90-R) total score (mean ± *SD*)	n.a.	49.44 ± 9.05
Positive and Negative Syndrome Scale for Schizophrenia (PANSS)		
Positive Scale (P) (mean ± *SD*)	22.17 ± 8.16	n.a.
Prevalence of Positive symptoms (n° – %)	10–43.48	n.a.
Delusions (mean ± *SD*)	3.65 ± 1,70	n.a.
Conceptual disorganization (mean ± *SD*)	2.78 ± 1.28	n.a.
Hallucinatory behavior (mean ± *SD*)	2.74 ± 1.54	n.a.
Excitement (mean ± *SD*)	3.00 ± 1.62	n.a.
Grandiosity (mean ± *SD*)	3.09 ± 1.70	n.a.
Suspiciousness/persecution (mean ± *SD*)	3.87 ± 1.58	n.a.
Hostility (mean ± *SD*)	3.04 ± 1.64	n.a.
Negative Scale (N) (mean ± *SD*)	25.74 ± 7.65	n.a.
Prevalence of Negative symptoms (n° – %)	13–56.52	n.a.
General Psychopathology Scale (G) (mean ± *SD*)	53.39 ± 12.42	n.a.
Composite Scale (mean ± *SD*)	−3.57 ± 10.45	n.a.
Total (mean ± *SD*)	101.30 ± 22.38	n.a.
State Anxiety Inventory (STAI-I) (mean ± *SD*)	47.23 ± 14.95	34.43 ± 7.49 *
Chlorpromazine Equivalent, mg/die (mean ± *SD*)	389.77 ± 762.35	n.a.
Intelligent Quotient (mean ± *SD*)	101.83 ± 13.10	n.a.
Atypical antipsychotic		
Risperidone, (n° – %)	3–13.04	n.a.
Olanzapine, (n° – %)	7–30.43	n.a.
Quetiapine, (n° – %)	1–4.34	n.a.
Ziprasidone, (n° – %)	1–4.34	n.a.
Aripiprazole, (n° – %)	4–17.39	n.a.

Numbers may not add to total due to missing data or rounding. n.a., not available; $^*p < 0.05$.

MATERIALS AND METHODS

Participants

Twenty-three schizophrenia patients (SCZ; 17 males, mean age 33.78 years ± 6.33) and 23 healthy controls (HC; 20 males; mean age 31.91 years ± 9.18) were included in the present study. SCZ participants were recruited from outpatient services at Perugia Mental Health Department and diagnosed according to the structured clinical interview for DSM-IV. The mean illness duration was 9.22 ± 3.61 months. Only SCZ participants treated with atypical antipsychotic were included in the study. Due to the large variety of atypical antipsychotics frequently used in the treatment of schizophrenia, an estimation of evidence-based and consistent therapeutic dose equivalence across these medications is needed to directly compare patients' exposed to different drugs, with different dosages and for different times. For this reason, Chlorpromazine equivalents were calculated following standard practices for antipsychotics (Woods, 2003). Exclusion criteria for all participants comprised significant medical, cardiac or neurological illnesses, substance abuse or dependence in the previous 6 months and mental retardation (IQ < 70). Solely for the HC participants either a personal history of Axis I/II disorders or a history of psychosis in first-degree relatives were considered as exclusion criteria.

All participants filled an anamnestic questionnaire through which their demographic and medical information was obtained. SCZ participants were further evaluated by structured clinical interviews for DSM-IV Axis I (SCID-I) and Axis II (SCID-II) disorders (First et al., 1996, 2012). They were rated for positive and negative symptoms severity using the PANSS for Schizophrenia (including Positive, Negative, and General Psychopathology scales) (Kay et al., 1987) and for their social functioning through the Global Assessment of Functioning scale (GAF) (Hall, 1995). Patients' intelligence quotient (IQ) was evaluated by means of the Raven Standard Progressive Matrices (SPM) (Raven et al., 1998a,b). Healthy controls' psychopathological symptoms were evaluated by means of the Symptom Checklist-90-Revised (SCL-90-R) (Derogatis and Savitz, 2000). Finally, to control for individual differences in anxiety at the time of the experiment, all participants filled the State Anxiety Inventory (STAI-I) (Pedrabissi and Santinello, 1989).

See **Table 1** for a detailed description of participants' information.

Procedure

This study was approved by the Bioethics Committee of Perugia University. Written informed consent was obtained from all participants after full explanation of the study procedure, in line with the Declaration of Helsinki 2013.

To avoid potential influences on participants' heart rate, the assumption of alcohol, caffeine, and tobacco for 2 h prior to the experiment was forbidden to all participants. On arrival, participants filled the self-report questionnaires (i.e., anamnestic questionnaire, SCL-90-R, STAI-I). Before this session, SCZ participants completed the clinical assessment (i.e., DSM-IV interviews, PANSS, GAF, and SPM) at the outpatient service of the Perugia Mental Health Department.

Interoceptive accuracy was measured using the heartbeat perception task (Schandry, 1981; Garfinkel et al., 2014) that has good test–retest reliability (up to 0.81) (Tsakiris et al., 2011) and highly correlates with other detection tasks (Knoll and Hodapp, 1992). Without taking advantage from biological feedback (e.g., by taking their wrist pulse), participants were instructed to silently count their own heartbeats following an audiovisual "start" signal until they received an audiovisual "stop" signal. "Start" and "stop" signals individuated four different time intervals of 100, 45, 35, and 25 s, presented in random order across participants. A brief training session (15 s) was arranged before the actual experiment intervals. At each "stop" signal participants were asked to orally communicate to the experimenter the number of heartbeats counted during the just completed time interval. Both the length of the intervals and the quality of task performance were never revealed to participants.

During the entire procedure, electrocardiogram (ECG) was recorded using three 10 mm Ag/AgCl pre-gelled electrodes (ADInstruments, UK) attached to the participants' wrists and left ankle following the ordinary Einthoven's triangle configuration. Before the execution of the heartbeat perception task, participants' ECG was recorded for 2 additional minutes in a rest condition to collect participants' baseline heart rate.

Interoceptive accuracy was then calculated, following standard procedure (Schandry, 1981; Garfinkel et al., 2014), as the mean score of four heartbeat perception intervals according to the following formula:

$$^1/_4\Sigma(1-(|\text{recorded heartbeats} - \text{counted heartbeats}|)/\text{recorded heartbeats}).$$

Consequently, interoceptive accuracy values vary between 0 and 1, with higher scores indicating small differences between recorded and counted heartbeats and therefore greater interoceptive accuracy.

RESULTS

Between-groups Differences in Age, Body Mass Index, STAI-I Score, and Heart Rate

In order to verify between-groups differences in participants' age, Body Mass Index (BMI), STAI-I score and heart rate (HR) possibly influencing participants' interoceptive accuracy (Jones, 1995; Khalsa et al., 2009; Pollatos et al., 2009), four independent sample t-tests (two-tailed) were performed comparing SCZ and HC participants. Results demonstrated a significant difference between SCZ and HC for STAI-I score (SCZ: 47.23, SE 3.19; HC: 34.04, SE 1.46; $t_{43} = 3.814$, $p = 0.001$) and HR (SCZ: 86.48 BPM SE 16.21; HC: 76.72 BPM, SE 3.25; $t_{44} = 2.083$, $p = 0.043$). No significant difference was found for age ($t_{44} = 0.748$, $p = 0.459$) and BMI ($t_{44} = 1.465$, $p = 0.15$).

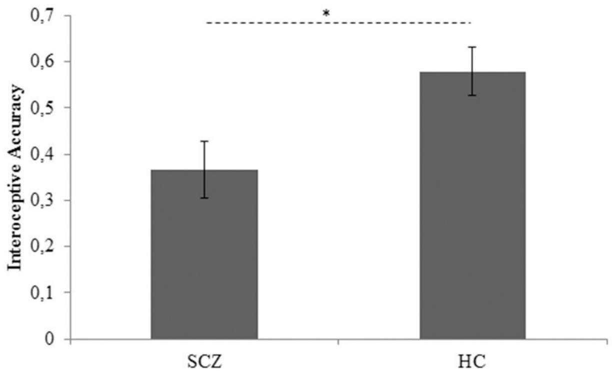

FIGURE 1 | Interoceptive accuracy marginal means for SCZ and HC participants. Covariates included in the model were estimated equal to the following values: age = 32.7778; BMI = 23.8401; STAI-I score = 40.6889; HR = 81.4887 SCZ: Schizophrenia patients; HC: Healthy controls. Error bars represent SE. *$p < 0.05$.

Between-Groups Difference in Interoceptive Accuracy

To pursue the first goal of the present study, between-groups difference in interoceptive accuracy, controlling for age, BMI, STAI-I score, and HR, was assessed by an ANCOVA analysis. Group (SCZ, HC) was entered as between-factor, whereas age, BMI, STAI-I score, and HR were included in the model as covariates. The Levene's test was not significant [$F_{(1,43)} = 1{,}558$, $p = 0.219$], revealing that the homogeneity of variance assumption was not violated. Results demonstrated that SCZ showed a significant lower interoceptive accuracy than HC (SCZ: 0.366, SE 0.063; HC: 0.579, SE 0.62; $F_{(1,39)} = 4.355$, $p = 0.043$, $\mu_p^2 = 0.10$) (**Figure 1**). None of the covariates included in the model resulted significant [age: $F_{(1,39)} = 3.183$, $p = 0.082$, $\mu_p^2 = 0.07$; BMI: $F_{(1,39)} = 0.211$, $p = 0.649$, $\mu_p^2 = 0.01$; STAI-I score: $F_{(1,39)} = 0.008$, $p = 0.928$, $\mu_p^2 = 0.01$; HR: $F_{(1,39)} = 0.777$, $p = 0.383$].

Impact of SCZ Participants' Illness Severity, Attention, and Pharmacological Treatment on Interoceptive Accuracy

Illness duration (computed in years from the first psychotic episode), number of hospital admissions and SCZ participants' score obtained to GAF scale were used as indexes of illness severity. In order to assess the possible influence of illness severity on SCZ participants' interoceptive accuracy three linear regression analyses were computed including years from the first psychotic event, number of hospital admissions and GAF score as predictors. Similarly, possible attention deficit could interfere with patients' performance in heartbeat perception task preventing the needed focus on internal bodily signals. For this reason another linear regression analysis was conducted on patients' interoceptive accuracy using the score obtained at Poor Attention item of PANSS as predictor (G11 score of PANSS). Finally, the possible role of pharmacological treatment (measured by Chlorpromazine equivalents; Woods, 2003) on SCZ participants' interoceptive accuracy was investigated performing a further linear regression analysis in which Chlorpromazine equivalents was treated as a predictor. Results demonstrated the absence of any significant effect of both illness severity [illness duration: $R^2 = 0.166$; $F_{(1,17)} = 3.188$; $p = 0.093$; $\beta = 0.408$; number of hospital admissions: $R^2 = 0.044$; $F_{(1,22)} = 0.977$; $p = 0.334$; GAF score: $R^2 = 0.156$; $F_{(1,22)} = 3.877$; $p = 0.062$]; attention [$R^2 = 0.054$; $F_{(1,22)} = 1.204$; $p = 0.285$; $\beta = 0.233$], and pharmacological treatment [$R^2 = 0.037$; $F_{(1,15)} = 0.532$; $p = 0.478$; $\beta = 0.191$] on SCZ participants' interoceptive accuracy.

Relation between Interoceptive Accuracy and Schizophrenia Symptoms

Pearsons' correlation analyses were conducted to pursue the second goal of this study, thus evaluating the relation between interoceptive accuracy and positive or negative symptomatology among SCZ participants. Bonferroni-corrected ($p < 0.025$) correlation analyses demonstrated a significant relation between SCZ participants' interoceptive accuracy and the score obtained with the Positive PANSS scale ($r_{23} = 0.483$; $p = 0.020$) (**Figure 2**). Conversely, SCZ participants' interoceptive accuracy was not related to the score obtained with the Negative PANSS scale ($r_{23} = 0.132$; $p = 0.547$).

To better explore the significant relation between interoceptive accuracy and SCZ participants' positive symptoms and hence to evaluate which of the seven different positive symptoms showed the strongest relation with SCZ participants' interoceptive accuracy, Bonferroni-corrected ($p < 0.007$) correlation analyses were calculated for the seven items of the Positive PANSS scale (P1, P2, P3, P4, P5, P6, P7). SCZ participants' P5-Grandiosity was the only item of the Positive PANSS scale turned out to have a near Bonferroni-corrected significant linear relation with interoceptive accuracy ($r_{23} = 0.531$; $p = 0.009$) (**Figure 3**). See **Table 2** for the Pearsons' correlation coefficients and p values obtained for the all seven items of Positive PANSS scale.

In order to substantiate the relevance of P5-Grandiosity in the relation between interoceptive accuracy and SCZ participants' positive symptoms, a partial correlation analysis was performed. Partial correlation analysis allows the study of the linear relationship between two variables after excluding the effect of one or more factors.

Thus, if the relation between SCZ participants' interoceptive accuracy and the score at Positive PANSS scale obtained by the sum of the six items with the exclusion of P5-Grandiosity, results not significant when controlling for the score at P5-Grandiosity, it is reasonable to conclude that P5-Grandiosity is a relevant positive symptom mediating the tested linear relation between interoceptive accuracy and positive symptoms. On the contrary, if the linear relation between interoceptive accuracy and the positive symptoms (with the exclusion of P5-Grandiosity) results significant, also when controlling for P5-Grandiosity, this last symptom can not be considered the principal mediator of the relation of interest. The inclusion of

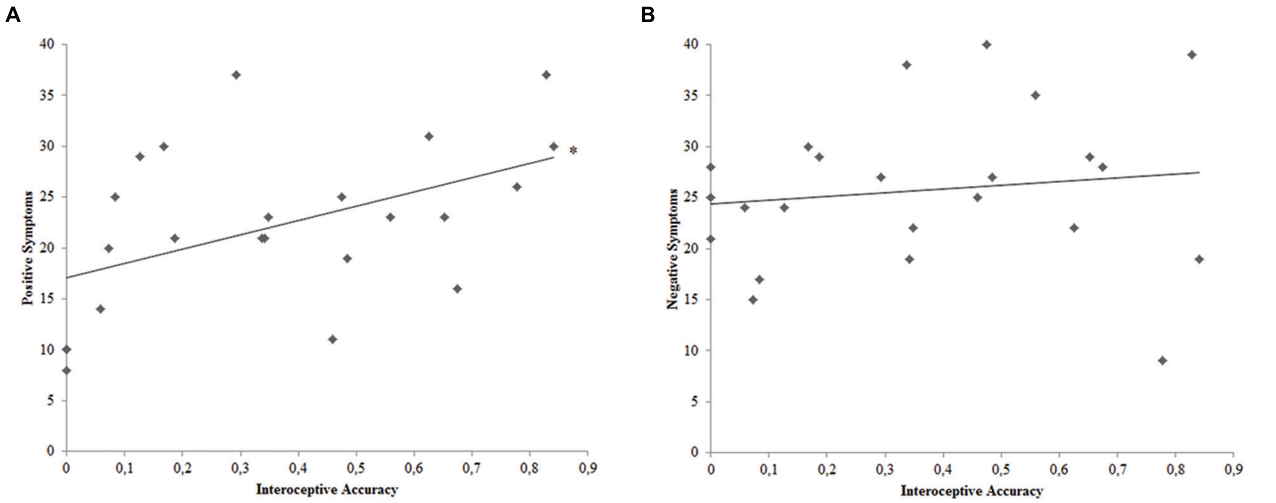

FIGURE 2 | (A) Correlation plot of the relation between interoceptive accuracy and PANSS Positive Symptoms Scale score for SCZ participants. **(B)** Correlation plot of the relation between interoceptive accuracy and PANSS Negative Symptoms Scale score for SCZ participants. * = Bonferroni corrected $p < 0.025$.

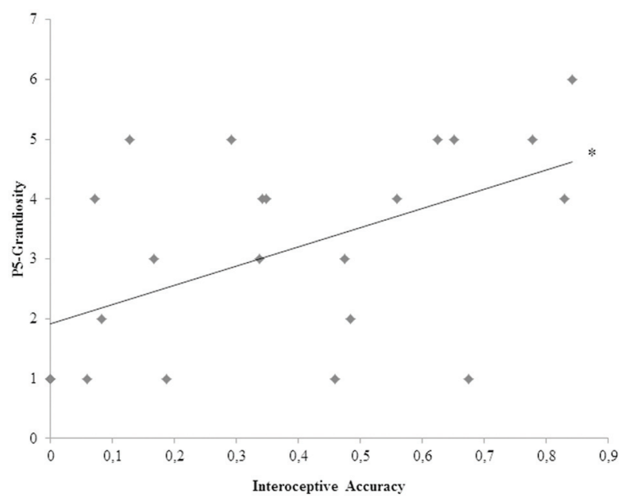

FIGURE 3 | Correlation plot of the relation between interoceptive accuracy and P5-Grandiosity positive symptom for SCZ participants. *p value near to the Bonferroni corrected threshold ($p < 0.007$).

P5-Grandiosity as control variable in this last analysis conducted on the score of Positive PANSS scale obtained by the sum of all items with the exclusion of P5 is necessary to avoid the possible influence of this specific symptom on the other positive symptoms scored in the PANSS positive symptoms scale.

Pearsons' partial correlation analysis did not show a significant linear relation between interoceptive accuracy and SCZ participants' score at Positive PANSS scale obtained by the sum of the six items with the exclusion of P5-Grandiosity, when controlling for P5-Grandiosity ($r_{20} = 0.132$; $p = 0.559$). Taken together, these analyses suggested a mediator role of P5-Grandiosity in the relation between SCZ participants' interoceptive accuracy and positive symptoms.

DISCUSSION

The present study focused on the basic experience of the self in schizophrenia, more specifically, on a not yet investigated aspect, which is interoceptive accuracy. Starting from the assumption that the effective detection and attribution of inner bodily sensations to oneself requires an intact basic sense of self, the aim of the present study was to explore the individual sensitivity to physiological stimuli originating inside of the body in a group of schizophrenia patients, compared to healthy controls. Furthermore, on the basis of the extended literature connecting altered basic self experiences, such as body ownership and sense of agency, with schizophrenia symptomatology, we also explored possible associations between interoceptive accuracy and positive or negative schizophrenia symptoms.

As expected, results demonstrated significantly lower interoceptive accuracy in schizophrenia patients when compared to healthy controls. This significant difference was not explained by participants' age, BMI, anxiety levels or HR. Furthermore, patients' illness severity, attention and pharmacological treatment did not affect their interoceptive accuracy. It is important to note that patients' attention was assessed by means of the score obtained at the corresponding item in the PANSS (G11 score of PANSS) instead of formal neuropsychological assessment. Future and more focused studies employing a direct evaluation of patients' attentive abilities are required to totally exclude a possible interfering role of attention on patients' interoceptive accuracy.

These results show, for the first time, that schizophrenia patients have a reduced sensitivity to their inner bodily signals.

TABLE 2 | Pearsons' correlation coefficients (r) and *p* values (two-tailed) calculated between SCZ participants' interoceptive accuracy and each item of the PANSS Positive Scale.

		P1	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*
Interoceptive Accuracy	*r*	0.437	0.378	0.238	0.410	0.531	0.095	0.384
	p (two-tailed)	0.037	0.075	0.274	0.052	0.009*	0.667	0.070
	N.	23	23	23	23	23	23	23

**p value near to the Bonferroni corrected threshold ($p < 0.007$).*

This suggests that, besides a feeble body ownership and an iper/ipo-trophic sense of agency, the basic experience of the self, as a body self, in schizophrenia is also characterized by damaged interoceptive accuracy.

Hence, the negative relationship between the malleability of the basic self and the interoceptive accuracy, previously evidenced in healthy participants (Tsakiris et al., 2011; Tajadura-Jiménez et al., 2012; Suzuki et al., 2013), seems to be preserved in schizophrenia patients, where both body ownership (Peled et al., 2000, 2003; Thakkar et al., 2011) and interoceptive accuracy are altered.

Furthermore, considering coenaesthesic symptoms in schizophrenia, described as unusual bodily and visceral sensations (Parnas et al., 2005b; Vollmer-Larsen et al., 2007), the reduced interoception in schizophrenia patients could constitute a previously neglected feature possibly involved in these clinical manifestations.

Several studies have shown that interoception is altered in different psychiatric disorders. Among others, low interoceptive accuracy was established in anorexia nervosa (Pollatos et al., 2008; Gaudio et al., 2014), major depression (Furman et al., 2013; Harshaw, 2015) and depersonalization-derealization disorders (Sedeño et al., 2014). In a different way, interoceptive accuracy was found abnormally higher among people suffering from anxiety disorders than healthy controls (Pollatos et al., 2009; Domschke et al., 2010). Frequently, deficit in interoceptive accuracy has been associated to anatomo-functional alterations of the Insular cortex (see for example, Frank, 2015; Kerr et al., 2015) and to clinical severity (Dunn et al., 2010b; Avery et al., 2014; Forrest et al., 2015; Yoris et al., 2015). In general, the fact that interoception is altered in several psychiatric diseases, suggests an unspecific interaction between mental illnesses and interoceptive accuracy. In the present study, however, we found no general effects of illness severity on patients' interoceptive accuracy. Rather, there was a linear relation between interoceptive accuracy and only positive symptoms suggesting a specific association between interoceptive abilities and illness qualities of schizophrenia. This specific association was mainly explained by the greater impact of Grandiosity (P5 score of PANSS), with respect to other positive symptoms. Grandiosity positive symptom refers to an "exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness".

A link between interoception and overstated explicit self representation has been established in a large sample of healthy controls (Lyons and Hughes, 2015). The authors demonstrated a positive relation between narcissistic traits and awareness of inner body sensations assessed through a formal questionnaire. In a similar vein, when healthy participants were asked to concentrate on their own mirror image (Ainley et al., 2012), the presentation of self-related words or photograph of themselves (Ainley et al., 2013) increased their interoceptive accuracy.

Overall, it seems that high self-opinion or focused attention on explicit aspects of the self are associated to increased sensitivity to the internal signals of the body. Drawing from this evidence, we speculated that while interoception might contribute to boost the explicit self representation in healthy controls, it might contribute to a pathologically hyperbolic explicit self representation in schizophrenia patients, characterized by a distorted sense of self. Grandiosity and grandiose delusions among schizophrenia patients, as well as narcissism traits in healthy participants, are indeed frequently described as defensive compensations against failures, dissatisfactions with life and traumatic events (Knowles et al., 2011; Lyons and Hughes, 2015). From this point of view, grandiosity and grandiose delusions might be protective also against the altered basic sense of self characterizing schizophrenia patients with higher sensibility to inner bodily sensations. The loss of "*the circumference centre*" might find its compensation by artificially building an explicit over-extended self, particularly among patients who are more in tune with their own internal bodily signals.

In sum, the present results suggest that even if interoceptive accuracy is altered in different psychiatric disorders, in the case of schizophrenia it has a specific association with the clinical profile of patients.

The present work specifically focuses on interoceptive accuracy (i.e., objective performance at behavioral task requiring the detection of visceral sensations), conceived as the most basic dimension of interoception underlying both interoceptive sensibility (i.e., explicit self-assessment of subjective interoception abilities by questionnaires) and interoceptive awareness (i.e., metacognitive awareness obtained by confidence-accuracy correspondence) (Garfinkel and Critchley, 2013; Garfinkel et al., 2014). The three interoceptive dimensions, however, were found to correlate only in people with high interoceptive accuracy (Garfinkel et al., 2014). Thus, despite the fundamental qualification of interoceptive accuracy, conclusions on this dimension cannot be generalized to the other two. Specifically, the fact that schizophrenia patients show lower interoceptive accuracy does not necessarily mean that they also would show low interoceptive sensibility. For example, the

Hyperreflexivity tendency, considered one of the complementary aspects of ipseity disorder (Sass and Parnas, 2003), predictive of schizophrenia symptomatology (Sass and Parnas, 2003, 2007; Sass et al., 2013), may be conceptually closer to interoceptive sensibility than to interoceptive accuracy. Hyperreflexivity refers to an exaggerated self-consciousness, a fundamentally non-volitional tendency for focal, objectifying attention directed toward processes and phenomena that would normally be "inhabited" or experienced as part of oneself. In schizophrenia this exaggerated self-reflection becomes automatic, leading to the popping-out of irrelevant background stimuli (Sass and Parnas, 2003, 2007; Sass et al., 2013). As a consequence, it may also result in an exaggerated interoceptive sensibility. Differently, metacognitive deficits, extensively established in schizophrenia (Gumley, 2011; Lysaker et al., 2014) also at the neural level (van der Meer et al., 2010), may be conceptually closer to altered interoceptive awareness, which is indeed defined as the metacognitive awareness of interoceptive accuracy. Further controlled studies are warranted to better clarify possible deficits of the different interoceptive dimensions in schizophrenia, as well as their specific association with different basic experiences of the self. For example, besides low body ownership and altered sense of agency, recent empirical evidence demonstrated that first-episode schizophrenia patients show an absence of the non-conceptual and pre-reflective experience of self underpinned by sensorimotor processes (Ferri et al., 2012). The relations between such processes and interoceptive dimensions have not been investigated yet, neither in healthy individuals nor in schizophrenia patients.

Finally, the here reported direct association between high interoceptive accuracy and positive symptoms can be more deepened by the additional involvement of larger clinical sample and by the formal assessment of patients' subjective self experiences through specific instruments (e.g., Examination of Anomalous Self Experience; Parnas et al., 2005a). This effort, adding operational depth to blur concepts, may also overcome critics (see for example, Mishara, 2007) frequently raised to schizophrenia phenomenological models.

CONCLUSION

The first time we investigated interoceptive accuracy in schizophrenia, shedding light on a new and not yet investigated aspect of basic self experiences. Schizophrenia patients showed a severe loss of the ability to detect internal bodily signals and to attribute them to themselves. Furthermore, interoceptive accuracy was associated to patients' positive symptomatology, likely fostering a grandiose, and probably defensive, self-opinion.

AUTHOR CONTRIBUTIONS

MAr designed the study, collected, analyzed, and interpreted the data, finally she wrote the manuscript. MAm was involved in the study design, data collection and analyses. She also contributed to the drafting of the manuscript. LB was principally engaged in participants recruitment and data collection, furthermore she gave her contribution to results interpretation. FF designed the study, interpreted the data and drafted the manuscript. MP, SD, and CM were involved in participants' recruitment and data collection, they also took part to the results interpretation. VG designed the study, interpreted the data and drafted the manuscript. All authors approved the final version of the manuscript.

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REFERENCES

Ainley, V., Maister, L., Brokfeld, J., Farmer, H., and Tsakiris, M. (2013). More of myself: manipulating interoceptive awareness by heightened attention to bodily and narrative aspects of the self. *Conscious. Cogn.* 22, 1231–1238. doi: 10.1016/j.concog.2013.08.004

Ainley, V., Tajadura-Jiménez, A., Fotopoulou, A., and Tsakiris, M. (2012). Looking into myself: changes in interoceptive sensitivity during mirror self-observation. *Psychophysiology* 49, 1504–1508. doi: 10.1111/j.1469-8986.2012.01468.x

Avery, J. A., Drevets, W. C., Moseman, S. E., Bodurka, J., Barcalow, J. C., and Simmons, W. K. (2014). Major depressive disorder is associated with abnormal interoceptive activity and functional connectivity in the insula. *Biol. Psychiatry* 76, 258–266. doi: 10.1016/j.biopsych.2013.11.027

Botvinick, M., and Cohen, J. (1998). Rubber hand "feels" touch that eyes see. *Nature* 391, 756. doi: 10.1038/35784

Brener, J., and Kluvitse, C. (1988). Heartbeat detection: judgments of the simultaneity of external stimuli and heartbeats. *Psychophysiology* 25, 554–561. doi: 10.1111/j.1469-8986.1988.tb01891.x

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* 3, 655–666. doi: 10.1038/nrn894

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* 13, 500–505. doi: 10.1016/S0959-4388(03)00090-4

Derogatis, L. R., and Savitz, K. L. (2000). "The SCL-90-R and the Brief Symptom Inventory (BSI) in primary care," in *Handbook of Psychological Assessment in Primary Care Settings*, ed. M. E. Maruish (Mahwah, NY: Lawrence Erlbaum Associates), 297–334.

Domschke, K., Stevens, S., Pfleiderer, B., and Gerlach, A. L. (2010). Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. *Clin. Psychol. Rev.* 30, 1–11. doi: 10.1016/j.cpr.2009.08.008

Dunn, B. D., Galton, H. C., Morgan, R., Evans, D., Oliver, C., Meyer, M., et al. (2010a). Listening to your heart. How interoception shapes emotion experience and intuitive decision making. *Psychol. Sci.* 21, 1835–1844. doi: 10.1177/0956797610389191

Dunn, B. D., Stefanovitch, I., Evans, D., Oliver, C., Hawkins, A., and Dalgleish, T. (2010b). Can you feel the beat? Interoceptive awareness is an interactive function of anxiety- and depression-specific symptom dimensions. *Behav. Res. Ther.* 48, 1133–1138. doi: 10.1016/j.brat.2010.07.006

Ebisch, S. J. H., Ferri, F., Salone, A., Perrucci, M. G., D'Amico, L., Ferro, F. M., et al. (2011). Differential involvement of somatosensory and interoceptive cortices during the observation of affective touch. *J. Cogn. Neurosci.* 23, 1808–1822. doi: 10.1162/jocn.2010.21551

Ebisch, S. J. H., Mantini, D., Northoff, G., Salone, A., De Berardis, D., Ferri, F., et al. (2014). Altered brain long-range functional interactions underlying the link between aberrant self-experience and self-other relationship in first-episode schizophrenia. *Schizophr. Bull.* 40, 1072–1082. doi: 10.1093/schbul/sbt153

Ebisch, S. J. H., Salone, A., Ferri, F., De Berardis, D., Romani, G. L., Ferro, F. M., et al. (2013). Out of touch with reality? Social perception in first-episode schizophrenia. *Soc. Cogn. Affect. Neurosci.* 8, 394–403. doi: 10.1093/scan/nss012

Ferri, F., Ardizzi, M., Ambrosecchia, M., and Gallese, V. (2013). Closing the gap between the inside and the outside: interoceptive sensitivity and social distances. *PLoS ONE* 8:e75758. doi: 10.1371/journal.pone.0075758

Ferri, F., Costantini, M., Salone, A., Di Iorio, G., Martinotti, G., Chiarelli, A., et al. (2014). Upcoming tactile events and body ownership in schizophrenia. *Schizophr. Res.* 152, 51–57. doi: 10.1016/j.schres.2013.06.026

Ferri, F., Frassinetti, F., Mastrangelo, F., Salone, A., Ferro, F. M., and Gallese, V. (2012). Bodily self and schizophrenia: The loss of implicit self-body knowledge. *Conscious. Cogn.* 21, 1365–1374. doi: 10.1016/j.concog.2012.05.001

First, M. B., Gibbon, M., Spitzer, R. L., First, M. B., Gibbon, M., and Spitzer, R. L. (1996). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II, Version 2.0)*. New York, NY: Biometrich Research.

First, M. B., Spitzer, R. L., Gibbon, M., and Williams, J. B. W. (2012). *Structured Clinical Interview for DSM-IV® Axis I Disorders (SCID-I), Clinician Version, Administration Booklet*. Available at: http://books.google.com/books?hl=it&lr=&id=jqeceksZPXcC&pgis=1 [Accessed March 24, 2015].

Forrest, L., Smith, A., White, R., and Joiner, T. (2015). (Dis)connected: An examination of interoception in individuals with suicidality. *J. Abnorm. Psychol.* 124, 754–763. doi: 10.1037/abn0000074

Fourneret, P., Franck, N., Slachevsky, A., and Jeannerod, M. (2001). Self-monitoring in schizophrenia revisited. *Neuroreport* 12, 1203–1208. doi: 10.2174/157340007782408897

Frank, G. K. W. (2015). Advances from neuroimaging studies in eating disorders. *CNS Spectr.* 20, 1–10. doi: 10.1017/S1092852915000012

Fuchs, T. (2005). Corporealized and disembodied minds: a phenomenological view of the body in melancholia and schizophrenia. *Philos. Psychiatry Psychol.* 12, 95–107. doi: 10.1353/ppp.2005.0040

Furman, D. J., Waugh, C. E., Bhattacharjee, K., Thompson, R. J., and Gotlib, I. H. (2013). Interoceptive awareness, positive affect, and decision making in major depressive disorder. *J. Affect. Disord.* 151, 780–785. doi: 10.1016/j.jad.2013.06.044

Garfinkel, S. N., and Critchley, H. D. (2013). Interoception, emotion and brain: new insights link internal physiology to social behaviour. *Soc. Cogn. Affect. Neurosci.* 8, 231–234. doi: 10.1093/scan/nss140

Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., and Critchley, H. D. (2014). Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol. Psychol.* 104, 65–74. doi: 10.1016/j.biopsycho.2014.11.004

Gaudio, S., Brooks, S. J., and Riva, G. (2014). Nonvisual multisensory impairment of body perception in anorexia nervosa: a systematic review of neuropsychological studies. *PLoS ONE* 9:e110087. doi: 10.1371/journal.pone.0110087

Germine, L., Benson, T. L., Cohen, F., and Hooker, C. I. L. (2013). Psychosis-proneness and the rubber hand illusion of body ownership. *Psychiatry Res.* 207, 45–52. doi: 10.1016/j.psychres.2012.11.022

Gumley, A. (2011). Metacognition, affect regulation and symptom expression: a transdiagnostic perspective. *Psychiatry Res.* 190, 72–78. doi: 10.1016/j.psychres.2011.09.025

Haase, L., Stewart, J. L., Youssef, B., May, A. C., Isakovic, S., Simmons, A. N., et al. (2016). When the brain does not adequately feel the body: links between low resilience and interoception. *Biol. Psychol.* 113, 37–45. doi: 10.1016/j.biopsycho.2015.11.004

Haggard, P., Martin, F., and Taylor-Clarke, M. (2003). Awareness of action in schizophrenia. *Cogn. Neurosci. Neuropsychol.* 14, 1081–1085.

Hall, R. C. (1995). Global assessment of functioning. A modified scale. *Psychosomatics* 36, 267–275. doi: 10.1016/S0033-3182(95)71666-8

Harshaw, C. (2015). Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychol. Bull.* 141, 311–363. doi: 10.1037/a0038101

Hur, J.-W., Kwon, J. S., Lee, T. Y., and Park, S. (2014). The crisis of minimal self-awareness in schizophrenia: a meta-analytic review. *Schizophr. Res.* 152, 58–64. doi: 10.1016/j.schres.2013.08.042

Jarrahi, B., Mantini, D., Balsters, J. H., Michels, L., Kessler, T. M., Mehnert, U., et al. (2015). Differential functional brain network connectivity during visceral interoception as revealed by independent component analysis of fMRI time-series. *Hum. Brain Mapp.* 36, 4438–4468. doi: 10.1002/hbm.22929

Jaspers, K. (1923). *General Psychopathology*. Chicago, IL: University Of Chicago Press.

Jeannerod, M. (2009). The sense of agency and its disturbances in schizophrenia: a reappraisal. *Exp. Brain Res.* 192, 527–532. doi: 10.1007/s00221-008-1533-3

Jones, G. E. (1995). "Constitutional and physiological factors in heartbeat perception," in *From the Heart to the Brain. The psychophysiology of circulation-brain interaction*, eds D. Vaitl and R. Schandry (Frankfurt: Peter Lang-Verlag), 173–192.

Kasai, K., Shenton, M. E., Salisbury, D. F., Onitsuka, T., Toner, S. K., Yurgelun-Todd, D., et al. (2003). Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. *Arch. Gen. Psychiatry* 60, 1069–1077. doi: 10.1001/archpsyc.60.11.1069

Kathirvel, N., and Mortimer, A. (2013). Causes, diagnosis and treatment of visceral hallucinations. *Prog. Neurol. Psychiatry* 17, 6–10.

Kay, S. R., Flszbein, A., and Opfer, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276. doi: 10.1093/schbul/13.2.261

Kerr, K. L., Moseman, S. E., Avery, J. A., Bodurka, J., Zucker, N. L., and Simmons, W. K. (2015). Altered insula activity during visceral interoception in weight-restored patients with anorexia nervosa. *Neuropsychopharmacology* 41, 521–528. doi: 10.1038/npp.2015.174

Khalsa, S. S., Rudrauf, D., and Tranel, D. (2009). Interoceptive awareness declines with age. *Psychophysiology* 46, 1130–1136. doi: 10.1111/j.1469-8986.2009.00859.x

Knoll, J. F., and Hodapp, V. (1992). A comparison between two methods for assessing heartbeat perception. *Psychophysiology* 29, 218–222. doi: 10.1111/j.1469-8986.1992.tb01689.x

Knowles, R., McCarthy-Jones, S., and Rowse, G. (2011). Grandiose delusions: a review and theoretical integration of cognitive and affective perspectives. *Clin. Psychol. Rev.* 31, 684–696. doi: 10.1016/j.cpr.2011.02.009

Lyons, M., and Hughes, S. (2015). Feeling me, feeling you? Links between the Dark Triad and internal body awareness. *Pers. Individ. Dif.* 86, 308–311. doi: 10.1016/j.paid.2015.06.039

Lysaker, P. H., Leonhardt, B. L., Pijnenborg, M., van Donkersgoed, R., de Jong, S., and Dimaggio, G. (2014). Metacognition in schizophrenia spectrum disorders: methods of assessment and associations with neurocognition, symptoms, cognitive style and function. *Isr. J. Psychiatry Relat. Sci.* 51, 54–62. doi: 10.4321/S0213-61632010000400004

Maeda, T., Kato, M., Muramatsu, T., Iwashita, S., Mimura, M., and Kashima, H. (2012). Aberrant sense of agency in patients with schizophrenia: forward and backward over-attribution of temporal causality during intentional action. *Psychiatry Res.* 198, 1–6. doi: 10.1016/j.psychres.2011.10.021

Maeda, T., Takahata, K., Muramatsu, T., Okimura, T., Koreki, A., Iwashita, S., et al. (2013). Reduced sense of agency in chronic schizophrenia with predominant negative symptoms. *Psychiatry Res.* 209, 386–392. doi: 10.1016/j.psychres.2013.04.017

Mishara, A. L. (2007). Missing links in phenomenological clinical neuroscience: why we still are not there yet. *Curr. Opin. Psychiatry* 20, 559–569. doi: 10.1097/YCO.0b013e3282f128b8

Morgan, H. L., Turner, D. C., Corlett, P. R., Absalom, A. R., Adapa, R., Arana, F. S., et al. (2011). Exploring the impact of ketamine on the experience of illusory body ownership. *Biol. Psychiatry* 69, 35–41. doi: 10.1016/j.biopsych.2010.07.032

Parnas, J., Handest, P., Jansson, L., and Saebye, D. (2005a). Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology* 38, 259–267. doi: 10.1159/000088442

Parnas, J., Møller, P., Kircher, T., Thalbitzer, J., Jansson, L., Handest, P., et al. (2005b). EASE: examination of anomalous self-experience. *Psychopathology* 38, 236–258. doi: 10.1159/000088441

Pedrabissi, L., and Santinello, M. (1989). *Inventario per l'Ansia di "Stato" e di "tratto": Nuova Versione Italiana dello STAI. Forma Y: Manuale*. Firenze: Organizzazioni Speciali.

Peled, A., Pressman, A., Geva, A. B., and Modai, I. (2003). Somatosensory evoked potentials during a rubber-hand illusion in schizophrenia. *Schizophr. Res.* 64, 157–163. doi: 10.1016/S0920-9964(03)00057-4

Peled, A., Ritsner, M., Hirschmann, S., Geva, A. B., and Modai, I. (2000). Touch feel illusion in schizophrenic patients. *Biol. Psychiatry* 48, 1105–1108. doi: 10.1016/S0006-3223(00)00947-1

Pollatos, O., Herbert, B. M., Matthias, E., and Schandry, R. (2007a). Heart rate response after emotional picture presentation is modulated by interoceptive awareness. *Int. J. Psychophysiol.* 63, 117–124. doi: 10.1016/j.ijpsycho.2006.09.003

Pollatos, O., Kurz, A. L., Albrecht, J., Schreder, T., Kleemann, A. M., Schopf, V., et al. (2008). Reduced perception of bodily signals in anorexia nervosa. *Eat Behav.* 9, 381–388. doi: 10.1016/j.eatbeh.2008.02.001

Pollatos, O., Schandry, R., Auer, D. P., and Kaufmann, C. (2007b). Brain structures mediating cardiovascular arousal and interoceptive awareness. *Brain Res.* 1141, 178–187. doi: 10.1016/j.brainres.2007.01.026

Pollatos, O., Traut-Mattausch, E., and Schandry, R. (2009). Differential effects of anxiety and depression on interoceptive accuracy. *Depress. Anxiety* 26, 167–173. doi: 10.1002/da.20504

Raven, J., Raven, J. C., and Court, J. H. (1998a). *Manual for Raven's Progressive Matrices and Vocabulary Scales—Section 1: General Overview*. Oxford: Oxford Psychologists Press.

Raven, J., Raven, J. C., and Court, J. H. (1998b). *Manual for Raven's progressive matrices and vocabulary scales—section 3: standard progressive matrices*. Oxford: Oxford Psychologists Press.

Renes, R. A., Vermeulen, L., Kahn, R. S., Aarts, H., and van Haren, N. E. M. (2013). Abnormalities in the establishment of feeling of self-agency in schizophrenia. *Schizophr. Res.* 143, 50–54. doi: 10.1016/j.schres.2012.10.024

Sass, L., Pienkos, E., and Nelson, B. (2013). Introspection and schizophrenia: a comparative investigation of anomalous self experiences. *Conscious. Cogn.* 22, 853–867. doi: 10.1016/j.concog.2013.05.004

Sass, L. A., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr. Bull.* 29, 427–444. doi: 10.1093/oxfordjournals.schbul.a007017

Sass, L. A., and Parnas, J. (2007). "Explaining schizophrenia: the relevance of phenomenology," in *Reconceiving Schizophrenia*, eds M. C. Chung, K. W. M. Filford, and G. Graham (Oxford: Oxford University Press), 63–95. doi: 10.1093/med/9780198526131.003.0004

Schandry, R. (1981). Heart beat perception and emotional experience. *Psychophysiology* 18, 483–488. doi: 10.1111/j.1469-8986.1981.tb02486.x

Sedeño, L., Couto, B., Melloni, M., Canales-Johnson, A., Yoris, A., Baez, S., et al. (2014). How do you feel when you can't feel your body? interoception, functional connectivity and emotional processing in depersonalization-derealization disorder. *PLoS ONE* 9:e98769. doi: 10.1371/journal.pone.0098769

Suzuki, K., Garfinkel, S. N., Critchley, H. D., and Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia* 51, 2909–2917. doi: 10.1016/j.neuropsychologia.2013.08.014

Synofzik, M., Thier, P., Leube, D. T., Schlotterbeck, P., and Lindner, A. (2010). Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. *Brain* 133, 262–271. doi: 10.1093/brain/awp291

Tajadura-Jiménez, A., Longo, M. R., Coleman, R., and Tsakiris, M. (2012). The person in the mirror: using the enfacement illusion to investigate the experiential structure of self-identification. *Conscious. Cogn.* 21, 1725–1738. doi: 10.1016/j.concog.2012.10.004

Thakkar, K. N., Nichols, H. S., McIntosh, L. G., and Park, S. (2011). Disturbances in body ownership in schizophrenia: evidence from the rubber hand illusion and case study of a spontaneous out-of-body experience. *PLoS ONE* 6:e27089. doi: 10.1371/journal.pone.0027089

Tsakiris, M., Tajadura-Jimenez, A., and Costantini, M. (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. *Proc. Biol. Sci.* 278, 2470–2476. doi: 10.1098/rspb.2010.2547

Tseng, H.-H., Bossong, M. G., Modinos, G., Chen, K.-M., McGuire, P., and Allen, P. (2015). A systematic review of multisensory cognitive-affective integration in schizophrenia. *Neurosci. Biobehav. Rev.* 55, 444–452. doi: 10.1016/j.neubiorev.2015.04.019

van der Meer, L., Costafreda, S., Aleman, A., and David, A. S. (2010). Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neurosci. Biobehav. Rev.* 34, 935–946. doi: 10.1016/j.neubiorev.2009.12.004

Vollmer-Larsen, A., Handest, P., and Parnas, J. (2007). Reliability of measuring anomalous experience: the bonn scale for the assessment of basic symptoms. *Psychopathology* 40, 345–348. doi: 10.1159/000106311

Voss, M., Moore, J., Hauser, M., Gallinat, J., Heinz, A., and Haggard, P. (2010). Altered awareness of action in schizophrenia: a specific deficit in predicting action consequences. *Brain* 133, 3104–3112. doi: 10.1093/brain/awq152

Waters, F. A. V., and Badcock, J. C. (2010). First-rank symptoms in schizophrenia: reexamining mechanisms of self-recognition. *Schizophr. Bull.* 36, 510–517. doi: 10.1093/schbul/sbn112

Werner, N. S., Jung, K., Duschek, S., and Schandry, R. (2009). Enhanced cardiac perception is associated with benefits in decision-making. *Psychophysiology* 46, 1123–1129. doi: 10.1111/j.1469-8986.2009.00855.x

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J. Clin. Psychiatry* 64, 663–667. doi: 10.4088/JCP.v64n0607

Wylie, K. P., and Tregellas, J. R. (2010). The role of the insula in schizophrenia. *Schizophr. Res.* 123, 93–104. doi: 10.1016/j.schres.2010.08.027

Yoris, A., Esteves, S., Couto, B., Melloni, M., Kichic, R., Cetkovich, M., et al. (2015). The roles of interoceptive sensitivity and metacognitive interoception in panic. *Behav. Brain Funct.* 11, 14. doi: 10.1186/s12993-015-0058-8

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Interoception and Autonomic Correlates during Social Interactions. Implications for Anorexia

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The aim of this study is to investigate the bodily-self in Restrictive Anorexia, focusing on two basic aspects related to the bodily self: autonomic strategies in social behavior, in which others' social desirability features, and social cues (e.g., gaze) are modulated, and interoception (i.e., the sensitivity to stimuli originating inside the body). Furthermore, since previous studies carried out on healthy individuals found that interoception seems to contribute to the autonomic regulation of social behavior, as measured by Respiratory Sinus Arrhythmia (RSA), we aimed to explore this link in anorexia patients, whose ability to perceive their bodily signal seems to be impaired. To this purpose, we compared a group of anorexia patients (ANg; restrictive type) with a group of Healthy Controls (HCg) for RSA responses during both a resting state and a social proxemics task, for their explicit judgments of comfort in social distances during a behavioral proxemics task, and for their Interoceptive Accuracy (IA). The results showed that ANg displayed significantly lower social disposition and a flattened autonomic reactivity during the proxemics task, irrespective of the presence of others' socially desirable features or social cues. Moreover, unlike HCg, the autonomic arousal of ANg did not guide behavioral judgments of social distances. Finally, IA was strictly related to social disposition in both groups, but with opposite trends in ANg. We conclude that autonomic imbalance and its altered relationship with interoception might have a crucial role in anorexia disturbances.

Keywords: anorexia nervosa, autonomic reactivity, bodily self, interoception, interoceptive accuracy, proxemics, sinus respiratory arrhythmia, social interaction

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INTRODUCTION

"How much, how much I enjoy the streamlinedness of it, the simplicity. I really care about that. But I couldn't stay alive. My "less is more" sort of thing, and also wishing to feel the consciousness of my body. So the coupling of a variety of things made me arrive at this very, very streamlined diet in which there clearly wasn't sufficient nutrition to sustain life" (Bruch, 1973).

"Sometimes I feel if I'm made of glass, like I'm transparent, and everyone can see right into my side, it makes me want to scream, get out, get out of me!" (Recovering anorexic personal communication, in Lester, 1997).

Anorexia nervosa (AN) is an eating disorder characterized by restriction of food energy intake due to an irrational fear of gaining weight and a distorted way in which body shape and weight are experienced that have an inappropriate influence on self- evaluation (DSM V—American Psychiatric Association, 2013). The serious loss of weight leads to severe malnutrition and an alarming high mortality risk compared with other psychiatric illnesses (Sullivan, 1995; Casiero and Frishman, 2006). In the last decades, the frequency of this illness and other eating disorders greatly increased (Fassino et al., 2004; Friederich et al., 2006; Keski-Rahkonen et al., 2007). Anorexia significantly impact health care, mostly in the female population, and represents a great challenge for physicians of various specialties (Mitchell and Crow, 2006).

To date, the etiology of this illness remains not yet fully understood. There is also increasing need for developing more effective treatments (Herzog et al., 1992; Vandereycken, 2003; Jacobi et al., 2004; Fairburn and Bohn, 2005; Tchanturia et al., 2005; Riva, 2014). In the last years, thanks to the support of neuroscience, several neurobiological models of eating disorders emerged; Kaye et al. (2009, 2010, 2013, 2015) for example, consider AN as the product of an altered serotonin and dopamine metabolism which in turn may leads to dysfunctional neural process involved in emotion and appetite. Such alterations would contribute to AN trait-related vulnerabilities like anxiety, emotional recognition and regulation deficits (Schmidt et al., 1993; Zonnevijlle-Bendek et al., 2002; Kucharska-Pietura et al., 2004; Schmidt and Treasure, 2006; Harrison et al., 2009; Rowsell et al., 2016), insensitivity to reward (Kaye et al., 2009; Harrison et al., 2010), disturbed perception of physical states (Fassino et al., 2004; Pollatos et al., 2008; see below) and cognitive inflexibility and rigidity (Katzman et al., 2001; Anderluh et al., 2003; Kucharska-Pietura et al., 2004; Tchanturia et al., 2004; Cassin and von Ranson, 2005; Chui et al., 2008; Titova et al., 2013) that may be exacerbated by puberty and social desirability, given rise to the onset of AN.

In addition, Treasure and Schmidt (2013) and Schmidt and Treasure (2006) in their cognitive—interpersonal maintenance model of eating disorders identified cognitive, socio-emotional, and interpersonal elements whose joint action would be involved in causing and maintaining eating disorders. Specifically, they suggest that obsessive compulsive and anxious avoidant traits may encourage anorexia beliefs and behaviors, determining widely documented problems in interpersonal relationships (Kog and Vandereycken, 1989; Kucharska-Pietura et al., 2004; Russell et al., 2009; Oldershaw et al., 2010; Watson et al., 2010; Claes et al., 2012; Zucker et al., 2013). Finally, Fairburn et al. (2003) proposed the Trans diagnostic theory of eating disorder, highlighting the role of self-esteem, perfectionism, and mood intolerance as core factors of eating disorder maintenance.

However, even if these models importantly increased the knowledge about the underpinnings of eating disorders, they only partially addressed the role of bodily experience in this pathology. Nonetheless, as previously mentioned (see above), disturbances in the way in which body weight or shape are experienced represent core symptoms of AN, (DSM V—American Psychiatric Association, 2013), in which the body is refused, lived as an object from which to get away (Noll and Fredrickson, 1998; Daubenmier, 2005; Riva et al., 2015). This gap has been recently filled by the Allocentric Lock Theory (see Riva, 2014; Riva et al., 2014), which conceives of EDs as the outcome of impaired ability in updating a negative bodily representation stored in autobiographical memory (allocentric) with real-time sensorimotor and proprioceptive data (egocentric; Riva, 2014). In line with Embodied Social Cognition theories, these authors highlighted the central role of the physical body in influencing the mind. This perspective emphasizes the link between altered (physical) subjective experience and both disturbed inter-subjectivity and neurobiological dysfunctions in the development of the mental illness (Matthews, 2004, 2007; Ratcliffe, 2008; Fuchs and Schlimme, 2009; Glannon, 2009; Gallese and Ferri, 2013; Gallese, 2014).

An embodied view of AN is also supported by patients' experiences (see above), through which it is quite evident that this disorder may reflect something more than a mere body image disorder (i.e., perceptual overestimation of one's body appearance and cognitive-evaluative dissatisfaction and disparagement—Cash and Deagle, 1997). Indeed, AN looks like a struggle with deeper and low-level aspects of the self, involving more implicit and unconscious aspects of the bodily-self such as action-oriented body schema (Guardia et al., 2010, 2012; Nico et al., 2010; Keizer et al., 2013), interoception (Fassino et al., 2004; Pollatos et al., 2008; Herbert and Pollatos, 2012; Strigo et al., 2013), multisensory body perception (see Gaudio et al., 2014 for a review), multisensory integration (Eshkevari et al., 2012), influencing both the body image and AN behaviors. For example, Epstein et al. (2001) found that patients in acute phase of AN showed poorer proprioceptive abilities compared to controls. In addition, Nico et al. (2010) tested body size perception implicitly, carrying out a psychophysical task in which participants had to predict whether a light beam would have hit/missed their body. They found that AN patients, like patients with right parietal lobe lesions, were significantly less precise than controls and underestimated eccentricity of their left body boundary.

Concerning interoception, it represents a core component of bodily-self experience, because it consists of the sensitivity to visceral stimuli originating inside of the body (Craig, 2002). It is often concomitant with emotional responses (Critchley et al., 2004; Gaudio et al., 2014). A strict relationship between IA and social attitudes in the context of real social interactions was the target of a recent study, carried out on healthy individuals (Ferri et al., 2013). This study demonstrated that IA contributes to inter-individual differences concerning social disposition and interpersonal space representation, via recruitment of different adaptive autonomic response strategies. The authors assessed Respiratory Sinus Arrhythmia (RSA) in both social and a non-social task. In the social task, participants viewed a caress-like movement, performed by an experimenter's hand, at different distances from participants' hand. In the non-social task, the movement of a metal stick replaced the hand. RSA is one of the periodic components of heart rate variability (Berntson et al., 1997) directly resulting from the interaction between the cardiovascular and respiratory systems (Grossman and Taylor, 2007). RSA is an index of social disposition (Porges et al., 2013) and positive social functioning both in healthy (Graziano et al., 2007) and clinical samples (Bal et al., 2010; Patriquin et al., 2013), and it can be modulated by emotional processing (Porges and Smilen, 1994).

The results showed that only good heartbeat perceivers with high IA levels displayed stronger autonomic responses in the social setting compared to the non-social setting. Particularly, when the experimenter's hand was moving at the boundary of participants' peri-personal space (i.e., 20 cm from the participants' hand). On the contrary, poor heartbeat perceivers with low IA levels were less predisposed to social engagement, as they required more intrusive social stimuli to be delivered in their personal space (i.e., touching their hand) to effectively predispose the autonomic response to them (Ferri et al., 2013).

Interoception in eating disorders has been poorly assessed. Some authors found that individuals suffering from anorexia showed difficulty to discriminate not only visceral sensations related to eating behaviors, such as hunger and satiety (Garner et al., 1983; Fassino et al., 2004; Lilenfeld et al., 2006; Matsumoto et al., 2006), but also visceral sensation in general (Pollatos et al., 2008). A study by Pollatos et al. (2008), for example, found that anorexic patients showed lower Interoceptive Accuracy (IA; performance on objective behavioral tests about visceral sensation detection, see Garfinkel et al., 2015) in a well-assessed heartbeat detection task (Schandry, 1981). Coherently, these patients show altered activation of the anterior insula (Wagner et al., 2008; Oberndorfer et al., 2013), which seems to play a crucial role in interoception (Critchley et al., 2004; Pollatos et al., 2007; Craig, 2009). Anterior insula is also relevant for emotional processing (Phan et al., 2002), and for the self-regulation of feelings and behavior (Beauregard et al., 2001) and it has been recently proposed to be responsible for the altered disgust sensitivity in AN (e.g., Vicario, 2013; Moncrieff-Boyd et al., 2014; Hildebrandt et al., 2015).

Considering that AN seems to be associated to low levels of IA (Pollatos et al., 2008), together with a wide range of autonomic system disturbances whose nature is far from clear (for a review see Mazurak et al., 2011), and taking into account the demonstrated link between IA levels and autonomic regulation in social context among healthy individuals, the purpose of the present study was to assess AN patients' autonomic regulation in social contexts and its possible relation with IA.

To this aim, we assessed RSA and IA of both a group of AN patients (restrictive type) and a group of Healthy Controls. To test participants' autonomic reactivity during social interactions, the two groups were also submitted to a Physiological proxemics task, a modified version of the "personal space regulation task" used by Kennedy et al. (2009). During the task, participants were instructed to view, one by one, two female experimenters (the one obese, the other underweight) slowly approaching them, from a distance of 470 cm across the room to a tip-to-tip distance (about 30 cm), or vice versa, slowly moving away from participants. We recruited two experimenters with different BMI to test its possible influence on participants' responses. Furthermore, to explore the role of social cues in modulating participants' responses during social interaction, the presence or the absence of eye contact (from the experimenter toward the participant) were also introduced. Participants' electrocardiogram (ECG) was recorded (to extract RSA) for the entire duration of the Physiological proxemics task.

As an explicit measure of participants' comfort during social interaction, and to help us with the interpretation of physiological results, they were also submitted to a Behavioral proxemics task, that is, the behavioral version of the Physiological proxemics task without ECG recordings. In this task, participants had to explicitly stop the experimenter as soon as she reached a distance at which they felt most comfortable (closer could be too much and farer could be too less).

IA was assessed throughout a well-assessed heartbeat perception task, the same used by Pollatos et al. (2008), following the Mental tracking Method by Schandry (1981).

On the basis of previous studies, we hypothesized lower resting RSA responses and IA in ANg compared to HCg. We also hypothesized a compromised relationship between IA and social disposition in AN. Given that this is a relatively uncharted territory, we explored both within and between group differences in autonomic and behavioral reactivity in the different social context, where the interacting experimenters' eye contact and BMI were manipulated.

MATERIALS AND METHOD

Participants

Twenty-four right-handed women diagnosed of Anorexia Nervosa, restrictive subtype, according to the DSM V criteria (American Psychiatric Association, 2013; AN group-ANg; mean age: 23.04 SE = 1.9; mean BMI: 16.1 Kg/m2 SE = 0.3; mean duration of illness: 6 years SE = 1.6; all females) were included in the study. The restrictive subtype of AN is characterized by the absence, during the last 3 months, of recurrent episodes of binge eating or purging behaviors as self-induced vomiting or the misuse of laxatives, diuretics, or enemas. All patients followed a controlled diet for the 10 days prior to the experiment in order to avoid the confounding effects of malnutrition on the performance.

Twenty-five control participants (HC group -HCg; mean age: 22.9 SE = 1.1; mean BMI: 21 Kg/m^2 SE = 0.58; all females) with normal Body Mass Index (BMI comprised between 18.5 and 24.9) were matched with AN patients for age and gender. Exclusion criteria for both groups included actual or past cognitive disorders (mental retardation), psychiatric disorders (psychosis), severe medical illnesses (head trauma, neurological, and cardio-respiratory diseases, and diabetes), substance dependence, and intake of medications altering the cardio-respiratory activity. Given the frequent comorbidity in anorexia nervosa with major depression, anxiety, and personality disorders, these were not comprised among exclusion criteria for ANg, but they were carefully clinically assessed (see below). Furthermore, since it is known that the autonomic tone, especially the vagal component (de Geus et al., 1995; Jurca et al., 2004), is affected by regular exercise, improving, in turn, IA as assessed by heartbeat detection (Bestler et al., 1990; Herbert et al., 2010), only individuals not regularly involved in athletic or endurance sports were recruited. A further exclusion criterion for the control group was a personal history of eating disorders, and a clinical risk to develop an eating disorder (high risk score in BSQ, EDE-Q, and EDRC scale of EDI3).

In a previous and separate session from the experiment, all participants filled in several questionnaires including an anamnestic questionnaire, the Eating Disorder Inventory (EDI-3; Giannini et al., 2008) and the Eating Disorder Examination Questionnaire (EDE Q; Fairburn, 2008), to assess both the eating disorder risk and the symptomatology associated with eating disorders, the Body Uneasiness Test (BUT; Cuzzolaro et al., 2006) and the Body Shape Questionnaire (BSQ; Stefanile et al., 2011), to measure concerns about body shape. In addition, participants were required to filled in the Symptom Checklist-90 (SCL-90; Derogatis et al., 1973), to assess their current psychological status and to exclude psychopathological symptoms in HC. They also filled in the Dissociative Experiences Scale (DES; Carlson and Putnam, 1993) to explore their possible dissociative symptoms.

Since there is evidence suggesting that depression symptoms and RSA interact (Yaroslavsky et al., 2013, 2014), participants were also required to fill in the Italian version of the Beck's Depression Inventory (BDI; Ghisi et al., 2006). The BDI is a widely used 21-items multiple-choice self-report inventory that measures the presence and severity of affective, cognitive, motivational, psychomotor, and vegetative symptoms of depression.

Similarly, because it has been shown that anxiety interacts with RSA (Gorka et al., 2013; Mathewson et al., 2013) and there is evidence suggesting positive association between IA and anxiety (Van der Does et al., 2000; Pollatos et al., 2007, 2009), participants filled in the Italian version of the State-Trait Anxiety Inventory (Pedrabissi and Santinello, 1989). The STAI is a 40 items scale, which assesses both state (this latter was administered during the experimental session) and trait anxiety. It represents widely-validated and reliable self-report measures of trait and state anxiety.

Sociodemographic features and questionnaire scores obtained from the two groups of participants are shown in **Table 1**.

The experimental protocol was approved by the Ethics Committee of Casa di Cura Villa Margherita, Arcugnano, Vicenza, Italy. The experiment was conducted in accordance with the ethical standards of the 2013 Declaration of Helsinki and all participants involved in the study gave written informed consent.

TABLE 1 | Comparison between the two groups with respect to socio-demographic and questionnaire data.

	ANg mean (SE)	HCg mean (SE)	*T*(*df*=1,47)	*p*
N(sex)	24 (f)	25 (f)	n.a.	n.a
Age	23 ± 9 (2)	23 ± 5.5 (1)	−0.7	n.s.
Illness duration, year	6 ± 8 (1.6)	n.a.	n.a.	n.a.
BMI	16 (0.3)	21 (0.6)	7.7	***
Weight	43.2 (0.8)	57 (1.9)	6.7	***
Height	1.6 (0.01)	1.6 (0.01)	0.18	n.s.
DES	20.5 (3.5)	9.1 (1.7)	−3	***
EDI 3-ID	77 (5.3)	32.8 (5.9)	−5.6	***
EDI3-LSE	81.9 (4.2)	30 (4.9)	−7.9	***
EDI3-II	71. (5.3)	42.2 (5.9)	−3.6	**
EDI3-ED	65.4 (5.9)	30.8 (5.6)	−3.9	***
EDI3-EDRC	74.2 (19.4)	27.9 (3.9)	−8.3	***
SCL-90	1.3 (0.12)	0.5(0.8)	−5.8	***
STAI- State	49.8 (2.2)	35(2.7)	−4.7	***
STAI- Trait	61.3 (2.2)	40.3 (2.2)	−6.8	***
BDI	27.2 (2.7)	6.5 (1.3)	−7	***
BUT (GSI)	2 (1.1)	0.8 (0.1)	−5	***
BUT (BIC)	1.9 (0.2)	0.9 (0.1)	−3.6	***
BSQ	121.3 (8.2)	56.3 (4)	−7.2	***

***p < 01, ***p < 001, n.s, not significant; n.a, not applicable.*

Procedure

Participants were required to abstain from caffeine, tobacco, and alcohol, for 2 h before the experimental session (Bal et al., 2010). After arrival at the laboratory, participants filled in the BDI (Ghisi et al., 2006) and the State-Trait STAI (Pedrabissi and Santinello, 1989).

Both groups of participants performed, in the following order: (1) the Physiological proxemics task; (2) the Heartbeat Perception Task; (3) the Behavioral proxemics task (Kennedy et al., 2009, see below and **Figure 1** for a description of the tasks). Participants' ECG was recorded for the entire duration of the Physiological proxemics task and the Heartbeat Perception Task. Furthermore, at the beginning and at the end of the experimental session, and after the Physiological proxemics task, a 2-min resting baseline ECG recording was done, during which participants were instructed to quietly stand up with their shoulders leaning against the wall, and to look at the blue circle in front of them.

Participants were fitted with 10 mm Ø Ag-AgCl pre-gelled disposable electrodes for ECG recording. ECG data were converted and amplified with an eight-channel amplifier (PowerLab8/30; ADInstruments UK) and displayed, stored, and reduced with LabChart 7.3.1 software package (ADInstruments Inc, 2011). All tasks were carried out in the same quiet and softly illuminated room and participants were instructed to relax and remain as still as possible during recording to minimize motion artifacts.

Physiological Proxemics Task

Participants stood up at an end of a 470 cm strip previously placed on the floor, in a comfortable and relaxed position, leaning against the wall.

The experiment consisted in two blocks in which a female experimenter slowly approached or distanced herself from the participant, along the strip, (from 470 to 30 cm, or vice versa, frontally). In the first block, the experimenter had an underweight BMI (Thin condition: 17.5 Kg/m2) and in the second block, the experimenter had an obese BMI (Fat condition: 34 Kg/m2). Both the experimenters were dressed in the same way, wearing a black tracksuit (**Figure 1**). The order of the two blocks was counterbalanced across participants.

Participants were instructed to pay attention and always follow with their gaze the experimenter and reassured that the experimenter would have never touched them.

Each experimental block consisted of 16 trials (4 for each condition presented in random order). Following audio cues, each experimenter could move along the strip:

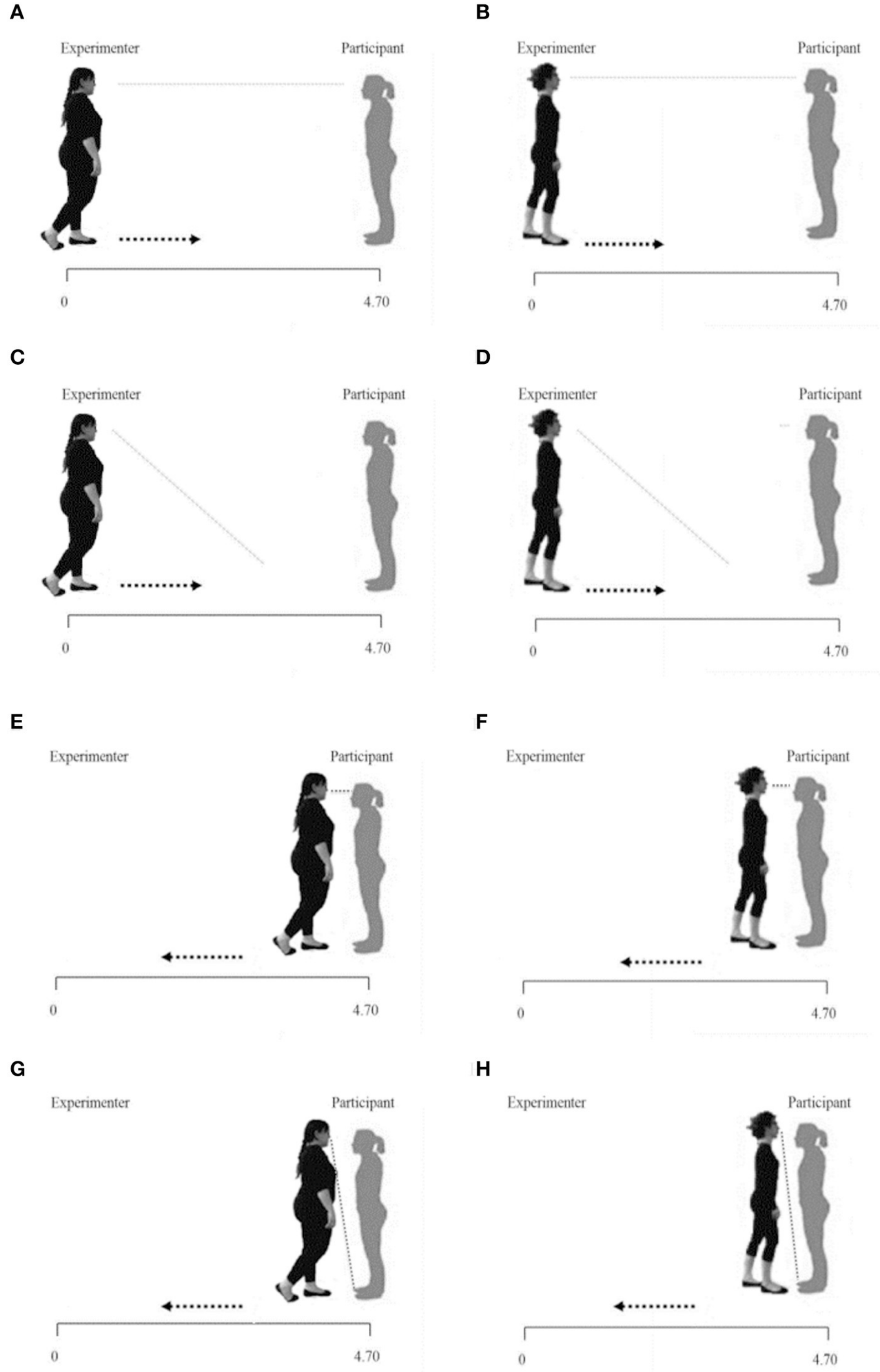

FIGURE 1 | Physiological and behavioral proxemics task representations. It show respectively the Fat/Thin Far-gaze conditions **(A,B)**; the Fat/Thin Far-No gaze conditions **(C,D)**; the Fat/Thin Near-gaze conditions **(E,F)**; the Fat/Thin Near-No gaze conditions **(G,H)**.

- starting from 470 to 30 cm from the participant while looking in the participant's eyes (Far-gaze condition);
- starting from 470 to 30 cm from the participant while glancing down (Far-No gaze condition);
- starting from 30 to 470 cm from the participant while looking in the participant's eyes (Near-gaze condition);
- starting from 30 to 470 cm from the participant while glancing down (Near-No gaze condition).

Each trial lasted 30 s with an inter-trial interval of 15 s.

Heartbeat Perception Task

Heartbeat perception was assessed using the Mental Tracking Method (Schandry, 1981), which is has been widely used in IA evaluation. It highly correlates with other heartbeat detection tasks (Knoll and Hodapp, 1992) and has good test–retest reliability (up to 0.81; Mussgay et al., 1999; Pollatos et al., 2007). Participants were required to start silently counting their own heartbeats, only the heartbeats about which they were sure, on an audio-visual start cue until they received an audio-visual stop cue. The experiment started after one brief familiarization period (15 s) and consisted of four different time intervals (25, 35, 45, and 100 s) presented in random order. Participants were asked to tell a third experimenter the number of heartbeats counted at the end of each interval. During the task, no feedback on the length of the counting phases or the quality of their performance was given and they were not permitted to take the pulse, and Heartbeat perception score, was calculated as the mean score of four separated heartbeat perception intervals according to the following transformation (Schandry, 1981; Pollatos et al., 2008):

$$\frac{1}{4}\sum \quad 1-\frac{\left(\left|\text{recorded beats} - \text{counted beats}\right|\right)}{\text{recorded beats}}\Bigg)$$

According to this transformation, heartbeat perception score vary between 0 and 1, with higher scores indicating small differences between recorded and counted heartbeats (i.e., higher interoceptive sensitivity).

Behavioral Proxemics Task

In this third phase, the Physiological proxemics task was repeated but in this case, participants stopped the experimenter at the distance at which they felt most comfortable. Shoulder-to-shoulder distance was recorded using a digital laser measurer. In this phase, the ECG was not recorded.

ECG Recording

Three Ag/AgCl pre-gelled electrodes (ADInstruments, UK) with a contact area of 10 mm diameter were placed on the wrists of the participants in an Einthoven's triangle configuration monitoring ECG (Powerlab and OctalBioAmp 8/30, ADInstruments, UK). The ECG was sampled at 1 KHz and filtered online by the mains filter, which have a negligible distorting effect on ECG waveforms. R-wave peak of the of the ECG was detected from each sequential heartbeat and the R-R interval was timed to the nearest ms. During the editing, a software artifacts detection (artifacts threshold 300 ms) was followed by a visual inspection of the recorded signal. Following standard practices (Berntson et al., 2007) artifacts were then edited by integer division or summation.

The amplitude of RSA was calculated with CMetX (available from http://apsychoserver.psych.arizona.edu). This is a time-domain method but allows derivation of components of heart rate variability within specified frequency bands (Berntson et al., 1997) as spectral techniques. RSA was evaluated as the natural log of variance of heart rate activity across the band of frequencies associated with spontaneous respiration.

RSA estimates were calculated as follows (Allen et al., 2007) (1) linear interpolation at 10 Hz sampling rate; (2) application of a 241-point FIR filter with a 0.12–0.40 Hz band pass; (3) extraction of the band passed variance; (4) transformation of the variance in its natural logarithm.

Coherently with guidelines (Berntson et al., 1997), these procedures were applied to epochs of 30 s, which was the duration of each experimental trial. Then, RSA-values corresponding to Far-gaze, Far- no gaze, Near- gaze, Near No-gaze conditions in each block (Thin or Fat) were separately computed as the average of four 30 s—epochs. Consistently, RSA-values corresponding to baseline and recovery were computed as the average of the four 30 s—epochs. RSA response to Far-gaze, Far- no gaze, Near-gaze, Near No-gaze condition were then separately obtained for the two Thin/Fat blocks as changes from the resting baseline RSA-values to the reactivity during each condition.

For assessing the heartbeat perception score, heart rate data were used.

RESULTS

Sample Description and Questionnaire Data

Group comparisons of socio-demographic features (age, BMI) and questionnaire data obtained for the two participant groups were performed with a series of independent samples two tailed *t*-tests, revealing a significantly lower weight and BMI for patients with anorexia nervosa than controls. No differences emerged with respect to height or age. Patients with anorexia nervosa also scored significantly higher in interoceptive awareness deficits (EDI3-ID), depression (BDI), state, and trait anxiety (STAI state and trait), dissociative experiences (DES), general psychopathology (SCL-90 total score), body image concerns (BSQ; BUT, BIC scale), and body image disturbances (BUT, GSI scale). Furthermore, ANg also obtained higher scores in problems with self-esteem (EDI3-LSE), interpersonal insecurity (EDI3-II), and emotive dysregulation (EDI3-ED; see **Table 1**).

Between-Groups Differences in Social Disposition at Rest, and Its Relations with Psychological Variables

To assess the presence of significant differences between ANg and HCg in social disposition at rest, we carried out a repeated measures ANCOVA with Group (ANg vs. HCg) as between factor and Condition (baseline vs. recovery) as within factor. In addition, since the previously found difference in terms of resting RSA between and within the two groups could be influenced by age, BMI, anxiety, and depression, age, BMI, scores obtained from STAI Trait, STAI State, and BDI questionnaires were added to the model as covariates. The factor Condition was introduced because it is well-known that in situations demanding sustained attention, or with challenging stimuli, RSA is suppressed (Porges, 1995). Therefore, we contrasted Baseline and Recovery in each Group to disentangle this possible confounding effect on our results. For this analysis, we excluded a participant in the control group because we did not entirely recorded RSA for technical problems.

The repeated measures ANCOVA only revealed the main effect of Group [$F_{(1, 40)} = 7.6$; $p > 0.01$, $\eta^2 = 0.16$; ANg: mean = 3.7 ln (ms)^2, SE = 0.32; HCg: 5.3 ln (ms)^2, SE = 0.33] even controlling for age, BMI, STAI-Trait, Stai-State, and BDI. Except age [$F_{(1, 40)} = 8.7$, $p < 0.01$, $\eta^2 = 0.18$], none of these covariates resulted significant [BMI: $F_{(1, 40)} = 0.29$, $p > 0.6$, $\eta^2 = 0.007$; STAI-Trait score: $F_{(1, 40)} = 2$, $p > 0.1$, $\eta^2 = 0.05$; STAI-State score: $F_{(1, 40)} < 0.001$, $p > 0.9$, $\eta^2 < 001$; BDI score: $F_{(1, 40)} = 1.15$, $p > 0.2$, $\eta^2 = 0.03$] (see **Figure 2**).

Additionally, neither the main effect of Condition [$F_{(1, 40)} = 3.8$ $p > 0.4$; $\eta^2 = 0.01$; ANg: marginal mean = 4.4 ln (ms)^2, SE = 0.17; HCg: marginal mean 4.7 ln (ms)^2, SE = 0.15] nor the interaction with Group were significant [$F_{(1, 40)} = 0.008$; $p > 9$; $\eta^2 < 0.001$], showing that after controlling for the inserted covariates, RSA responses in baseline (ANg: marginal mean = 3.8, SE = 0.32; HCg: marginal mean = 5.5, SE = 0.33) and recovery conditions (ANg: marginal mean = 3.6, SE = 0.36; HCg: marginal mean = 5.2, SE = 0.38) did not differ within each group.

To assess the possible influence of the different age of onset and duration of the illness for each AN patient (see **Table 2**) on her resting RSA we conducted two separate correlations. The first correlation was performed between Resting RSA and Age of Onset, the second between resting RSA and Duration of the Illness (in years). Since the variables "Duration of Illness" and "Age of Onset" were not distributed normally (Age of Onset: Shapiro-Wilk test $p < 0.05$, Duration of Illness: Shapiro-Wilk test, $p < 0.001$)] we chose non-parametric Spearman correlations.

Bonferroni-corrected ($p < 0.025$) correlation analysis excluded the significant relationship between resting RSA and Age of Onset ($r_s = -0.16$; $p = 0.23$). In addition, neither the relationship between resting RSA and duration of illness was significant ($r_s = 0.27$; $p = 0.103$).

Between-Groups Differences in IA, and Its Relations with Psychological Variables

Since previous data indicated that IA could be influenced by age, BMI, anxiety and depression (see Introduction), between-groups difference in IA were assesses by and ANCOVA, controlling for age, BMI, and the scores obtained from STAI-Trait and STAI -State and BDI that entered as covariates. The factor Group (ANg vs. HCg) was included as between-factor. Results did not show any significant difference in IA between the two groups [$F_{(1, 42)} = 0.82$; $p > 0.3$, $\eta^2 = 0.02$] since ANg did not show a lower heartbeat perception score compared to HCg (ANg: mean = 0.53 SE = 0.07, HCg: mean = 0.41 SE = 0.07). None of the covariates included in the model resulted significant [age: $F_{(1, 42)} = 0.36$, $p > 0.5$, $\eta^2 = 0.001$; BMI: $F_{(1, 42)} = 0.9$, $p > 0.3$, $\eta^2 = 0.02$; STAI-Trait score: $F_{(1, 42)} = 0.76$, $p > 0.3$, $\eta^2 = 0.02$; STAI-State score: $F_{(1, 42)} = 0.68$, $p > 0.4$, $\eta^2 = 0.02$; BDI score: $F_{(1, 42)} = 3.27$, $p > 0.05$, $\eta^2 = 0.07$].

To evaluate the possible influence of the different age of onset and duration of the illness (see **Table 2**) on patients' IA, we conducted two separate non-parametric Spearman correlations.

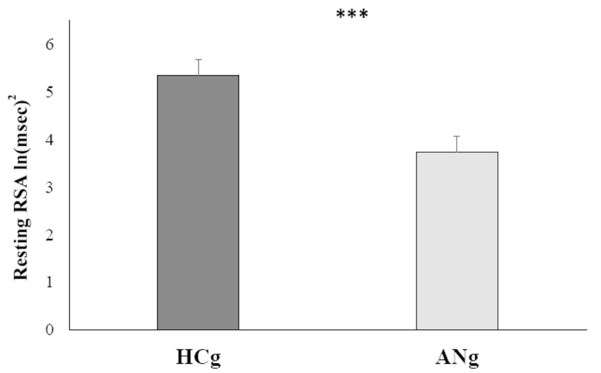

FIGURE 2 | Marginal means of resting RSA levels for both HCg and ANg. Covariates included in the model were estimated to the following values: age = 22.8, BMI = 18.46, STAI-Trait = 51.63, STAI-State = 42.98, BDI = 17.31. Error bars depict the standard error of the mean; ***$p < 0.001$.

TABLE 2 | Information relative to age, age of onset, and duration of the illness, IA, and resting RSA of ANg.

ID	Age	Age of the onset	Duration of the illness (year)	IA	Resting RSA ln (ms)^2
1	22	19	3	0.36	5.08
2	13	12	1	0.30	3.86
3	19	17	2	0.51	2.80
4	39	18	21	0.71	3.23
5	44	17	27	0.41	2.15
6	31	15	16	0.25	2.39
7	15	15	0	0.53	1.79
8	17	16	1	0.35	4.03
9	32	17	15	0.30	3.67
10	16	15	1	0.33	5.93
12	23	15	8	0.36	6.14
13	22	14	8	0.66	2.65
14	23	16	7	0.69	5.10
15	17	14	3	0.37	3.48
16	21	20	1	0.67	3.61
17	21	21	0	0.36	3.82
18	27	24	3	0.55	2.03
19	48	24	24	0.73	1.55
20	24	19	5	0.34	5.06
21	15	14	1	0.59	2.76
22	16	14	2	0.84	3.07
23	17	16	1	0.37	4.19
24	16	15	1	0.57	4.90
25	15	14	1	0.35	6.25

The first correlation was performed between IA and Age of Onset, the second, between IA and Duration of the Illness (in years).

Bonferroni-corrected ($p < 0.025$) correlation analysis showed that the variables IA and Age of Onset were not significantly correlated ($r_s = 0.14$; $p = 0.25$) as well as the variables IA and Duration of Illness ($r_s = 0.115$; $p = 0.3$).

Relationship between IA and Social Disposition

To better understand the relationship between IA and social disposition in AN, we carried out a Pearson correlation between IA and resting RSA (mean score between baseline and recovery). To compare the correlation coefficients of the different groups, we used the Fisher r to z transformation (Lowry, 2004; Cohen et al., 2013; Eid and Lischetzke, 2013). For this analysis, we excluded a participant in the HCg because she resulted as a multivariate outlier, with unusual combination of scores on the considered variables.

The analysis showed a significant relationship between IA and RSA at rest in the two groups, but positive in HCg ($r_{21} = 0.40$; $p = 0.03$) and negative in AN ($r_{22} = -0.39$; $p = 0.03$; $z = 2.67$, $p = 0.008$). This result suggests that, even if we did not find significant differences in IA between HCg and ANg, there is a different association between the two variables in the individuals affected by AN (see **Figure 3**).

Physiological Proxemics Task

To assess changes in autonomic reactivity both in ANg and HCg during social interactions, participants' RSA responses entered in a repeated measures ANOVA with experimenter's BMI (Fat vs. Thin), Distance (far vs. near) and Gaze (gaze vs. no gaze) as within factors and Group (ANg vs. HCg) as between factor. The Tukey test was used for all *post-hoc* comparisons.

The most relevant significant result (overall results of the ANOVA are reported in **Table 3**) was the interaction among BMI, Distance, Gaze and Group [$F_{(1, 46)} = 5.11$; $p < 0.05$, $\eta^2 = 0.10$], because of the greater RSA responses for the Thin-Far-Gaze condition than all other conditions [mean = -0.11 ln $(ms)^2$; SE = 0.14; all $ps < 0.05$]. This modulation across the experimental conditions was present only for HCg (see **Figure 4**).

Behavioral Proxemics Task

To assess changes in behavioral responses both in ANg and HCg during social interactions and to explore possible differences in autonomic reactivity between the two groups, participants' rating of comfort (reciprocal normalized data; Barbaranelli and D'Olimpio, 2006) entered in a repeated measures ANOVA. Experimenter's BMI (Fat vs. Thin), Distance (far vs. near) and Gaze (gaze vs. no gaze) were inserted as within factors, and Group (ANg vs. HCg) as between factor. We used the Tukey test for all *post-hoc* comparisons.

The ANOVA showed that (overall results of the ANOVA are reported in **Table 4**) the main factors BMI [$F_{(1, 46)} = 40.2$; $p < 0.001$; $\eta^2 = 0.47$] was significant: both groups, indeed, felt comfortable with the thin experimenter, stopping her 13 cm closer than the fat one (Fat: mean = 132 cm SE = 0.06 vs. Thin: mean = 119 cm, SE = 0.06; see **Figure 5A**).

The interaction between BMI and Distance was significant [$F_{(1, 46)} = 15.6$; $p < 0.001$; $\eta^2 = 0.25$), since participants felt more comfortable with both the thin and fat experimenter in the Far condition than in the Near condition [(Fat-Far: mean = 119 cm, SE = 0.06; Fat-Near: mean = 145 cm SE = 0.07; $p < 0.01$); (Thin-Far: mean = 116 cm, SE = 0.07; Thin-Near: mean = 122 cm SE = 0.06; $p < 0.001$)].

Also the factor Gaze resulted significant [$F_{(1, 46)} = 7$; $p < 0.05$; $\eta^2 = 0.13$], showing that both groups stopped the experimenter 7 cm closer when she was glancing down than when the experimenter maintained the eye contact with participants (Gaze: mean = 129 SE = 0.07 vs. No Gaze: mean = 123 SE = 0.06; see **Figure 5B**).

Relations between Social Disposition at Rest and Tolerance of Social Distances

In order to investigate the role of autonomic arousal in guiding behavioral responses in social distances, two linear regression analyses, having Distance as criterion (calculated as the overall mean among participants' rating of comfort) and RSA at rest as predictor were independently performed for the two groups. Results revealed a significance relationship in HCg ($t = -2.5$, $b = -0.47$, $p < 0.05$) explaining the 22% of the variance [$F_{(1, 22)} = 6.3$, $p < 0.05$, $R^2 = 0.22$, R^2 adjusted = 0.19, see **Figure 6A**). When the same regression was conducted on ANg, the regression model was not significant ($t = 0.45$, $b = -0.1$, $p > 0.6$), explaining only the 0.2%) of the variance [$F_{(1, 21)} = 0.20$, $p > 0.6$, $R^2 = 0.002$; R^2 adjusted = -0.04, see **Figure 6B**).

DISCUSSION

Basing on the idea that the ability to adapt oneself to the social settings does not depend only from high sensitivity in

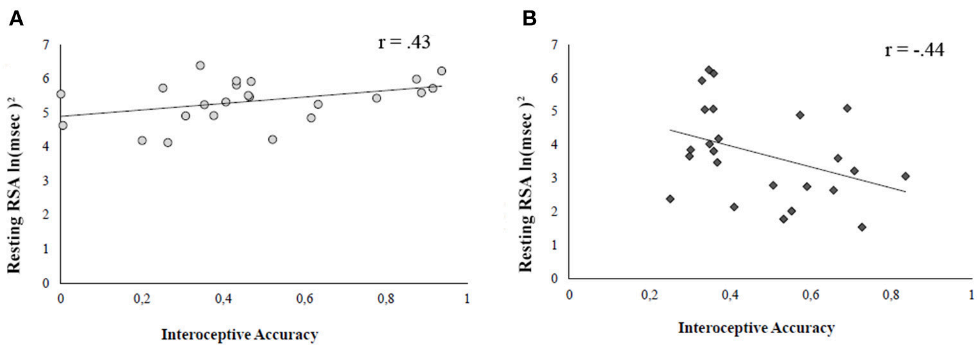

FIGURE 3 | Pearson correlations between IA and resting RSA for both HCg (A) and ANg **(B)**.

TABLE 3 | ANOVA significant effects of the Physiological proxemics task on RSA responses of ANg and HCg.

Effect	*F*(*df* = 1,46)	*p*	η^2	Mean [ln(ms)2](*SE*)
Distance	6.38	<0.05	0.12	Far = −0.35 (0.10) vs. near = −43 (0.11)
Distance*Gaze	8.59	<0.01	0.16	Far eye = −0.27 (0.10) vs. far no eye = −0.43 (0.11), near eye = −0.44 (0.10), near no eye = −0.41 (0.11); all *ps* < 0.01
Distance*Gaze*Group	4.6	<0.05	0.09	**HCg.** Higher RSA responses in far eye = −22 (0.13); vs. far no eye = −50 (0.16), near eye = −0.48 (0.15), near no eye = −0.45 (0.16); all *ps* < 0.01. ANg. No differences among conditions: far eye = −0.32 (0.13), far no eye = −0.36 (0.16), near eye = −0.39 (0.15), near no eye = −0.38 (0.16); all *ps* = n.s.
BMI*Gaze*Group	6.57	<0.05	0.12	**HCg.** Higher RSA responses in thin eye = −0.25 (0.16) vs. thin no eye = −0.49 (0.17), fat eye = −0.44 (0.15), fat no eye = −0.46 (0.17); all p_S < 0.05. ANg. No differences among conditions: thin Eye = −0.36 (0.15) vs. thin no eye = −0.33 (0.16), fat eye = −36 (0.15), fat no eye = −0.41(0.15); all p_S n.s.
BMI*Distance*Gaze*Group	5.11	<0.05	0.10	**HCg.** Greater RSA responses in the thin far−eye condition = −0.1 (0.14) than all other conditions: thin far−no eye = −0.55 (16), thin near eye = −0.41 (16), thin near−no gaze = −0.44 (0.17), fat far eye = −0.34 (0.15), fat far− no-eye = −0.45 (0.17), fat near eye = −54 (0.15), fat near-no eye = −0.46 (0.17); all *ps* < 0.05. ANg. No differences among conditions: fat far eye = −0.30 (0.15), fat far −no eye = −0.41 (0.17), fat near eye = −0.42 (0.15), fat near-no eye = −0.40 (0.17), thin far eye = −0.35 (0.14), thin far-no eye = −0.30 (0.16), thin near eye = −0.37 (0.16), thin near-no eye = −0.35 (0.17); all *ps* n.s.

*n.s, not significant; * = interacting.*

assessing information from the outer environment, but also from the inner body (Paladino et al., 2010; Tsakiris et al., 2011; Tajadura-Jiménez et al., 2012; Gaudio et al., 2014), the present study aimed to explore both the relationship between autonomic functioning and IA, in a population of restrictive anorexic patients whose interoception is impaired (Fassino et al., 2004; Friederich et al., 2006; Nunn et al., 2008; Pollatos et al., 2008; Paladino et al., 2010; Strigo et al., 2013; Gaudio et al., 2014). Furthermore, the autonomic reactivity of ANg during social interactions and their behavioral judgment of social distances was explored, manipulating social cues and social desirability traits of experimenters (BMI) interacting with participants.

To these purposes, we recorded RSA responses of both HCg and ANg during both a resting condition and social interaction (Physiological proxemics task). Then we submitted both groups to a well-assessed heartbeat perception task (Schandry, 1981). Finally, to better interpret our results, we submitted participants to an "overt" behavioral version of the Physiological proxemics task.

In line with our hypothesis, we found that ANg showed lower RSA at rest than HCg. Since higher resting RSA is an index of self-regulation, social disposition, and it is considered a marker of positive social functioning in autism (Bal et al., 2010; Patriquin et al., 2013), our results revealed a lower social disposition in ANg.

Concerning IA, contrary to Pollatos et al. (2008), in the heartbeat detection task ANg did not perform differently from HCg. It should be emphasized that even our HCg showed lower IA compared to the literature (Pollatos et al., 2008; Ainley et al., 2012; Herbert et al., 2012; Klabunde et al., 2013; Krautwurst et al., 2014). An explanation of this result may be that the difficulty of this task lead to higher level of stress and arousal in our sample.

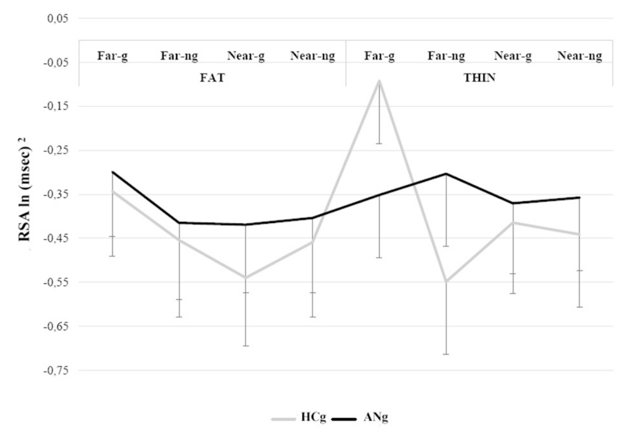

FIGURE 4 | RSA responses during the Physiological proxemics task of HCg and ANg. Error bars depict the standard error of the mean; g, gaze; ng, no gaze.

As recently showed by Khalsa et al. (2015), AN and HC did not differ in the detection of interoceptive changes occurring during isoprotenol infusion in situations of high arousal (see Khalsa et al., 2015 for full details). Our results do not necessarily entail that IA is not compromised in anorexic patients, or that IA might not have a role in AN disturbances (e.g., Herbert and Pollatos, 2012; Eshkevari et al., 2014). The most interesting and novel result of our study is the different association between IA and RSA between ANg and HCg. In fact, even if we did not found a reduced IA in ANg, as espected we found that higher IA is related to higher social disposition (higher RSA at rest) in HCg, but not in ANg, in which these two variables are disfunctionally associated.

TABLE 4 | ANOVA significant effects of the Behavioral proxemics task on RSA responses of ANg and HCg.

Effect	F(*df* = 1,46)	*p*	η^2	Mean (cm) (SE)
BMI	40.2	<0.001	0.47	Fat = 132 (0.06) vs. thin = 119 (0.11)
Distance	24.2	<0.001	0.34	Far = 118 (0.06) vs. near = 133 (0.07)
Gaze	7	<0.05	0.13	Gaze = 129 (0.07), no gaze = 123 (0.06)
BMI*Distance	15.6	<0.001	0.25	Fat far = 119 (0.13) vs. fat near = 145 (0.07); $p < 0.01$; thin far = 116 (0.07), thin near = 122 (0.06); $p > 0.05$
Distance*Gaze	8.4	<0.01	0.15	Participants stopped closer the experimenter in the far condition, approaching them and glancing down than all other condition (all ps < 0.001): far-gaze = 122 (0.07); far-no gaze = mean = 113 (0.06), near gaze: = 135 (0.07); near-no gaze = 133 (0.06).
Distance*Group	4.1	<0.05	0.08	**HCg**. Differentiate between the starting distance of the experimenter; far = 103 (0.08) vs. near = 127 (0.09); $p = < 0.001$. **ANg**. On the contrary, did not differentiate between far = 131 (0.08) and near = 141 (0.1) p = n.s.

Interacting; n.s, not significant.

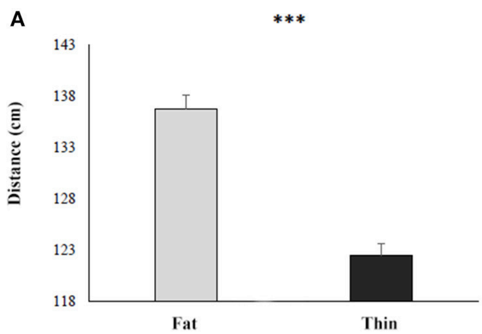

FIGURE 5 | Responses during the Behavioral proxemics task of both HCg and ANg in function of the BMI (A) and the Gaze **(B)**. Error bars depict the standard error of the mean. ***$p > 0.001$.

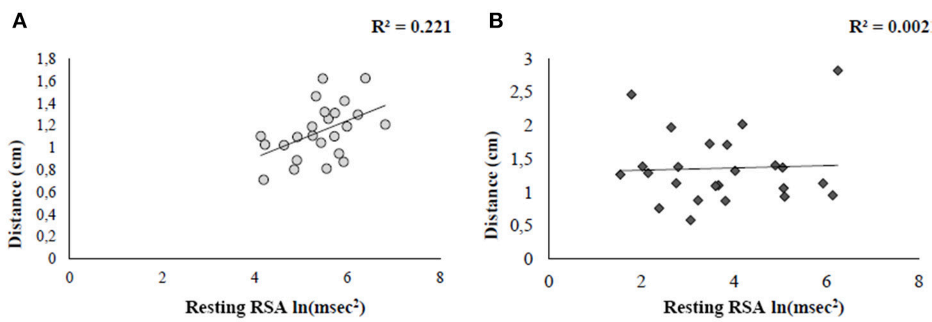

FIGURE 6 | Linear regression plots showing the relation between comfort ratings and social disposition (resting RSA) for both HCg (A) and ANg **(B).**

In the Physiological proxemics task, ANg showed flattened autonomic reactivity across all experimental conditions. Anorexic patients seemed not to be engaged in social interactions; they did not respond differently to the presence of two different experimenters, and to the manipulation of significant social cues, such as the eye contact (Argyle and Dean, 1965; for a review see Kleinke, 1986) and the body size of the experimenter. On the contrary, HCg showed better autonomic reactivity to social stimuli, showing higher RSA responses when the underweight experimenter approached them keeping the eye contact, which has a crucial role for the relevance and intention of social stimuli (Carlston, 2013).

It is possible, however, that the higher RSA in the social task could also reflect effortful emotion regulation in presence of a moderately stressful stimulus (Porges, 2007) caused by social anxiety or by unpleasantness. We can exclude this interpretation of our results for the following reasons: first, regression analysis revealed that participants' anxiety did not significantly contribute to the association between IA and RSA responses; second, the Behavioral proxemics task showed that both ANg and HCg felt more comfortable when interacting with the thin experimenter than with the fat one.

In the overt judgment of comfort in defining social distances, both ANg and HCg felt more comfortable (i.e., stopped the experimenters at closer distance) when the experimenters were glancing down. This results is coherent with several studies suggesting that while direct glance is affiliative, without eye contact we do not feel that we are fully in communication with others (e.g., Argyle and Dean, 1965; Wieser et al., 2009). However, during social interactions, people look at each other frequently, most when they are listening to each other, but for short periods of time (about -10 s). When glances are longer than this, anxiety is aroused (Argyle and Dean, 1965).

A further result of this task concerns the fact that both ANg and HCg (only the latter also showed coherent autonomic responses), felt less comfortable with the obese experimenter, stopping her at longer distances than the thin experimenter. We speculate that these results could reflect the internalization of cultural beliefs related to obese individuals, who are perceived to be less attractive than their thinner counterparts (Harris, 1990; Sobal et al., 2006; Puhl and Heuer, 2009). A recent study indeed showed that medical students' level of visual contact with their patient differed depending on the patient's weight (Persky and Eccleston, 2011). This result is in line with the "objectification theory" suggested by Fredrickson and Roberts (1997) stating that every culture has a shared concept of ideal beauty that is internalized by individuals (especially by women) whose satisfaction or dissatisfaction depends on to what extent they meet such a standard. Self-objectification is more pervasive in eating disorders (e.g., Calogero et al., 2005) and is also inversely related to interoception (Myers and Crowther, 2008).

The last point to be addressed is the relationship between resting RSA and the comfort rating of social distances. While we found a clear positive association between these two variables in HCg, this relation was lacking in ANg. In other words, the higher is the autonomic social disposition in HCg, the wider is their tolerated proxemics distance, suggesting that the higher is the social disposition, the wider is the distance at which they are socially engaged/efficient. The lack of this relation in ANg finds support in studies showing lack of emotional clarity in ANg (Damasio, 2004; Merwin et al., 2010). Emotional clarity is conceptualized as the clarity regarding one's internal experiences/arousal (Merwin et al., 2010), which is nothing but another way to define interoception.

Taken together, our results suggests that ANg, contrarily to HCg, are affected both by lower social disposition and more flattened autonomic reactivity in social context, irrespective of social cues and body size of the interacting experimenters. Moreover, while in HCg the autonomic functioning supports the behavioral regulation of social distances, this is not true for ANg whose altered autonomic functioning is not only abnormally related to interoceptive accuracy, but also coherently correlates with lack of emotional clarity and abnormal conditioned responses such as binging, purging, fasting, and other compensatory behaviors (Brogan et al., 2010). These findings support an embodied view of this illness, emphasizing that AN might be a more pervasive disorder involving, beyond mere cognitive factors, a sort of "flattened sense of the physical body," which may contribute to reinforcing AN symptoms and generate altered meanings, emotions and social behaviors. These results can be also predicted by the etiological model of Riva (2014; see Introduction), which suggests that eating disorders, in the course of the evolution of their bodily experience integrating the manifold levels of bodily representation over time, may be locked in the "objectified body" (Riva, 2014), that is, in an allocentric perspective in which the body is experienced as an object, disconnected and not updated by multisensory perception, which normally contribute to the egocentric view of the body (Riva and Gaudio, 2012).

Possible limitations of this study are the small sample of participants and the fact that the HCg a was restricted to students. We also did not introduce measures for alexithymia, disgust propensity and sensitivity, which seem to be related to interoception and have some implications for social cognition. However, to the best of our knowledge, this is the first study exploring the autonomic correlates of social contexts in eating disorder and its link with the ability to perceive the inside of the body. Even if further studies are necessary to formulate a complete etiologic model of this illness, we suggest that future treatments should take into account the altered bodily correlates of self-experience and their neurobiological dysfunctions. That would allow the development of more effective strategies able to reduce treatment resistance, a frequent issue in eating disorders (Kaye et al., 2009; Treasure and Schmidt, 2013).

AUTHOR CONTRIBUTIONS

MAm designed the study, collected, analyzed, and interpreted the data, she wrote the manuscript. MAr was involved in study design, collection of data and analyses. She also contributed to the drafting of the manuscript. ER and Fd were principally engaged in the recruitment of participants and data collection, furthermore they contributed to results interpretation. MS, PV, PT, and SM were involved in the recruitment of participants and data collection and took part to the results interpretation. VG designed the study, interpreted the data and drafted the manuscript. All the authors approved the final version of the manuscript.

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REFERENCES

ADInstruments Inc. (2011). *Labchart Information [online]*. Available online at: http://www.adinstruments.com/products/https://www.adinstruments.com/products/labchart

Ainley, V., Tajadura-Jiménez, A., Fotopoulou, A., and Tsakiris, M. (2012). Looking into myself: the effect of self-focused attention on interoceptive sensitivity. *Psychophysiology* 49:1504. doi: 10.1111/j.1469-8986.2012.01468.x

Allen, J. J. B., Chambers, A. S., and Towers, D. N. (2007). The many metrics of cardiac chronotropy: a pragmatic primer and a brief comparison of metrics. *Biol. Psychol*. 74, 243–262. doi: 10.1016/j.biopsycho.2006.08.005

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub.

Anderluh, M. B., Tchanturia, K., Rabe-Hesketh, S., and Treasure, J. (2003). Childhood obsessive-compulsive personality traits in adult women with eating disorders: defining a broader eating disorder phenotype. *Am. J. Psychiatry* 160, 242–247. doi: 10.1176/appi.ajp.160.2.242

Argyle, M., and Dean, J. (1965). Eye-contact, distance and affiliation. *Sociometry* 28, 289–304. doi: 10.2307/2786027

Bal, E., Harden, E., Lamb, D., Van Hecke, A. V., Denver, J. W., and Porges, S. W. (2010). Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. *J. Autism Dev. Disord*. 40, 358–370. doi: 10.1007/s10803-009-0884-3

Barbaranelli, C., and D'Olimpio, F. (2006). *Analisi Dei Dati Con SPSS*. Milano: Led.

Beauregard, M., Levesque, J., and Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *J. Neurosci.* 21, RC165.

Berntson, G. G., Bigger, J. T., Eckberg, D. L., Grossman, P., Kaufmann, P. G., Malik, M., et al. (1997). Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 34, 623–648. doi: 10.1111/j.1469-8986.1997.tb02140.x

Berntson, G. G., Cacioppo, J. T., and Grossman, P. (2007). Whither vagal tone. *Biol. Psychol*. 74, 295–300. doi: 10.1016/j.biopsycho.2006.08.006

Bestler, M., Schandry, R., Weitkunat, R., and Alt, E. (1990). Kardiodynamische determinanten der herzwahrnehmung. *Z. Für Exp. Angew. Psychol.* 37, 361–377. doi: 10.1371/journal.pone.0036646

Brogan, A., Hevey, D., and Pignatti, R. (2010). Anorexia, bulimia, and obesity: shared decision making deficits on the Iowa Gambling Task (IGT). *J. Int. Neuropsychol. Soc*. 16, 711–715. doi: 10.1017/S1355617710000354

Bruch, H. (1973). *Eating Disorders: Obesity, Anorexia Nervosa, and the Person Within.* Chicago, IL: Basic Books.

Calogero, R. M., Davis, W. N., and Thompson, J. K. (2005). The role of self-objectification in the experience of women with eating disorders. *Sex Roles* 52, 43–50. doi: 10.1007/s11199-005-1192-9

Carlston, D. E. (2013). *The Oxford Handbook of Social Cognition.* Oxford: Oxford University Press.

Carlson, E. B., and Putnam, F. W. (1993). An update on the dissociative experiences scale. *Dissociation Prog. Dissoc. Disord*. 6, 16–27.

Cash, T. F., and Deagle, E. A. (1997). The nature and extent of body−image disturbances in anorexia nervosa and bulimia nervosa: a meta−analysis. *Int. J. Eat. Disord*. 22, 107–126.

Casiero, D., and Frishman, W. H. (2006). Cardiovascular complications of eating disorders. *Cardiol. Rev*. 14, 227–231. doi: 10.1097/01.crd.0000216745.96062.7c

Cassin, S. E., and von Ranson, K. M. (2005). Personality and eating disorders: a decade in review. *Clin. Psychol. Rev*. 25, 895–916. doi: 10.1016/j.cpr.2005.04.012

Chui, H. T., Christensen, B. K., Zipursky, R. B., Richards, B. A., Hanratty, M. K., Kabani, N. J., et al. (2008). Cognitive function and brain structure in females with a history of adolescent-onset anorexia nervosa. *Pediatrics* 122, e426–e437. doi: 10.1542/peds.2008-0170

Claes, L., Jiménez−Murcia, S., Santamaría, J. J., Moussa, M. B., Sánchez, I., Forcano, L., et al. (2012). The facial and subjective emotional reaction in response to a video game designed to train emotional regulation (Playmancer). *Eur. Eat. Disord. Rev*. 20, 484–489. doi: 10.1002/erv.2212

Cohen, J., Cohen, P., West, S. G., and Aiken, L. S. (2013). *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. Oxford: Routledge.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci*. 3, 655–666. doi: 10.1038/nrn894

Craig, A. D. (2009). How do you feel—now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. doi: 10.1038/nrn2555

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., and Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nat. Neurosci*. 7, 189–195. doi: 10.1038/nn1176

Cuzzolaro, M., Vetrone, G., Marano, G., and Garfinkel, P. E. (2006). The Body Uneasiness Test (BUT): development and validation of a new body image assessment scale. *Eat. Weight Disord.* 11, 1–13. doi: 10.1007/BF03327738

Damasio, A. R. (2004). "Emotions and feelings," in *Feelings and Emotions: The Amsterdam Symposium*, eds A. S. R. Manstead, N. Frijda, and A. Fischer (Cambridge: Cambridge University Press), 49–57.

Daubenmier, J. J. (2005). The relationship of yoga, body awareness, and body responsiveness to self-objectification and disordered eating. *Psychol. Women Q*. 29, 207–219. doi: 10.1111/j.1471-6402.2005.00183.x

de Geus, E. J., Willemsen, G. H., Klaver, C. H., and van Doornen, L. J. (1995). Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. *Biol. Psychol.* 41, 205–227. doi: 10.1016/0301-0511(95)05137-6

Derogatis, L. R., Lipman, R. S., and Covi, L. (1973). SCL-90. *Psychopharmacol. Bull.* 9, 13–28.

Eid, M., and Lischetzke, T. (2013). "Statistische Methoden der Auswertung kulturvergleichender Studien," in *Handbuch Stress und Kultur. Interkulturelle und kulturvergleichende Perspektiven,* eds P. Genkova, T. Ringeisen, and F. T. L. Leong (Wiesbaden: Springer), 189–206.

Epstein, J., Wiseman, C. V., Sunday, S. R., Klapper, F., Alkalay, L., and Halmi, K. A. (2001). Neurocognitive evidence favors "top down" over "bottom up" mechanisms in the pathogenesis of body size distortions in anorexia nervosa. *Eat. Weight Disord.* 6, 140–147. doi: 10.1007/BF03339763

Eshkevari, E., Rieger, E., Longo, M. R., Haggard, P., and Treasure, J. (2012). Increased plasticity of the bodily self in eating disorders. *Psychol. Med*. 42, 819–828. doi: 10.1017/S0033291711002091

Eshkevari, E., Rieger, E., Musiat, P., and Treasure, J. (2014). An investigation of interoceptive sensitivity in eating disorders using a heartbeat detection task and a self−report measure. *Eur. Eat. Disord. Rev*. 22, 383–388. doi: 10.1002/erv.2305

Fairburn, C. G. (2008). *Cognitive Behavior Therapy and Eating Disorders*. New York, NY: Guilford Press.

Fairburn, C. G., and Bohn, K. (2005). Eating disorder NOS (EDNOS): an example of the troublesome "not otherwise specified" (NOS) category in DSM-IV. *Behav. Res. Ther*. 43, 691–701. doi: 10.1016/j.brat.2004.06.011

Fairburn, C. G., Cooper, Z., and Shafran, R. (2003). Cognitive behaviour therapy for eating disorders: a "transdiagnostic" theory and treatment. *Behav. Res. Ther*. 41, 509–528. doi: 10.1016/S0005-7967(02)00088-8

Fassino, S., Pierò, A., Gramaglia, C., and Abbate-Daga, G. (2004). Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity. *Psychopathology* 37, 168–174. doi: 10.1159/000079420

Ferri, F., Ardizzi, M., Ambrosecchia, M., and Gallese, V. (2013). Closing the gap between the inside and the outside: interoceptive sensitivity and social distances. *PLoS ONE* 8:e75758. doi: 10.1371/journal.pone.0075758

Friederich, H.-C., Kumari, V., Uher, R., Riga, M., Schmidt, U., Campbell, I. C., et al. (2006). Differential motivational responses to food and pleasurable cues in anorexia and bulimia nervosa: a startle reflex paradigm. *Psychol. Med*. 36, 1327–1335. doi: 10.1017/S0033291706008129

Fredrickson, B. L., and Roberts, T.-A. (1997). Objectification theory: toward understanding women's lived experiences and mental health risks. *Psychol. Women Q*. 21, 173–206. doi: 10.1111/j.1471-6402.1997.tb00108.x

Fuchs, T., and Schlimme, J. E. (2009). Embodiment and psychopathology: a phenomenological perspective. *Curr. Opin. Psychiatry* 22, 570–575. doi: 10.1097/YCO.0b013e3283318e5c

Gallese, V. (2014). Bodily selves in relation: embodied simulation as second-person perspective on intersubjectivity. *Phil. Trans. R. Soc. B* 369:20130177. doi: 10.1098/rstb.2013.0177

Gallese, V., and Ferri, F. (2013). Jaspers, the body, and schizophrenia: the bodily self. *Psychopathology* 46, 330–336. doi: 10.1159/000353258

Garner, D. M., Olmstead, M. P., and Polivy, J. (1983). Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. *Int. J. Eat. Disord*. 2, 15–34. doi: 10.1002/1098-108X(198321)2:2<15::AID-EAT2260020203>3.0.CO;2-6

Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., and Critchley, H. D. (2015). Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol. Psychol*. 104, 65–74. doi: 10.1016/j.biopsycho.2014.11.004

Gaudio, S., Brooks, S. J., and Riva, G. (2014). Nonvisual multisensory impairment of body perception in anorexia nervosa: a systematic review of neuropsychological studies. *PLoS ONE* 9:e110087. doi: 10.1371/journal.pone.0110087

Ghisi, M., Flebus, G. B., Montano, A., Sanavio, E., and Sica, C. (2006). *Beck Depression Inventory*. Manuale. Firenze: Organizzazioni Speciali, Adattamento italiano.

Giannini, M., Pannocchia, P., Dalle Grave, R., Muratori, F., and Viglione, V. (2008). *Eating Disorder Inventory-3*. Firenze: Giunti OS.

Glannon, W. (2009). Our brains are not us. *Bioethics* 23, 321–329. doi: 10.1111/j.1467-8519.2009.01727.x

Gorka, S. M., Nelson, B. D., Sarapas, C., Campbell, M., Lewis, G. F., Bishop, J. R., et al. (2013). Relation between respiratory sinus arrythymia and startle response during predictable and unpredictable threat. *J. Psychophysiol*. 7, 95–104. doi: 10.1027/0269-8803/a000091

Graziano, P. A., Reavis, R. D., Keane, S. P., and Calkins, S. D. (2007). The role of emotion regulation in children's early academic success. *J. Sch. Psychol*. 45, 3–19. doi: 10.1016/j.jsp.2006.09.002

Grossman, P., and Taylor, E. W. (2007). Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. *Biol. Psychol*. 74, 263–285. doi: 10.1016/j.biopsycho.2005.11.014

Guardia, D., Conversy, L., Jardri, R., Lafargue, G., Thomas, P., Dodin, V., et al. (2012). Imagining one's own and someone else's body actions: dissociation in anorexia nervosa. *PLoS ONE* 7:e43241. doi: 10.1371/journal.pone.0043241

Guardia, D., Lafargue, G., Thomas, P., Dodin, V., Cottencin, O., and Luyat, M. (2010). Anticipation of body-scaled action is modified in anorexia nervosa. *Neuropsychologia* 48, 3961–3966. doi: 10.1016/j.neuropsychologia.2010.09.004

Harris, A. P. (1990). Race and essentialism in feminist legal theory. *Stanford Law Rev*. 42, 581–616. doi: 10.2307/1228886

Harrison, A., O'Brien, N., Lopez, C., and Treasure, J. (2010). Sensitivity to reward and punishment in eating disorders. *Psychiatry Res*. 177, 1–11. doi: 10.1016/j.psychres.2009.06.010

Harrison, A., Sullivan, S., Tchanturia, K., and Treasure, J. (2009). Emotion recognition and regulation in anorexia nervosa. *Clin. Psychol. Psychother*. 16, 348–356. doi: 10.1002/cpp.628

Herbert, B. M., Muth, E. R., Pollatos, O., and Herbert, C. (2012). Interoception across modalities: on the relationship between cardiac awareness and the sensitivity for gastric functions. *PLoS ONE* 7:e36646. doi: 10.1371/journal.pone.0036646

Herbert, B. M., and Pollatos, O. (2012). The body in the mind: on the relationship between interoception and embodiment. *Top. Cogn. Sci*. 4, 692–704. doi: 10.1111/j.1756-8765.2012.01189.x

Herbert, B. M., Pollatos, O., Flor, H., Enck, P., and Schandry, R. (2010). Cardiac awareness and autonomic cardiac reactivity during emotional picture viewing and mental stress. *Psychophysiology* 47, 342–354. doi: 10.1111/j.1469-8986.2009.00931.x

Herzog, D. B., Keller, M. B., Sacks, N. R., Yeh, C. J., and Lavori, P. W. (1992). Psychiatric comorbidity in treatment-seeking anorexics and bulimics. *J. Am. Acad. Child Adolesc. Psychiatry* 31, 810–818. doi: 10.1097/00004583-199209000-00006

Hildebrandt, T., Grotzinger, A., Reddan, M., Greif, R., Levy, I., Goodman, W., et al. (2015). Testing the disgust conditioning theory of food-avoidance in adolescents with recent onset anorexia nervosa. *Behav. Res. Ther*. 71, 131–138. doi: 10.1016/j.brat.2015.06.008

Jacobi, C., Hayward, C., de Zwaan, M., Kraemer, H. C., and Agras, W. S. (2004). Coming to terms with risk factors for eating disorders: application of risk terminology and suggestions for a general taxonomy. *Psychol. Bull*. 130:19. doi: 10.1037/0033-2909.130.1.19

Jurca, R., Church, T. S., Morss, G. M., Jordan, A. N., and Earnest, C. P. (2004). Eight weeks of moderate-intensity exercise training increases heart rate variability in sedentary postmenopausal women. *Am. Heart J*. 147, e8–e15. doi: 10.1016/j.ahj.2003.10.024

Katzman, D. K., Christensen, B., Young, A. R., and Zipursky, R. B. (2001). Starving the brain: structural abnormalities and cognitive impairment in adolescents with anorexia nervosa. *Semin. Clin. Neuropsychiatry* 6, 146–152. doi: 10.1053/scnp.2001.22263

Kaye, W. H., Fudge, J. L., and Paulus, M. (2009). New insights into symptoms and neurocircuit function of anorexia nervosa. *Nat. Rev. Neurosci*. 10, 573–584. doi: 10.1038/nrn2682

Kaye, W. H., Wagner, A., Fudge, J. L., and Paulus, M. (2010). "Neurocircuity of eating disorders," in *Behavioral Neurobiology of Eating Disorders*, eds R. A. H. Adan and W. H. Kaye (Berlin; Heidelberg: Springer), 37–57.

Kaye, W. H., Wierenga, C. E., Bailer, U. F., Simmons, A. N., and Bischoff-Grethe, A. (2013). Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends Neurosci*. 36, 110–120. doi: 10.1016/j.tins.2013.01.003

Kaye, W. H., Wierenga, C. E., Knatz, S., Liang, J., Boutelle, K., Hill, L., et al. (2015). Temperament—based treatment for anorexia nervosa. *Eur. Eat. Disord. Rev*. 23, 12–18. doi: 10.1002/erv.2330

Keizer, A., Smeets, M. A., Dijkerman, H. C., Uzunbajakau, S. A., van Elburg, A., and Postma, A. (2013). Too fat to fit through the door: first evidence for disturbed body-scaled action in anorexia nervosa during locomotion. *PLoS ONE* 8:e64602. doi: 10.1371/journal.pone.0064602

Kennedy, D. P., Gläscher, J., Tyszka, J. M., and Adolphs, R. (2009). Personal space regulation by the human amygdala. *Nat. Neurosci*. 12, 1226–1227. doi: 10.1038/nn.2381

Keski-Rahkonen, A., Hoek, H. W., Susser, E. S., Linna, M. S., Sihvola, E., Raevuori, A., et al. (2007). Epidemiology and course of anorexia nervosa in the community. *Am. J. Psychiatry*. 164, 1259–1265. doi: 10.1176/appi.ajp.2007.06081388

Khalsa, S. S., Craske, M. G., Li, W., Vangala, S., Strober, M., and Feusner, J. D. (2015). Altered interoceptive awareness in anorexia nervosa: effects of meal anticipation, consumption and bodily arousal. *Int. J. Eat. Disord*. 48, 889–897. doi: 10.1002/eat.22387

Klabunde, M., Acheson, D. T., Boutelle, K. N., Matthews, S. C., and Kaye, W. H. (2013). Interoceptive sensitivity deficits in women recovered from bulimia nervosa. *Eat. Behav*. 14, 488–492. doi: 10.1016/j.eatbeh.2013.08.002

Kleinke, C. L. (1986). Gaze and eye contact: a research review. *Psychol. Bull*. 100:78. doi: 10.1037/0033-2909.100.1.78

Knoll, J. F., and Hodapp, V. (1992). A comparison between two methods for assessing heartbeat perception. *Psychophysiology* 29, 218–222. doi: 10.1111/j.1469-8986.1992.tb01689.x

Kog, E., and Vandereycken, W. (1989). Family interaction in eating disorder patients and normal controls. *Int. J. Eat. Disord*. 8, 11–23. doi: 10.1002/1098-108X(198901)8:1<11::AID-EAT2260080103>3.0.CO;2-1

Krautwurst, S., Gerlach, A. L., Gomille, L., Hiller, W., and Witthöft, M. (2014). Health anxiety–An indicator of higher interoceptive sensitivity? *J. Behav. Ther. Exp. Psychiatry* 45, 303–309. doi: 10.1016/j.jbtep.2014.02.001

Kucharska-Pietura, K., Nikolaou, V., Masiak, M., and Treasure, J. (2004). The recognition of emotion in the faces and voice of anorexia nervosa. *Int. J. Eat. Disord*. 35, 42–47. doi: 10.1002/eat.10219

Lester, R. J. (1997). The (dis) embodied self in anorexia nervosa. *Soc. Sci. Med*. 44, 479–489. doi: 10.1016/S0277-9536(96)00166-9

Lilenfeld, L. R. R., Wonderlich, S., Riso, L. P., Crosby, R., and Mitchell, J. (2006). Eating disorders and personality: a methodological and empirical review. *Clin. Psychol. Rev*. 26, 299–320. doi: 10.1016/j.cpr.2005.10.003

Lowry, R. (2004). *VassarStats: Website for Statistical Computation*. Vassar College. Available online at: http://vassarstats.net/tabs.html#fisher

Mathewson, K. J., Schmidt, L. A., Miskovic, V., Santesso, D. L., Duku, E., McCabe, R. E., et al. (2013). Does respiratory sinus arrhythmia (RSA) predict anxiety reduction during cognitive behavioral therapy (CBT) for social anxiety disorder (SAD)? *Int. J. Psychophysiol*. 88, 171–181. doi: 10.1016/j.ijpsycho.2013.03.016

Matsumoto, R., Kitabayashi, Y., Narumoto, J., Wada, Y., Okamoto, A., Ushijima, Y., et al. (2006). Regional cerebral blood flow changes associated with interoceptive awareness in the recovery process of anorexia nervosa. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 30, 1265–1270. doi: 10.1016/j.pnpbp.2006.03.042

Matthews, E. (2007). *Body-Subjects and Disordered Minds: Treating the'whole'Person in Psychiatry.* Oxford: Oxford University Press.

Matthews, E. H. (2004). Merleau-Ponty's body-subject and psychiatry. *Int. Rev. Psychiatry* 16, 190–198. doi: 10.1080/09540260400003867

Mazurak, N., Enck, P., Muth, E., Teufel, M., and Zipfel, S. (2011). Heart rate variability as a measure of cardiac autonomic function in anorexia nervosa: a review of the literature. *Eur. Eat. Disord. Rev*. 19, 87–99. doi: 10.1002/erv.1081

Merwin, R. M., Zucker, N. L., Lacy, J. L., and Elliott, C. A. (2010). Interoceptive awareness in eating disorders: distinguishing lack of clarity from non-acceptance of internal experience. *Cogn. Emot*. 24, 892–902. doi: 10.1080/02699930902985845

Mitchell, J. E., and Crow, S. (2006). Medical complications of anorexia nervosa and bulimia nervosa. *Curr. Opin. Psychiatry* 19, 438–443. doi: 10.1097/01.yco.0000228768.79097.3e

Moncrieff-Boyd, J., Byrne, S., and Nunn, K. (2014). Disgust and anorexia nervosa: confusion between self and non-self. *Adv. Eat. Disord. Theory Res. Pract*. 2, 4–18. doi: 10.1080/21662630.2013.820376

Mussgay, L., Klinkenberg, N., and Rüddel, H. (1999). Heart beat perception in patients with depressive, somatoform, and personality disorders. *J. Psychophysiol*. 13, 27–36. doi: 10.1027//0269-8803.13.1.27

Myers, T. A., and Crowther, J. H. (2008). Is self-objectification related to interoceptive awareness? An examination of potential mediating pathways to disordered eating attitudes. *Psychol. Women Q*. 32, 172–180. doi: 10.1111/j.1471-6402.2008.00421.x

Nico, D., Daprati, E., Nighoghossian, N., Carrier, E., Duhamel, J.-R., and Sirigu, A. (2010). The role of the right parietal lobe in anorexia nervosa. *Psychol. Med*. 40, 1531–1539. doi: 10.1017/S0033291709991851

Noll, S. M., and Fredrickson, B. L. (1998). A mediational model linking self−objectification, body shame, and disordered eating. *Psychol. Women Q*. 22, 623–636. doi: 10.1111/j.1471-6402.1998.tb00181.x

Nunn, K., Frampton, I., Gordon, I., and Lask, B. (2008). The fault is not in her parents but in her insula—a neurobiological hypothesis of anorexia nervosa. *Eur. Eat. Disord. Rev*. 16, 355–360. doi: 10.1002/erv.890

Oberndorfer, T. A., Frank, G. K., Simmons, A. N., Wagner, A., McCurdy, D., Fudge, J. L., et al. (2013). Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. *Am. J. Psychiatry* 170, 1143–1151. doi: 10.1176/appi.ajp.2013.11111745

Oldershaw, A., Hambrook, D., Tchanturia, K., Treasure, J., and Schmidt, U. (2010). Emotional theory of mind and emotional awareness in recovered anorexia nervosa patients. *Psychosom. Med*. 72, 73–79. doi: 10.1097/PSY.0b013e3181c6c7ca

Paladino, M.-P., Mazzurega, M., Pavani, F., and Schubert, T. W. (2010). Synchronous multisensory stimulation blurs self-other boundaries. *Psychol. Sci*. 21, 1202–1207. doi: 10.1177/0956797610379234

Patriquin, M. A., Scarpa, A., Friedman, B. H., and Porges, S. W. (2013). Respiratory sinus arrhythmia: a marker for positive social functioning and receptive language skills in children with autism spectrum disorders. *Dev. Psychobiol*. 55, 101–112. doi: 10.1002/dev.21002

Pedrabissi, L., and Santinello, M. (1989). *Inventario per L'ansia di ≪Stato≫ e di ≪Tratto≫: Nuova Versione Italiana Dello STAI Forma Y: Manuale*. Firenze: Organ Specification.

Persky, S., and Eccleston, C. P. (2011). Medical student bias and care recommendations for an obese versus non-obese virtual patient. *Int. J. Obes*. 35, 728–735. doi: 10.1038/ijo.2010.173

Phan, K. L., Wager, T., Taylor, S. F., and Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 16, 331–348. doi: 10.1006/nimg.2002.1087

Pollatos, O., Gramann, K., and Schandry, R. (2007). Neural systems connecting interoceptive awareness and feelings. *Hum. Brain Mapp*. 28, 9–18. doi: 10.1002/hbm.20258

Pollatos, O., Kurz, A.-L., Albrecht, J., Schreder, T., Kleemann, A. M., Schöpf, V., et al. (2008). Reduced perception of bodily signals in anorexia nervosa. *Eat. Behav*. 9, 381–388. doi: 10.1016/j.eatbeh.2008.02.001

Pollatos, O., Traut-Mattausch, E., and Schandry, R. (2009). On perceiving bodily changes, depression and anxiety. *Depress Anxiety* 26, 167–173. doi: 10.1002/da.20504

Porges, R. F., and Smilen, S. W. (1994). Long-term analysis of the surgical management of pelvic support defects. *Am. J. Obstet. Gynecol*. 171, 1518–1528. doi: 10.1016/0002-9378(94)90395-6

Porges, S. W. (1995). Orienting in a defensive world: mammalian modifications of our evolutionary heritage. A polyvagal theory. *Psychophysiology* 32, 301–318. doi: 10.1111/j.1469-8986.1995.tb01213.x

Porges, S. W. (2007). The polyvagal perspective. *Biol. Psychol*. 74, 116–143. doi: 10.1016/j.biopsycho.2006.06.009

Porges, S. W., Macellaio, M., Stanfill, S. D., McCue, K., Lewis, G. F., Harden, E. R., et al. (2013). Respiratory sinus arrhythmia and auditory processing in autism: modifiable deficits of an integrated social engagement system? *Int. J. Psychophysiol*. 88, 261–270. doi: 10.1016/j.ijpsycho.2012.11.009

Puhl, R. M., and Heuer, C. A. (2009). The stigma of obesity: a review and update. *Obesity* 17, 941–964. doi: 10.1038/oby.2008.636

Ratcliffe, M. (2008). *Feelings of Being: Phenomenology, Psychiatry and the Sense of Reality*. Oxford: Oxford University Press.

Riva, G. (2014). Out of my real body: cognitive neuroscience meets eating disorders. *Front. Hum. Neurosci*. 8:236. doi: 10.3389/fnhum.2014.00236

Riva, G., and Gaudio, S. (2012). Allocentric lock in anorexia nervosa: new evidences from neuroimaging studies. *Med. Hypotheses* 79, 113–117. doi: 10.1016/j.mehy.2012.03.036

Riva, G., Gaudio, S., and Dakanalis, A. (2014). I'm in a virtual body: a locked allocentric memory may impair the experience of the body in both obesity and anorexia nervosa. *Eat. Weight Disord*. 19, 133–134. doi: 10.1007/s40519-013-0066-3

Riva, G., Gaudio, S., and Dakanalis, A. (2015). The neuropsychology of self-objectification. *Eur. Psychol*. 20, 34–43. doi: 10.1027/1016-9040/a000190

Rowsell, M., MacDonald, D. E., and Carter, J. C. (2016). Emotion regulation difficulties in anorexia nervosa: associations with improvements in eating psychopathology. *J. Eat. Disord*. 4, 1. doi: 10.1186/s40337-016-0108-0

Russell, L. M., Bahadur, R., Hawkins, L. N., Allan, J., Baumgardner, D., Quinn, P. K., et al. (2009). Organic aerosol characterization by complementary measurements of chemical bonds and molecular fragments. *Atmos. Environ*. 43, 6100–6105. doi: 10.1016/j.atmosenv.2009.09.036

Schandry, R. (1981). Heart beat perception and emotional experience. *Psychophysiology* 18, 483–488. doi: 10.1111/j.1469-8986.1981.tb02486.x

Schmidt, U., Jiwany, A., and Treasure, J. (1993). A controlled study of alexithymia in eating disorders. *Compr. Psychiatry* 34, 54–58. doi: 10.1016/0010-440X(93)90036-4

Schmidt, U., and Treasure, J. (2006). Anorexia nervosa: valued and visible. A cognitive−interpersonal maintenance model and its implications for research and practice. *Br. J. Clin. Psychol*. 45, 343–366. doi: 10.1348/014466505X53902

Sobal, J., Bisogni, C. A., Devine, C. M., and Jastran, M. (2006). A conceptual model of the food choice process over the life course. *Front. Nutr. Sci*. 3:1. doi: 10.1079/9780851990323.0001

Stefanile, C., Matera, C., Nerini, A., and Pisani, E. (2011). Validation of an italian version of the sociocultural attitudes towards appearance questionnaire-3 (SATAQ-3) on adolescent girls. *Body Image* 8, 432–436. doi: 10.1016/j.bodyim.2011.06.001

Strigo, I. A., Matthews, S. C., Simmons, A. N., Oberndorfer, T., Klabunde, M., Reinhardt, L. E., et al. (2013). Altered insula activation during pain anticipation in individuals recovered from anorexia nervosa: evidence of interoceptive dysregulation. *Int. J. Eat. Disord*. 46, 23–33. doi: 10.1002/eat.22045

Sullivan, P. F. (1995). Mortality in anorexia nervosa. *Am. J. Psychiatry* 152, 1073–1074. doi: 10.1176/ajp.152.7.1073

Tajadura-Jiménez, A., Grehl, S., and Tsakiris, M. (2012). The other in me: interpersonal multisensory stimulation changes the mental representation of the self. *PLoS ONE* 7:e40682. doi: 10.1371/journal.pone.0040682

Tchanturia, K., Campbell, I. C., Morris, R., and Treasure, J. (2005). Neuropsychological studies in anorexia nervosa. *Int. J. Eat. Disord*. 37, S72–S76. doi: 10.1002/eat.20119

Tchanturia, K., Morris, R. G., Anderluh, M. B., Collier, D. A., Nikolaou, V., and Treasure, J. (2004). Set shifting in anorexia nervosa: an examination before and after weight gain, in full recovery and relationship to childhood and adult OCPD traits. *J. Psychiatr. Res*. 38, 545–552. doi: 10.1016/j.jpsychires.2004.03.001

Titova, O. E., Hjorth, O. C., Schiöth, H. B., and Brooks, S. J. (2013). Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. *BMC Psychiatry* 13:110. doi: 10.1186/1471-244X-13-110

Treasure, J., and Schmidt, U. (2013). The cognitive-interpersonal maintenance model of anorexia nervosa revisited: a summary of the evidence for cognitive, socio-emotional and interpersonal predisposing and perpetuating factors. *J. Eat. Disord*. 1:13. doi: 10.1186/2050-2974-1-13

Tsakiris, M., Tajadura-Jiménez, A., and Costantini, M. (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. *Proc. R. Soc. Lond. B Biol. Sci*. 278, 2470–2476. doi: 10.1098/rspb.2010.2547

Van der Does, A. W., Antony, M. M., Ehlers, A., and Barsky, A. J. (2000). Heartbeat perception in panic disorder: a reanalysis. *Behav. Res. Ther*. 38, 47–62. doi: 10.1016/S0005-7967(98)00184-3

Vandereycken, W. (2003). The place of inpatient care in the treatment of anorexia nervosa: questions to be answered. *Int. J. Eat. Disord*. 34, 409–422. doi: 10.1002/eat.10223

Vicario, C. M. (2013). Altered insula response to sweet taste processing in recovered anorexia and bulimia nervosa: a matter of disgust sensitivity? *Am. J. Psychiatry* 170, 1497–1497. doi: 10.1176/appi.ajp.2013.13060748

Wagner, A., Aizenstein, H., Mazurkewicz, L., Fudge, J., Frank, G. K., Putnam, K., et al. (2008). Altered insula response to taste stimuli in individuals recovered from restricting-type anorexia nervosa. *Neuropsychopharmacology* 33, 513–523. doi: 10.1038/sj.npp.1301443

Watson, K. K., Werling, D. M., Zucker, N., and Platt, M. (2010). Altered social reward and attention in anorexia nervosa. *Front. Psychol*. 1:36. doi: 10.3389/fpsyg.2010.00036

Wieser, M. J., Pauli, P., Alpers, G. W., and Mühlberger, A. (2009). Is eye to eye contact really threatening and avoided in social anxiety?—An eye-tracking and psychophysiology study. *J. Anxiety Disord*. 23, 93–103. doi: 10.1016/j.janxdis.2008.04.004

Yaroslavsky, I., Rottenberg, J., and Kovacs, M. (2013). The utility of combining RSA indices in depression prediction. *J. Abnorm. Psychol*. 122:314. doi: 10.1037/a0032385

Yaroslavsky, I., Rottenberg, J., and Kovacs, M. (2014). Atypical patterns of respiratory sinus arrhythmia index an endophenotype for depression. *Dev. Psychopathol*. 26, 1337–1352. doi: 10.1017/S0954579414001060

Zonnevijlle-Bendek, M. J. S., Van Goozen, S. H. M., Cohen-Kettenis, P. T., Van Elburg, A., and Van Engeland, H. (2002). Do adolescent anorexia nervosa patients have deficits in emotional functioning? *Eur. Child Adolesc. Psychiatry* 11, 38–42. doi: 10.1007/s007870200006

Zucker, N., Moskovich, A., Bulik, C. M., Merwin, R., Gaddis, K., Losh, M., et al. (2013). Perception of affect in biological motion cues in anorexia nervosa. *Int. J. Eat. Disord*. 46, 12–22. doi: 10.1002/eat.22062

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Atypical Self-Focus Effect on Interoceptive Accuracy in Anorexia Nervosa

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Background: Interoceptive abilities are known to be affected in anorexia nervosa (AN). Previous studies could show that private self-focus can enhance interoceptive accuracy (IAcc) in healthy participants. As body dissatisfaction is high in AN, confrontation with bodily features such as the own face might have a directly opposed effect in AN. Whether patients with AN can benefit from self-focus in their IAcc and whether this pattern changes over the time-course of cognitive behavioral therapy was investigated in this study.

Methods: Fifteen patients with AN from the Psychosomatic Clinic in Windach were assessed three times in the time course of a standardized cognitive-behavioral therapy. They were compared to 15 controls, recruited from Ulm University and tested in a comparable setting. Both groups performed the heartbeat perception task assessing IAcc under two conditions either enhancing ("Self") or decreasing ("Other") self-focused attention. Furthermore, body dissatisfaction was assessed by a subscale of the Eating Disorder (ED) Inventory 2.

Results: Patients with AN scored higher in IAcc when watching others' faces as compared to one's own face while performing the heartbeat perception task. The opposite pattern was observed in controls. IAcc remained reduced in AN as compared to controls in the time-course of cognitive-behavioral therapy, while body-dissatisfaction improved in AN. High body dissatisfaction was related to poorer IAcc in the "Self" condition.

Conclusions: Our findings suggest that using self-focused attention reduces IAcc in AN while the opposite pattern was observed in controls. Confronting anorexic patients with bodily features might increase body-related avoidance and therefore decrease IAcc. The current study introduces a new perspective concerning the role of interoceptive processes in AN and generates further questions regarding the therapeutic utility of methods targeting self-focus in the treatment of AN.

Keywords: anorexia nervosa, interoceptive accuracy, self-focused attention, body dissatisfaction, heartbeat perception, cognitive-behavioral therapy

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INTRODUCTION

Anorexia nervosa (AN) is a psychiatric disorder defined by excessive weight loss, fear of gaining weight, a disturbed body image and a rejection of the own body (Klein and Walsh, 2003). Friederich et al. (2010) describe body dissatisfaction as an important precipitating and maintenance factor in AN. Interestingly, the perceptual disturbance of one's own body is highlighted as important for the pathophysiology of AN (Friederich et al., 2010). Friederich et al. (2010) suggest that observed hyperactivation in insula along with hypoactivation in anterior cingulate may be critical for altered interoceptive processes involved in body self-comparisons in AN as both insula and anterior cingulate are central structures associated with the processing of interoceptive signals (see e.g., Craig, 2003; Critchley et al., 2004; Seth et al., 2012). This is in accordance to previous studies (Fassino et al., 2004; Matsumoto et al., 2006; Pollatos et al., 2008; Klabunde et al., 2013) showing that patients with eating disorders (ED) and especially patients with AN have difficulties in interoceptive functions assessed with different methods, e.g., when using questionnaires or behavioral tests targeting accuracy in detecting internal signals such as heartbeat detection.

Interoception is the body-to-brain axis of sensation concerning the state of the internal body and its visceral organs (Cameron, 2001; Craig, 2002). The generation and perception (interoception) of internal states of bodily arousal are central to many theoretical accounts of emotion (e.g., James, 1884; Damasio, 1999). As a general concept, interoception includes two forms of perception: proprioception (signals from the skin and musculoskeletal apparatus) and visceroception (signals from the inner organs like heart rate, breath and hunger). Garfinkel and Critchley (2013) first emphasized the importance to differentiate between different facets of interoceptive processing, suggesting to distinguish between interoceptive accuracy (IAcc; e.g., behavioral testing such as performance on heartbeat perception tests), metacognitive awareness (e.g., confidence-accuracy correspondence) and subjective interoceptive sensibility (e.g., as assessed via self-report questionnaires, e.g., body perception questionnaire). In former research these different levels were often used in an interchangeable way which could have contributed to diverging results.

Referring to a recent study of Garfinkel et al. (2015) IAcc might be the core ability within the construct of interoception underpinning other interoceptive measures. Individuals differ substantially in measures of IAcc, the ability to perceive consciously signals arising from the body. Measuring a person's ability to perceive and accurately report one's heartbeats at rest is often used to quantify these differences (Schandry, 1981; Cameron, 2001; Critchley et al., 2004; Pollatos and Schandry, 2004; Pollatos et al., 2005; Dunn et al., 2007). First evidence indicates that a focus on self-related stimuli can manipulate IAcc suggesting a dynamic relationship between self-awareness and interoception. IAcc can be improved when persons attend to their self as operationalized with looking in the mirror (Ainley et al., 2012). This effect was most pronounced in persons with low IAcc at the baseline condition. Similar results were achieved when persons paid attention to bodily and narrative aspects of the self (Ainley et al., 2013).

Another set of studies has looked at the role of IAcc in body-awareness using various established paradigms of bodily illusions that have been shown to alter the sense of body-ownership. For example, it has been demonstrated that interoceptive processes modulate the integration of multisensory body percepts as shown by Tsakiris et al. (2011) and Suzuki et al. (2013). Further research has also demonstrated that interoceptive signals can also be used for inducing bodily illusions as cardio-visual stimulation was associated with an affected sense of self in one patient before and after insula resection surgery (Ronchi et al., 2015). Interoceptive influences extend from the basic levels of multisensory integration to the conscious attitudes that we hold about our body, highlighting the role that interoception potentially plays across different hierarchical levels of body-representations. Pollatos et al. (2008) have shown that patients with ED show reduced IAcc relative to controls. Ainley and Tsakiris (2013) recently showed an inverse relation between levels of IAcc and self-objectification (Ainley and Tsakiris, 2013), suggesting that better IAcc is associated with a lower tendency to experience one's body as an object. The body as object describes an attitude of evaluation of its appearance and a position as if seen through the eyes of others. Similarly, a negative relation has been shown between IAcc and body-image dissatisfaction (Emanuelsen et al., 2015) in a sample of 82 high school students (mean age 17). Of relevance, other studies have reported that levels of IAcc influence eating habits, e.g., IAcc is inversely related to intuitive eating (Herbert et al., 2013). Although these findings are suggestive of the role that interoception may have for body-image satisfaction and related behaviors (e.g., eating), the question of how experimentally manipulating self-focus may change IAcc in AN, as it does in healthy individuals has not been examined before.

A negative evaluation of one's own body is often associated with body-related avoidance (e.g., not looking in the mirror or hiding one's body under baggy clothes, see Trautmann et al., 2007). Therefore, it is an open question whether self-focus using bodily features can indeed improve IAcc in AN as demonstrated in healthy participants. The role of body-dissatisfaction in this context has not been elucidated so far. The aim of this study was to investigate possible changes in IAcc using a paradigm manipulating the self-focus during the interoceptive task. Anorexic patients from the psychosomatic clinic Windach am Ammersee were examined three times during stationary therapy (first week of clinic stay, 4–6 weeks later respectively after a gain of 2 body mass index (BMI) points, and before their dismissals at the end of their therapy) and compared to healthy controls. We were primarily interested in testing whether AN patients will benefit in IAcc from self-focus in the same extent as healthy controls, as well as if IAcc is improved over time by cognitive-behavioral therapy.

MATERIALS AND METHODS

Participants

Female patients with current AN were recruited from the Psychosomatic Clinic Windach am Ammersee. Reflecting clinical routine, diagnoses were determined according to International Classification of Disease 10 criteria based on semi-structured clinical interviews administered by a senior staff member. The patients took part in a cognitive behavioral therapy with special attention to maladaptive emotional processes and the systemic context. They agreed with the therapists on a target weight and a weight gain of 700 g per week.

Data for this study were collected in a longitudinal design targeting IAcc under two conditions: looking at the own face (condition "Self") and looking at another face (of an unknown person; condition "Other") while the heartbeat perception task was carried out (details see below). Body weight and height were assessed at the end of each session. Participants were tested three times based on the therapy-process at the beginning (T1), after 4–6 weeks respectively after an increase of 2 BMI points (T2) and at the end of therapy (T3). On average, patients stayed in the clinic 12–14 weeks and were included in the study in the first or second week of their therapy. Fifteen women with AN were included in the experiments. Mean age in the AN group was 27.4 years (SD = 7.8) and mean BMI was 15.7 (SD = 1.3) at T1. Exclusion criteria were any purging at the moment or former diagnosis of bulimia nervosa.

Fifteen female healthy controls were recruited from staff or students at the Ulm University and matched according age and educational background. They received a compensation of €20. Controls had a mean age of 27.9 (SD = 7.6) and a mean BMI of 21.0 (SD = 1.8). None of them were taking medication (except of contraceptives), had a past or current ED or any other psychiatric or severe somatic illness as assessed by anamnestic questionnaire. Both groups did not differ significantly concerning age ($t_{(\mathrm{df}=28)} = 0.19$, $p =$ n.s.) and educational level (educational level assessed by a scoring system for the German school system: (1) without educational qualification; (2) secondary general school certificate; (3) intermediate school certificate; (4) entrance qualification for technical college; (5) entrance qualification for university; AN: mean 3.13 (SD = 1.0); controls: mean 3.4 (SD = 0.9); $t_{(\mathrm{df}=28)} = -0.74$, $p =$ n.s.). The study was conducted in accordance with the Declaration of Helsinki, ethical approval was obtained from an institutional review board. Prior to testing, informed consent was obtained.

Instruments

A short questionnaire explored health status and personal data (e.g., age, educational background). Different standard psychological questionnaires were applied including the subscale "body dissatisfaction" from the ED-Inventory-2 (Garner, 1984). Questions are rated on a 6-point scale, ranging from 1 (never) to 6 (always). High scores indicate higher body dissatisfaction.

IAcc was assessed by a heartbeat perception task in two counterbalanced conditions: looking at the own ("self") or looking at another face ("other"; a non-familiar female face) while doing the heartbeat perception task. Condition "self" was realized by using a laptop camera focusing on the face of the participant, while during the "Other" condition participants watched a pre-recorded video of a female model (age of the model 21, 24, 26 years; BMI within normal range: 22.6 kg/m^2, and 20.8 kg/m^2, 20.5 kg/m^2) who was looking directly into camera. There were three different female models used, so that for each time point (T1, T2, T3) another pre-recorded video was presented. The order of the models was randomized. Participants were instructed to attentively watch either "Self" or "Other" during the following heartbeat perception tasks. For each condition three heartbeat counting trials of the Mental Tracking Method were used as proposed by Schandry (1981). The three trials per conditions were presented in a random order across participants. A short training interval of 15 s was followed by four intervals of 25, 45 and 35. Participants were asked to count their own heartbeats silently and to verbally report the number of counted heartbeats at the end of each counting phase. The beginning and the end of the counting intervals were indicated by the supervisor. During heartbeat counting, participants were instructed not to take their own pulse or attempt to use other forms of manipulation in order to support counting of their heartbeats. Furthermore, they did not receive any information about the length of the counting phases or the quality of their performances.

IAcc was calculated as the mean heartbeat perception score according to the following transformation:

$$\frac{1}{3}\sum\left(1-\frac{(|\text{recorded heartbeats}-\ \text{counted heartbeats}|)}{\text{recorded heartbeats}}\right)$$

IAcc scores range from 0 to 1. Higher scores indicate small differences between the counted and recorded heartbeat and consequently a better IAcc. Other experimental paradigms (e.g., emotional picture presentation and evaluation, attention task) conducted later are not reported here. Each session lasted about 45 min.

Procedure

Patients were informed about the study by staff and they received written information about the experiment. At each point of data collection, patients were tested individually in a separate, quiet room of the clinic. Controls were examined at the laboratories of the Clinical and Health Psychology department in Ulm. Patients were tested three times based on the therapy-process at the beginning (T1), after 4–6 weeks (T2) and at the end of therapy (T3). Controls were also tested three times using a comparable timetable and setting.

Patients and controls filled in the questionnaires prior to each testing session. Then the assessment of IAcc took place under two conditions. Therefore, cardiac activity was recorded using the mobile heart frequency monitor RS800CX (Polar Electro Oy, Kempele, Finland). The RS800CX is easy to use, non-invasive and -reactive recording of inter-beat-intervals whose validity and reliability compared to alternative ECG measurement devices are established (Koch and Pollatos, 2014a,b).

Data Analyses

Data analyses were performed with the program SPSS (version 22). Referring to questionnaire and BMI data, repeated measurements ANOVAs were calculated with the factors Group (AN, controls) and Time (T1, T2, T3). Furthermore, IAcc was examined with the factors Group (AN, controls), Time (T1, T2, T3) and Condition (Self, Other). Pearson correlation analyses were carried out between body dissatisfaction scores and IAcc during the "self" and "other" condition at T1, T2 and T3. With respect to the correlation analyses, we used Bonferroni correction to adjust the alpha errors for multiple comparisons. Statistical significance levels reported correspond to *p*-values less than 0.05, 0.01 and 0.001, respectively. In the "Results" Section, uncorrected *F*-values are reported together with the Greenhouse-Geiser epsilon values and corrected degrees of freedom.

RESULTS

Sample Description and Questionnaire Data

The relevant sample characteristics obtained from both participant groups concerning BMI and body dissatisfaction are shown in **Table 1**. Results of the repeated measurements ANOVAs are also summarized there.

BMI significantly increased in AN patients only; BMI of AN patients always was smaller than the BMI of controls (at all time points T1–T3; $ps < 0.001$). Only AN patients exhibited a decrease in body dissatisfaction over time; differences to controls were significant for T1 ($p < 0.001$) and T2 ($p < 0.01$), but not for T3 ($p = 0.17$).

Interoceptive Accuracy

The mean obtained heartbeat perception scores for the two conditions averaged across all time points (**Figure 1A**) as well as contrasting both groups at time points T1, T2 and T3 (**Figure 1B**) are summarized in **Figure 1**.

We observed a significant interaction effect Condition × Group ($F_{(1,28)} = 10.92$; $p < 0.01$; $\eta^2 = 0.28$; $\varepsilon = 0.89$) as well as a significant main effect Group ($F_{(1,28)} = 5.13$; $p < 0.05$; $\eta^2 = 0.16$; $\varepsilon = 0.59$). While mean IAcc was higher for controls (mean 0.68) as compared to anorexic patients (mean 0.58), separate ANOVAs for each group showed that in controls IAcc during the condition "Self" was always higher as compared to "Other"(Condition × Time ($F_{(1,14)} = 6.18$; $p < 0.05$; $\eta^2 = 0.28$; $\varepsilon = 0.80$). The opposite effect was observed for anorexic patients (Condition × Time ($F_{(1,14)} = 4.96$; $p < 0.05$; $\eta^2 = 0.31$; $\varepsilon = 0.64$). The main effects Time were not significant in both groups.

Correlations Between Body Dissatisfaction and IAcc During "Self" Condition

In a last step we correlated IAcc during "self" and "other" with mean body dissatisfaction score obtained from questionnaire ($N = 30$, total sample). Due to multiple comparisons, we corrected the alpha error accordingly (*p* values smaller 0.008 are considered significant). We observed significant inverse correlations between IAcc during "Self" condition and body dissatisfaction at T1 ($r = -0.49$, $p = 0.006$) and T2 ($r = -0.53$; $p = 0.002$), while all other correlation coefficients were also inverse, but substantially smaller and did not reach significance ("Self" at T3: $r = -0.33$, $p = 0.07$; "Other" at T1: $r = -0.37$, $p = 0.04$; T2: $r = -0.33$, $p = 0.07$; T3: $r = -0.35$, $p = 0.06$). To compare the distribution between both groups, we plotted the scatter plots between IAcc during the condition "Self" at T1 contrasting anorexics and controls (see **Figure 2**).

DISCUSSION

The aim of the present study was to investigate whether AN patients benefit in IAcc from self-focus in the same extent as healthy controls, and whether possible differences change in the time course of an inpatient cognitive-behavioral therapy. In line with former research (Pollatos et al., 2008), anorexic patients exhibited a reduced IAcc averaged across both conditions. Furthermore, IAcc remained reduced in AN during the time course of cognitive-behavioral therapy compared to controls. Remaining deficient IAcc signaling disturbed processing of bodily signals may represent an ongoing risk factor for maintenance of AN. Recent studies using mindfulness-based

TABLE 1 | Body mass index (BMI) and body dissatisfaction during the time course of therapy contrasting anorexic patients ($N = 15$) and controls ($N = 15$).

	T1 Mean (SD)		T2 Mean (SD)		T3 Mean (SD)	
	Anorexics	Controls	Anorexics	Controls	Anorexics	Controls
BMI (kg/m^2)	15.72 (1.27)	21.19 (1.79)	16.93 (1.29)	21.17 (1.85)	18.25 (0.98)	21.11 (1.86)
ANOVA	Time $F_{(2,56)} = 81.03$; $p < 0.001$; $\eta^2 = 0.74$; $\varepsilon = 1.00$					
	Time × Group: $F_{(2,56)} = 93.33$; $p < 0.001$; $\eta^2 = 0.77$; $\varepsilon = 1.00$					
	Group: $F_{(1,28)} = 57.46$; $p < 0.001$; $\eta^2 = 0.67$; $\varepsilon = 1.00$					
Body dissatisfaction (range 1–6)	4.38 (0.87)	2.96 (0.94)	3.93 (0.89)	2.90 (1.02)	3.51 (1.18)	2.95 (1.01)
ANOVA	Time: $F_{(2,56)} = 6.67$; $p < 0.01$; $\eta^2 = 0.19$; $\varepsilon = 0.85$					
	Time × Group: $F_{(2,56)} = 6.11$; $p < 0.01$; $\eta^2 = 0.18$; $\varepsilon = 0.83$					
	Group: $F_{(1,28)} = 9.06$; $p < 0.01$; $\eta^2 = 0.24$; $\varepsilon = 0.83$					

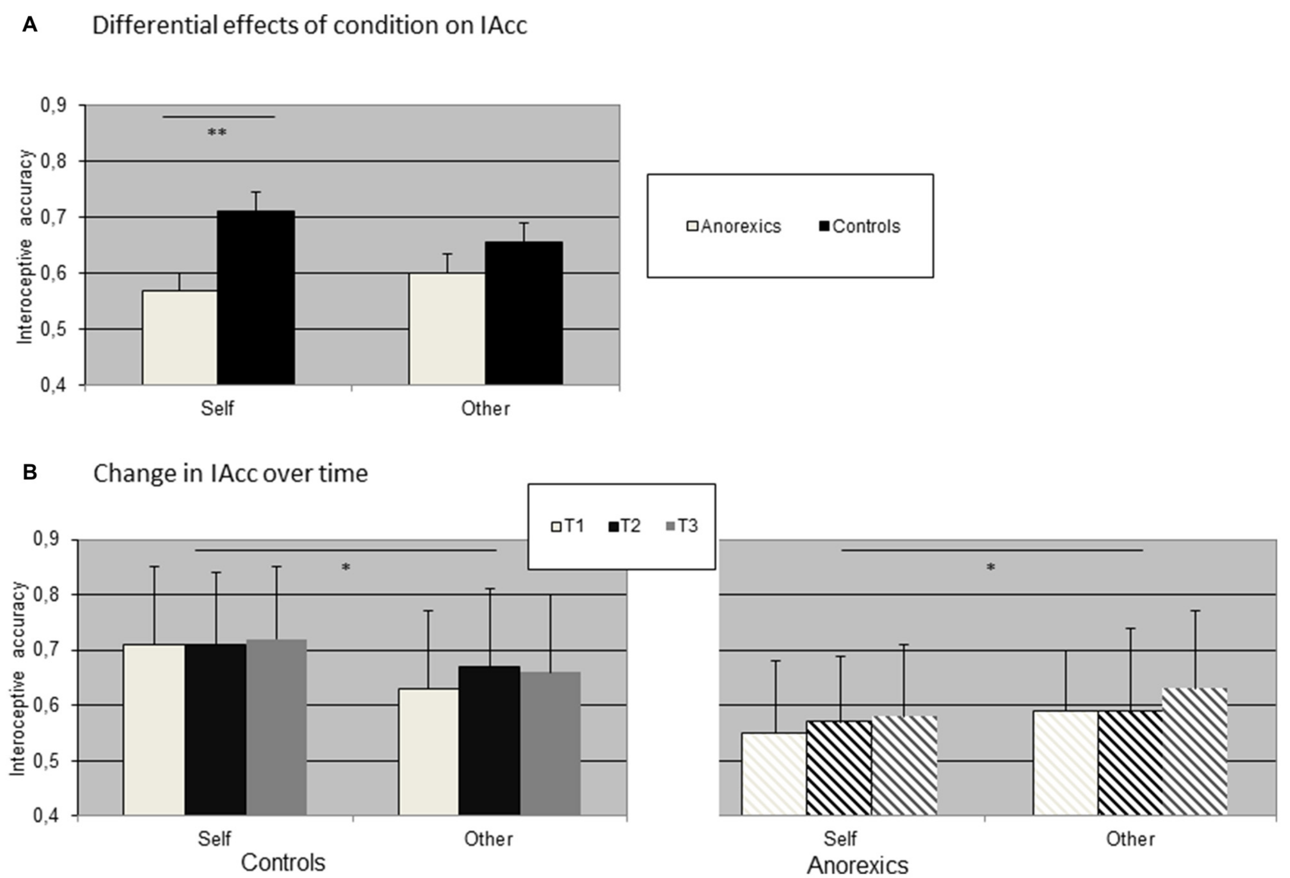

FIGURE 1 | Distribution of interoceptive accuracy (IAcc) contrasting controls and anorexics in (A) both conditions and (B) over time. (Bars represent standard error of means, SEM; $^{*}p < 0.05$; $^{**}p < 0.01$). **(A)** Differential effects of condition on IAcc. **(B)** Change in IAcc over time.

methods focusing on the body in a non-judging way such as the so-called body-scan could show that interoceptive sensibility as assessed by questionnaire could be improved when trained over a time period of 3 months in healthy controls (Bornemann et al., 2015). Farb et al. (2013) also reported an increase in neural plasticity in interoceptive network structures after daily practices of contemplative techniques such as breath monitoring. Whether these techniques could improve deficits in IAcc using them together with cognitive-behavioral therapy is a relevant future research question. One can assume that observed deficits could be transferred to the perception of bodily signals in general, including accuracy of bodily signals such as hunger and satiety as observed in healthy participants (Herbert et al., 2012). Recent studies also suggest that deficient IAcc might contribute to social problems in healthy populations, demonstrating that higher IAcc is associated with better coping of social exclusion (Werner et al., 2013; Pollatos et al., 2015) and a higher sensitivity to emotions of others (Terasawa et al., 2014). Whether this is also the case in AN needs further evaluation.

Furthermore, AN patients demonstrated differences in the processing of stimuli enhancing self-focus compared to healthy controls: while in accordance to former studies (Ainley et al., 2013) controls showed higher IAcc when watching their face during heartbeat perception, anorexics scored lower when watching their own face as compared to another person's face. As body dissatisfaction was higher in AN with most pronounced differences at T1, one might assume that the observed atypical lack of a self-observation enhancement effect in IAcc could be related to higher degrees of body-dissatisfaction in the AN group. As we did not ask our participants to evaluate their own face in the experimental situation, we can only speculate that this stimulus is seen as critical as other parts of the body in anorexic females, which then leads to an avoidance of attention on general aspects of the body including interoceptive signal processing. Supporting this interpretation, Trautmann et al. (2007) demonstrated that the own face is a stimulus associated with high avoidance in AN, and also other studies reported alterations in brain activation in anorexics for bodily (see e.g., Uher et al., 2005; Sachdev et al., 2008; Blechert et al., 2010; Miyake et al., 2010). It is an open question whether other methods inducing a self-focus such as self-related words or imagination of positive autobiographic episodes could facilitate IAcc in AN as shown in healthy participants (Ainley et al., 2012, 2013), which could be a promising avenue for future therapeutic methods.

In accordance to Emanuelsen et al. (2015) who showed that body dissatisfaction is related to IAcc in healthy persons,

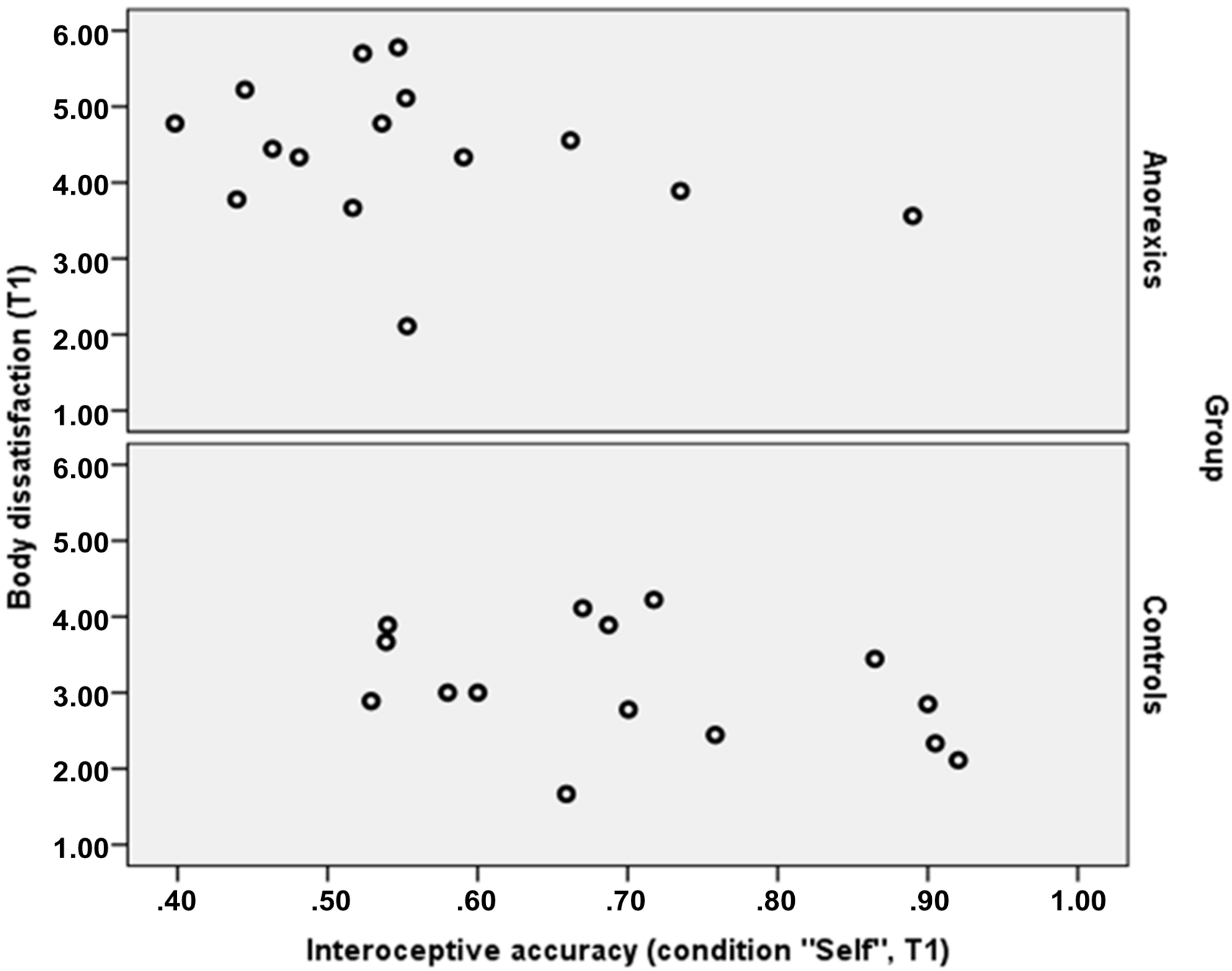

FIGURE 2 | Distribution of IAcc (condition "Self") and body dissatisfaction contrasting controls and anorexics at T1.

we also observed inverse correlations between IAcc (during "Self") and body dissatisfaction in this study. As depicted in **Figure 2**, the pattern of relationship was quite similar both in the groups of anorexics and in the control group at T1, highlighting that the observed results are comparable between controls and patients, though due to the small sample size more data are needed to support this result. It is important to note that the fact that IAcc did not change over the course of therapy, though body dissatisfaction improved, signals that deficient IAcc may represent an independent and stable factor of AN associated with ongoing symptoms and characteristic features of AN, that is not touched by state-of-the-art cognitive behavioral therapies. This also suggests further mechanisms underlying deficient IAcc in AN going beyond body dissatisfaction. Future research could use experimental designs or longitudinal data to examine whether theories of objectification claiming that an evaluative third person view of the body leads to decreased interoceptive abilities (Frederickson and Roberts, 1997; Emanuelsen et al., 2015) or the alternative causal chain suggesting that low levels of IAcc might cause high self-objectification (Ainley and Tsakiris, 2013) are valid.

We suggest that our results highlight a lack of self-focus effect on interoceptive processes in AN, interpreted as dysfunctional integration of bodily information. As known from other studies, lower IAcc is associated with a higher malleability of body-representations (Tsakiris et al., 2011) which was also demonstrated for AN using different experimental paradigms (see e.g., Eshkevari et al., 2012, 2014; Keizer et al., 2014). The atypical pattern of self-focus on IAcc might be interpreted as additional evidence that the dynamic modulation of interoceptive abilities is affected in AN. As we did not assess other aspects of interoception such as confidence in one's perception, we can only speculate whether the different levels of interoceptive processing respectively the interplay between those levels is affected in AN. Supporting this idea, a recent study by Pollatos and Georgiou (2016) observed such an abnormal overlap between different levels of interoceptive signal processing in bulimic patients. Our observation can be interpreted as potential risk configuration for processes related to a higher malleability of interoceptive signal processing and evaluation of interoceptive signals in AN.

We conclude that anorexic patients, unlike healthy controls, show a significant decrease in their IAcc during self-focus. Limitations of the current study are referred to the small sample of AN patients examined that did also not allow to split into groups for the correlational analyses, and the fact that other facets of interoceptive processes, such as subjective feelings and thoughts of one's body and interoceptive sensations and metacognitive beliefs, were not systematically addressed. So far, our results questions methods confronting anorexic patients with their body before improving body satisfaction as using bodily stimuli might be associated with greater avoidance and a higher malleability of body-representations in AN as reflected by a decrease in IAcc. Future research highlighting longitudinal data and exploring more facets of interoceptive processes would help understand the pattern observed in AN.

AUTHOR CONTRIBUTIONS

OP, MT, TK, MZ and GB substantially contributed to conception, design and acquisition of the data. OP analyzed the data. OP, BMH, MT and GB interpreted the data and drafted the manuscript. All authors approved the version submitted.

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REFERENCES

Ainley, V., Maister, L., Brokfeld, J., Farmer, H., and Tsakiris, M. (2013). More of myself: manipulating interoceptive awareness by heightened attention to bodily and narrative aspects of the self. *Conscious. Cogn.* 22, 1231–1238. doi: 10.1016/j.concog.2013.08.004

Ainley, V., Tajadura-Jiménez, A., Fotopoulou, A., and Tsakiris, M. (2012). Looking into myself: changes in interoceptive sensitivity during mirror self-observation. *Psychophysiology* 49, 1504–1508. doi: 10.1111/j.1469-8986.2012.01468.x

Ainley, V., and Tsakiris, M. (2013). Body Conscious? Interoceptive awareness, measured by heartbeat perception, is negatively correlated with self-objectification. *PLoS One* 8:e55568. doi: 10.1371/journal.pone.0055568

Blechert, J., Ansorge, U., and Tuschen-Caffier, B. (2010). A body-related dot-probe task reveals distinct attentional patterns for bulimia nervosa and anorexia nervosa. *J. Abnorm. Psychol.* 119, 575–585. doi: 10.1037/a0019531

Bornemann, B., Herbert, B. M., Mehling, W. E., and Singer, T. (2015). Differential changes in self-reported aspects of interoceptive awareness through three months of contemplative training. *Front. Psychol.* 5:1504. doi: 10.3389/fpsyg.2014.01504

Cameron, O. G. (2001). Interoception: the inside story—a model for psychosomatic processes. *Psychosom. Med.* 63, 697–710. doi: 10.1097/00006842-200109000-00001

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev. Neurosci.* 3, 655–666. doi: 10.1038/nrn894

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* 13, 500–505. doi: 10.1016/s0959-4388(03)00090-4

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., and Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195. doi: 10.1038/nn1176

Damasio, A. R. (1999). *The Feeling of What Happens: Body and Emotion in the Making of Consciousness.* New York, NY: Harcourt Brace.

Dunn, B. D., Dalgleish, T., Ogilvie, A. D., and Lawrence, A. D. (2007). Heartbeat perception in depression. *Behav. Res. Ther.* 45, 1921–1930. doi: 10.1016/j.brat.2006.09.008

Emanuelsen, L., Drew, R., and Köteles, F. (2015). Interoceptive sensitivity, body image dissatisfaction and body awareness in healthy individuals. *Scand. J. Psychol.* 56, 167–174. doi: 10.1111/sjop.12183

Eshkevari, E., Rieger, E., Longo, M. R., Haggard, P., and Treasure, J. (2012). Increased plasticity of the bodily self in eating disorders. *Psychol. Med.* 42, 819–828. doi: 10.1017/s0033291711002091

Eshkevari, E., Rieger, E., Longo, M. R., Haggard, P., and Treasure, J. (2014). Persistent body image disturbance following recovery from eating disorders. *Int. J. Eat. Disord.* 47, 400–409. doi: 10.1002/eat.22219

Farb, N. A. S., Segal, Z. V., and Anderson, A. K. (2013). Mindfulness meditation training alters cortical representations of interoceptive attention. *Soc. Cogn. Affect. Neurosci.* 8, 15–26. doi: 10.1093/scan/nss066

Fassino, S., Pierò, A., Gramaglia, C., and Abbate-Daga, G. (2004). Clinical, psychopathological and personality correlates of interoceptive awareness in anorexia nervosa, bulimia nervosa and obesity. *Psychopathology* 37, 168–174. doi: 10.1159/000079420

Frederickson, B. L., and Roberts, T. A. (1997). Objectification theory: toward understanding women's lived experiences and mental health risks. *Psychol. Women Q.* 21, 173–206. doi: 10.1111/j.1471-6402.1997.tb00108.x

Friederich, H. C., Brooks, S., Uher, R., Campbell, C. II, Giampietro, V., Brammer, M., et al. (2010). Neural correlates of body dissatisfaction in anorexia nervosa. *Neuropsychologia* 48, 2878–2885. doi: 10.1016/j.neuropsychologia.2010.04.036

Garfinkel, S. N., and Critchley, H. D. (2013). Interoception, emotion and brain: new insights link internal physiology to social behaviour. Commentary on: "anterior insular cortex mediates bodily sensibility and social anxiety by" Terasawa et al. (2012). *Soc. Cogn. Affect. Neurosci.* 8, 231–234. doi: 10.1093/scan/nss140

Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., and Critchley, H. D. (2015). Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. *Biol. Psychology* 104, 65–74. doi: 10.1016/j.biopsycho.2014.11.004

Garner, D. M. (1984). *Eating Disorder Inventory 2.* Firenze: Organizzazioni Speciali.

Herbert, B. M., Blechert, J., Hautzinger, M., Matthias, E., and Herbert, C. (2013). Intuitive eating is associated with interoceptive sensitivity. Effects on body mass index? *Appetite* 70, 22–30. doi: 10.1016/j.appet.2013.06.082

Herbert, B. M., Muth, E. R., Pollatos, O., and Herbert, C. (2012). Interoception across modalities: on the relationship between cardiac awareness and the sensitivity for gastric functions. *PLoS One* 7:e36646. doi: 10.1371/journal.pone.0036646

James, W. (1884). What is an emotion? *Mind* 9, 188–205. doi: 10.1093/mind/os-IX.34.188

Keizer, A., Smeets, M. A. M., Postma, A., van Elburg, A., and Dijkerman, H. C. (2014). Does the experience of ownership over a rubber hand change body size perception in anorexia nervosa patients? *Neuropsychologia* 62, 26–37. doi: 10.1016/j.neuropsychologia.2014.07.003

Klabunde, M., Acheson, D. T., Boutelle, K. N., Matthews, S. C., and Kaye, W. H. (2013). Interoceptive sensitivity deficits in women recovered from bulimia nervosa. *Eat. Behav.* 14, 488–492. doi: 10.1016/j.eatbeh.2013.08.002

Klein, D. A., and Walsh, B. T. (2003). Eating disorders. *Int. Rev. Psychiatry* 15, 205–216. doi: 10.1080/0954026031000136839

Koch, A., and Pollatos, O. (2014a). Cardiac sensitivity in children: sex differences and its relationship to parameters of emotional processing. *Psychophysiology* 51, 932–941. doi: 10.1111/psyp.12233

Koch, A., and Pollatos, O. (2014b). Interoceptive sensitivity, body weight and eating behavior in children: a prospective study. *Front. Psychol.* 5:1003. doi: 10.3389/fpsyg.2014.01003

Matsumoto, R., Kitabayashi, Y., Narumoto, J., Wada, Y., Okamoto, A., Ushijima, Y., et al. (2006). Regional cerebral blood flow changes associated with interoceptive awareness in the recovery process of anorexia nervosa. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 30, 1265–1270. doi: 10.1016/j.pnpbp.2006.03.042

Miyake, Y., Okamoto, Y., Onoda, K., Kurosaki, M., Shirao, N., Okamoto, Y., et al. (2010). Brain activation during the perception of distorted body images in eating disorders. *Psychiatry Res.* 181, 183–192. doi: 10.1016/j.pscychresns.2009.09.001

Pollatos, O., and Georgiou, E. (2016). Normal interoceptive accuracy in women with bulimia nervosa. *Psychiatry Res.* 240, 328–332. doi: 10.1016/j.psychres.2016.04.072

Pollatos, O., and Schandry, R. (2004). Accuracy of heartbeat perception is reflected in the amplitude of the heartbeat-evoked brain potential. *Psychophysiology* 41, 476–482. doi: 10.1111/1469-8986.2004.00170.x

Pollatos, O., Kirsch, W., and Schandry, R. (2005). Brain structures involved in interoceptive awareness and cardioafferent signal processing: a dipole source localization study. *Hum. Brain Mapp.* 26, 54–64. doi: 10.1002/hbm.20121

Pollatos, O., Kurz, A. L., Albrecht, J., Schreder, T., Kleemann, A. M., Schöpf, V., et al. (2008). Reduced perception of bodily signals in anorexia nervosa. *Eat. Behav.* 9, 381–388. doi: 10.1016/j.eatbeh.2008.02.001

Pollatos, O., Matthias, E., and Keller, J. (2015). When interoception helps to overcome negative feelings caused by social exclusion. *Front. Psychol.* 6:786. doi: 10.3389/fpsyg.2015.00786

Ronchi, R., Bello-Ruiz, J., Lukowska, M., Herbelin, B., Cabrilo, I., Schaller, K., et al. (2015). Right insular damage decreases heartbeat awareness and alters cardio-visual effects on bodily self-consciousness. *Neuropsychologia* 70, 11–20. doi: 10.1016/j.neuropsychologia.2015.02.010

Sachdev, P., Mondraty, N., Wen, W., and Gulliford, K. (2008). Brains of anorexia nervosa patients process self-images differently from non-self-images: an fMRI study. *Neuropsychologia* 46, 2161–2168. doi: 10.1016/j.neuropsychologia.2008.02.031

Schandry, R. (1981). Heart beat perception and emotional experience. *Psychophysiology* 18, 483–488. doi: 10.1111/j.1469-8986.1981.tb02486.x

Seth, A. K., Suzuki, K., and Critchley, H. D. (2012). An interoceptive predictive coding model of conscious presence. *Front. Psychol.* 2:395. doi: 10.3389/fpsyg.2011.00395

Suzuki, K., Garfinkel, S. N., Critchley, H. D., and Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia* 51, 2909–2917. doi: 10.1016/j.neuropsychologia.2013.08.014

Terasawa, Y., Moriguchi, Y., Tochizawa, S., and Umeda, S. (2014). Interoceptive sensitivity predicts sensitivity to the emotions of others. *Cogn. Emot.* 28, 1435–1448. doi: 10.1080/02699931.2014.888988

Trautmann, J., Worthy, S. L., and Lokken, K. L. (2007). Body dissatisfaction, bulimic symptoms and clothing practices among college women. *J. Psychol.* 141, 485–498. doi: 10.3200/jrlp.141.5.485-498

Tsakiris, M., Tajadura-Jiménez, A., and Costantini, M. (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. *Proc. Biol. Sci.* 278, 2470–2476. doi: 10.1098/rspb.2010.2547

Uher, R., Murphy, T., Friederich, H. C., Dalgleish, T., Brammer, M. J., Giampietro, V., et al. (2005). Functional neuroanatomy of body shape perception in healthy and eating-disordered women. *Biol. Psychiatry* 58, 990–997. doi: 10.1016/j.biopsych.2005.06.001

Werner, N. S., Kerschreiter, R., Kindermann, N. K., and Duschek, S. (2013). Interoceptive awareness as a moderator of affective responses to social exclusion. *J. Psychophysiol.* 27, 39–50. doi: 10.1027/0269-8803/a000086

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Bodily Sensory Inputs and Anomalous Bodily Experiences in Complex Regional Pain Syndrome: Evaluation of the Potential Effects of Sound Feedback

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Neuroscientific studies have shown that human's mental body representations are not fixed but are constantly updated through sensory feedback, including sound feedback. This suggests potential new therapeutic sensory approaches for patients experiencing body-perception disturbances (BPD). BPD can occur in association with chronic pain, for example in Complex Regional Pain Syndrome (CRPS). BPD often impacts on emotional, social, and motor functioning. Here we present the results from a proof-of-principle pilot study investigating the potential value of using sound feedback for altering BPD and its related emotional state and motor behavior in those with CRPS. We build on previous findings that real-time alteration of the sounds produced by walking can alter healthy people's perception of their own body size, while also resulting in more active gait patterns and a more positive emotional state. In the present study we quantified the emotional state, BPD, pain levels and gait of twelve people with CRPS Type 1, who were exposed to real-time alteration of their walking sounds. Results confirm previous reports of the complexity of the BPD linked to CRPS, as participants could be classified into four BPD subgroups according to how they mentally visualize their body. Further, results suggest that sound feedback may affect the perceived size of the CRPS affected limb and the pain experienced, but that the effects may differ according to the type of BPD. Sound feedback affected CRPS descriptors and other bodily feelings and emotions including feelings of emotional dominance, limb detachment, position awareness, attention and negative feelings toward the limb. Gait also varied with sound feedback, affecting the foot contact time with the ground in a way consistent with experienced changes in body weight. Although, findings from this small pilot study should be interpreted with caution, they suggest potential applications for regenerating BDP and its related bodily feelings in a clinical setting for patients with chronic pain and BPD.

Keywords: body perception, body representation, anomalous bodily experiences, complex regional pain syndrome, action sounds, body-related sensory inputs, multisensory interaction, technologies for self-management

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INTRODUCTION

Anomalous bodily experiences accompany a number of chronic pain conditions, such as in the case of complex regional pain syndrome (CRPS), also known as Reflex Sympathetic Dystrophy Syndrome (RSD). CRPS may initially affect a single limb, but rarely may then spread throughout the body. It may occur following injury and major nerve damage (Type 2), or after minor trauma with no apparent nerve injury, or spontaneously (Type 1). The cause of CRPS is unclear and is likely to involve multiple different mechanisms involving inflammation, the immune system, and the autonomic, peripheral and central nervous systems (Rockett, 2014). The incidence of CRPS type 1 varies from 5.46 per 100,000 person-years at risk with a prevalence of 20.57 per 100,000 (Sandroni et al., 2003), to 26.2 per 100,000 person-years (de Mos et al., 2007). Sufferers of CRPS describe a severe, continuous, and debilitating pain in their affected limb, and 55–85% of these sufferers experience some sort of body perception disturbances (Lewis and McCabe, 2010).

They describe abnormal sensations such as segments of their limb being perceived as being much larger, heavier, or different in shape, temperature, or pressure from objective assessment; sometimes sections of the limb may also be reported as being missing during mental visualization (some examples are given in **Figure 1**; Moseley, 2005; Lewis and McCabe, 2010; Turton et al., 2013). Other disturbances include a sense of disowning the affected limb or difficulties in moving it; lack of awareness as to the position of the impaired limb; and hostile feelings toward the limb, such as hate, anger, disgust, or repulsion, that often lead to a desire to amputate this limb (Galer and Jensen, 1999; Förderreuther et al., 2004; Lewis et al., 2007; Harden et al., 2010; Lewis and McCabe, 2010). Furthermore, significant motor dysfunction is a common symptom in people with CRPS (Galer et al., 1999). CRPS is a deeply distressing condition that has a significant impact on the sufferer's quality of life. A significant number experience lasting symptoms, and some experience chronic pain and disability (Bean et al., 2014). There is currently no cure for this condition, and pain may continue indefinitely despite treatment attempts. While CRPS affects far fewer people than other chronic pain conditions such as fibromyalgia, patients with CRPS may present extreme body-perception disturbances (BPD) and thus CRPS becomes a good model condition to study anomalous bodily experiences.

Previous works have described that some people with CRPS have referred sensations (i.e., the perception of a stimulus at a location distant from the stimulated body site; McCabe et al., 2003). These sensations are thought to be a clinical correlate of the cortical reorganization found in neuroimaging, psychophysical and transcranial magnetic stimulation studies in areas of the primary and secondary somatosensory cortex responsible for the representation of the affected limb (Flor et al., 1995, 1997; Maihöfner et al., 2003, 2004; McCabe et al., 2003; Eisenberg et al., 2005; Pleger et al., 2005; Marinus et al., 2011). There is also clinical evidence that in people with CRPS there can be dysfunction of parietal regions (Schwoebel et al., 2001; Cohen et al., 2013). These regions overlap with multisensory parietal areas integrating somatosensory, visual and auditory signals to form mental body representations (Serino et al., 2013).

The term body-representation refers to the internal knowledge of the size and shape of one's body parts and its position in space relative to each other (Longo et al., 2010; Medina and Coslett, 2010). Body-representations are not only essential for everyday motor functioning, but are also tightly linked to emotional processes (Carruthers, 2008; Pollatos et al., 2008). As demonstrated by neuroscientific and psychological research, body-representations are continuously updated by multisensory information received during bodily interactions with the environment (Tsakiris, 2010). Indeed, whereas one's body does not often change appearance very quickly, the mental representation of body appearance can update very quickly in response to sensory feedback (Botvinick and Cohen, 1998; Maravita and Iriki, 2004; Serino and Haggard, 2010; Longo and Haggard, 2012). There are now numerous examples of artificial manipulations of body-representations using specially designed sensory feedback. For instance, in the so-called *rubber hand* illusion, people experience an artificial rubber hand as their own if they see the rubber hand being touched and in synchrony they feel their own hand being touched (Botvinick and Cohen, 1998). A related illusion is the so-called *body swap* illusion, in which people experience an entire artificial body as their own if they are administered tactile stimulation on their chest while they observe a synchronous touch on a manikin's chest (Petkova and Ehrsson, 2008; van der Hoort et al., 2011). These changes in body-representation are triggered by integration of discrepant visual, tactile, and proprioceptive information. A few recent studies have shown that sound can also be used for inducing changes in the perceived physical appearance of one's own body and that these changes have an effect in the related emotional state and patterns of bodily movement (Tajadura-Jiménez et al., 2012, 2015a,b, 2016). We highlight one of these studies in which we showed that the altering of walking sounds to make them consistent with those produced by a lighter body leads to represent one's body as slimmer, as well as enhancing emotional state and changing gait biomechanics in a way consistent with having a lighter body (Tajadura-Jiménez et al., 2015a).

The above studies show that sensory inputs are responsible for forming and updating mental body-representation. Of relevance to the present research, some of these studies have proposed that the altering of sensory cues related to one's body can result in reorganization within the somatosensory cortex (Taylor-Clarke et al., 2004; de Vignemont et al., 2005; Haggard et al., 2007; Cardinali et al., 2009, 2012; Cardini et al., 2011, 2012, 2013; Tajadura-Jiménez et al., 2012, 2016; Canzoneri et al., 2013a,b; Miller et al., 2014; Cardini and Longo, 2016). In relation to people with CRPS, it has been suggested that the lack of sensory input from the limb may contribute to the perpetuation of their BPD, as they are often reluctant to look at or touch their affected limb, choosing to position it in such a way that it is outside their field of view and even trying to avoid thinking about it (Lewis et al., 2007; Lewis and McCabe, 2010).

Treatment for CRPS often utilizes a combination of cognitive strategies which encourage patients to visualize their affected limb and think about it in a positive way, and sensory-motor

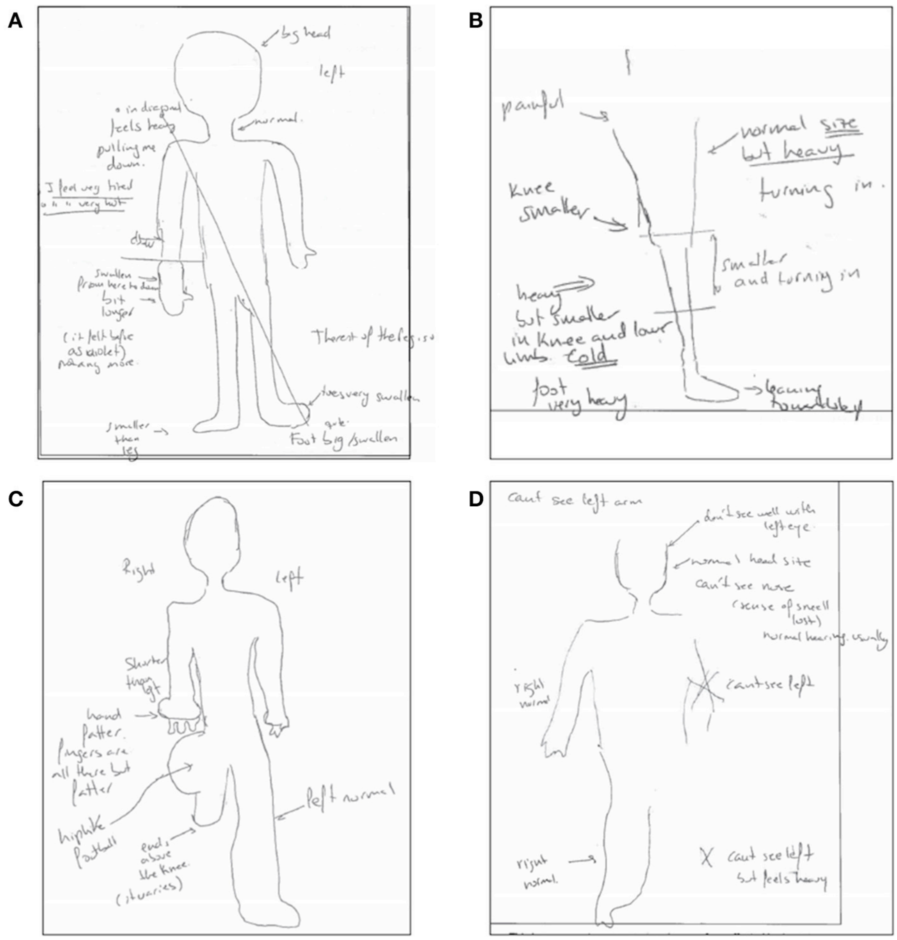

FIGURE 1 | Examples of anomalous bodily experiences in CRPS. The Figure displays four drawings generated from descriptions provided by participants when asked to visualize their body with eyes closed as part of the Bath CRPS Body Perception Disturbance Scale. Notes on the drawing read: **(A)** "big head," "feels heavy, pulling me down," "I feel very tired," "I feel very hot," "swollen from here to down and a bit longer. Before it felt as violet" [referring to the lower part of the right arm], "foot is big and swollen, toe is very swollen" [referring to the left foot], "the rest of the leg is ok"; **(B)** "painful," "heavy but smaller in knee and lower limb; turning in and cold," "foot very heavy and leaning toward left," "normal size but heavy; turning in" [referring to the rest of the leg]; **(C)** "shorter than left, hand fatter, fingers are all there but fatter" [referring to right arm], "hip like a football," "ends above the knee" [referring to right leg]; "left side is normal"; **(D)** "can't see the left arm," "don't see well with left eye," "can't see the nose (the sense of smell is lost, hearing is usually normal), "can't see left leg, but feels heavy," "right side is normal."

strategies encouraging them to move, look and touch the limb to provide accurate sensory inputs that help correct the BPD. Other sensory therapies, known as sensory discrimination training or desensitization therapy involve subjecting the limb to a range of textures and other stimuli such as thermal challenges (Moseley, 2008; Lewis and McCabe, 2010). Such approaches are recommended in therapeutic guidelines for CRPS (Goebel et al., 2012) and they are a core component of multi-disciplinary rehabilitation programs, but there is little published evidence to support this practice (Stanton-Hicks et al., 1998, 2002).

Some people with CRPS may find sensory interventions involving looking at or touching their affected limb upsetting for them, given the previously mentioned reluctance to look at or touch the limb (Lewis et al., 2007; Lewis and McCabe, 2010). In some of these cases mirror-visual feedback may become a useful aid in CRPS rehabilitation because it avoids direct contact with the affected limb, yet it provides visual inputs that help updating limb representations (Lewis and McCabe, 2010). Here, we explored for the first time the possibility of using sound-feedback to help with regenerating distorted mental body-representations in people with CRPS. The use of sound feedback in this case offers a number of interesting advantages, as apart from removing the need for direct visual contact with the affected limb, it can provide a continuous flow of information, as audition never "turns off" in the same way that vision is blocked when shutting our eyes, and it does not interfere with movement. Further, for the specific design of the sound feedback, we built on our previous findings on healthy people that real-time alteration of self-produced walking sounds can alter people's perceptions of their body size/weight, while enhancing gait patterns and people's positivity toward their bodies (Tajadura-Jiménez et al., 2015a). Of relevance, other recent studies from our group have demonstrated that real-time sound-feedback on one's movement can be used for sensory substitution of defective proprioception in people with low back pain, increasing confidence and motivation for physical activity in these populations (Singh et al., 2014, 2016).

While it has been demonstrated that sound can alter body perception in healthy controls, it is unknown whether this is possible in the context of chronic pain and BPD. The aim of this proof-of-principle pilot study was to establish whether sound can be used to alter BPD in CRPS. The hypothesis was that the altering of the auditory feedback derived from one's footsteps would lead to an enhanced perception of one's body and its related emotional state and gait in those with CRPS. To date this approach has not been trialed in CRPS. The findings may help to ascertain the feasibility and potential value of auditory simulation for regenerating BPD and its related bodily feelings in a clinical setting.

TABLE 1 | Demographic characteristics of participants with CRPS.

Gender	Age at experiment	Duration CRPS (years and months)	Body part affected	BPD group
Female	40	1 year and 6 months	Right lower limb	Big
Female	48	1 year and 9 months	Right upper limb/left lower limb	Big
Female	62	3 years and 2 months	Right upper limb	Big
Female	49	8 years	Right lower limb	Mixed
Female	56	3 years and 7 months	Right lower limb	Mixed
Female	46	4 years and 2 months	Right lower limb	Small
Male	36	1 year	Right lower limb	Nothing
Female	39	17 years and 4 months	Left upper limb	Nothing
Male	64	4 years and 5 months	Both lower limbs	Nothing
Female	52	9 years	Both lower limbs (left worse than right)	Nothing
Female	52	16 years	Both upper limbs (possibly left lower limb)	Nothing
Female	44	1 year and 8 months	Left lower limb	Nothing

MATERIALS AND METHODS

Participants

Twelve participants were recruited (10 female and 2 male; mean age ± *SD*: 49.0 ± 8.4 years; age range from 36 to 64 years—see individual demographic characteristics of participants in **Table 1**). The inclusion criteria were the following: (1) age comprised between 18 and 70 years old; (2) meet the recognized diagnostic research criteria for CRPS Type I; and (3) able to walk continuously for at least 60 s with or without walking aids. The exclusion criteria were the following: (1) diagnosis of any other neurological, psychopathologic, motor disorder, or major nerve damage (CRPS Type II); (2) disability significantly affecting physical mobility/activity; (3) the presence of any other limb pathology or pain on the affected CRPS limb; (4) hearing impairment; (5) weight <40 kg or more than 135 kg; (6) severe Postural Orthostatic Tachycardia Syndrome (POTS); (7) insufficient mental capacity to take part in the study; and (8) unable to understand written or verbal English and give informed consent. The characteristics of each participant, including demographics, duration of CRPS condition and body part affected are listed in **Table 1**.

Participants were recruited through the Royal National Orthopaedic Hospital (RNOH) at Stanmore from a tertiary referral service for those with CRPS. Potential participants were identified from current patients and from patients who have previously received treatment for CRPS at RNOH and sent an invitation to voluntary take part in the study. Participants were naïve as to the purposes of the study. This study was carried out in accordance with the recommendations of the 1964 Declaration of Helsinki and the ethics committee of the UK National Health Service. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the UK National Health Service Research Ethics Committee.

Apparatus and Materials

The experiment was conducted at the local motor learning lab of the RNOH, which is a quiet environment. Participants were asked to walk on the spot (i.e., to imitate the motions of walking, lifting one leg after the other, without actually resulting in any displacement) for short periods of 1 min on the hard rubber platform of a stationary treadmill. This stationary treadmill was used for safety and comfort reasons, as this setting allowed participants to hold onto two parallel bars placed on the sides of the platform. The height of these bars could be adjusted according to the height of participants. A functioning treadmill was not used because early exploratory work had shown that the sound of the treadmill motor interferes with the sound used in the study. During the walking periods participants were asked to wear a system, which is displayed in **Figure 2**. This system allows the dynamic modification of footstep sounds, as people walk, and measurement of walking behavior changes. Three sound feedback conditions were designed, as described in Section Sound Feedback Conditions. The system was an adaptation of the system used in Tajadura-Jiménez et al. (2015a), with some modifications in the part involved in gait data collection that allowed minimizing the system thus making it easier to carry. The system is comprised by commercial components, including a pair of strap sandals that are easy to wear (EU size 42); two microphones attached to the sandals and that capture the walking sounds (Core Sound, frequency response 20 Hz–20 kHz); and four force-sensitive resistors (FSR; 1.75 × 1.5″ sensing area) attached to the front and the rear part of each sandal insole and that detect the exerted force by feet against the ground (as in Tajadura-Jiménez et al., 2015a). In addition, the device includes two 3-axis accelerometers attached to the participant's ankles (Sparkfun). FSRs and accelerometer in each foot are connected to a Microduino microcontroller board, which combined a Microduino Core, a Microduino Shield Bluetooth 4.0, and a Microduino USBTTL Shield. This board allowed linking the sensors via Bluetooth to a smartphone that acquired their data. The microphones are connected to a small stereo pre-amplifier (SP-24B) and a sound equalizer (Behringer FBQ800) that modify the sound spectra and these connect to a pair of headphones participants wore (Sennheiser HDA 300). These headphones

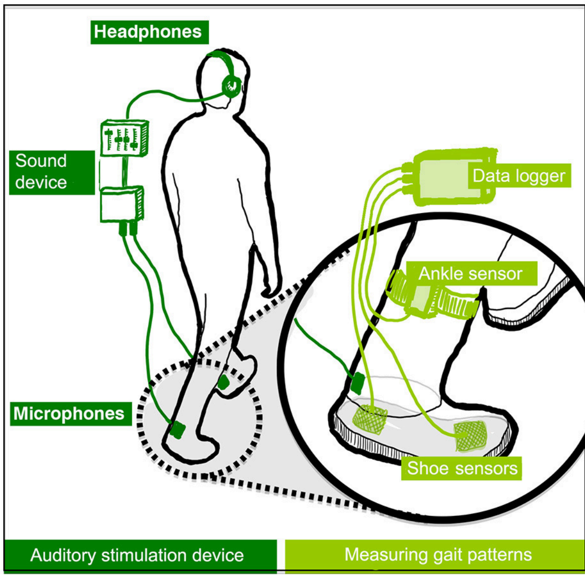

FIGURE 2 | Overview of the auditory stimulation device **(left)** and sensors used for sensing gait **(right)**. In healthy participants, short adaptation periods to altered walking sounds led to lower perceived body weight, to the adoption of gait patterns typical of lighter bodies and to an enhanced emotional state. (Tajadura-Jiménez et al., 2015a), © 2015 ACM, Inc. https://doi.org/10.1145/2702123.2702374. Reprinted by permission. This figure is published in color in the online version.

had high passive ambient noise attenuation (>30 dBA) that muffled the actual sound of footsteps. The analog sound loop had minimal latency (<1 ms). Pre-amp and equalizer were fitted into a small backpack the walker could carry (~2 Kg, 35 × 29 × 10 cm).

A 22-inches computer screen, linked to a laptop computer, was placed in front of participants at the edge of the walking platform (~50 cm away from participants), and it was used for the tasks involving estimating body dimensions (see Section Measures). A keypad, placed on the top of one of the parallel bars, was used to collect participants' responses on body estimates. Presentation® software was used to control the stimulus delivery and to record the participant's body estimates.

Experimental Design

Sound Feedback Conditions

Three sound feedback conditions were designed (based on Li et al., 1991; Tajadura-Jiménez et al., 2015a) for the walking periods. These conditions were created by dynamically modifying the footstep sounds people produce as they walk: a "Control" condition in which no sound feedback was provided (headphones were put inside the backpack); a "High frequency" condition in which the frequency components of the footsteps sounds in the range 1–4 kHz were amplified by 12 dB and those in the range 83–250 Hz were attenuated by 12 dB; and a "Low Frequency" condition in which the frequency components in the range 83–250 Hz were amplified by 12 dB and those above 1 kHz were attenuated by 12 dB.

Measures

This mixed methods study utilized qualitative and quantitative outcome measures. The effects of sound feedback received during the 1-min walking periods on BPD and the related bodily feelings and patterns of bodily movement were evaluated by combining self-reporting and objective behavioral measures. Specifically, the effects of sound feedback on BPD were measured in three ways: (1) by assessing the effect of sound on perceived body dimensions; (2) by quantifying changes on gait mechanics, as an implicit measure of changes in perceived body weight; and (3) by looking at the effect of sound on CRPS descriptors, pain and other bodily/emotional feelings that may indicate changes in perceived body parts. Data collected included estimates of body dimensions and verbal descriptions of limb perception; questionnaire data on perceived pain and emotional state; and capture of gait data. The measures used are detailed below:

a) Assessment of perceived body dimensions ("avatar," "aperture," and "hands" tasks): participants were asked to estimate the size of their affected body part by indicating this size using their two hands ("hands" task). They were also asked to use a line task visualization tool which involved two white vertical lines displayed on the screen on a black background and which could be moved toward each other, or moved further apart, with use of the keypad. With this tool, participants adjusted the distance between the two lines to correspond to the perceived width of their affected body part ("aperture" task; adapted from studies by Linkenauger et al., 2009; Keizer et al., 2013). Participants were also asked to use a body visualization tool (bodyvisualizer.com; used by Tajadura-Jiménez et al., 2015a for the same purpose) in which they adjusted the weight related dimension of the body of a 3D avatar displayed on the screen to correspond to their perceived body size ("avatar" task). Participants' actual weight and the actual dimensions of their entire body and affected body part(s) were recorded as reference.

b) The Short Form McGill Pain Questionnaire (SF-MPQ; Melzack, 1987): This is a self-report questionnaire, which provides a comprehensive assessment of participants' pain. It includes a 0–10 cm visual analog rating scale of pain intensity as well as a comprehensive list of pain descriptors that capture the quality of that pain. Three pain scores are derived from the sum of the intensity rank values of the words chosen for sensory, affective, and total descriptors. This questionnaire is commonly used in pain clinical routine and pain research. Both the SF-MPQ and the longer MPQ from which it is derived have been shown to have good validity (Dubuisson and Melzack, 1976; Wright et al., 2001; Zinke et al., 2010) and reliability (Graham et al., 1980; Strand et al., 2008). The SF-MPQ also includes the Present Pain Intensity (PPI) index of the standard MPQ.

c) Assessment of participants body feelings—The Bath CRPS Body perception Disturbance Scale (referred in this paper as CRPS BPD scale; Lewis and McCabe, 2010) and "questionnaire on body feelings": The CRPS BPD scale is standardly used in clinical routine with CRPS patients, and includes a set of items and a drawing based on a verbal description of participants' perception of their painful limb with their eyes closed. This is a routine clinical assessment, which is thought to provide an insight into the extent of cortical reorganization (Förderreuther et al., 2004). We quantified other aspects of the experience by asking participants to select a score that best expresses their feelings using 7-point Likert-type response items adapted from previous studies on healthy participants (Tajadura-Jiménez et al., 2015a). It was comprised by 4 statements which range from: "I feel slow" to "I feel quick" (Speed); "I feel light" to "I feel heavy" (Weight); "I feel weak" to "I feel strong" (Strength); "I feel crouched/stooped" to "I feel elongated/extended" (Extension). In addition, in the following four statements participants rated their level of agreement (from "I strongly disagree" to "I strongly agree"): "It seems like the sounds I hear are produced by my own footsteps/body" (Agency); "It seems the feeling of my body is less vivid than normal" (Vividness); "The feelings about my body are surprising and unexpected" (Surprise); "It seems like I could really tell where my feet are" (Feet localization).

d) Assessment of changes in emotional state ("questionnaire on emotional feelings"): Emotional valence, dominance, and arousal felt by participants were quantified by using the 9-item graphic scales of the self-assessment manikin questionnaire (Bradley and Lang, 1994).

e) Assessment of changes in gait patterns: Gait biomechanics were taken as an implicit measure of changes in perceived body weight (Tajadura-Jiménez et al., 2015a). The "stance" and the "swing" of the two phases of a gait cycle (i.e., the time between two successive steps made by one foot, Cunado et al., 2003) were analyzed. The stance phase starts with the strike of the heel on the ground and ends when the toes lose contact with the ground. Data from the FSR sensors placed on the sandal insoles were used to quantify the mean exerted force of the heel and toes against the ground and their contact times, as well as the stance and the gait cycle times. The swing phase starts with the foot lifting, first accelerating and then decelerating (midswing) while preparing for the next heel strike and while the other foot is on the ground. The foot accelerates again when the flexor muscles are activated to move the foot forward and downwards (Vaughan et al., 1992). The accelerometers data were used to quantify the foot lifting acceleration (as in Tajadura-Jiménez et al., 2015a).

To extract the gait parameters a specifically developed piece of software was used. Raw sensor data are parsed by this software, which then isolates the accelerometer and FSR readings and creates separate data sets for the left and right foot. FSR data for heel and toe are separated further. As in the paper by Tajadura-Jiménez et al. (2015a), the net acceleration is calculated as the square root of the sum of the squares of the three acceleration axes. The resultant acceleration, FSR of heel and FSR of toe data are low passed filtered to limit the effects of noise (as in Kavanagh and Menz, 2008; Harle et al., 2012). Finally, the first derivative of the resultant acceleration is calculated. For the FSR readings, the software considers that the foot touches the ground when the FSR value exceeds a threshold value. Erroneous detections of the foot leaving the ground are avoided by considering the rate of change of the acceleration readings. Once all steps have been identified within the data sets, the following parameters are extracted for each foot and for each step: mean exerted force of the heel and toes against the ground, stance or contact time (difference between initial strike time and last contact time), gait cycle times and maximum foot lifting acceleration (see **Figure 3**). For each trial and for each extracted parameter we calculated the average of all steps in the walking phase.

Procedure

Verbal and written instructions about the tasks were given to participants at the beginning of the session. Next, participants' actual weight and height were recorded as reference. We also asked participants to indicate which was the part of their limb that was more affected (e.g., the knee, the ankle, etc.), and the actual width of this affected body part was also recorded as reference. This body part would be the one referred to during the "aperture" task and the "hands" task. Participants were then asked to complete, in this order, the questionnaire on emotional feelings, the questionnaire on body feelings, the SF-MPQ and the CRPS BPD Scale. Next, participants were equipped with all the sensors and sound-feedback system and were instructed on the tasks for the experiment. They were asked to complete a set of three experimental blocks differing in the sound feedback condition ("Low frequency," "High frequency," and "Control") and presented in a randomized order. In each block, participants were asked to walk on the spot for 60 s, at a self-paced, comfortable speed, while holding the parallel bars on the sides of the treadmill platform. After this 60-s period, participants were asked to complete twice the "aperture" task. In one of the "aperture" trials the lines started together and in the other trial they started 54 cm apart. The order of presentation of these two conditions was randomized, and an average of the two measures was calculated for each of the sound condition (as in Keizer et al., 2013). After the "aperture" task, they completed twice the "avatar" task. The avatar would be proportional to the participant in terms of gender and height, but its initial weight would either be 25% more, or 25% less compared to the participant's actual weight. The order of the two was randomized, and an average of these two weight measures in kilograms was calculated (as in Tajadura-Jiménez et al., 2015a). Finally, after the "avatar" task they completed once the "hands" task, in which participants were asked to close their eyes and used their hands in parallel separated a distance that corresponded to their felt width of their affected body part. The experimenter measured this distance by using a ruler. After providing these body size estimates, participants were removed of the headphones and backpack, and then asked to sit down and to complete in this order, the questionnaire on emotional feelings, the questionnaire on body feelings, the SF-MPQ, and the CRPS BPD scale. Prior to the three experimental blocks, participants performed an initial practice block which was similar to the experimental blocks in terms of tasks and in which they wore the headphones through which they could listen to non-manipulated versions of their footsteps sounds in order to familiarize themselves with the task and the sound feedback.

Data Analyses

We analyzed normal parametrical data (normality tested with Shaphiro–Wilk) with repeated measures analyses of variance (ANOVA), with sound condition ("Control," "High frequency," and "Low frequency") as within-subject factor, except for the gait data for which we conducted for each parameter an ANOVA

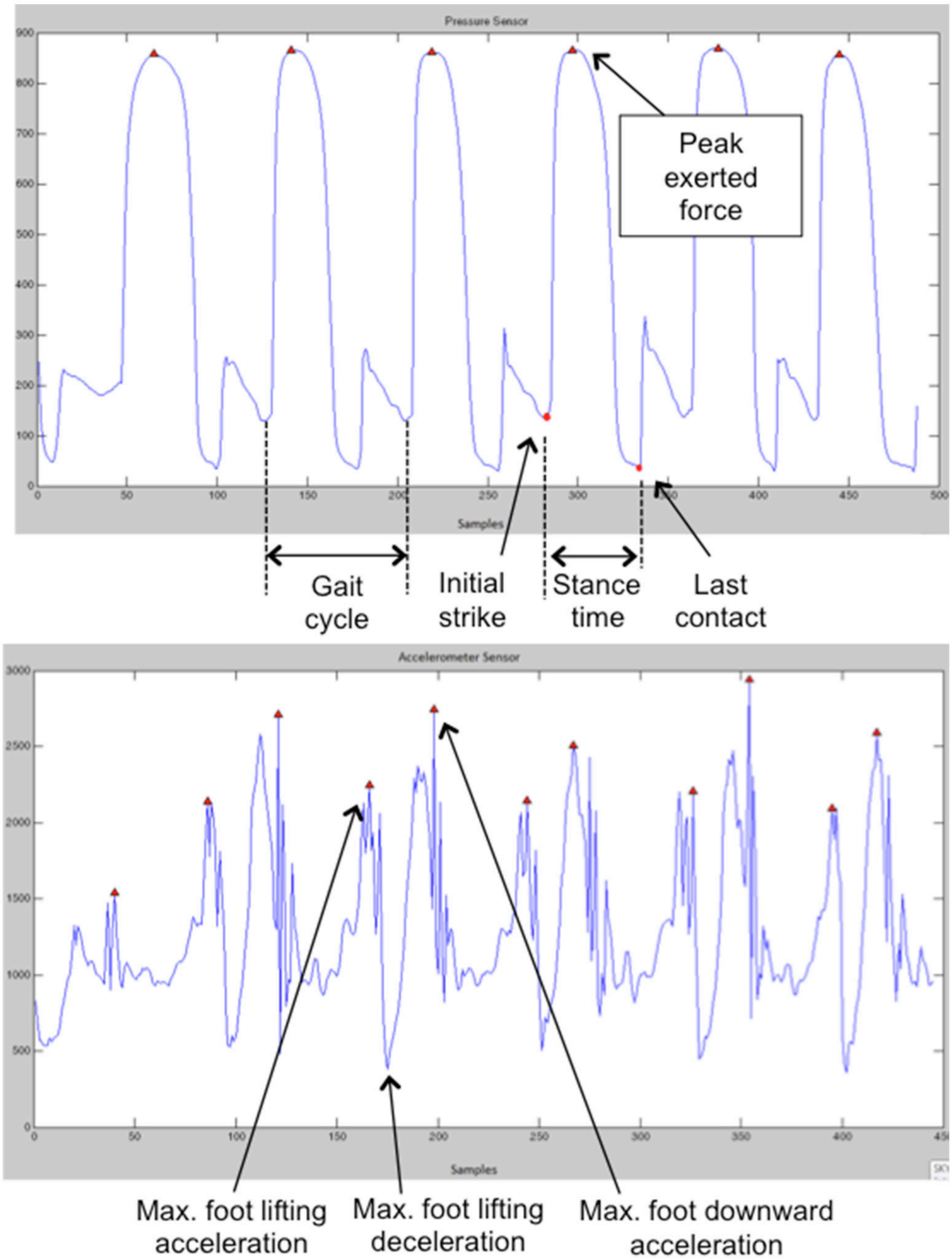

FIGURE 3 | (Top) Examples of FSR and **(Bottom)** and accelerometer data. This figure is published in color in the online version.

with 3 × 2 within-subject factors sound condition ("Control," "High frequency," and "Low frequency") and foot (left or right). Significant effects were followed by paired samples two-tailed *t*-tests, with the significance alpha level adjusted for multiple comparisons. We analyzed non-parametrical data with Friedman tests with sound condition ("Control," "High frequency," and "Low frequency") as within-subject factor. Significant effects were followed by Wilcoxon tests, with the significance alpha level adjusted to multiple comparisons. Given the group sizes, we did not use statistical tests for comparison within the four BPD subgroups we identified based on the pre-test body-representation drawings ("Big," "Small," "Mixed," and "Nothing" groups, as described in the Results Section) but we discuss the observed trends for each subgroup as displayed in figures and tables as these trends may provide some insight and inform the design of a larger study conducted in order to establish whether the type of BPD modulates the effect of sound feedback in CRPS.

RESULTS

Pre-test Values

As previously indicated, pre-test body-representation drawings were produced based on participants verbal descriptions of their body perception when asked to visualize it with eyes closed as part of the CRPS BPD scale. The results of this indicated four types of BPD (see **Table 1**): "Big" (i.e., limb represented as unusually big; 3 participants), "Small" (i.e., limb represented as unusually small; 1 participant), "Nothing" (i.e., not able to visualize his/her limb; 6 participants), and "Mixed" (i.e., a mixture of two or all the other groups; 2 participants). An example of each BPD group is displayed in **Figure 1**. The pre-test values for each individual corresponding to BPD scores, actual and estimated body dimensions, reported pain, emotional and bodily feelings are presented in Tables S1–S4. As previously mentioned, an analysis of the above by BPD group is out the scope of this study given the small population; a qualitative analysis, instead, aims to provide some insight into whether the type of BPD modulates the effect of sound feedback in CRPS.

Table 2 summarizes the pre-test CRPS total score (CRPS BPD), the ratio between estimated and actual body dimensions, reported pain and emotional feelings, for each BPD group. As it can be seen, CRPS total scores and pain scores were higher in the "Mixed" and "Nothing" groups than in the "Big" and "Small" groups. As shown in **Figure 4**, in the "Mixed" and "Nothing" groups, BPD scores for feelings of one's body part being detached, not paying attention to limb and negative feelings were higher than in the "Big" and "Small" groups; the feelings of body part position unawareness were higher for the "Small" and the "Nothing" groups than for the "Big" and "Mixed" groups.

Comments from the "Mixed" and "Nothing" groups when asked to visualize their body in order to produce the body visualization drawings, include the following (see also comments in **Figure 1**):

Mixed:

- "my right arm feels shorter, but hand and fingers are fatter; my right hip feels like a football and my right leg seems to end above the knee" (Participant P03)
- "my right arm feels heavy and slightly bigger than the left, and the hand feels twice bigger and longer; my right tight feels heavy and much bigger than normal, with some parts missing; I cannot visualize the right calf but it feels heavy and cold" (Participant P08).

Nothing:

- "I cannot visualize at all the left side of my body, but left arm and left leg feel heavy" (Participant P06)
- "I cannot visualize my left leg from half tight down, it is too painful; I don't know what to think about it, I hate it" (Participant P09)
- "my left tight feels skinny and I can't visualize the leg from above the knee down; the right knee feels ugly and distorted" (Participant P11)
- "I cannot visualize most of my left body (no arm, no leg) but feels heavy" (Participant P02)
- "below the knee the leg is blurry, it feels wooden ("like a pirate leg"); I don't know if it is big or small but it feels cold and wet" (Participant P05)
- "it is difficult to visualize the left arm; it is blurry and feels different than right arm and heavy" (Participant P12).

Effects of Sound Condition in BPD

The sections below summarize the effects of sound feedback received during the 1-min walking periods on the alteration of BPD. These effects were quantified in three different ways. First, by assessing the effect of sound on perceived body dimensions, using the avatar, aperture and hands task. Second, by quantifying changes on gait mechanics, as an implicit measure of changes in perceived body weight. And third, by looking at the effect of sound on CRPS descriptors (including drawings), pain and other bodily/emotional feelings that may indicate changes in perceived body parts.

Effect of Sound Condition on Perceived Body Dimensions

The mean values ± SE for the "avatar," "aperture," and "hands" tasks for all sound conditions ("Control," "High frequency," and

TABLE 2 | Mean (±SE) CRPS score, ratio between estimated and actual body dimensions, reported pain, and emotional feelings during the pre-test for each participant, according to their BPD group.

BPD group	CRPS Total score	Ratio between estimated and actual body dimensions			SF-MPQ Pain scores				Emotional feelings		
		Avatar task	Aperture task	Hands task	Sensory descript.	Affective descript.	PPI	VAS	Val	Aro	Dom
Big	26.33 (3.84)	0.96 (0.05)	1.58 (0.23)	1.61 (0.24)	9.00 (0.58)	0.00 (0.00)	1.67 (0.33)	5.62 (1.47)	5.33 (0.33)	5.67 (0.33)	3.67 (0.67)
Mixed	41.50 (3.50)	1.22 (0.05)	1.73 (0.1)	1.89 (0.11)	19.50 (0.50)	6.00 (4.00)	3.50 (0.50)	6.83 (0.08)	4.50 (2.50)	5.50 (2.50)	3.50 (1.50)
Small	23.00 (0)	1.15 (0)	2.76 (0)	2.13 (0)	14.00 (0)	3.00 (0)	2.00 (0)	6.25 (0)	7.00 (0)	5.00 (0)	5.00 (0)
Nothing	35.33 (2.76)	0.86 (0.09)	2.05 (0.4)	1.73 (0.31)	15.50 (3.89)	5.17 (1.64)	3.17 (0.40)	6.33 (0.60)	6.00 (1.03)	5.33 (0.56)	4.33 (1.15)

Estimates of body weight were quantified by the "avatar" task and estimates of the width of the affected body part were quantified by the "aperture" and the "hands" tasks. SF-MPQ scores include sensory and affective descriptors, Present Pain Intensity (PPI) score, VAS pain intensity score. Ratings of emotional feelings include emotional valence (Val), arousal (Aro), and dominance (Dom). The SF-MPQ scores correspond to the sum of the intensity rank values of the words chosen for sensory and affective descriptors. The PPI score ranges from 0 (no pain) to 5 (excruciating). The VAS pain score is a value between 0 and 10 cm, corresponding to a visual analog rating scale. Valence, Arousal, and Dominance ratings refer to the 9-item graphic scales of the self-assessment Manikin questionnaire.

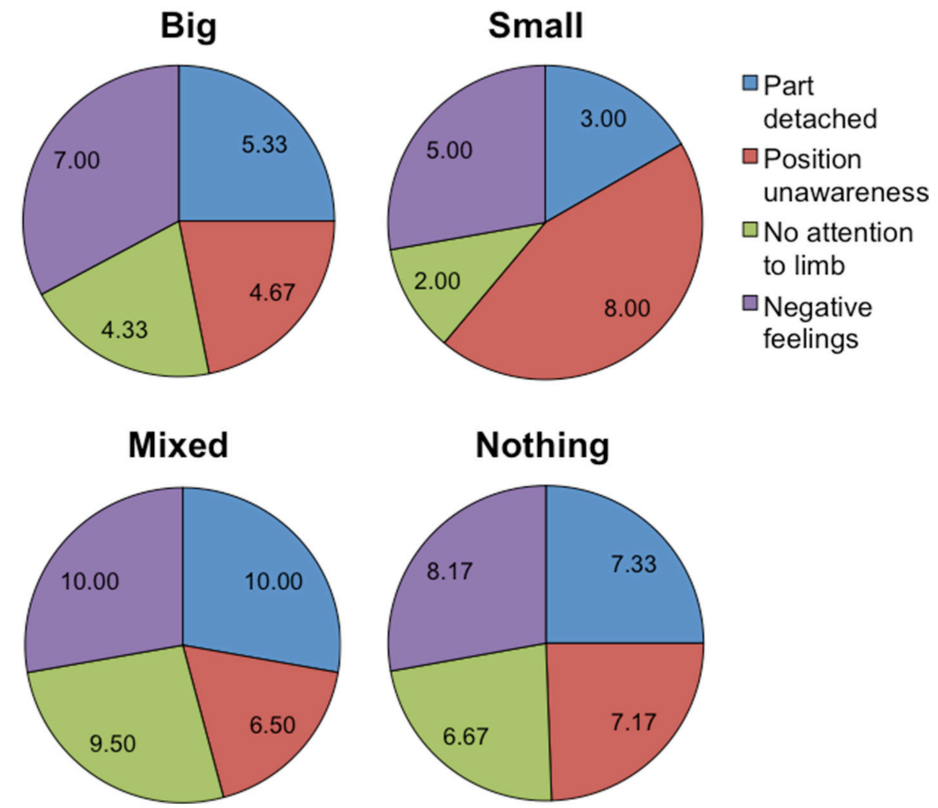

FIGURE 4 | Pie charts summarizing the mean pre-test body perception disturbance scores ($N = 12$). The four charts correspond to the four body disturbance groups: "Big" ($N = 3$), "Mixed" ($N = 2$), "Small" ($N = 1$), "Nothing" ($N = 6$). The pie sectors correspond to the first four 11-level Likert items of the Bath CRPS Body Perception Disturbance questionnaire. For the item "Part detached" the scale ranges from "very much a part" (0) to "completely detached" (11); for the item "Position unawareness" the scale ranges from "very aware" (0) to "completely unaware" (11); for the item "No attention to limb" the scale ranges from "full attention" (0) to "no attention" (11); for the item "Negative feelings" the scale ranges from "strongly positive" (0) to "strongly negative" (11). This figure is published in color in the online version.

"Low frequency") are presented in **Figure 5** and individual data are presented in Tables S5–S7. While there were no statistically significant effects of sound on perceived body dimensions, the results shown in **Figure 5** suggest that the sound condition affects perceived body dimensions differently according to the BPD group. This is evident on the data from the "aperture" and "hands" tasks. Indeed, **Figures 5E,F** suggest that sound feedback has larger effect on participants not able to visualize their affected body part (i.e., from the "Nothing" group). These participants represented their body part larger in the sound conditions, especially in the "High frequency" condition compared to the no sound ("Control") condition.

Effect of Sound Condition on Pain

The mean values ± SE for the McGill Pain PPI index for the pre-test and for all sound conditions ("Control," "High frequency," and "Low frequency") are presented in **Figure 6**. The mean values ± SE for the other McGill Pain data are presented in Figure S1 and the individual data are presented in Tables S8, S9.

Reviewing the effects of sound on the sensory descriptors, affective descriptors, total descriptors, and on the PPI and visual analog rating scale (VAS) of pain intensity, only the PPI showed a significant effect of sound condition [$X^2(2) = 7.28$, $p = 0.026$]. Follow-up Wilcoxon tests showed that the "High frequency" condition elicited higher ratings of pain than the "Low frequency" condition ($Z = -2.33$, $p = 0.020$). The effect of sound on the PPI suggests an effect of sound on the *unpleasantness* dimension of pain quantified by this index, rather than in the *intensity* dimension of pain, which the VAS scale quantifies. Data from each BPD group suggests that the sound condition may affect the pain ratings differently according to the BPD group.

Effect of Sound Condition on CRPS Descriptors and Other Bodily/Emotional Feelings

Participants reported that sound did have an effect on how the CRPS affected limb felt, and their associated bodily and emotional feelings. Group data (Median and range) are displayed in **Tables 3–5** and Figure S2 and the individual data are presented in Tables S10–S12. These did not reach statistical significance except for the dominance scale [$X^2(2) = 6.70$, $p = 0.035$]. People reported feeling more dominant in the Low frequency condition than in the High frequency condition ($Z = -2.33$, $p = 0.020$), with the rating for the Control condition falling in between the other two ratings (see **Figure 7** and **Table 3**).

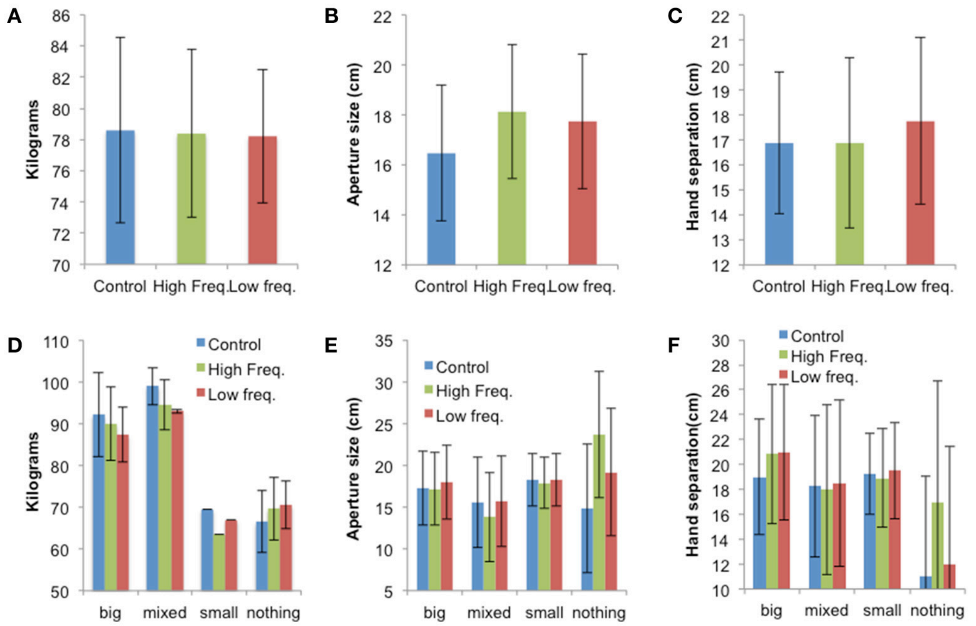

FIGURE 5 | (A) Mean perceived body weight (±SE), **(B)** mean aperture size (±SE), and **(C)** mean hand separation (±SE) for all three sound conditions ($N = 12$). Panels **(D–F)** show the mean results (±SE) for each BPD group: "Big" ($N = 3$), "Mixed" ($N = 2$), "Small" ($N = 1$), "Nothing" ($N = 6$). This figure is published in color in the online version.

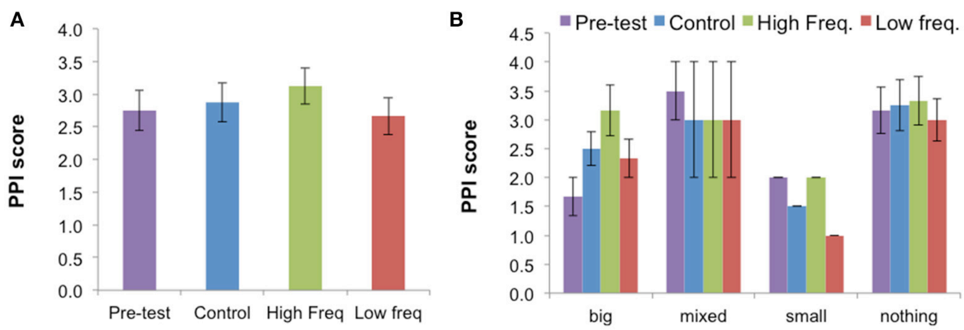

FIGURE 6 | (A) Mean Present Pain Intensity (PPI) score (±SE) for all three sound conditions and pre-test condition for all participants ($N = 12$). **(B)** Mean results (±SE) for each BPD group: "Big" ($N = 3$), "Mixed" ($N = 2$), "Small" ($N = 1$), "Nothing" ($N = 6$). The PPI (Present Pain Intensity) index is a pain score ranging from 0 (no pain) to 5 (excruciating). This figure is published in color in the online version.

TABLE 3 | Emotional valence (Val), Arousal (Aro), and Dominance (Dom) for all three sound conditions according to BPD group.

BPD group	Control condition			High frequency condition			Low frequency condition		
	Val	Aro	Dom	Val	Aro	Dom	Val	Aro	Dom
"Big"	5 (3–8)	6 (5–7)	5 (3–7)	6 (3–7)	7 (3–7)	6 (2–6)	7 (3–7)	7 (6–7)	7 (3–7)
"Mixed"	3.5 (1–6)	5.5 (3–8)	3 (1–5)	4 (1–7)	5 (2–8)	3 (1–5)	4 (1–7)	5 (2–8)	3 (1–5)
"Small"	7	7	6	7	6	4	7	7	6
"Nothing"	5.5 (2–7)	6 (4–7)	5.5 (2–7)	6 (2–8)	5.5 (3–7)	5 (2–7)	6 (2–7)	6 (4–7)	5 (2–8)
All participants	5.5 (1–8)	6 (3–8)	5 (1–7)	6 (1–8)	6 (2–8)	5 (1–7)	6.5 (1–7)	6.5 (2–8)	5 (1–8)

The values correspond to 9-level Likert items of the self-assessment Manikin questionnaire (Median value and range are indicated).

Other reported effects of sound included how detached their limb felt, limb position awareness, attention to the affected limb and negative feelings toward the limb. Some quotes of participants from the "Nothing" group, for which these effects of sound seemed more evident, are given below:

TABLE 4 | Bath CRPS Body perception Disturbance questionnaire data for all three sound conditions according to BPD group.

Condition	BPD group	Part detached	Position unawareness	No attention to limb	Negative feelings	Change size	Change temperature	Change pressure	Change weight
Control	"Big"	7 (4–8)	7 (5–8)	5 (1–7)	8 (3–8)	3	3	3	3
	"Mixed"	10 (10–10)	6.5 (3–10)	10 (10–10)	10 (10–10)	2	2	2	2
	"Small"	3	3	4	5	1	1	1	1
	"Nothing"	8.5 (5–10)	8.5 (5–9)	8 (4–10)	7.5 (6–10)	5	6	4	6
	All participants	7 (2–10)	7.5 (3–10)	7 (1–10)	8 (3–10)	11	12	10	12
High frequency	"Big"	8 (3–9)	8 (5–9)	7 (5–7)	7 (3–8)	3	3	3	3
	"Mixed"	9.5 (9–10)	6.5 (3–10)	10 (10–10)	10 (10–10)	2	2	2	2
	"Small"	4	0	2	5	1	1	1	1
	"Nothing"	5 (3–10)	4.5 (3–10)	4 (3–10)	7.5 (4–10)	5	6	6	6
	All participants	7 (3–10)	5 (0–10)	6 (2–10)	7.5 (3–10)	11	12	11	12
Low frequency	"Big"	7 (2–7)	8 (5–8)	5 (1–7)	7 (5–8)	2	3	3	3
	"Mixed"	9.5 (9–10)	6.5 (3–10)	10 (10–10)	10 (10–10)	2	2	2	2
	"Small"	7	7	7	3	0	1	0	1
	"Nothing"	7 (3–10)	6.5 (3–9)	6 (3–10)	8.5 (5–10)	5	5	5	6
	All participants	8 (3–10)	7.5 (3–10)	7 (1–10)	8 (3–10)	9	11	10	12

The values correspond to 11-level Likert items for the first four items (Median value and range are indicated) and frequency data for the other four items. For the item "Part detached" the scale ranges from "very much a part" (0) to "completely detached" (11); for the item "Position unawareness" the scale ranges from "very aware" (0) to "completely unaware" (11); for the item "No attention to limb" the scale ranges from "full attention" (0) to "no attention" (11); for the item "Negative feelings" the scale ranges from "strongly positive" (0) to "strongly negative" (11).

TABLE 5 | Body feelings questionnaire data for all three sound conditions according to BPD group.

Condition	BPD group	Speed	Weight	Strength	Extended	Agency	Vividness	Surprise	Feet localization
Control	"Big"	3 (2–4)	6 (2–6)	4 (3–5)	4 (2–6)	4 (4–6)	5 (3–5)	4 (4–5)	4 (2–6)
	"Mixed"	2.5 (1–4)	6 (5–7)	2.5 (1–4)	3.5 (3–4)	2.5 (1–4)	2 (1–3)	5.5 (4–7)	2 (1–3)
	"Small"	4	3	4	5	2	2	6	5
	"Nothing"	2 (1–6)	6 (5–6)	2 (1–5)	2 (1–5)	3 (1–6)	4 (1–6)	4.5 (2–7)	3.5 (1–6)
	All participants	2.5 (1–6)	6 (2–7)	3 (1–5)	3.5 (1–6)	3.5 (1–6)	3.5 (1–6)	4.5 (2–7)	3.5 (1–6)
High frequency	"Big"	4 (3–6)	3 (3–7)	4 (1–5)	5 (1–6)	3 (1–6)	2 (2–4)	5 (2–6)	5 (1–6)
	"Mixed"	2.5 (1–4)	6 (5–7)	2 (1–3)	3.5 (3–4)	4 (1–7)	2 (1–3)	5.5 (4–7)	3 (3–3)
	"Small"	3	5	2	2	6	4	2	7
	"Nothing"	3 (1–5)	5 (3–7)	2 (2–4)	2.5 (2–5)	5 (1–6)	5 (2–6)	5 (2–6)	5 (1–5)
	All participants	3 (1–6)	5 (3–7)	2 (1–5)	3 (1–6)	5 (1–7)	3.5 (1–6)	5 (2–7)	5 (1–7)
Low frequency	"Big"	5 (2–5)	4 (2–6)	4 (2–5)	6 (2–6)	6 (2–6)	6 (3–6)	5 (2–6)	5 (2–6)
	"Mixed"	2.5 (1–4)	5.5 (4–7)	2.5 (1–4)	3 (3–3)	7 (7–7)	2.5 (1–4)	5.5 (4–7)	4.5 (3–6)
	"Small"	5	3	4	6	6	2	5	6
	"Nothing"	2.5 (1–6)	6 (5–6)	2.5 (2–4)	2.5 (1–5)	5 (1–6)	3.5 (2–6)	5 (3–6)	3.5 (2–5)
	All participants	3 (1–6)	6 (2–7)	3.5 (1–5)	3 (1–6)	5.5 (1–7)	3.5 (1–6)	5 (2–7)	4.5 (2–6)

The values correspond to 7-level Likert items (Median value and range are indicated). For the item "Speed" the scale ranges from "slow" (1) to "quick" (7); for the item "Weight" the scale ranges from "light" (1) to "heavy" (7); for the item "Strength" the scale ranges from "weak" (1) to "strong" (7); for the item "Straight" the scale ranges from "crouched, stoop" (1) to "elongated, extended" (7). For the remaining items ("Agency," "Vividness," "Surprise," "Feet localization"), the scale indicates the level of agreement with the statement, ranging from "I strongly disagree" (1) to "I strongly agree" (7).

- "below the knee the leg is less blurry than before" (Participant P05—"High frequency" condition); "below the knee the leg is still blurry, feels very thin, but more like a limb than wood." (Participant P05—"Low frequency" condition);
- "I can now slightly vaguely visualize both of my hips, but nothing else on the left side" (Participant P06—both sound conditions);
- "I have a sense of the left side of the body (arm and leg), even if I don't see them (they are not solid); I can clearly see the

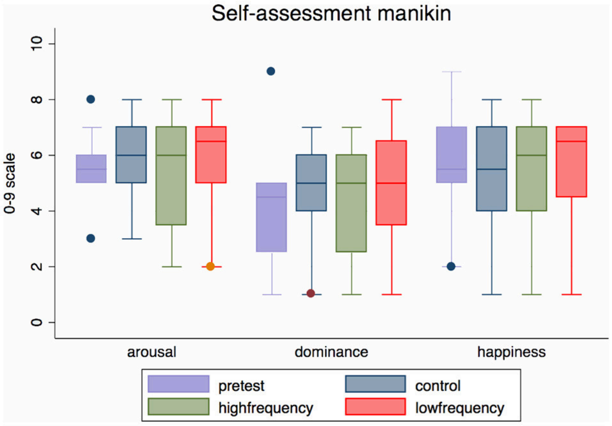

FIGURE 7 | Median (range) emotional arousal, dominance and happiness (valence) for all three sound conditions and pre-test condition for all participants ($N = 12$). Valence, Arousal, and Dominance ratings refer to the 9-item graphic scales of the self-assessment Manikin questionnaire. This figure is published in color in the online version.

left hip." (Participant P02—"High frequency" condition); "I cannot visualize the left arm and leg, but I can visualize the left hip, which usually I can't" (Participant P02—"Low frequency" condition).

It should be noted that the increase in attention to limb and restoring of body representations sometimes came accompanied by an increase in negative sensations, as in the case of one of the participants from the "Nothing" group, who said: *"I can feel my left arm big all the way down, but I feel more pressure in it (blood pumping)"* (Participant P12—"High frequency" condition); *"I can feel my left arm big all the way down, but the pumping in the hand has increased; I feel more pain and more aware of my arm—If I don't do anything, I feel nothing, I don't see it, I try to forget about it. But you asked me to focus on it and now I visualize it—it feels bigger and painful"* (Participant P12—"Low frequency" condition). Another participant from the "Big" group, however, reported less pain in the sound conditions than in the control condition: *"My knee feels a little uncomfortable behind, touching, a little painful"* (Participant P04—"Control" condition); *"My knee feels a little uncomfortable behind, but less than before"* (Participant P04—"High frequency" condition); *"My knee feels a little uncomfortable behind, but not really. It doesn't hurt"* (Participant P04—"Low frequency" condition).

Although, not significant, for most descriptors of bodily feelings we observed differences between the median scores for the sound conditions and the control condition. In particular, people reported feeling **faster** in both sound conditions than in the "Control" condition, **less heavy** in the "High frequency" condition than in the other conditions and **stronger** in the "Low frequency" condition than in the other conditions. They also felt **more able to localize their feet**, **more surprised about their bodily feelings**, and more **agent of the sounds** in both sound conditions than in the "Control" condition. There were observable differences between groups for most descriptors, as for instance, the effect of the "Low frequency" condition in feelings of strength was more obvious in the "Nothing" group.

We found a clear beneficial effect of one or both sound conditions compared to the control condition for seven out of the twelve participants (one participant from the "Big" group, all three participants comprising the "Small" and the "Mixed" groups, and three participants from the "Nothing" group). For three participants in the "Nothing" group we observed an improvement of the BPD for one or both of the sound conditions as well as the control condition compared to the pre-test, BPD. For two participants in the "Big" group we found that either both sound conditions worsened the participant's body-representation in terms of exacerbating the disturbance, or one of the conditions was worse and the other did not have an effect.

Effect of Sound Condition on Gait

Gait data for three participants were lost. For the remaining 9 participants, gait parameters were extracted as described in Section Methods. Reviewing the effects of sound on all the gait parameters, the **stance time** showed a significant effect of sound condition [$F_{(2, 16)} = 3.91$, $p = 0.041$]. Participants spent more time with their foot in contact with the ground in the Low frequency condition than in the High Frequency condition [$t_{(8)} = 3.89$, $p = 0.005$], with the average contact time for the Control condition falling in between the time for the other two conditions. A similar related effect of sound condition was found for the **toe contact time** [$F_{(2, 16)} = 4.62$, $p = 0.026$]: People spent more time with their toe in contact with the ground in the Low frequency condition than in the High Frequency condition [$t_{(8)} = 3.84$, $p = 0.005$]. The mean stance times ± SE for all sound conditions ("Control," "High frequency," and "Low frequency") are presented in **Figure 8**. The mean values ± SE for other gait parameters are presented in Figures S3–S6.

DISCUSSION

Previous research has shown that sound can affect body perception in healthy controls (Tajadura-Jiménez et al., 2012, 2015a,b, 2016). This proof-of-principle pilot study has suggested that sound can alter body perception in patients with CRPS and chronic pain with body perception disturbances (BPD). However, while in healthy controls the effect of high or low frequency alterations of own walking sounds on body perception is predictable (i.e., the body feels lighter in the high frequency condition than in the low frequency condition; Tajadura-Jiménez et al., 2015a), this relationship is not consistent in CRPS. The patients with CRPS in this study all had BPD of varying types and therefore it is not surprising that the effect of sound would not be as predictable. The data suggests that the type of BPD may influence the effect of sound feedback on body perception. Sound feedback seems to have larger effect on perceived body dimensions and on CRPS descriptors in participants not able to visualize their affected body part (i.e., from the "Nothing" group). A much larger study would be required to establish whether the type of BPD modulates the effect of the frequency of sound feedback in CRPS, or whether in the context of chronic pain and

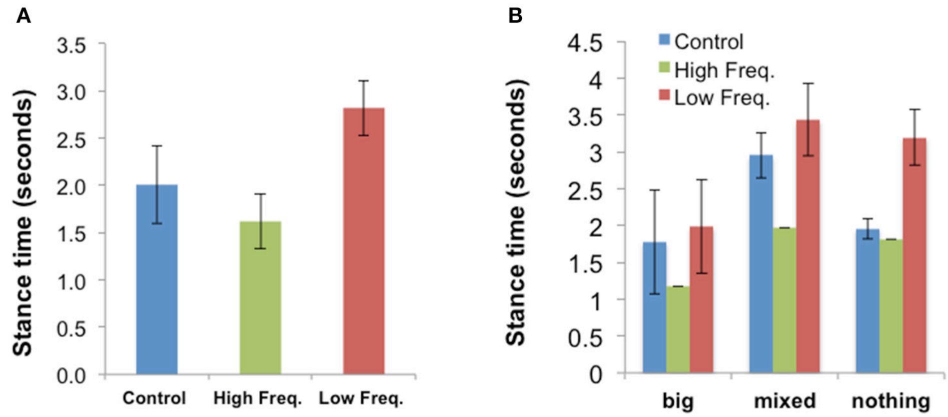

FIGURE 8 | (A) Mean stance time (±SE) for all three sound conditions ($N = 9$). **(B)** Shows the mean results for each body disturbance group: "Big" ($N = 3$), "Mixed" ($N = 1$), "Nothing" ($N = 5$). This figure is published in color in the online version.

BPD the frequency has any importance or it is more an effect of sound per-se and/or an interaction with attention and distractive factors.

In the current study the effects of sound feedback received during the 1-min walking periods on the alteration of BPD were quantified in three different ways: by assessing the effect of sound on perceived body dimensions; by quantifying the effects on the related gain mechanics; and by looking at the effect of sound on CRPS descriptors, pain, and other bodily/emotional feelings, which may indicate changes in perceived body parts. Our data suggest that sound feedback can affect the perceived size of the CRPS affected limb, and the observed trends within BPD subgroups suggest that this may differ according to the type of BPD. Effects on perceived body dimensions were more evident on the data assessing specifically the perceived size of the affected limb (i.e., "aperture" and "hands" tasks), than in the data assessing the perceived overall body size (i.e., data collected with the avatar tool). It is important to take into account that this avatar tool we used, which we adopted from our previous study with healthy population (Tajadura-Jiménez et al., 2015a), did not allow modifying the size of the individual limbs of the avatar. An avatar tool allowing modifications of all body parts has been used previously to explore BPD in CRPS (Turton et al., 2013). Patients found this an acceptable tool for communicating their BPD, and described a positive impact being able to see an image they had previously only imagined. Peltz and colleagues used schematic drawings to explore hand size perception in upper limb of people with CRPS, and found a tendency to overestimation which correlated with disease duration, neglect score, and increase of two-point-discrimination-thresholds (Peltz et al., 2011). Other work has revealed that more extensive BPD is associated with worse tactile acuity, and correlates positively with pain (Lewis and Schweinhardt, 2012). In our study, the schematic drawings of participants' body visualizations revealed both tendencies to overestimation and underestimation with some participants not able to visualize parts of their body (those in the "Nothing" group or "Mixed" groups). The qualitative data suggest that sound may cause these body parts to remerge.

We demonstrated that sound feedback can affect the pain experienced in CRPS, and that this is bidirectional (i.e., pain may increase or decrease with sound) and may vary according to the type of BPD. It has been previously demonstrated that ambiguous visual stimuli can enhance pain in CRPS (Hall et al., 2011; Cohen et al., 2012). In our study, the qualitative descriptors from one of the participants in the "Nothing" group suggested that when the sound feedback enhanced the awareness of the affected limb, it resulted in increased pain. Neglect-like phenomena are recognized in CRPS (Kolb et al., 2012), and this participant described using neglect-like strategies to cope. Therefore, the type of BPD may be an important factor in determining how sound feedback may affect CRPS pain. We also found that sound feedback affected CRPS descriptors and other bodily feelings and emotions including feelings of emotional dominance, limb detachment, position awareness, attention and negative feelings toward the limb. Future work would need to carefully phenotype patients and explore their particular BPD and bodily feelings and emotions in order to better understand how to utilize sound feedback optimally.

We also demonstrated an effect of sound feedback on gait. Time of foot contact with the ground increased in the low frequency condition compared to the high frequency condition. This is consistent with previous work in healthy controls where in the high frequency condition, participants experience their body as lighter, the time of foot contact with the ground reduces and the foot lifting acceleration increases in a way consistent with actually having a lighter body (Tajadura-Jiménez et al., 2015a). This may have relevance to rehabilitation, particularly where lower limb CRPS patients perceive the limbs as heavy and weak, which may contribute to the gait impairment that is often observed in CRPS population (Galer et al., 1999). Visual manipulation is established in CRPS treatment in mirror visual feedback therapy (Méndez-Rebolledo et al., 2016), and in therapies using prisms (Moseley et al., 2013). There is potential to combine manipulation of auditory and visual stimuli in the treatment of CRPS and future work would be needed to discover if this is practical, and offers the potential for a synergistic effect.

The possibility of using sensory feedback to "retrain" the brain of people with CRPS might offer a new treatment approach. Alterations in the somatosensory cortex are thought to be behind the anomalous bodily experiences of people with CRPS (Flor et al., 1995, 1997; Maihöfner et al., 2003, 2004; McCabe et al., 2003; Pleger et al., 2005; Marinus et al., 2011) and previous studies using sensory feedback to manipulate people's body representations have linked their results to recalibration of somatosensory receptive fields (RF) in the somatosensory cortex (Taylor-Clarke et al., 2004; de Vignemont et al., 2005; Haggard et al., 2007; Cardinali et al., 2009, 2012; Cardini et al., 2011, 2012, 2013; Tajadura-Jiménez et al., 2012, 2016; Canzoneri et al., 2013a,b; Miller et al., 2014; Cardini and Longo, 2016). We suggest that the observed changes in body-representation in the current study may also indicate reorganization within the somatosensory cortex The observed changes in kinematics of gait may also support this suggestion, if it is considered that the control of body movements relies on somatosensory representations of body dimensions (Holmes and Spence, 2004; Maravita and Iriki, 2004; Cardinali et al., 2009; Tajadura-Jiménez et al., 2016). Consistent with the theories of "forward internal models" of motor-to-sensory transformations (Wolpert and Ghahramani, 2000), body-representations are used among other inputs when planning actions and predicting the sensory feedback (e.g., the sound of one's footsteps) that should be received from such actions. When the sensory feedback received from one's actions does not match these predictions, an update of the internal somatosensory body model may occur. It has been suggested that the observed gait changes may result from an attempt to reduce the sensory discrepancies introduced by the sound feedback, and that these gait changes may contribute to maintain the bodily illusion induced by the sound (Tajadura-Jiménez et al., 2015a). It is possible that changes in body perception, emotion and gait, may reinforce each other during the period of exposure to the stimulation.

This is a proof-of-principle pilot study and thus there are limitations in the design and generalization of findings. The most significant limitation is the number of participants; this is a consistent difficulty encountered in clinical studies of CRPS (O'Connell et al., 2013) due to the relatively rare nature of the condition and difficulties in recruitment. This could be addressed in future studies and by multicenter collaboration. Our study had a predominance of lower limb affected CRPS patients, but data on our upper limb affected CRPS patients suggest that the effects of manipulating footstep sounds may extend to other body parts apart from lower limbs. Further work should aim to balance the distribution of affected limbs, and establish whether the limb/s affected has any relevance upon the effect and utility of sound feedback. The participants in our study also had a wide range of disease duration and future work with larger numbers should characterize whether this also a significant factor. Our work has demonstrated the possible importance of the type of BPD and further work should aim to explore the CRPS phenotype in detail including the BPD and associated emotions and bodily feelings together with other potentially linked aspects such as tactile discrimination (Peltz et al., 2011; Lewis and Schweinhardt, 2012) and neglect-like phenomena (Kolb et al., 2012). Our research has demonstrated that sound feedback can affect BPD and pain, and may potentially inform the design of currently available sensorimotor based therapy combining visual, tactile and motor strategies; this should be explored in clinical studies with CRPS and other patients with chronic pain and BPD such as fibromyalgia and phantom limb phenomena in amputees.

CONCLUSION

Our results suggest that sound feedback may be used to alter body perception and its related emotional state and gait in those with CRPS. They suggest that sound feedback may affect the perceived size of the CRPS affected limb and the pain experienced, but that the effects may differ according to the type of body perception disturbance. Further, there are indications that sound feedback affected CRPS descriptors and other bodily feelings and emotions including feelings of emotional dominance, limb detachment, position awareness, attention, and negative feelings toward the limb. Gait varied with sound feedback, affecting the foot contact time with the ground in a way consistent with experienced changes in body weight. These findings may inform the experiment protocol for larger studies and have potential application for regenerating altered body-representation and its related bodily feelings in a clinical setting for patients with chronic pain and body perception disturbances.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the work, interpretation of data and revision of the drafts of the work. AT acquired and analyzed the data, and drafted the work. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and approved this final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00379/full#supplementary-material

REFERENCES

Bean, D. J., Johnson, M. H., and Kydd, R. R. (2014). The outcome of complex regional pain syndrome type 1: a systematic review. *J. Pain* 15, 677–690. doi: 10.1016/j.jpain.2014.01.500

Botvinick, M., and Cohen, J. (1998). Rubber hands 'feel' touch that eyes see. *Nature* 391:756. doi: 10.1038/35784

Bradley, M. M., and Lang, P. J. (1994). Measuring emotion: the self-assessment manikin and the semantic differential. *J. Behav. Ther. Exp. Psychiatry* 25, 49–59. doi: 10.1016/0005-7916(94)90063-9

Canzoneri, E., Marzolla, M., Amoresano, A., Verni, G., and Serino, A. (2013a). Amputation and prosthesis implantation shape body and peripersonal space representations. *Sci. Rep.* 3:2844. doi: 10.1038/srep02844

Canzoneri, E., Ubaldi, S., Rastelli, V., Finisguerra, A., Bassolino, M., and Serino, A. (2013b). Tool-use reshapes the boundaries of body and peripersonal space representations. *Exp. Brain Res.* 228, 25–42. doi: 10.1007/s00221-013-3532-2

Cardinali, L., Frassinetti, F., Brozzoli, C., Urquizar, C., Roy, A. C., and Farne, A. (2009). Tool-use induces morphological updating of the body schema. *Curr. Biol.* 19, R478–R479. doi: 10.1016/j.cub.2009.06.048

Cardinali, L., Jacobs, S., Brozzoli, C., Frassinetti, F., Roy, A. C., and Farne, A. (2012). Grab an object with a tool and change your body: tool-use-dependent changes of body representation for action. *Exp. Brain Res.* 218, 259–271. doi: 10.1007/s00221-012-3028-5

Cardini, F., and Longo, M. R. (2016). Congruency of body-related information induces somatosensory reorganization. *Neuropsychologia* 84, 213–221. doi: 10.1016/j.neuropsychologia.2016.02.013

Cardini, F., Longo, M. R., Driver, J., and Haggard, P. (2012). Rapid enhancement of touch from non-informative vision of the hand. *Neuropsychologia* 50, 1954–1960. doi: 10.1016/j.neuropsychologia.2012.04.020

Cardini, F., Longo, M. R., and Haggard, P. (2011). Vision of the body modulate somatosensory intracortical inhibition. *Cereb. Cortex* 21, 2014–2022. doi: 10.1093/cercor/bhq267

Cardini, F., Tajadura-Jiménez, A., Serino, A., and Tsakiris, M. (2013). It feels like it's me: interpersonal multisensory stimulation enhances visual remapping of touch from other to self. *J. Exp. Psychol. Hum. Percept. Perform.* 39, 630–637. doi: 10.1037/a0031049

Carruthers, G. (2008). Types of body representation and the sense of embodiment. *Conscious. Cogn.* 17, 1302–1316. doi: 10.1016/j.concog.2008.02.001

Cohen, H. E., Hall, J., Harris, N., McCabe, C. S., Blake, D. R., and Jänig, W. (2012). Enhanced pain and autonomic responses to ambiguous visual stimuli in chronic Complex Regional Pain Syndrome (CRPS) type I. *Eur. J. Pain* 16, 182–195. doi: 10.1016/j.ejpain.2011.06.016

Cohen, H., McCabe, C., Harris, N., Hall, J., Lewis, J., and Blake, D. R. (2013). Clinical evidence of parietal cortex dysfunction and correlation with extent of allodynia in CRPS type 1. *Eur. J. Pain* 17, 527–538. doi: 10.1002/j.1532-2149.2012.00213.x

Cunado, D., Nixon, M. S., and Carter, J. N. (2003). Automatic extraction and description of human gait models for recognition purposes. *Comput. Vis. Image Underst.* 90, 1–41. doi: 10.1016/S1077-3142(03)00008-0

de Mos, M., de Bruijn, A. G., Huygen, F. J., Dieleman, J. P., Stricker, B. H., and Sturkenboom, M. C. (2007). The incidence of complex regional pain syndrome: a population-based study. *J. Pain* 129, 12–20. doi: 10.1016/j.pain.2006.09.008

de Vignemont, F., Ehrsson, H. H., and Haggard, P. (2005). Bodily illusions modulate tactile perception. *Curr. Biol.* 15, 1286–1290. doi: 10.1016/j.cub.2005.06.067

Dubuisson, D., and Melzack, R. (1976). Classifications of clinical pain descriptions by multiple group discriminate analysis. *Exp. Neurol.* 51, 480–487. doi: 10.1016/0014-4886(76)90271-5

Eisenberg, E., Chistyakov, A. V., Yudashkin, M., Kaplan, B., Hafner, H., and Feinsod, M. (2005). Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. *J. Pain* 113, 99–105. doi: 10.1016/j.pain.2004.09.030

Flor, H., Braun, C., Elbert, T., and Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neurosci. Lett.* 224, 5–8. doi: 10.1016/S0304-3940(97)13441-3

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., et al. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 375, 482–484. doi: 10.1038/375482a0

Förderreuther, S., Sailer, U., and Straube, A. (2004). Impaired self-perception of the hand in complex regional pain syndrome (CRPS). *J. Pain* 110, 756–761 doi: 10.1016/j.pain.2004.05.019

Galer, B. S., and Jensen, M. (1999). Neglect-like symptoms in complex regional pain syndrome: results of a self-administered survey. *J. Pain Symptom Manage.* 18, 213–217. doi: 10.1016/S0885-3924(99)00076-7

Galer, B. S., Henderson, J., Perander, J., and Jensen, M. (1999). Course of symptoms and quality of life measurement in complex regional pain syndrome: a pilot survey. *J. Pain Symptom Manage.* 20, 286–292. doi: 10.1016/S0885-3924(00)00183-4

Goebel, A., Barker, C. H., Turner-Stokes, L., Atkins, R. M., Cameron, H., and Cossins, L. (2012). *Complex Regional Pain Syndrome in Adults: UK Guidelines for Diagnosis, Referral and Management in Primary and Secondary Care*. London: RCP.

Graham, C., Bond, S. S., Gerkovich, M. M., and Cook, M. R. (1980). Use of the McGill pain questionnaire in the assessment of cancer pain: reliability and consistency. *J. Pain* 6:377. doi: 10.1016/0304-3959(80)90081-0

Haggard, P., Christakou, A., and Serino, A. (2007). Viewing the body modulates tactile receptive fields. *Exp. Brain Res.* 180, 187–193. doi: 10.1007/s00221-007-0971-7

Hall, J., Harrison, S., Cohen, H., McCabe, C. S., Harris, N., and Blake, D. R. (2011). Pain and other symptoms of CRPS can be increased by ambiguous visual stimuli–an exploratory study. *Eur. J. Pain* 15, 17–22. doi: 10.1016/j.ejpain.2010.04.009

Harden, R. N., Bruehl, S., Perez, R. S., Birklein, F., Marinus, J., Maihofner, C., et al. (2010). Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. *J. Pain* 150, 268–274. doi: 10.1016/j.pain.2010.04.030

Harle, R., Taherian, S., Pias, M., Coulouris, G., Hopper, A., Cameron, J., et al. (2012). Towards real-time profiling of sprints using wearable pressure sensors. *Comput. Commun.* 35, 650–660. doi: 10.1016/j.comcom.2011.03.019

Holmes, N. P., and Spence, C. (2004). The body schema and multisensory representation (s) of peripersonal space. *Cogn. Process.* 5, 1–21. doi: 10.1007/s10339-004-0013-3

Kavanagh, J. J., and Menz, H. B. (2008). Accelerometry: a technique for quantifying movement patterns during walking. *Gait Posture* 28, 1–15. doi: 10.1016/j.gaitpost.2007.10.010

Keizer, A., Smeets, M. A. M., Dijkerman, H. C., Uzunbajakau, S. A., van Elburg, A., and Postma, A. (2013). Too fat to fit through the door: first evidence for disturbed body-scaled action in anorexia nervosa during locomotion. *PLoS ONE* 8:e64602. doi: 10.1371/journal.pone.0064602

Kolb, L., Lang, C., Seifert, F., and Maihöfner, C. (2012). Cognitive correlates of "neglect-like syndrome" in patients with complex regional pain syndrome. *J. Pain* 153, 1063–1073. doi: 10.1016/j.pain.2012.02.014

Lewis, J. S., Kersten, P., McCabe, C. S., McPherson, K. M., and Blake, D. R. (2007). Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). *J. Pain* 133, 111–119. doi: 10.1016/j.pain.2007.03.013

Lewis, J.S., and McCabe, C.S. (2010). Body Perception Disturbance (BPD) in CRPS. *Pract. Pain Manage.*

Lewis, J. S., and Schweinhardt, P. (2012). Perceptions of the painful body: the relationship between body perception disturbance, pain and tactile discrimination in complex regional pain syndrome. *Eur. J. Pain* 16, 1320–1330. doi: 10.1002/j.1532-2149.2012.00120.x

Li, X. F., Logan, R. J., and Pastore, R. E. (1991). Perception of acoustic source characteristics: walking sounds. *J. Acoust. Soc. Am.* 90, 3036–3049. doi: 10.1121/1.401778

Linkenauger, S. A., Witt, J. K., Bakdash, J. Z., Stefanucci, J. K., and Proffitt, D. R. (2009). Asymmetrical body perception: A possible role for neural body representations. *Psychol. Sci.* 20, 1373–1380. doi: 10.1111/j.1467-9280.2009.02447.x

Longo, M., and Haggard, P. (2012). What is it like to have a body? *Curr. Dir. Psychol.* 21, 140–145. doi: 10.1177/0963721411434982

Longo, M. R., Azañón, E., and Haggard, P. (2010). More than skin deep: body representation beyond primary somatosensory cortex. *Neuropsychologia* 48, 655–668. doi: 10.1016/j.neuropsychologia.2009.08.022.

Maihöfner, C., Handwerker, H., Neundörfer, B., and Birklein, F. (2003). Patterns of cortical reorganisation in complex regional pain syndrome. *Neurology* 61, 1707–1715. doi: 10.1212/01.WNL.0000098939.02752.8E

Maihöfner, C., Handwerker, H., Neundörfer, B., and Birklein, F. (2004). Cortical reorganisation during recovery from complex regional pain syndrome. *Neurology* 63, 693–701 doi: 10.1212/01.WNL.0000134661.46658.B0

Maravita, A., and Iriki, A. (2004). Tools for the body (schema). *Trends Cogn. Sci.* 8, 79–86. doi: 10.1016/j.tics.2003.12.008

Marinus, J., Moseley, G. L., Birklein, F., Baron, R., Maihöfner, C., Kingery, W. S., et al. (2011). Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol.* 10, 637–648. doi: 10.1016/S1474-4422(11)70106-5

McCabe, C. S., Haigh, R. C., Halligan, P. W., and Blake, D. R. (2003). Referred sensations in complex regional pain syndrome type 1. *Rheumatology* 42, 1067–1073. doi: 10.1093/rheumatology/keg298

Medina, J., and Coslett, H. B. (2010). From maps to form to space: touch and the body schema. *Neuropsychologia* 48, 645–654. doi: 10.1016/j.neuropsychologia.2009.08.017

Melzack, R. (1987). The short-form McGill Pain Questionnaire. *J. Pain* 30, 191–197. doi: 10.1016/0304-3959(87)91074-8

Méndez-Rebolledo, G., Gatica-Rojas, V., Torres-Cueco, R., Albornoz-Verdugo, M., and Guzmán-Muñoz, E. (2016). Update on the effects of graded motor imagery and mirror therapy on complex regional pain syndrome type 1: a systematic review. *J. Back Musculoskelet. Rehabil.* 30, 441–449. doi: 10.3233/BMR-150500

Miller, L. E., Longo, M. R., and Saygin, A. P. (2014). Tool morphology constrains the effects of tool use on body representations. *J. Exp. Psychol. Hum. Percept. Perform.* 40, 2143–2153. doi: 10.1037/a0037777

Moseley, G. L. (2005). Distorted body image in complex regional pain syndrome. *Neurology* 65:773. doi: 10.1212/01.wnl.0000174515.07205.11

Moseley, G. L. (2008). I can't find it! Distorted body image and tactile dysfunction in patients with chronic back pain. *Pain* 140, 239–243. doi: 10.1016/j.pain.2008.08.001

Moseley, G.L., Gallace, A., Di Pietro, F., Spence, C., and Iannetti, G. D. (2013). Limb-specific autonomic dysfunction in complex regional pain syndrome modulated by wearing prism glasses. *J. Pain* 154, 2463–2468. doi: 10.1016/j.pain.2013.07.026

O'Connell, N. E., Wand, B. M., McAuley, J., Marston, L., and Moseley, G. L. (2013). Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst. Rev.* 30:CD009416. doi: 10.1002/14651858.CD009416.pub2

Peltz, E., Seifert, F., Lanz, S., Müller, R., and Maihöfner, C. (2011). Impaired hand size estimation in CRPS. *J. Pain* 12, 1095–1101. doi: 10.1016/j.jpain.2011.05.001

Petkova, V. I., and Ehrsson, H. H. (2008). If I were you: perceptual illusion of body swapping. *PLoS ONE* 3:e3832. doi: 10.1371/journal.pone.0003832

Pleger, B., Tegenthoff, M., Ragert, P., et al. (2005). Sensorimotor returning in complex regional pain syndrome parallels pain reduction. *Ann. Neurol.* 57, 425–429. doi: 10.1002/ana.20394

Pollatos, O., Kurz, A.-L., Albrecht, J., Schreder, T., et al. (2008). Reduced perception of bodily signals in anorexia nervosa. *Eat. Behav.* 9, 381–388. doi: 10.1016/j.eatbeh.2008.02.001

Rockett, M. (2014). Diagnosis, mechanisms and treatment of complex regional pain syndrome. *Curr. Opin. Anaesthesiol.* 27, 494–500. doi: 10.1097/ACO.0000000000000114

Sandroni, P., Benrud-Larson, L. M., McClelland, R. L., and Low, P. A. (2003). Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. *J. Pain* 103, 199–207. doi: 10.1016/S0304-3959(03)00065-4

Schwoebel, J., Friedman, R., Duda, N., and Coslett, H. B. (2001). Pain and the body schema: evidence for peripheral effects on mental representations of movement. *Brain* 124, 2098–2104. doi: 10.1093/brain/124.10.2098

Serino, A., Alsmith, A., Costantini, M., Mandrigin, A., Tajadura-Jiménez, A., and Lopez, C. (2013). Bodily ownership and self-location: components of bodily self-consciousness. *Conscious. Cogn.* 22, 1239–1252. doi: 10.1016/j.concog.2013.08.013

Serino, A., and Haggard, P. (2010). Touch and the body. *Neurosci. Biobehav. Rev.* 34, 224–236. doi: 10.1016/j.neubiorev.2009.04.004

Singh, A., Klapper, A., Jia, J., Fidalgo, A., Tajadura-Jiménez, A., Kanakam, N., et al. (2014). "Motivating people with chronic pain to do physical activity: opportunities for technology design," in *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems* (Toronto, ON: ACM Press), 2803–2812. doi: 10.1145/2556288.2557268

Singh, A., Piana, S., Pollarolo, D., Volpe, G., Varni, G., Tajadura-Jiménez, A., et al. (2016). Go-with-the-flow: tracking, analysis and sonification of movement and breathing to build confidence in activity despite chronic pain. *Int. J. Hum. Comput. Interact.* 31, 1–40. doi: 10.1080/07370024.2015.1085310

Stanton-Hicks, M., Baron, R., Boas, R., Gordh, T., Harden, R. N., Hendler, N., et al. (1998). Complex regional pain syndromes: guidelines for therapy. *Clin. J. Pain* 14, 155–166. doi: 10.1097/00002508-199806000-00012

Stanton-Hicks, M., Burton, A. W., Bruehl, S., Carr, D., Harden, R. N., Hassenbusch, S., et al. (2002). An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract.* 2, 1–16. doi: 10.1046/j.1533-2500.2002.02009.x

Strand, L. I., Ljunggren, A. E., Bogen, B., Ask, T., and Johnsen, T. B. (2008). The Short-Form McGill Pain Questionnaire as an outcome measure: test–retest reliability and responsiveness to change. *Eur. J. Pain* 12, 917–925. doi: 10.1016/j.ejpain.2007.12.013

Tajadura-Jiménez, A., Basia, M., Deroy, O., Fairhust, M., Marquardt, N., and Berthouze, N. (2015a). "As light as your footsteps: altering walking sounds to change perceived body weight, emotional state and gait," in *Proceedings of the 33rd Annual ACM Conference on Human Factors in Computing Systems* (Seoul: ACM Press), 2943–2952. doi: 10.1145/2702123.2702374

Tajadura-Jiménez, A., Marquardt, T., Swapp, D., Kitagawa, N., and Bianchi-Berthouze, N. (2016). Action sounds modulate arm reaching movements. *Front. Psychol.* 7:1391. doi: 10.3389/fpsyg.2016.01391

Tajadura-Jiménez, A., Tsakiris, M., Marquardt, T., and Nadia, B. B. (2015b). Action sounds update the mental representation of arm dimension: contributions of kinaesthesia and agency. *Front. Psychol.* 6:689. doi: 10.3389/fpsyg.2015.00689

Tajadura-Jiménez, A., Väljamäe, A., Toshima, I., Kimura, T., Tsakiris, M., and Kitagawa, N. (2012). Action sounds recalibrate perceived tactile distance. *Curr. Biol.* 22, R516–R517. doi: 10.1016/j.cub.2012.04.028

Taylor-Clarke, M., Jacobsen, P., and Haggard, P. (2004). Keeping the world a constant size: object constancy in human touch. *Nat. Neurosci.* 7, 219–220. doi: 10.1038/nn1199

Tsakiris, M. (2010). My body in the brain: a neurocognitive model of body-ownership. *Neuropsychologia* 48, 703–712. doi: 10.1016/j.neuropsychologia.2009.09.034

Turton, A. J., Palmer, M., Grieve, S., Moss, T. P., Lewis, J., and McCabe, C. S. (2013). Evaluation of a prototype tool for communicating body perception disturbances in complex regional pain syndrome. *Front. Hum. Neurosci.* 7:517. doi: 10.3389/fnhum.2013.00517

van der Hoort, B., Guterstam, A., and Ehrsson, H. H. (2011). Being barbie: the size of one's own body determines the perceived size of the world. *PLoS ONE* 6:e20195. doi: 10.1371/journal.pone.0020195

Vaughan, C. L., Davis, B. L., and O'connor, J. C. (1992). *Dynamics of Human Gait*. Champaign, IL: Human Kinetics Publishers.

Wolpert, D. M., and Ghahramani, Z. (2000). Computational principles of movement neuroscience. *Nat. Neurosci.* 3, 1212–1217. doi: 10.1038/81497

Wright, K. D., Asmundson, G. J., and McCreary, D. R. (2001). Factorial validity of the short-form McGill pain questionnaire (SF-MPQ). *Eur. J. Pain* 5, 279–284. doi: 10.1053/eujp.2001.0243

Zinke, J. L., Lam, C. S., Harden, R. N., and Fogg, L. (2010). Examining the cross-cultural validity of the english short-form McGill Pain Questionnaire using the matched moderated regression methodology. *Clin. J. Pain* 26, 153–162. doi: 10.1097/AJP.0b013e3181b99f56

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Exteroceptive and Interoceptive Body-Self Awareness in Fibromyalgia Patients

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Fibromyalgia is a widespread chronic pain disease characterized by generalized musculoskeletal pain and fatigue. It substantially affects patients' relationship with their bodies and quality of life, but few studies have investigated the relationship between pain and body awareness in fibromyalgia. We examined exteroceptive and interoceptive aspects of body awareness in 30 women with fibromyalgia and 29 control participants. Exteroceptive body awareness was assessed by a body-scaled action-anticipation task in which participants estimated whether they could pass through apertures of different widths. Interoceptive sensitivity (IS) was assessed by a heartbeat detection task where participants counted their heartbeats during different time intervals. Interoceptive awareness was assessed by the Multidimensional Assessment of Interoceptive Awareness (MAIA). The "passability ratio" (the aperture size for a 50% positive response rate, divided by shoulder width), assessed by the body-scaled action-anticipation task, was higher for fibromyalgia participants, indicating disrupted exteroceptive awareness. Overestimating body size correlated positively with pain and its impact on functionality, but not with pain intensity. There was no difference in IS between groups. Fibromyalgia patients exhibited a higher tendency to note bodily sensations and decreased body confidence. In addition, the passability ratio and IS score correlated negatively across the whole sample, suggesting an inverse relationship between exteroceptive and interoceptive body awareness. There was a lower tendency to actively listen to the body for insight, with higher passability ratios across the whole sample. Based on our results and building on the fear-avoidance model, we outline a proposal that highlights possible interactions between exteroceptive and interoceptive body awareness and pain. Movement based contemplative practices that target sensory-motor integration and foster non-judgmental reconnection with bodily sensations are suggested to improve body confidence, functionality, and quality of life.

Keywords: exteroception, interoception, body awareness, chronic pain, fibromyalgia

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INTRODUCTION

> "It is as if all of my joints were locked and I am caught inside, as though imprisoned in a kind of body or an envelope that has padlocks inside, like doors that I cannot open."
>
> Fibromyalgia patient interview (Valenzuela-Moguillansky, 2012).

The present study was performed to assess two aspects of body awareness in fibromyalgia patients: exteroception and interoception. Fibromyalgia is a chronic disease characterized by generalized musculoskeletal pain and fatigue. It is diagnosed based on the presence of at least 11 of 18 tender point sites on digital palpation (Wolfe et al., 2010; see Wolfe and Häuser, 2011 for an up to-date discussion). Dysfunction in processing and modulation of noxious stimuli by the central nervous system, and hyperactivity of the sympathetic nervous system are purportedly involved (Cohen et al., 2000; Martinez-Lavin, 2007; McEwen and Kalia, 2010; Bellato et al., 2012), as are psychiatric conditions including anxiety, panic disorder, post-traumatic stress disorder, and general depression (Epstein et al., 1999; Bair et al., 2003; Raphael et al., 2004; van Houdenhove et al., 2005; Arnold et al., 2006; Van Houdenhove and Luyten, 2006). The etiology and pathogenesis of fibromyalgia remain unclear. Pregabalin, duloxetine, and milnacipran are approved pharmacological therapies, but their use is limited by side effects, and not all patients experience improvement (Ablin and Buskila, 2010). The prevalence of fibromyalgia is between 1.6 and 2.1% in Europe and the United States (Wolfe et al., 1995, 2013; Perrot et al., 2011), and 1–2% in Chile, where the present study was performed (Trujillo-Lira, 2007).

Fibromyalgia impacts an individual's relationship with their bodies. As illustrated by the opening quote, the body becomes an obstacle. While pain loci might change from patient to patient or from 1 day to another, pain and fatigue are felt over the whole body (Valenzuela-Moguillansky, 2013; Calsius et al., 2015). The body becomes a salient, unfamiliar presence that prevents daily activities and affects quality of life, social relationships, and functionality (Burckhardt et al., 1993; Arnold et al., 2008). Valenzuela-Moguillansky (2013) investigated the bodily experience in fibromyalgia over the course of a pain crisis from a phenomenological perspective. As pain increased, a series of changes in patients' body perception were observed. They described changes in the perception of their body size and its relationship with space: they felt their body becoming larger and as though space was shrinking. These results are in line with those of Akkaya et al. (2012) who report that body image is disrupted in fibromyalgia. Moreover, patients with fibromyalgia exhibit a higher frequency of falls and loss of balance despite an absence of inflammatory joint damage (Jones et al., 2009; Meireles et al., 2014), suggesting that a sensorimotor aspect of body awareness is also affected.

Body awareness involves aspects differentially conceptualized by discipline or researcher (Gallagher, 2000; de Preester and Knockaert, 2005; de Vignemont, 2010). In the present work, we refer to the notions of exteroceptive awareness, interoceptive sensitivity, and interoceptive awareness. Exteroceptive body awareness (or "the body schema") refers to the implicit knowledge we have of our body in relation to space and movement. It results from the integration of multimodal exteroceptive signals (e.g., vision, sound, touch), vestibular and proprioceptive systems, and voluntary motor systems. Even though the term "body schema" is more commonly used, we refer to exteroceptive body awareness to highlight the relationship with interoceptive body awareness (Harshaw, 2015). Both terms emphasize the internal representation we have of our body and posture in guiding action and are thus interchangeable. Previous work has revealed alterations of exteroceptive body awareness in other chronic pain syndromes (e.g., Schwoebel et al., 2001, 2002; Bray and Moseley, 2011). Whether exteroceptive body awareness is affected in fibromyalgia has not been evaluated.

Interoception refers to the perception of our internal state. Originally introduced by Sherrington (1906), this term was linked to visceral sensitivity, meaning the ability to detect signals coming from our "internal milieu." This term was redefined by Craig (2002) as the sense of the physiological condition of the body beyond the viscera, thus expanding the notion and positioning it in the afferent pathway of the autonomic nervous system. Under this view, afferent signals from the various body tissues that contribute to the regulation of physiological parameters constitute "a basis for the subjective evaluation of one's condition," allowing better understanding of organic body function and its relationship to mental and emotional experiences. In recent years, diverse lines of research including emotional and social cognition, mental health, and sense of the bodily self have incorporated interoception in investigations as a key element of the mind-body relationship. It is therefore of interest to investigate whether interoception is altered in persons with fibromyalgia.

The notion of interoception has multiple aspects. Harshaw (2015) presented a detailed taxonomy of interoceptive dysfunction; however, the defined terms are liable to ambiguous and interchangeable use. Further, they are based on assessment methods rather than a clear conceptual construct. For example, using the heartbeat detection task, a widely used method to measure interoception, enhanced interoception associated with emotional liability, anxiety, lower pain thresholds, and lower pain tolerability (Schandry, 1981; Ehlers and Breuer, 1992; Cameron, 2002; Eley et al., 2004; Pollatos et al., 2012), while diminished interoception associated with depression and alexithymia (Pollatos et al., 2009; Herbert et al., 2011; Terhaar et al., 2012). Under a different framework, enhanced interoception is related to non-judgmental acceptance of bodily sensations and a sense of self grounded in experiencing physical sensations in the present moment (Mehling et al., 2009). Mehling et al. (2012) elaborated a self-report questionnaire called the Multidimensional Assessment of Interoceptive Awareness (MAIA) to assess this type of interoception. With the heartbeat detection task, we refer to *interoceptive sensitivity*, while with the MAIA we refer to *interoceptive awareness*.

Given the impact fibromyalgia has on patients' bodily experience and functionality, we consider it relevant to investigate whether exteroceptive and interoceptive aspects of body awareness are altered in fibromyalgia patients in greater detail. Developing from previous work, we hypothesize that fibromyalgia patients exhibit disrupted exteroceptive body awareness and disrupted interoceptive sensitivity (IS). As fibromyalgia has been related to traits such as anxiety and depression, each associated with heightened and diminished IS, respectively, we will not propose a specific *a priori* hypothesis, but rather explore responses in this area. In addition, we propose that interoceptive awareness is decreased in fibromyalgia patients, hypothesizing a reduced sense of self grounded in experiencing physical sensations, and reduced ability to regulate emotional responses based on a connection with one's own body, in situation of chronic pain.

Finally, as exteroceptive and interoceptive body awareness are constructs that point to different aspects of an integrated experience of the bodily self, we consider relevant to assess whether these are related. Tsakiris et al. (2011) found that people with low IS are more prone to body illusions that involve ownership of a foreign body part, concluding that interoceptive awareness modulates the online integration of multisensory body stimuli. Moseley et al. (2008) found that inducing the illusion of ownership of a rubber hand decreases the temperature of participants' "disowned" hand, suggesting that changes in body schema impact homeostatic regulation of physiological parameters (see Harshaw, 2015 for a comprehensive review and additional examples). We hypothesize that there is a relationship between exteroceptive and interoceptive body awareness in both fibromyalgia and control participants.

Investigating in greater detail which aspects of body awareness are altered in fibromyalgia patients, and determining how this occurs might improve therapeutic strategies and their evaluation, as well as encourage reflection on the relationship between pain and body awareness.

METHODS

Design and Participants

This comparative, cross-sectional study was performed in a laboratory setting. Fifty-nine female participants aged 22–71 years were included. Thirty fibromyalgia patients were recruited from the Valparaíso (Chile) Regional Fibromyalgia Association, and 29 healthy controls were recruited among patients' immediate social environment, aiming for similarity between groups in socioeconomic, cultural, and educational aspects. Fibromyalgia was diagnosed according to the American College of Rheumatology (ACR) criteria. Patients were included if they were over 18 years of age, reported pain equal to or >4(on a scale from 0 to 10), experienced pain at least 4 days per week and over at least the previous 6 months, consented to participate, and demonstrated the ability to read and understand the informed consent form and questionnaires. In addition, patients who received medical treatment for pain were asked to have a constant medication dosage during the 2 weeks prior to inclusion. Exclusion criteria included treatment for major depression; history of neurological conditions such as epilepsy, stroke, organic brain impairment, and dementia; autoimmune diseases or diseases affecting the autonomic nervous system; cardiovascular disease; diabetes mellitus; pain <6 months; attentional or intellectual deficits; eating disorders; use of drugs or excessive alcohol use; pregnancy; and amputees or a physical disability. Additionally, controls were excluded if they had any chronic pain condition. Due to low prevalence, male fibromyalgia patients were not recruited. There were no significant differences in age, body mass, or educational level between the two groups (**Table 1**).

The Institutional Bioethics Committee of the University of Valparaíso (Chile) approved the study. Each participant received an information sheet and provided written, informed consent to participate.

MATERIALS

Clinical Assessments

The Fibromyalgia Impact Questionnaire (FIQ)

The Fibromyalgia Impact Questionnaire (FIQ) is a 19-item self-report questionnaire that covers three domains: "physical function," "overall impact," and "symptoms." The physical function domain contains 10 items that use a 4-point Likert scale with a response set ranging from "always" to "never." The overall impact domain contains two items measured by number of days in the previous week. The symptoms domain contains 7 items using 100-mm anchored visual analog scales. The FIQ has been used in large-scale clinical trials for fibromyalgia therapies (Williams and Arnold, 2011). We used an adaptation of a validated Spanish translation of the FIQ (Esteve-Vives et al., 2007) to assess fibromyalgia symptoms. Internal consistency of the FIQ, measured by Cronbach's alpha coefficient, was estimated at 0.93.

The Symptoms Impact Questionnaire (SIQ)

The Symptoms Impact Questionnaire (SIQ) is identical to the FIQ but does not refer to fibromyalgia and is used to compare fibromyalgia patients to other groups (Friend and Bennett, 2011). We used the SIQ to identify symptoms of discomfort in the control group.

The Short Form of the Brief Pain Inventory (BPI)

The short form of the Brief Pain Inventory (BPI) is a two-dimensional, self-report questionnaire that assesses pain intensity (*Severity* dimension) and the impact of pain on functioning (*Interference* dimension). Answers are given across a 10-point Likert scale (0 meaning no severity or interference and 10 meaning worse intensity or complete interference). The BPI is recommended for use in clinical settings to monitor the severity and impact of general pain (Williams and Arnold, 2011). We used a validated Spanish translation of the BPI (Cleeland, 1991) in fibromyalgia and control groups. Internal consistency of the BPI was estimated at a Cronbach's alpha coefficient of 0.97 for the overall score, with 0.95 and 0.97 for the *Severity* and *Interference* dimensions, respectively.

The Depression Anxiety Stress Scale (DASS-21)

The Depression Anxiety Stress Scale (DASS-21) is a three-dimensional, 21-item, self-report questionnaire that assesses

TABLE 1 | Summary of the demographic characteristics of fibromyalgia patients and the participants of the control group.

	Fibromyalgia group ($n = 30$)				Control group ($n = 29$)						
Variables	***Min.***	***Max.***	***M***	***SD***	***Min.***	***Max.***	***M***	***SD***	***t-z***	***p-value***	***d***
Age (years)	22	71	46.77	12.66	22	61	43.52	10.97	1.052	0.30^{a}	0.27
Weight (Kg)	53	110	66.15	11.58	50	85	66.62	10.47	−0.164	0.74^{b}	−0.04
Size (m)	1.50	1.70	1.60	0.05	1.50	1.86	1.63	0.07	−1.761	0.08^{a}	−0.46
BMI (kg/m^2)	19.47	39.44	26.00	4.46	19.72	35.56	25.29	4.38	0.614	0.41^{b}	0.16
Duration of the pain (months)	21	540	173.33	164.60	0	0	–	–	–	–	–
Current pain intensity (0 to 10)	0	9	5.00	2.26	0	5	0.28	1.07	−6.277	0.00^{b}	2.67
Educational level	*n*	%			*n*	%					
Primary	0	0			2	6.9			−1.46	0.143^{c}	
Secondary complete	1	3.3			1	3.4			−0.02	0.983^{c}	
Secondary incomplete	1	3.3			2	6.9			−0.63	0.529^{c}	
Technical-professional	13	43.3			11	37.9			0.42	0.673^{c}	
College degree	10	33.3			7	24.1			0.78	0.435^{c}	
Postgraduate studies	5	16.7			6	20.7			−0.39	0.693^{c}	

n, Sample size; M, Mean; SD, Standard Deviation; BMI, body mass index; a, t-test; b, Mann-Whitney U-Test; c, Z-Test; d, Cohen's d.

depression, anxiety, and stress. Answers are given according to a 4-point Likert scale (0 meaning "this statement does not describe what happened to me during the last week" and 3 meaning "this statement describes much of what happened to me during the last week"). We used a Spanish translation validated in a Chilean population (Antúnez and Vinet, 2012) to assess depression, anxiety, and stress in fibromyalgia and control groups. Internal consistency was estimated at a Cronbach's alpha of 0.96 for the total score, with coefficients of 0.93, 0.84, and 0.91 for the dimensions of *Depression*, *Anxiety*, and *Stress*, respectively.

Participants were also asked to report their current pain intensity on a scale from 0 to 10.

Exteroceptive Body Awareness

Body-Scaled Action Task

The body scale action task was performed following the protocol of Guardia et al. (2010). Fifty-one apertures varying from 35 to 78 cm were projected onto a wall in random fashion (constant stimuli method, E-prime software). The video projector was positioned sufficiently far (4.3 m) to allow the projection zone to reach the floor and present a 2-m-high aperture such that the projection was similar to a real door. The participant stood upright behind the video projector, 4.8 m from the wall on which the aperture was projected. Participants were instructed to imagine themselves walking at a normal speed and to say, without performing the action, whether they would be able to pass through the presented aperture without turning sideways, pressing a button for "yes" or "no." Each aperture was presented four times for a total of 204 randomly ordered trials. When the task was completed, the experimenter measured the participant's shoulder width. As performed by Guardia et al., we calculated participants' perceptual threshold as the aperture for which they gave a 50% positive response rate ("Yes, I can walk through without turning sideways").

We calculated the slope of the psychometric curve as follows:

$$\text{Answer} = 1/1 + \exp^{(-\mathrm{k}(\mathrm{c}-\text{aperture}))}$$

Where c is the aperture corresponding to the perceptual threshold and k is the slope of the curve around the point c. The slope indicates the discriminability of the participants: steep and shallow slopes correspond to good and poor discrimination, respectively. Dividing the perceptual threshold by the participants' shoulder width, we calculated the perceived passability ratio (π_{p}). The passability ratio is an index that indicates the estimate that a person makes of her body size in relation to the width of her shoulders. Thus, if the index is equal to 1, the perceptual threshold is equal to the width of shoulders of the person. The larger the index, the greater the width that the person needs to estimate that she passes through the aperture. Warren and Whang (1987) used a similar task to show that the passability ratio in healthy subjects is 1.16.

Interoceptive Sensitivity

Heartbeat Detection-Task

The heartbeat-detection task was performed following the protocol of Tsakiris et al. (2011). Participants were asked to silently count their heartbeats during an interval determined by two auditory cues while their heartbeats were monitored using a three-electrode electrocardiogram (ECG, Biopac MP36R). There were four different intervals of 75, 45, 35, and 25 s, presented in random order per participant, who was then asked to report the number of heartbeats counted at the end of each interval.

IS was estimated as the mean heartbeat perception score:

$$\text{IS score} = 1/4\,\mathrm{S}\,(1 - [|\text{recorded heartbeats—counted heartbeats}|]/\text{recorded heartbeats})$$

Accordingly, the IS score ranges from 0 to 1, with higher scores indicating smaller differences between counted and recorded heartbeats.

Interoceptive Awareness

The MAIA

The MAIA is a 32-item self-report questionnaire composed of eight subscales, evaluating the following per category. *Noticing*, awareness of uncomfortable, comfortable, and neutral body sensations; *Not distracting*, not ignoring or distracting oneself from sensations of pain or discomfort; *Not worrying*, not worrying or experiencing emotional distress with sensations of pain or discomfort; *Attention regulation*, ability to sustain and control attention to body sensation; *Emotional awareness*, awareness of the connection between body sensations and emotional states; *Self-regulation*, ability to regulate psychological distress by attention to body sensations; *Body listening*, actively listening to the body for insight; and *Trusting*, experiencing one's body as safe and trustworthy.

Items are answered on a Likert scale, with six levels of ordinal responses coded from 0 (never) to 5 (always). We translated the MAIA questionnaire to Spanish and evaluated the Spanish version's psychometric properties (Valenzuela-Moguillansky and Reyes-Reyes, 2015). It was used in the present study to assess interoceptive body awareness in fibromyalgia and control groups. In terms of reliability, a Cronbach's alpha value of 0.90 was estimated for the total score, while subscales ranged from 0.21 to 0.85: Noticing ($\alpha = 0.74$), Not distracting ($\alpha = 0.21$), Not worrying ($\alpha = 0.39$), Attention regulation ($\alpha = 0.85$), Emotional awareness ($\alpha = 0.84$), Self-regulation ($\alpha = 0.85$), Body listening ($\alpha = 0.85$), and Trusting ($\alpha = 0.78$).

Procedure

Prior to the experimental session, participants were contacted by telephone to agree to an appointment and register personal information (age, educational level, duration of the pain, intensity of the pain, description of other symptoms, medications, and other illnesses). On arrival, participants were provided with written information about the experiment, and informed consent was obtained. Next, they answered four questionnaires: the FIQ/SIQ[1], BPI, DASS-21, and MAIA. They were then seated in a comfortable chair, ECG electrodes were placed, and the heartbeat detection task commenced. Two training trials were performed prior to four experimental trials (described above). At the end of the heartbeat perception task, a short interview was given about the participants' performance. Between the heartbeat detection and body-scaled action tasks, we registered participants' cardiac activity during 5 min of rest and 5 min of a cognitive stress task (objective of a parallel study). ECG electrodes were removed, participants asked to stand up-right and the body-scaled action task was performed (described above). The experimental session lasted approximately 75 min.

[1] As explained in Method, the SIQ is equivalent to the FIQ but does not contain any reference to fibromyalgia; it was used for comparing the fibromyalgia and control groups.

Statistical Analysis

Student's t-tests for independent samples were used to compare the means of variables between fibromyalgia and control groups. Correlations between variables were assessed with the Pearson coefficient. Mann-Whitney and Spearman tests were applied for non-normal distributions and non-homogeneous between group variances. The Shapiro-Wilk test was used to test normality. The Z-test was used to compare proportions of two independent samples. A two-tailed hypothesis test was performed using a significance level of 0.05.

The Expectation Maximization (EM) method was used to impute missing data with a likelihood function based on a Student t distribution. Little's Missing Completely at Random (MCAR) test was applied over the data set.

Analyses were performed using IBM SPSS Statistics 22 (IBM Corp, 2011) and with StataSE (StataCorp, 2015).

RESULTS

Group Comparisons

There were no significant differences between the fibromyalgia and control groups in age, weight, height and body mass index (**Table 1**). Education level was similar in both groups (all $p > 0.05$).

Clinical Assessments

The FIQ scores of the fibromyalgia group were higher than the SIQ scores of the control group. The *Severity* and *Interference* scores of the BPI were higher in fibromyalgia patients, as were the *Depression*, *Anxiety*, and *Stress* dimensions of the DASS-21 (**Table 2**). Distribution of pain and the frequency at each location are shown in **Table 3**.

Exteroceptive Body Awareness

The passability ratio was higher in the fibromyalgia group (**Figure 1**, mean $\pi_{FM} \pm$ SD: 1.61 $\pm$ 0.26; mean $\pi_C \pm$ SD: 1.46 $\pm$ 0.23; $t = 2.209$, $p = 0.03$; $d = 0.61$). We compared the means of the psychometric curves slopes of both groups and found no differences in discriminability (**Table 4**, mean slope $_{FM} \pm$ SD: -0.77 ± 0.41; mean slope $_C \pm$ SD: -0.91 ± 0.43; $U = 346.5$; $z = -1.342$, $p = 0.18$; $d = 0.33$).

A correlation analysis was performed to test the relationship between the passability ratio and clinical variables (FIQ/SIQ, BPI, current pain score, and DASS-21). Correlations were observed between the passability ratio and FIQ/SIQ score ($r = 0.364$, $p = 0.006$) and the *Interference* dimension of the BPI ($r = 0.334$, $p = 0.012$). No correlation was found between the passability ratio and BPI severity or the current pain score. There was no correlation between the passability ratio and the DASS-21. We also tested the relationship between the passability ratio and pain duration but did not find a significant correlation. Though not significant, a progressive increment of the mean ratio was observed when pain duration was stratified in three categories: 0 months (absence of pain), 1–96 months, and 97–540 months (mean $\pi_{0\ months} = 1.48 \pm 0.25$, mean $\pi_{21\ to\ 96\ months} = 1.55 \pm 0.247$, mean $\pi_{97\ to\ 540\ months} = 1.60 \pm 0.305$).

TABLE 2 | Comparison of clinical assessment of the participants with fibromyalgia and control group.

Variables	Fibromyalgia group ($n = 30$)				Control group ($n = 29$)						
	Min.	*Max.*	*M*	*SD*	*Min.*	*Max.*	*M*	*SD*	*t-z*	*p-value*	*d*
FIQ/SIQ	20.50	90.96	59.72	19.51	.00	54.72	18.45	13.40	9.497	0.000[a]	2.47
BPI severity	7	40	20.23	6.20	0	25	4.17	6.50	−5.973	0.0001[b]	2.53
BPI interference	7	65	37.57	16.00	0	40	4.62	9.58	−6.161	0.0001[b]	2.45
DASS-21 total	3	56	26.00	14.78	0	19	6.69	5.01	5.26	<0.001[b]	1.75
DASS-21 depression	0	21	7.63	6.53	0	8	1.90	2.24	3.87	<0.001[b]	1.17
DASS-21 anxiety	0	17	7.53	4.58	0	5	1.55	1.50	5.55	<0.001[b]	1.75
DASS-21 stress	0	20	10.83	5.17	0	10	3.24	3.02	5.13	<0.001[b]	1.79

FIQ, Fibromyalgia impact questionnaire; SIQ, Symptoms impact questionnaire; BPI, Brief pain inventory; DASS-21, Depression, anxiety, stress scale. n, Sample size; M, Mean; SD, Standard Deviation; a, t-test; b, Mann-Whitney U-Test; d, Cohen's d.

Interoceptive Sensitivity

No difference between groups was observed for the IS score (mean $_{FM}$ ± SD: 0.49 ± 0.31, mean $_{C}$ ± SD: 0.50 ± 0.26; $t = -0.169$; $p = 0.867$; $d = -0.035$).

To assess relationships between IS and clinical variables, we performed a correlation analysis over the whole sample between the IS score and the FIQ/SIQ, BPI, and DASS-21 results. There was a negative correlation between IS and the *Depression* dimension of the DASS-21 (**Table 5**). Examining each group, a negative correlation was found between the IS score and the *Depression* dimension, *Stress* dimension, and total DASS-21 score among participants with fibromyalgia. In the control group, a positive correlation was observed between the IS score and the *Anxiety* dimension of the DASS-21.

Interoceptive Awareness

The MAIA questionnaire scores are displayed in **Table 6**. Participants with fibromyalgia registered lower scores in the dimensions *Not distracting* ($F = 5.153$, $p = 0.027$, $\eta_p^2 = 0.084$) and *Trusting* ($F = 12.113$, $p = 0.001$, $\eta_p^2 = 0.178$) and higher scores in *Noticing* ($F = 6.031$, $p = 0.017$, $\eta_p^2 = 0.097$).

A negative correlation was found between the total MAIA score and the FIQ/SIQ (**Table 7**). The dimension *Noticing* correlated positively, while *Not distracting*, *Not worrying*, *Self-regulation*, and *Trusting* correlated negatively.

The *Severity* dimension of the BPI correlated negatively with the total MAIA score. The *Not distracting*, *Self-regulation*, and *Trusting* dimensions of the MAIA correlated negatively with BPI severity. The total MAIA score exhibited a negative correlation with *Interference,* as did the individual dimensions of *Not distracting*, *Not worrying, Self-regulation*, and *Trusting.*

There was a negative correlation between total DASS-21 score and that of the MAIA. The total MAIA score correlated negatively with the *Depression* dimension of the DASS-21. *Noticing* on the MAIA correlated positively with *Anxiety, Stress*, and the total DASS-21 score. *Not distracting* correlated negatively with *Depression*, *Stress*, and total DASS-21 score. *Not worrying* correlated negatively with *Depression, Anxiety*, and *Stress* on the DASS-21, as well as the total score. *Self-regulation* correlated negatively with *Depression* and the total DASS-21 score. *Trusting* correlated negatively with *Anxiety*, *Stress*, and total DASS-21 score.

Exteroceptive and Interoceptive Body Awareness

To evaluate whether there is a relationship between exteroceptive and interoceptive body awareness, we tested correlations between a) the passability ratio and IS score and b) the passability ratio and MAIA. The passability ratio and the IS score correlated inversely ($r = -0.291$, $p = 0.05$), as did the passability ratio and *Body listening* dimension of the MAIA ($r = -0.355$, $p = 0.001$), although it did not correlate with any other MAIA dimension or its total score.

DISCUSSION

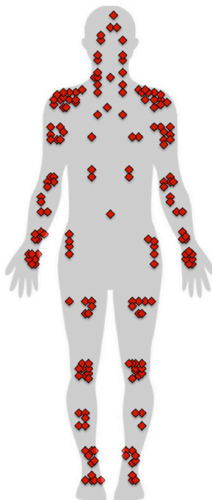
The aims of the present study were to evaluate exteroceptive and interoceptive self-body awareness of persons suffering from fibromyalgia and to assess whether there is a relationship between exteroceptive and interoceptive body awareness. Our hypotheses were (a) fibromyalgia patients have disrupted exteroceptive body awareness, overestimating their body size; (b) fibromyalgia patients present disrupted IS; (c) fibromyalgia patients have diminished interoceptive awareness compared with control subjects; and (d) there is a relationship between exteroceptive and interoceptive self-body awareness within the whole sample.

Exteroceptive Body Awareness

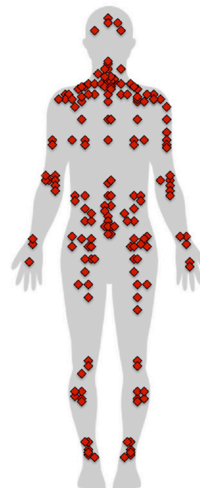
Consistent with our first hypothesis, the passability ratio of the body-scaled action-anticipation task was higher among fibromyalgia patients. They overestimated the passability of an aperture relative to their shoulder width, suggesting a disruption in their exteroceptive body awareness. To our knowledge, this is the first study to report such a result. The lack of difference in the slope of the psychometric curve compared to controls suggests that the difference in the passability ratio is not due to group differences in the ability to perform the task. This result extends on our previous findings (Valenzuela-Moguillansky, 2013), where fibromyalgia patients described feeling a larger body over the course of a pain crisis.

TABLE 3 | Distribution and frequency of pain in fibromyalgia patients.

Anterior		
Body zone	**Side**	**Frequency**
Head		4
Face		1
Jaw	Right	2
	Left	2
Neck	Middle	1
	Right	5
	Left	4
Shoulders	Right	13
	Left	10
Upper arm	Right	7
	Left	8
Elbow	Right	5
	Left	5
Forearm	Right	4
	Left	4
Wrist	Right	5
	Left	4
Hand	Right	7
	Left	7
Chest	Middle	1
	Right	3
	Left	4
Ribs	Right	2
	Left	2
Belly	Middle	1
Hip	Right	4
	Left	5
Thigh	Right	6
	Left	7
Knee	Right	9
	Left	10
Shin	Right	5
	Left	3
Ankle	Right	6
	Left	6
Foot	Right	5
	Left	3



Posterior		
Body zone	**Side**	**Frequency**
Head		5
Cervical	Middle	13
	Right	5
	Left	6
Shoulders	Right	7
	Left	5
Upper arm	Right	5
	Left	2
Elbow	Right	6
	Left	7
Wrist	Right	3
	Left	2
Hand	Right	2
	Left	1
Upper thorax	Middle	3
	Right	6
	Left	6
Lower thorax	Middle	4
	Right	4
	Left	4
Lumbar region	Middle	14
	Right	7
	Left	7
Sacrum region	Middle	1
	Right	2
	Left	2
Buttocks	Right	8
	Left	8
Thigh	Right	4
	Left	3
Knee	Right	2
	Left	3
Calf	Right	5
	Left	5
Ankle	Right	6
	Left	6



Notably, the passability ratio in our control group (1.46) was larger than ratios obtained in previous studies employing the body-scaled action task. Warren and Whang (1987) obtained a passability ratio of 1.16 in controls, whiles 2010 and 2012 studies by Guardia et al. reported 1.15 and 1.14, respectively. Group differences between the samples might explain this disparity. Warren and Wang included male undergraduates, while Guardia et al. (2010, 2012) included young women with a mean age around 24. The mean age of the women participating in the present study was 45. Increase in hip width with age is generally larger than that of shoulder width. Normalization of the critical opening (the aperture for which participants gave a 50% positive response rate) is performed by shoulder rather than hip width, so it is plausible that the passability ratio increases with age in women. There was no difference in age between the two groups; thus, this difference in the passability ratio compared to previous studies has no bearing on the results with respect to our hypotheses.

Our results show that body size overestimation correlates positively with the *Interference* dimension of the BPI but not the *Severity* dimension or current pain intensity. This suggests that the change in exteroceptive body awareness is not due to moment-to-moment incorporation of sensory (nociceptive) changes, as proposed by Schwoebel et al. (2001, 2002), where we would have expected the passability ratio and pain intensity to correlate due to an impact of pain on functionality. Pain-related fear and fear-avoidance behavior have been extensively reported in different chronic pain conditions (e.g., Jensen and Karoly, 1992; Asmundson et al., 1997; Crombez et al., 1999; Leeuw et al., 2007; Wideman et al., 2009). Pain-related avoidance behavior affects range of movement and muscular strength, changing the motor response patterns (Vlaeyen and Linton, 2000). Disrupted body awareness in fibromyalgia patients might be the result of such a process. This is in line with findings by Moseley (2004) and Peltz et al. (2011). Moseley applied the hand laterality task in complex regional pain syndrome (CRPS) patients to test: (a) if chronic disuse is responsible for a delay in hand recognition, reaction times should be proportional to duration of symptoms and (b) if a guarding response contributes to the delay in hand recognition, reaction times should be proportional to the pain evoked by performing the mental movement but not to current pain intensity. Patients' reaction times correlated with symptom duration and pain that would be evoked by executing a movement but not with pain intensity. Moseley proposed the existence of a "guarding-type" mechanism, affecting motor processes at the level of planning movements and the involvement of long-term changes in the cortical brain regions that participate in body representation. In the same line, Peltz et al. (2011) found that CRPS patients overestimated the size of their hand, and the degree correlated with disease duration, tactile discrimination, and neglect symptoms. Although not significant, we observed a tendency of a progressive increase in the mean passability ratio stratified by pain symptom duration. A larger sample size might evidence a significant relationship with symptom duration.

It is noteworthy that the pain distribution results show greater concentration of pain in the shoulders and cervical and lumbar regions. The question arises whether there is a relationship between the passability ratio and pain location. Since the body-scaled action-anticipation task specifically involves shoulder width, one could hypothesize that overestimation of body size is due to the concentration of pain in the shoulder area alone. We compared the mean passability ratio for subsamples of patients that had pain in different locations with the total fibromyalgia group (see supplementary material) and found a significantly higher mean ratio in subsamples with pain in the thighs, cervical, upper arms, shoulders, wrists, elbows, neck, and lumbar region. Given the small number of cases for some pain locations, it was not possible to perform a comparison. A further limitation was that patients felt pain in more than one location; therefore, we were unable to determine whether the fact of obtaining a higher passability ratio in a subsample presenting pain at a given location is exclusively related to the presence of pain at that location.

To assess the hypothesis that overestimation of body size was due to concentration of pain in the shoulder area alone,

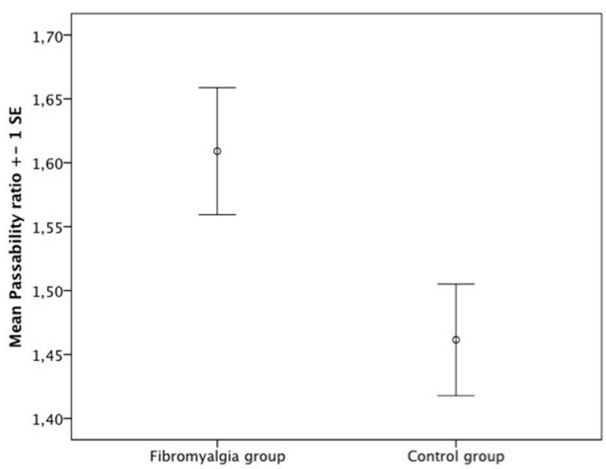


FIGURE 1 | Comparison between groups of mean passability ratio.

TABLE 5 | Pearson correlation coefficient between the interoceptive sensitivity (IS) score and the DASS-21 in the fibromyalgia and control groups.

Variables	IS score		
	Whole Sample	Fibromyalgia group	Control group
FIQ/SIQ	−0.129	−0.294	0.023
BPI *Severity*	−0.094	−0.245	0.013
BPI *Interference*	−0.112	−0.304	0.131
DASS-21 Depression	−0.298*	−0.431*	−0.108
DASS-21 Anxiety	−0.051	−0.201	0.450*
DASS-21 Stress	−0.184	−0.403*	0.117
DASS-21 Total score	−0.203	−0.394*	0.157

** $p < 0.05$.*

TABLE 4 | Summary of the slope, critical aperture, shoulder width and the passability ratio (π_p) in the two groups.

	Fibromyalgia group				Control group						
	Min.	*Max.*	*M*	*SD*	*Min.*	*Max.*	*M*	*SD*	*t-z*	*p-value*	*d*
Slope	−1.93	−0.29	−0.77	0.41	−1.89	−0.23	−0.91	0.43	−1.342	0.18[b]	0.33
Critical aperture (cm)	43.6	73.0	56.09	8.16	34.50	73.0	53.77	8.50	1.067	0.29[a]	0.28
Shoulder width (cm)	32	40	35.59	2.35	32	40	36.46	2.35	−1.394	0.169[a]	−0.37
Passability ratio (π_p)	1.23	2.15	1.61	0.26	0.91	1.87	1.46	.23	2.231	0.030[a]	0.61

M, Mean; DS, Standard Deviation; a, t-test; b, Mann-Whitney U-Test; d, Cohen's d.

TABLE 6 | Descriptive statistics of the MAIA dimensions according to the fibromyalgia and control groups.

Dimensions	Fibromyalgia group					Control group							
	Min.	*Max.*	*M*	*Md*	*SD*	*Min.*	*Max.*	*M*	*Md*	*SD*	*F*	*p*	η_p^2
Noticing	6	20	15.57	16.00	3.70	3	20	12.82	13.00	4.78	6.031	0.017	0.097
Not distracting	0	11	5.97	6.50	3.02	2	13	7.71	8.00	2.83	5.153	0.027	0.084
Not worrying	0	15	7.17	7.00	3.46	1	15	8.64	9.50	3.27	2.785	0.101	0.047
Attention regulation	5	33	18.27	18.50	7.53	1	32	19.36	20.50	7.91	0.289	0.593	0.005
Emotional awareness	0	25	18.43	19.50	6.53	4	25	19.11	21.00	5.63	0.176	0.676	0.003
Self-regulation	0	20	9.40	10.00	5.45	3	20	11.89	12.00	4.92	3.329	0.073	0.056
Body listening	0	14	6.67	6.00	4.19	0	13	6.43	6.50	3.99	0.049	0.826	0.001
Trusting	1	15	7.87	8.00	3.32	0	15	10.96	12.00	3.46	12.113	0.001	0.178
MAIA total	35	127	89.33	90.50	24.22	43	147	96.93	97.00	25.03	1.379	0.245	0.024

M, Mean; DS, Standard Deviation; η_p^2, Partial eta squared; Md, Median.

TABLE 7 | Pearson correlation coefficient between the MAIA and the FIQ, BPI, and DASS-21 considering the whole sample.

		BPI		DASS-21			
MAIA	**FIQ/SIQ**	***Severity***	***Interference***	***Depression***	***Anxiety***	***Stress***	**Total**
Noticing	0.362**	0.168	0.170	0.202	0.385**	0.336**	0.327*
Not distracting	−0.329*	−0.296*	−0.359**	−0.392**	−0.210	−0.334*	−0.345**
Not worrying	−0.392**	−0.251	−0.327*	−0.449**	−0.363**	−0.414**	−0.445**
Attention regulation	−0.076	−0.207	−0.178	−0.196	−0.013	−0.072	−0.107
Emotional awareness	−0.109	−0.092	−0.113	−0.221	−0.079	−0.087	−0.143
Self-regulation	−0.299*	−0.287*	−0.363**	−0.292*	−0.205	−0.258*	−0.276*
Body listening	−0.088	−0.046	−0.136	−0.189	−0.043	−0.003	−0.087
Trusting	−0.442**	−0.416**	−0.439**	−0.247	−0.379**	−0.338**	−0.343**
MAIA Total	−0.289*	−0.297*	−0.364**	−0.370**	−0.194	−0.242	−0.296*

$*p < 0.05$, $**p < 0.01$.

we compared the mean passability ratio of a subsample of patients who had no shoulder pain (NSP) with that of the total fibromyalgia group. The result indicated that the NSP subsample had a higher passability ratio than the fibromyalgia group, discarding that hypothesis (mean $\pi_{NSP} \pm$ SD: 1.72 $\pm$ 0.26; mean $\pi_{FM} \pm$ SD: 1.61 $\pm$ 0.26, $p = 0.016$). These results, together with the fact that body size overestimation correlates positively with the *Interference* dimension of the BPI but not with the *Severity* dimension or with current pain intensity, led us to consider that it was not current pain in a specific location that directly affected oversize estimation. Nevertheless, the relationship between body size overestimation and pain location warrants further investigation.

Interoceptive Sensitivity

Our second hypothesis was that fibromyalgia patients experience disrupted IS compared with controls. There was no difference in *IS*-values between groups for the heartbeat detection task, which does not support our hypothesis.

The correlation analysis over the whole sample showed no relationship between IS and the FIQ/SIQ, in agreement with the lack of difference in IS between groups. Likewise, there was no association between IS and the *Severity* and *Interference* dimensions of the BPI. Taken together, these results indicate that IS is not related to fibromyalgia symptoms.

In contrast to our findings, Duschek et al. (2015) found decreased IS in fibromyalgia patients and a negative linear association between IS and fibromyalgia symptom severity using a similar experimental paradigm. The difference may be due to an interaction between interoception and emotional variables. Dunn et al. (2010) argued that contradictory clinical evidence regarding interoception might be explained by an interaction with depression and anxiety. The authors applied the Clark and Watson (1991) tripartite model in which depression and anxiety are not considered monolithic typologies, but dimensional constructs that share a common component of negative affect differentiated by specific symptoms: anhedonia for depression and hyperarousal for anxiety. Assessing IS with the heartbeat detection task and symptoms with a short form of the Mood and Anxiety Symptom Questionnaire, Dunn et al. showed that the relationship between arousal and interoceptive accuracy weakened as anhedonia symptoms increased, suggesting interactions among interoception, depression, and anxiety (Dunn et al., 2010).

In the present work, fibromyalgia patients exhibited depression, anxiety, and stress as assessed by the DASS-21.

Considering the IS score and mental health variables, an inverse association was observed: higher scores on depressive symptoms were coincident with lower IS, in agreement with previous studies (Pollatos et al., 2009; Terhaar et al., 2012). However, assessing groups individually, we found an inverse association between IS and depressive and stress symptoms in the fibromyalgia group, while the control group exhibited a positive correlation between the IS score and *Anxiety*. This contrast could suggest a different emotional-affective background in patients and controls, which could interact differently with IS. Taking into account the findings of Dunn et al. (2010) anhedonic and/or hyperarousal symptoms could have interacted with interoceptive performance, resulting in a lack of difference between the groups. A limitation of our study is that these symptoms were not specifically assessed.

No explanatory conclusions regarding IS can be extrapolated from the present findings. The interplay of emotional variables, particularly depressive and anxiety symptoms, between pain and IS in fibromyalgia, should be explored in future works using more complex models and larger participant samples.

Interoceptive Awareness

The MAIA total score did not differ between the fibromyalgia and control groups. Scores for *Noticing* were higher in the fibromyalgia group, suggesting patients are more aware of uncomfortable, comfortable, and neutral body sensations than controls. In addition, *Trusting* scores were lower among patients with fibromyalgia.

Notably, Cronbach's alpha estimates for *Not distracting* and *Not worrying* were low ($\alpha = 0.21$; $\alpha = 0.39$, respectively), indicating that these two dimensions cannot be reliably interpreted. Low Cronbach's alpha values were obtained for *Not Distracting* and *Not Worrying* in our evaluation of MAIA psychometric properties ($\alpha = 0.487$; $\alpha = 0.402$, respectively; Valenzuela-Moguillansky and Reyes-Reyes, 2015), suggesting cautious interpretation with respect to these dimensions and a need to verify the survey's Spanish translation.

An inverse relation was found between the total MAIA score and the FIQ/SIQ and the *Severity* and *Interference* dimensions of the BPI over the whole sample, indicating lower interoceptive awareness with a higher impact of fibromyalgia/any discomfort symptoms. In agreement with comparisons between groups, *Noticing* correlated positively with the FIQ/SIQ over the whole sample. On the other hand, *Self-regulation* and *Trusting* negatively associated with the FIQ/SIQ and both dimensions of the BPI, indicating that fibromyalgia/any discomfort symptoms are related to a reduced ability to regulate distress by attending to body sensations, as well as experiencing one's body as safe or trustworthy. These results suggest that while fibromyalgia patients exhibit greater awareness of uncomfortable, comfortable, and neutral body sensations, they cannot use this awareness to regulate distress. This idea is supported by correlations between the MAIA and mental health variables. The total MAIA score correlated negatively with *Depression* on the DASS-21, suggesting lower general interoceptive awareness with higher depressive symptoms. *Noticing* associated positively with the *Anxiety* and *Stress* dimensions of the DASS-21, indicating greater awareness of body sensations as anxiety or stress increase. *Self-regulation* associated negatively with the *Depression* and *Stress* dimensions of the DASS-21, indicating reduced ability to regulate distress by attending to body sensations as depression or stress increase. *Trusting* associated negatively with *Anxiety* and *Stress*, suggesting diminished experience of one's body as safe or trustworthy with elevated anxiety or stress.

The correlation between *Noticing* with *Anxiety* and *Stress* could be understood as expressing some form of "somatosensory amplification" (Barsky and Wyshak, 1990; Barsky et al., 1990; Cameron, 2002; Mailloux and Brener, 2002; De Berardis et al., 2007), described as a heightened attentional focus on the body, anxious vigilance of bodily signals, and self-focusing (as in hypochondriasis). This might explain the lower scores in *Trusting*. For fibromyalgia patients, bodily sensations are a source of anxiety and distress. Thus, it is consistent that body awareness is an alarm rather than an experience of non-judgmental acceptance of and connection with bodily sensations. Such body awareness can lead to a process of "objectification of body sensations," in which body sensations are experienced as an object of perception rather than constituting the subject that perceives. Accordingly, bodily sensations are no longer part of the background of patients' embodied experience of the world; rather, they become a foreign object from which they need to protect themselves. Consequently, although attention to bodily sensations is increased, there is a concomitant process of taking distance and disconnection from body sensations, leaving the individual without bodily based emotional tools for self-regulation processes (Damasio, 2005). Such a process is coherent with fibromyalgia patients' reports of an "alienated" (Calsius et al., 2015) or "foreigner" body (Valenzuela-Moguillansky, 2013). This experience, different from the experience of "alienated" body in schizophrenia patients that directly expresses an "alienated" embodied self or disembodiment (Parnas and Handest, 2003; Fuchs and Schlimme, 2009; Parnas and Sass, 2010; Sestito et al., 2015a,b), expresses an aching body "as if" it was foreigner to the patient but experienced within a preserved sense of self. In this regard, the *embodied affectivity model* (Fuchs, 2013; Fuchs and Koch, 2014; Gaete and Fuchs, 2016) proposes that bodily resonance of emotions plays a key role in the experience of affects. Such model considers that without bodily resonance of emotions the experience of the world is devoid of meaning, as is the case of the bodily constriction observed in depressive patients, of which the so-called *Cotard's* syndrome is its main expression, or the case of alexithymia traits of somatoform or eating disorders. The negative association between the total MAIA score and *Depression* could indicate difficulties in patients' bodily resonance of emotions, as some authors have proposed (Brosschot and Aarsse, 2001; van Middendorp et al., 2008). In this regard, Hsu et al. (2010) treated fibromyalgia using Affective Self-Awareness (ASA), proposing that affects and how they are regulated (inhibition and avoidance or identification and expression) play a role in pain experience. They reported a significant reduction in pain severity, improved self-reported physical function, and a higher tender points threshold following ASA, applying mindfulness techniques toward breath, body, and emotions without judgment.

Relationship between Exteroceptive and Interoceptive Body Awareness

Confirming our hypothesis, we observed a relationship between exteroceptive and interoceptive body awareness. The passability ratio and the IS score correlated negatively across the whole sample, meaning lower sensitivity to internal signals with higher passability ratios, i.e., higher the disruption of exteroceptive body awareness. To our knowledge, this is the first result showing that the estimation of body size relates to the perception of inner sensations. This result expands on Tsakiris et al. (2011) who report greater IS measured by the heartbeat detection task with reduced illusion of ownership of a rubber hand. In addition, through the MAIA we assessed an attitudinal disposition to being connected to internal states. There was a negative association between the passability ratio and *Body Listening* dimension of the MAIA, indicating a lower tendency to actively listen to the body for insight among subjects with higher passability ratios. These results suggest an interaction between mechanisms underlying the perception of our body in relation to space, sensibility to internal signals, and awareness of our inner state.

Finally, we would like to relate our unique results in a schematic (**Figure 2**) inspired by the Vlaeyen and Linton fear-avoidance model (see Crombez et al., 2012; Vlaeyen and Linton, 2012, for an up to-date discussion), which was originally conceived to understand how acute injury pain becomes chronic. In such a context, rumination, and catastrophizing, cognitive aspects of pain-related fear, were considered as determinants in the evolution of the state of pain. In our work, we take as a point of departure a situation of chronic pain. Although catastrophizing and rumination are probably involved in aggravating pain in patients with fibromyalgia, we will not emphasize this aspect. We believe that considering the immediate behavioral aspect of pain-related fear—"it hurts, therefore I avoid it"—is sufficient to discuss possible interactions between exteroceptive and interoceptive body awareness and pain, which is the aim of our model.

We take as a starting point the situation of chronic pain that typically includes symptoms of depression and anxiety. As proposed by Vlaeyen and Linton (2000), pain-related fear promotes avoidance behaviors, which modifies patients' motor patterns. We proposed that the modification in motor patterns alter patients' exteroceptive body awareness, decreasing agility and physical dexterity, which is supported by the higher rate of falls and balance loss in people with fibromyalgia (Jones et al., 2009; Meireles et al., 2014). This experience of a clumsy body might lead to decreased confidence, as suggested by a negative correlation between the *Trusting* dimension of the MAIA and FIQ/SIQ scores. Lack of confidence in one's body might lead to decreased functionality and isolation; impacting social relationships and emotional wellbeing; and enhancing depression, anxiety, and pain. Such emotional states can impact interoceptive body awareness and foster objectification of body sensations. Here, attention to body sensations is coupled with a disconnection from them, contributing to decreased self-confidence and leaving the patient without bodily based emotional tools for self-regulation processes. These factors contribute to dysfunctionality and isolation, aggravating pain and patients' emotional state. In addition, the inverse relationship between the passability ratio and *Body listening* support the idea that exteroceptive and interoceptive body awareness are related; disconnection from bodily sensations might aggravate the distortion of exteroceptive body awareness and vice versa.

A two-pronged strategy aimed at re-establishing appropriate sensorimotor processing and enabling connection with emotions

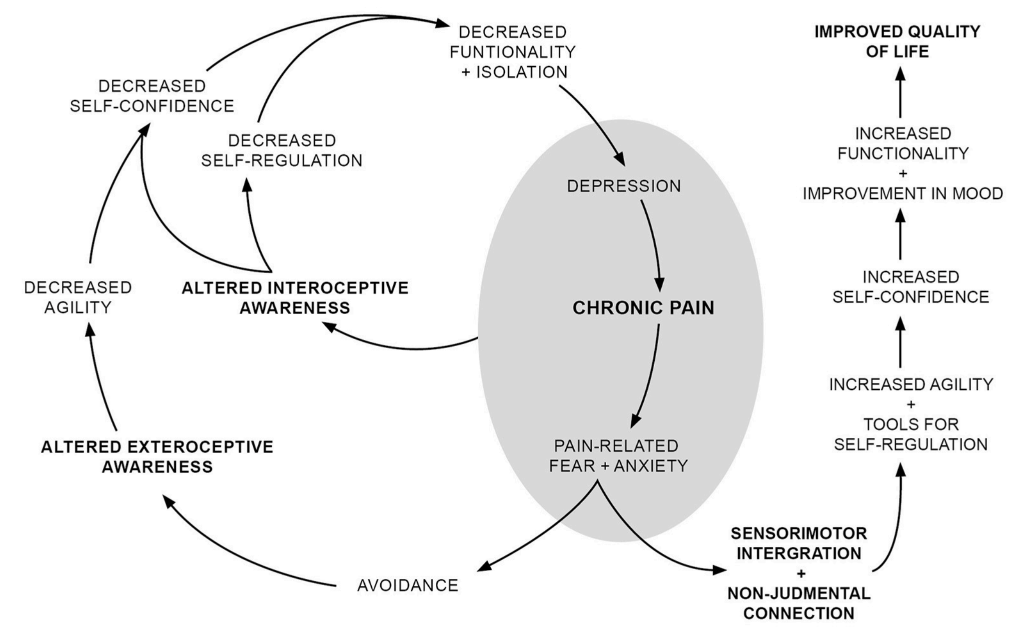


FIGURE 2 | Outline model of the relationship between pain, exteroceptive and interoceptive body awareness.

TABLE 8 | Pearson correlation coefficient between the MAIA and IS score within the whole sample.

MAIA	IS score
Noticing	0.183
Not distracting	0.079
Not worrying	0.095
Attention regulation	0.446**
Emotional awareness	0.416**
Self-regulation	0.209
Body listening	0.372**
Trusting	−0.022
MAIA total	0.382**

$^{**}p < 0.001$.

and bodily sensations in a non-judgmental manner is suggested to overcome these vicious cycles and improve patients' quality of life. A movement-based embodied contemplative practice such as yoga, the Feldenkrais method, or tai chi could be suitable to fulfill those objectives (Schmalzl and Kerr, 2016). Such practices can modify sensorimotor processing (Kerr et al., 2016) and foster non-judgmental connections with emotions and bodily sensations (Gard et al., 2014). This could help re-establish coherent exteroceptive body awareness and regaining familiarity with bodily sensations as part of patients' embodied subjectivity. In turn, coherent exteroceptive body awareness would improve patients' agility and self-confidence, and connection with bodily sensations would provide tools for emotional regulation, also improving self-confidence. Altogether, this would increase functionality, decreasing depression, and anxiety, and improving patient quality of life. The inverse relationship between the passability ratio and *Body listening* supports the idea that targeting both exteroceptive and interoceptive body awareness may be synergistic, enhancing the therapeutic effect of each dimension of the treatment.

Before concluding, we would like to refer to the relationship between interoceptive awareness and IS. Contrary to a dichotomized vision of interoceptive awareness and IS—one being adaptive and the other maladaptive—our results suggest these constructs share some aspects. Both the MAIA total score and IS score associated negatively with depression, indicating that these two aspects of interoception (a sense of self grounded in experiencing physical sensations in a non-judgmental way and accuracy in sensing an internal signal) decrease with higher depressive symptom burden. In addition, we found a positive association between the IS score and MAIA total score (**Table 8**). The following MAIA dimensions associated with the IS score were *Attention regulation*, *Emotional awareness*, and *Body listening*. Interestingly, these dimensions did not associate with pain or mental health variables, and there was no difference between groups. This is coherent with the lack of a difference in IS scores. Understanding the different modes of body awareness underlying the constructs of IS and interoceptive awareness, as well as the circumstances and individual characteristics in which these attentional modes might be adaptive or maladaptive, warrant further investigation.

In summary, the present findings more precisely define which aspects of body awareness are altered in fibromyalgia patients and how. We outlined a model highlighting the interaction between pain and exteroceptive and interoceptive aspects of body awareness. Movement-based embodied contemplative practices aimed at re-establishing sensorimotor integration and foster non-judgmental reconnection with bodily sensations are suggested to improve body confidence, functionality, and quality of life. Our results expand the scope of reflection regarding the relationship between body awareness and pain, including interoceptive and emotional aspects of the pain-body relationship.

AUTHOR CONTRIBUTIONS

CVM conceived, designed and performed the study. ARR performed the statistical analysis and gave critical revision to the draft. MIG contributed with the interpretation of the data and gave critical revision to the draft.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00117/full#supplementary-material

REFERENCES

Ablin, N., and Buskila, D. (2010). Emerging therapies for fibromyalgia: an update. *Expert Opin. Emerg. Drugs* 15, 521–533. doi: 10.1517/14728214.2010.491509

Akkaya, N., Akkaya, S., Atalay, N. S., Balci, C. S., and Sahin, F. (2012). Relationship between the body image and level of pain, functional status, severity of depression, and quality of life in patients with fibromyalgia syndrome. *Clin. Rheumatol.* 31, 983–988. doi: 10.1007/s10067-012-1965-9

Antúnez, Z., and Vinet, E. V. (2012). Escalas de Depresión, Ansiedad y Estrés (DASS - 21): Validación de la Versión abreviada en Estudiantes Universitarios Chilenos. *Terapia Psicol.* 30, 49–55. doi: 10.4067/S0718-48082012000300005

Arnold, L. M., Crofford, L. J., Mease, P. J., Burgess, S. M., Palmer, S. C., Abetz, L., et al. (2008). Patient perspectives on the impact of fibromyalgia. *Patient Educ. Couns.* 73, 114–120. doi: 10.1016/j.pec.2008.06.005

Arnold, L. M., Hudson, J. I., Keck, P. E., Auchenbach, M. B., Javaras, K. N., and Hess, E. V. (2006). Comorbidity of fibromyalgia and psychiatric disorders. *J. Clin. Psychiatry* 67, 1219–1225. doi: 10.4088/JCP.v67n0807

Asmundson, G. J. G., Norton, G. R., and Allerdings, M. D. (1997). Fear and avoidance in dysfunctional chronic back pain patients. *Pain* 69, 231–236.

Bair, M. J., Robinson, R. L., Katon, W., and Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Arch. Intern. Med.* 163, 2433–2445. doi: 10.1001/archinte.163.20.2433

Barsky, A. J., and Wyshak, G. (1990). Hypochondriasis and somatosensory amplification. *Br. J. Psychiatry* 157, 404–409.

Barsky, A. J., Wyshak, G., and Klerman, G. L. (1990). The somatosensory amplification scale and its relationship to hypochondriasis. *J. Psychiatr. Res.* 24, 323–334.

Bellato, E., Marini, E., Castoldi, F., Barbasetti, N., Mattei, L., Bonasia, D. E., et al. (2012). Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. *Pain Res. Treat.* 2012:426130. doi: 10.1155/2012/426130

Bray, H., and Moseley, G. L. (2011). Disrupted working body schema of the trunk in people with back pain. *Br. J. Sports Med.* 45, 168–173. doi: 10.1136/bjsm.2009.061978

Brosschot, J. F., and Aarsse, H. R. (2001). Restricted emotional processing and somatic attribution in fibromyalgia. *Int. J. Psychiatry Med.* 31, 127–146. doi: 10.2190/K7AU-9UX9-W8BW-TETL

Burckhardt, C. S., Clark, S. R., and Bennett, R. (Rob). (1993). Fibromyalgia and quality of life. *J. Rheumatol.* 20, 475–479.

Calsius, J., Courtois, I., Stiers, J., and Bie, J. D. (2015). How do fibromyalgia patients with alexithymia experience their body? A qualitative approach. *SAGE Open* 5, 1–10. doi: 10.1177/2158244015574631

Cameron, O. G. (2002). *Visceral Sensory Neuroscience: Interoception*. Oxford ; New York, NY: Oxford University Press.

Clark, L. A., and Watson, D. (1991). Tripartite model of anxiety and depression: psychometric evidence and taxonomic implications. *J. Abnorm. Psychol.* 100, 316–336.

Cleeland, C. (1991). *The Brief Pain Inventory | MD Anderson Cancer Center*. Texas.

Cohen, H., Neumann, L., Shore, M., Amir, M., Cassuto, Y., and Buskila, D. (2000). Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Semin. Arthritis Rheum.* 29, 217–227. doi: 10.1016/S0049-0172(00)80010-4

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev.* 3, 655–666. doi: 10.1038/nrn894

Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J. W. S., and Karoly, P. (2012). Fear-avoidance model of chronic pain: the next generation. *Clin. J. Pain* 28, 475–483. doi: 10.1097/AJP.0b013e3182385392

Crombez, G., Vlaeyen, J. W. S., Heuts, P. H. T. G., and Lysens, R. (1999). Fear of pain is more disabling than pain itself. Evidence on the role of pain-related fear in chronic back pain disability. *Pain* 80, 329–339.

Damasio, A. (2005). *Descartes' Error: Emotion, Reason, and the Human Brain (Reprint edition)*. London: Penguin Books.

De Berardis, D., Campanella, D., Gambi, F., La Rovere, R., Sepede, G., Core, L., et al. (2007). Alexithymia, fear of bodily sensations, and somatosensory amplification in young outpatients with panic disorder. *Psychosomatics* 48, 239–246. doi: 10.1176/appi.psy.48.3.239

de Preester, H., and Knockaert, V. (2005). *Body Image and Body Schema: Interdisciplinary Perspectives on the Body*. Portland, OR: John Benjamins Publishing.

de Vignemont, F. (2010). Body schema and body image–pros and cons. *Neuropsychologia* 48, 669–680. doi: 10.1016/j.neuropsychologia.2009.09.022

Dunn, B. D., Stefanovitch, I., Evans, D., Oliver, C., Hawkins, A., and Dalgleish, T. (2010). Can you feel the beat? Interoceptive awareness is an interactive function of anxiety- and depression-specific symptom dimensions. *Behav. Res. Ther.* 48, 1133–1138. doi: 10.1016/j.brat.2010.07.006

Duschek, S., Montoro, C. I., and Reyes Del Paso, G. A. (2015). Diminished interoceptive awareness in fibromyalgia syndrome. *Behav. Med.* doi: 10.1080/08964289.2015.1094442. [Epub ahead of print].

Ehlers, A., and Breuer, P. (1992). Increased cardiac awareness in panic disorder. *J. Abnorm. Psychol.* 101, 371–382.

Eley, T. C., Stirling, L., Ehlers, A., Gregory, A. M., and Clark, D. M. (2004). Heart-beat perception, panic/somatic symptoms and anxiety sensitivity in children. *Behav. Res. Ther.* 42, 439–448. doi: 10.1016/S0005-7967(03)00152-9

Epstein, S. A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., et al. (1999). Psychiatric disorders in patients with fibromyalgia. *Psychosomatics* 40, 57–63. doi: 10.1016/S0033-3182(99)71272-7

Esteve-Vives, J., Rivera-Redondo, J., Salvat-Salvat, M. I., de Gracia-Blanco, M., and de Miquel, C. A. (2007). [Proposal for a consensus version of the Fibromyalgia Impact Questionnaire (FIQ) for the Spanish population]. *Reumatol. Clin.* 3, 21–24. doi: 10.1016/S1699-258X(07)73594-5

Friend, R., and Bennett, R. M. (2011). Distinguishing fibromyalgia from rheumatoid arthritis and systemic lupus in clinical questionnaires: an analysis of the revised Fibromyalgia Impact Questionnaire (FIQR) and its variant, the Symptom Impact Questionnaire (SIQR), along with pain locations. *Arthritis Res. Ther.* 13, R58. doi: 10.1186/ar3311

Fuchs, T. (2013). "The phenomenology of affectivity," in *Oxford Handbook of the Philosophy of Psychiatry,* eds K. W. M. Fulford, M. Davies, R. G. T. Gipps, G. Graham, J. Z. Sadler, G. Stanghellini et al. (Oxford: Oxford University Press), 612–631.

Fuchs, T., and Koch, S. C. (2014). Embodied affectivity: on moving and being moved. *Front. Psychol*. 5:508. doi: 10.3389/fpsyg.2014.00508

Fuchs, T., and Schlimme, J. (2009). Embodiment and psychopathology: a phenomenological perspective. *Curr. Opin. Psychiatry* 22, 570–575. doi: 10.1097/YCO.0b013e3283318e5c

Gaete, M. I., and Fuchs, T. (2016). From body image to emotional bodily experience in eating disorders. *J. Phenomenol. Psychol.* 47, 17–40. doi: 10.1163/15691624-12341303

Gallagher, S. (2000). Philosophical conceptions of the self: implications for cognitive science. *Trends Cogn. Sci.* 4, 14–21. doi: 10.1016/S1364-6613(99)01417-5

Gard, T., Noggle, J. J., Park, C. L., Vago, D. R., and Wilson, A. (2014). Potential self-regulatory mechanisms of yoga for psychological health. *Front. Hum. Neurosci.* 8:770. doi: 10.3389/fnhum.2014.00770

Guardia, D., Conversy, L., Jardri, R., Lafargue, G., Thomas, P., Dodin, V., et al. (2012). Imagining one's own and someone else's body actions: dissociation in anorexia nervosa. *PLoS ONE* 7:e43241. doi: 10.1371/journal.pone.0043241

Guardia, D., Lafargue, G., Thomas, P., Dodin, V., Cottencin, O., and Luyat, M. (2010). Anticipation of body-scaled action is modified in anorexia nervosa. *Neuropsychologia* 48, 3961–3966. doi: 10.1016/j.neuropsychologia.2010.09.004

Harshaw, C. (2015). Interoceptive dysfunction: toward an integrated framework for understanding somatic and affective disturbance in depression. *Psychol. Bull.* 141, 311–363. doi: 10.1037/a0038101

Herbert, B. M., Herbert, C., and Pollatos, O. (2011). On the relationship between interoceptive awareness and alexithymia: is interoceptive awareness related to emotional awareness? *J. Personal* 79, 1149–1175. doi: 10.1111/j.1467-6494.2011.00717.x

Hsu, M. C., Schubiner, H., Lumley, M. A., Stracks, J. S., Clauw, D. J., and Williams, D. A. (2010). Sustained pain reduction through affective self-awareness in fibromyalgia: a randomized controlled trial. *J. Gen. Intern. Med.* 25, 1064–1070. doi: 10.1007/s11606-010-1418-6

IBM Corp. (2011). *IBM SPSS Statistics for Windows, Version 22.* Armonk, NY: IBM Corp.

Jensen, M. P., and Karoly, P. (1992). Pain-specific beliefs, perceived symptom severity, and adjustment to chronic pain. *Clin. J. Pain* 8, 123–130.

Jones, K. D., Horak, F. B., Winters-Stone, K., Irvine, J. M., and Bennett, R. M. (2009). Fibromyalgia is associated with impaired balance and falls. *J. Clin. Rheumatol.* 15, 16–21. doi: 10.1097/RHU.0b013e318190f991

Kerr, C. E., Agrawal, U., and Nayak, S. (2016). The effects of tai chi practice on intermuscular beta coherence and the rubber hand illusion. *Front. Hum. Neurosci.* 10:37. doi: 10.3389/fnhum.2016.00037

Leeuw, M., Goossens, M. E. J. B., Linton, S. J., Crombez, G., Boersma, K., and Vlaeyen, J. W. S. (2007). The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J. Behav. Med.* 30, 77–94. doi: 10.1007/s10865-006-9085-0

Mailloux, J., and Brener, J. (2002). Somatosensory amplification and its relationship to heartbeat detection ability. *Psychosom. Med.* 64, 353–357. doi: 10.1097/00006842-200203000-00020

Martinez-Lavin, M. (2007). Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arth. Res. Ther.* 9, 216. doi: 10.1186/ar2146

McEwen, B. S., and Kalia, M. (2010). The role of corticosteroids and stress in chronic pain conditions. *Metab. Clin. Exp.* 59(Suppl. 1), S9–S15. doi: 10.1016/j.metabol.2010.07.012

Mehling, W. E., Gopisetty, V., Daubenmier, J., Price, C. J., Hecht, F. M., and Stewart, A. (2009). Body awareness: construct and self-report measures. *PLoS ONE* 4:e5614. doi: 10.1371/journal.pone.0005614

Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E., and Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS ONE* 7:e48230. doi: 10.1371/journal.pone.0048230

Meireles, S. A., Antero, D. C., Kulczycki, M. M., and Skare, T. L. (2014). Prevalence of falls in fibromyalgia patients. *Acta Ortop. Bras.* 22, 163–166. doi: 10.1590/1413-78522014220300386

Moseley, G. L. (2004). Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology* 62, 2182–2186. doi: 10.1212/01.WNL.0000130156.05828.43

Moseley, G. L., Olthof, N., Venema, A., Don, S., Wijers, M., Gallace, A., et al. (2008). Psychologically induced cooling of a specific body part caused by the illusory ownership of an artificial counterpart. *Proc. Natl. Acad. Sci. U.S.A.* 105, 13169–13173. doi: 10.1073/pnas.0803768105

Parnas, J., and Handest, P. (2003). Phenomenology of anomalous self-experience in early schizophrenia. *Compr. Psychiatry* 44, 121–134. doi: 10.1053/comp.2003.50017

Parnas, J., and Sass, L. (2010). "Phenomenology of self-disorders. The Spectrum of Schizophrenia," in *The Embodied Self: Dimensions, Coherence, and Disorders*, eds T. Fuchs, H. C. Sattel, and P. Henningsen (Stuttgart: Schattauer Verlag), 227–244.

Peltz, E., Seifert, F., Lanz, S., Müller, R., and Maihöfner, C. (2011). Impaired hand size estimation in CRPS. *J. Pain.* 12, 1095–1101. doi: 10.1016/j.jpain.2011.05.001

Perrot, S., Vicaut, E., Servant, D., and Ravaus, P. (2011). Prevalence of fibromyalgia in France: a multi-step study research combining national screening and clinical confirmation: The DEFI study (Determination of Epidemiology of Fibromyalgia). *BMC Musculoskelet. Disord.* 12, 224–233. doi: 10.1186/1471-2474-12-224

Pollatos, O., Füstös, J., and Critchley, H. D. (2012). On the generalised embodiment of pain: how interoceptive sensitivity modulates cutaneous pain perception. *Pain* 153, 1680–1686. doi: 10.1016/j.pain.2012.04.030

Pollatos, O., Traut-Mattausch, E., and Schandry, R. (2009). Differential effects of anxiety and depression on interoceptive accuracy. *Depress. Anxiety* 26, 167–173. doi: 10.1002/da.20504

Raphael, K. G., Janal, M. N., and Nayak, S. (2004). Comorbidity of fibromyalgia and posttraumatic stress disorder symptoms in a community sample of women. *Pain Med.* 5, 33–41. doi: 10.1111/j.1526-4637.2004.04003.x

Schandry, R. (1981). Heart beat perception and emotional experience. *Psychophysiology* 18, 483–488.

Schmalzl, L., and Kerr, C. E. (2016). Editorial: neural mechanisms underlying movement-based embodied contemplative practices. *Front. Hum. Neurosci.* 10:169. doi: 10.3389/fnhum.2016.00169

Schwoebel, J., Coslett, H. B., Bradt, J., Friedman, R., and Dileo, C. (2002). Pain and the body schema: effects of pain severity on mental representations of movement. *Neurology* 59, 775–777. doi: 10.1212/WNL.59.5.775

Schwoebel, J., Friedman, R., Duda, N., and Coslett, H. B. (2001). Pain and the body schema: evidence for peripheral effects on mental representations of movement. *Brain* 124(Pt 10), 2098–2104. doi: 10.1093/brain/124.10.2098

Sestito, M., Raballo, A., Umiltà, M. A., Amore, M., Maggini, C., and Gallese, V. (2015a). Anomalous echo: exploring abnormal experience correlates of emotional motor resonance in Schizophrenia Spectrum. *Psychiatry Res.* 30, 229, 559–564. doi: 10.1016/j.psychres.2015.05.038

Sestito, M., Raballo, A., Umiltà, M. A., Leuci, E., Tonna, M., Fortunati, R., et al. (2015b). Mirroring the self: testing neurophysiological correlates of disturbed self-experience in schizophrenia spectrum. *Psychopathology* 48, 184–191. doi: 10.1159/000380884

Sherrington, C. S. (1906). *The Integrative Action of the Nervous System*. New York, NY: C Scribner's sons.

StataCorp. (2015). *Stata Statistical Software, Version 14.* College Station, TX: StataCorp LP.

Terhaar, J., Viola, F. C., Bär, K.-J., and Debener, S. (2012). Heartbeat evoked potentials mirror altered body perception in depressed patients. *Clin. Neurophysiol.* 123, 1950–1957. doi: 10.1016/j.clinph.2012.02.086

Trujillo-Lira, M. (2007). Complementary medicine in patients with fibromyalgia. *Medwave* 7:e2565. doi: 10.5867/medwave.2007.08.2565

Tsakiris, M., Tajadura-Jiménez, A., and Costantini, M. (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. *Proc. Biol. Sci.* 278, 2470–2476. doi: 10.1098/rspb.2010.2547

Valenzuela-Moguillansky, C. (2013). *Pain and Body Awareness.* An Exploration of the Bodily Experience of Persons Suffering from Fibromyalgia. Constructivist Foundations, Vol. 8.

Valenzuela-Moguillansky, C., and Reyes-Reyes, A. (2015). Psychometric properties of the multidimensional assessment of interoceptive awareness (MAIA) in a Chilean population. *Front. Psychol.* 6:120. doi: 10.3389/fpsyg.2015.00120

Valenzuela-Moguillansky (2012). *The Relationship between Pain and Body Awareness: an Investigation Using Experimental and Experiential Methods.* Ph.D. thesis, Université Pierre et Marie Curie, Paris.

van Houdenhove, B., Egle, U., and Luyten, P. (2005). The role of life stress in fibromyalgia. *Curr. Rheumatol. Rep.* 7, 365–370. doi: 10.1007/s11926-005-0021-z

Van Houdenhove, B., and Luyten, P. (2006). Stress, depression and fibromyalgia. *Acta Neurol. Belg.* 106, 149–156. Retrived from: http://www.actaneurologica.be/acta/article.asp?lang=en&navid=137&id=14153&mod=acta

van Middendorp, H., Lumley, M. A., Jacobs, J. W. G., van Doornen, L. J. P., Bijlsma, J. W. J., and Geenen, R. (2008). Emotions and emotional approach and avoidance strategies in fibromyalgia. *J. Psychosom. Res.* 64, 159–167. doi: 10.1016/j.jpsychores.2007.08.009

Vlaeyen, J. W., and Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain* 85, 317–332. doi: 10.1016/S0304-3959(99)00242-0

Vlaeyen, J. W. S., and Linton, S. J. (2012). Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain* 153, 1144–1147. doi: 10.1016/j.pain.2011.12.009

Warren, W. H., and Whang, S. (1987). Visual guidance of walking through apertures: body-scaled information for affordances. *J. Exp. Psychol. Hum. Percept. Perform.* 13, 371–383.

Wideman, T. H., Adams, H., and Sullivan, M. J. L. (2009). A prospective sequential analysis of the fear-avoidance model of pain. *Pain* 145, 45–51. doi: 10.1016/j.pain.2009.04.022

Williams, D. A., and Arnold, L. M. (2011). Measures of fibromyalgia: Fibromyalgia Impact Questionnaire (FIQ), Brief Pain Inventory (BPI), Multidimensional Fatigue Inventory (MFI-20), Medical Outcomes Study (MOS) Sleep Scale, and Multiple Ability Self-Report Questionnaire (MASQ). *Arthritis Care Res.* 63(Suppl. 11), S86–S97. doi: 10.1002/acr.20531

Wolfe, F., Brähler, E., Hinz, A., and Häuser, W. (2013). Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. *Arthritis Care Res.* 65, 777–785. doi: 10.1002/acr.21931.

Wolfe, F., Clauw, D., Fitzcharles, M., Goldenberg, D. L., Katz, R. S., Mease, P., et al. (2010). The American College of rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res.* 62, 600–610. doi: 10.1002/acr.20140

Wolfe, F., and Häuser, W. (2011). Fibromyalgia diagnosis and diagnostic criteria. *Ann. Med.* 43, 1–8. doi: 10.3109/07853890.2011.595734

Wolfe, F., Ross, K., Anderson, J., Russell, J., and Helbert, L. (1995). The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 38, 19–28.

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REVIEW
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Genetics of Schizophrenia: Overview of Methods, Findings and Limitations

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Genetics constitute a crucial risk factor to schizophrenia. In the last decade, molecular genetic research has produced novel findings, infusing optimism about discovering the biological roots of schizophrenia. However, the complexity of the object of inquiry makes it almost impossible for non-specialists in genetics (e.g., many clinicians and researchers) to get a proper understanding and appreciation of the genetic findings and their limitations. This study aims at facilitating such an understanding by providing a brief overview of some of the central methods and findings in schizophrenia genetics, from its historical origins to its current status, and also by addressing some limitations and challenges that confront this field of research. In short, the genetic architecture of schizophrenia has proven to be highly complex, heterogeneous and polygenic. The disease risk is constituted by numerous common genetic variants of only very small individual effect and by rare, highly penetrant genetic variants of larger effects. In spite of recent advances in molecular genetics, our knowledge of the etiopathogenesis of schizophrenia and the genotype-environment interactions remain limited.

Keywords: twin, adoption, linkage, candidate-gene, GWAS, CNVs, SNVs, self-disorders

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INTRODUCTION

Despite a century of research, our knowledge of the etiology and pathogenetic unfolding of schizophrenia remains scarce. A persistent scientific problem may have several overlapping sources: it may be due to the intrinsic difficulty of the object of inquiry, to methodological or technological inadequacies, or to a mistaken formulation of the research problem. As we shall see, some of these sources have played a role in the history of research on schizophrenia genetics.

In the last decade, genetic research in schizophrenia has experienced a new dawn infused by a regained optimism due to newly developed, far more advanced molecular, technological and statistical methods. Given the rapid progress and intrinsic complexity of molecular genetic research (reflected, e.g., in the technical language of many molecular genetic studies), it may be difficult for outsiders to the field to grasp and appreciate the results from studies on schizophrenia genetics. Since genes are considered the strongest risk factor for schizophrenia, some grasp of this complex research domain is relevant in many clinical contexts.

The purpose of this article is to contribute to facilitate such an understanding by providing an accessible overview of some of the central methods and findings in genetic research in schizophrenia, from its historical origins to current status. In other words, we are not offering a comprehensive review of the entire field but a brief overview that may provide the reader with an initial orientation in the field. For this reason, we generally refrain from discussing the details of the manifold findings in especially molecular genetics. Finally, we seek to articulate certain limitations and challenges that tend to be deemphasized in this field of psychiatric research.

MODELS OF GENETIC TRANSMISSION

It has for a long time been known that madness (and many other human afflictions and characteristics) runs in families. After Mendel's discovery of the laws of monogenic transmission of phenotypic traits, some of the earliest authors, describing schizophrenia, assumed an inherited basis of schizophrenia risk due to familial aggregation of the disease or its milder variants (Bleuler and Jung, 1908). The monogenic model of schizophrenia was attractive for a variety of reasons, e.g., simplicity, a hope of discovering a corresponding, simple pathophysiological mechanism, and because it fitted into available theoretical options (i.e., recessive, dominant, with varying penetrance). The strictly monogenic theory was, however, quickly abandoned, because it did not fit the empirical data (even with the quantitative help of the concept of penetrance). Yet, the very idea of one specific gene or, later, a few specific genes as being etiologically necessary but not sufficient for the emergence of schizophrenia survived until fairly recently. For example, Meehl (1962) believed in a monogenic necessary gene, whose action was modified by polygenic factors. Holzman (1989) proposed the "latent trait model", suggesting that a dominant gene results in a latent trait, a postulated neural deficit with potentially pleiotropic manifestations (e.g., schizophrenia, schizotypy or eye-movement disorder). Risch and Baron (1984) offered the "mixed model", claiming that a specific gene in combination with a few oligogenes and a polygenic-multifactorial background formed the genetic substrate. All these models have been tried to fit, with varying degree of success, to the available epidemiological data of schizophrenia. In this context, it merits special attention that Gottesman and Shields (1967) already proposed a polygenic model for schizophrenia. As we shall see, research in molecular genetics documents that schizophrenia is in fact best accounted for by complex, polygenic model.

PRE-MOLECULAR GENETICS

In the first half of the 20th century, family studies demonstrated that the rate of schizophrenia was higher in relatives of patients with schizophrenia than in the general population (Rüdin, 1916; Kahn, 1923; Schulz, 1932; Kallmann, 1938). Twin studies documented that the concordance rate (i.e., both twins suffering from schizophrenia) was elevated in monozygotic (MZ) twins compared to dizygotic (DZ) twins (Luxenburger, 1928; Kallmann, 1946; Slater, 1953). These early twin studies were later criticized for various methodological reasons (Rosenthal, 1959, 1962; vide infra). From the 1960s, improved twin (Kringlen, 1967; Fischer, 1973) and adoption studies (Heston, 1966; Rosenthal et al., 1968; Kety et al., 1975; Tienari et al., 1985) became crucial in determining the familial clustering and concordance rates for schizophrenia. By indicating a strong genetic component in the etiology of the illness, the studies contributed to undermine the psychoanalytical hypothesis of schizophrenic causation, claiming that schizophrenogenic rearing was either a necessary or sufficient cause for developing schizophrenia. The basic intuition behind the twin studies is the following: given that MZ twins (sharing 100% of their genes) and DZ twins (sharing 50% of their genes) share the environment they are raised in, higher concordance rates in MZ over DZ twins most likely result from genetic similarity. Estimates of concordance rates for schizophrenia, based on European twin studies from 1963 to 1987, show higher rates for MZ (48%) than for DZ twins (17%; Gottesman, 1991), and similar concordance rates were reported in European and Japanese twin studies from 1992 to 1999—41%–65% for MZ vs. 0%–28% for DZ twins (Cardno and Gottesman, 2000). A meta-analysis (Sullivan et al., 2003) of twin studies estimates the genetic liability to schizophrenia at 81% (95% CI, 73%–90%), whereas shared environmental influences were estimated to be 11% (95% CI, 3%–19%). Finally, a few studies of children of discordant MZ twins found a similar risk of schizophrenia spectrum disorders in the children of the affected and unaffected MZ twin (Gottesman and Bertelsen, 1989; Kringlen and Cramer, 1989), presumably indicating that unaffected MZ twins carry silent (non-expressed) susceptibility genes for schizophrenia. By contrast, for children of discordant DZ twins, the risk was higher in the children of the affected DZ twin compared to the children of the unaffected DZ twin (Gottesman and Bertelsen, 1989).

Adoption studies have documented that schizophrenia spectrum disorders are more frequent in adopted-away children of mothers with schizophrenia than in their control adoptees (Heston, 1966; Rosenthal et al., 1968; Kety et al., 1975, 1994). A cross-fostering study (Wender et al., 1974) found that children of healthy parents, adopted by a family where one of the parents later developed schizophrenia, did not have an increased risk of developing schizophrenia. Other studies (Heston, 1966; Higgins, 1976) found that children of mothers with schizophrenia had the same risk of developing the disorder independent of whether they were raised by their biological mothers or by adopting parents with no history of mental illness. A Finish adoption study (Tienari et al., 1985, 2004) found that markedly dysfunctional rearing environments (the adoptive families were initially assessed and classified on a scale ranging from "1. healthy" to "5. severely disturbed") predicted schizophrenia spectrum disorders in adopted-away children of mothers with schizophrenia but not in their genetically undisposed controls. Interestingly, similar results were reported in the Danish High-Risk study (Mednick et al., 1987), which found increased risk of schizophrenia in children of mothers with schizophrenia, who were exposed to unstable parenting or raised in public childcare institutions (Parnas et al., 1985).

MOLECULAR GENETICS

The Human Genome Project (1990–2003) has been instrumental in molecular genetic research in schizophrenia. The Human

Genome Project was an international research effort to determine the sequence of the human genome's three billion base pairs and to map all of its genes. At the dawn of molecular genetics in the early 1980s, some researchers, though certainly not all, believed that within a fairly limited period of time the availability of DNA would reveal the biological causes of the disorder (e.g., Andreasen, 1984), as jointly indicated by twin and adoption studies.

The first DNA-based method was "linkage analysis", which aimed at discovering genomic regions in samples of affected extended or nuclear families and sibling pairs without implicating a specific allelic variant. By examining the degree of co-segregation of genetic markers and predefined phenotypic traits (e.g., schizophrenia spectrum diagnosis), estimates of linkage between the illness and genomic loci were obtained. Linkage analysis is based on the observation that genetic markers, which are located physically close on the same chromosome, tend to be inherited together, i.e., they remain "linked" during meiosis. Numerous linkage studies of schizophrenia have been conducted, but positive findings have generally proved difficult to replicate in subsequent studies (Risch and Merikangas, 1996). In brief, results from meta-analyses (Badner and Gershon, 2002; Lewis et al., 2003; Ng et al., 2009) suggest that many chromosomal regions may contain schizophrenia susceptibility loci. Notably, these loci do not themselves confer risk but they may harbor variants that do. These results also made it clear that the power of the linkage design was too weak to address genomic loci with small effects; the sample size requirement necessary to detect linkage was simply practically unachievable (Risch and Merikangas, 1996). Hence, other DNA-based methods were required to key in on the genes potentially involved in the etiology of schizophrenia.

The next wave of molecular genetic research in schizophrenia employed the "candidate gene" approach, which, using a case-control study design, explored if potential susceptibility genes correlate with the disorder. In contrast to linkage analysis, the candidate gene approach can detect genes with small effect alleles provided that the sample size is adequate. Candidate genes have usually been selected due to their position (e.g., from findings in linkage analyses) or functionality (e.g., genes coding for proteins related to dopamine or serotonin neurotransmission). Today, more than 1000 candidate genes have been tested (for details see http://www.szgene.org) but despite identification of some genes with small effect alleles (see e.g., Haraldsson et al., 2011), the overall results from the candidate gene studies have been disappointing (Gejman et al., 2011). Some of the most cited candidate genes are *DISC1*, *DTNBP1*, *NRG1* and *COMT*, but their potential pathogenetic involvement in schizophrenia remains debated. The absence of significant discoveries may have several reasons, e.g., difficulties in replicating positive findings, inadequate statistical power, and limited knowledge of the genes believed to be involved in the pathophysiology of schizophrenia (which obviously makes it difficult to select relevant candidate genes for testing).

In contrast to the hypothesis-driven candidate gene approach that typically could test only relatively few genetic markers in delimited genomic loci in each study, the genome-wide association studies (GWAS), which also often employ a case-control study design, interrogate the genome purely empirically (i.e., GWAS do not rely on any *a priori* selected candidate genes) for associations between common genomic variants or loci and the disorder. The identification and mapping of millions of common single nucleotide polymorphisms (SNPs), as facilitated by initiatives such as the International HapMap Project and the 1000 Genomes Project (continued by The International Genome Sample Resource), has been instrumental for the GWAS approach. GWAS are based on linkage disequilibrium, i.e., a non-random association of alleles at two or more loci. Recent technological advances such as microarrays and chips have made it possible to quickly and inexpensively scan a million SNPs genome-wide. The reasoning behind the GWAS approach is that if specific allele variants are found more frequently in patients than in their controls, then the allele variants may be indicative of a genetic association. To minimize the risk of Type I errors (i.e., false positives), most GWAS operate with a stringent threshold of significance ($p < 5 \times 10^{-8}$). Since 2007, schizophrenia GWAS have been published (for details see http://www.genome.gov/gwastudies). Overall, the studies have failed to support the findings from linkage and candidate gene studies, but the GWAS have instead identified a large number of new susceptibility loci of only very small individual effects—and many of these genomic loci have in fact been replicated in subsequent GWAS and have reached meta-analytic genome-wide significance (see e.g., Shi et al., 2009; Stefansson et al., 2009; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011; Aberg et al., 2013; Ripke et al., 2013; Xiao and Li, 2016; Yu et al., 2016). One seminal study (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) combined available schizophrenia GWAS samples into a single analysis and successfully identified 128 independent schizophrenia associations, spanning 108 risk loci of genome-wide significance, 83 of which were novel findings. For example, associations were found at dopamine receptor D2, in several genes involved in glutamatergic neurotransmission and synaptic plasticity, and in tissues with central immune functions. The authors suggest that these results provide some genetic support for the hypothesized links between schizophrenia and dopamine and immune dysregulation, respectively.

Furthermore, associations have repeatedly been found between schizophrenia and genetic markers across the extended Major Histocompatibility Complex (MHC) locus on chromosome 6 (25–34 Mb), implicating the MHC locus as strongest of the >100 loci of genome-wide significance (see e.g., Shi et al., 2009; Stefansson et al., 2009; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The MHC locus is known to harbor genes with immune functions and attempts to link the locus to schizophrenia date back to the 1970s (Gejman et al., 2011). A recent study (Sekar et al., 2016) found that the association between schizophrenia and the MHC locus to a considerable extent stems from many common, structurally distinct alleles of the complement component 4 (*C4*), and these alleles were moreover found to affect the expression of *C4A* and *C4B* in the brain and to be associated with schizophrenia in proportion to their effect on *C4A* expression. Finally, it merits attention that several GWAS have found shared genetic risk loci in schizophrenia and bipolar disorder (e.g., Moskvina et al., 2009; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Sleiman et al., 2013); we discuss these findings in the section on limitations and challenges.

The rationale behind GWAS is the "common-disease common-variants" hypothesis, which suggests that schizophrenia is mainly associated with common genetic variants (SNPs). As we have seen, large-scale GWAS have identified more than 100 risk loci.

However, it merits attention that a seminal study (International Schizophrenia Consortium et al., 2009) demonstrated that a substantial polygenic component of schizophrenia risk is in fact not to be found in a large number of strongly associated loci but rather in thousands of common alleles of only a very small effect that individually do not attain significance. The predictive accuracy of polygenic risk scores is likely to further improve as sample sizes continue to grow (Dudbridge, 2013). Still, there is an increasing awareness that common variants only explain a proportion of the heritability of schizophrenia, which refers to the proportion of variance between individuals that is accounted for by genetic factors. Individually, most of these common alleles confer only relatively small risk (typically odds ratios <1.2) but cumulatively they have been estimated to explain between a quarter and half of the variance in genetic liability (e.g., International Schizophrenia Consortium et al., 2009; Lee et al., 2012; Ripke et al., 2013; Arnedo et al., 2015). In other words, a proportion of the variance in genetic liability is apparently not accounted for by common genetic variants. Addressing this issues, the "common-disease rare-variants" hypothesis (McClellan et al., 2007) proposes that highly penetrant, rare (<1%) genetic variants, including copy number variations (CNVs), single nucleotide variants (SNVs), and small insertions and deletions (indels), contribute to the genetic component of schizophrenia. The two hypotheses are complementary to each other. In the following, we briefly address some of the most significant rare genetic variants, which, in the last few years, substantially have increased our understanding of the spectrum of genetic risk variants.

First, there is now strong evidence that rare, *de novo* (i.e., new, not inherited) or inherited CNVs, i.e., structural genomic variants that consist primarily of duplication or deletion, confer high risk for schizophrenia. CNVs range in size from one kilobase (kb) to several megabase (Mb) pairs. Several studies have found elevated levels of rare CNVs in patients with schizophrenia compared to controls (International Schizophrenia Consortium, 2008; Xu et al., 2008; International Schizophrenia Consortium et al., 2009; Malhotra et al., 2011; Szatkiewicz et al., 2014; Chang et al., 2016; Ruderfer et al., 2016). For example, robust associations have been uncovered between schizophrenia and rare, large (>100 kb) CNVs, including deletions on chromosome 1q21.1, 3q29, 15q13.3 and 22q11.2, and duplications on chromosome 16p11.2 and 16p13.11—the odds ratios of these CNVs range from approximately 2 to 60 (Rees et al., 2015). Moreover, deletions of *NRXN1* have been substantially linked to schizophrenia (e.g., Kirov et al., 2009).

Second, exome sequencing, a technology that allows for identification of DNA variants within the 1% protein-coding regions or genes (exons) of the genome (the exome), has enabled scans of genes for mutations at single-base resolution, which previously could not be detected, i.e., SNVs and indels. The rationale behind exome sequencing is that variations in these sequences are likely to entail more severe consequences than variations in the remaining 99% of the genome. Several studies have now used exome sequencing to explore SNVs and indels in schizophrenia. Some studies have reported a slightly increased exome-wide level of rare and/or *de novo* SNVs in patients with schizophrenia compared to controls (Xu et al., 2012; McCarthy et al., 2014a, 2016) but this finding has not been replicated in larger studies (Fromer et al., 2014; Purcell et al., 2014). Interestingly, Fromer et al. (2014) found *de novo* SNVs and indels to be significantly enriched in glutamatergic postsynaptic proteins, comprising the ARC (activity-regulated cytoskeleton-associated protein) and N-methyl-D-aspartate receptor (NMDAR) postsynaptic protein complexes, which previously have been linked to schizophrenia in CNV studies (Glessner et al., 2010). Finally, Purcell et al. (2014) used exome sequencing to explore rare SNVs and indels in schizophrenia and found a polygenic burden of very rare (<1/10,000), disruptive variants distributed across many genes in a set of 2546 genes previously implicated in schizophrenia by GWAS, and CNV and *de novo* SNV studies (see Richards et al., 2016).

In sum, pre-molecular and molecular genetics have demonstrated beyond doubt that genetics constitute a strong risk factor for schizophrenia. In contrast to the initial monogenic and oligogenic models of genetic transmission, there is now compelling evidence that the genetic architecture of schizophrenia is very complex, heterogeneous, and polygenic—the disease risk is constituted by numerous common genetic variants of only very small individual effects (e.g., SNPs) and by uncommon, highly penetrant genetic variants of larger effect (e.g., CNVs).

LIMITATIONS AND CHALLENGES

As any research question, pre-molecular and molecular genetic studies in schizophrenia are based on certain assumptions and confront various limitations and challenges that must be made explicit if we are to properly appreciate the empirical findings. In the following, we discuss what we believe are six of the most important ones.

First, the classical twin design remains controversial and its validity has regularly been called into question (e.g., Charney, 2012; Turkheimer and Harden, 2014). Although the intuition behind the twin studies seems straightforward (*vide supra*), it is, in fact, not unproblematic. In order to take the higher concordance rates in MZ than in DZ twins as evidence for a genetic component, some fairly unlikely assumptions are required, e.g., we must statistically hold the environment constant, i.e., we must assume that the environments experienced by MZ and DZ twins do not differ in any way that may be relevant for the development of schizophrenia; and we must assume that genes and environment are both mutually independent and jointly additive (inclusive) for the development of schizophrenia. The problem with the classical twin design is that many, if not most, behavioral traits seem to act quite similarly, i.e., definitely heritable with some variance ascribable to the non-shared environment and little to the shared environment. Notably, these remarks do not undermine the identified concordance rates for schizophrenia in MZ and DZ twins, but they do put into perspective the problem of making inferences and estimations of the size of the genetic component in schizophrenia on the basis of the classical twin design. Although the classical twin design does not play a major role in genetic studies today, estimates of the genetic contribution to schizophrenia, based on previous twin studies, are often stated as facts in many textbooks and research articles on schizophrenia, and therefore we believe it is still important to voice these concerns.

Second, a challenge confronting molecular genetic research is, in our view, the apparent variability in the clinical manifestation of schizophrenia and the absence of a biomarker to compensate for the shortcomings in phenotypic demarcation. According to Baron (2001), attempts to circumvent this problem have involved dissecting schizophrenia into clinical subtypes aggregating in families (e.g., periodic catatonia), replacing the phenotype (schizophrenia) with symptom-based analysis (e.g., positive and negative symptoms) or endophenotypes (e.g., impaired sensory gating and ocular movement dysfunction), and blurring the diagnostic boundaries between schizophrenia and other major mental disorders (e.g., bipolar disorder). The elimination of diagnostic boundaries has led to potentially interesting genetic findings indicative of an overlap of genetic susceptibility loci between schizophrenia and bipolar disorder (Moskvina et al., 2009; Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Sleiman et al., 2013). These results are somewhat surprising given that family studies usually have found that these disorders do not co-aggregate in families (Kendler et al., 1993; Maier et al., 1993). Yet, a large, population-based study of approximately 75,000 affected Swedish families with schizophrenia or bipolar disorder found a co-aggregation in the families, providing some epidemiological support for the hypothesis of an at least partially shared genetic basis (Lichtenstein et al., 2009). Crucially, however, this study was based on hospital discharge rather than research diagnoses, and we may speculate if the apparent co-aggregation perhaps could result from different diagnostic practices.

Third, it merits attention that the symptom-based analysis, the blurring of diagnostic boundaries, the case-control design of many GWAS, CNV and exome sequencing studies, and the detection of shared genetic risk loci between schizophrenia, bipolar disorder, and sometimes also autism is indicative of a genetic vulnerability to mental disorders more broadly and not to schizophrenia specifically (i.e., genetic pleiotropy). While identifying shared genetic vulnerability is crucial in its own right, keying in on what is specific for schizophrenia presents an obvious target for contemporary and future molecular genetic research. One way of keying in on what is specific to schizophrenia is illustrated in a GWAS (Ruderfer et al., 2014), where the authors explored the discriminability of schizophrenia from bipolar disorder and found that no SNPs reached genome-wide significance but, on the basis of computed risk scores, the authors identified a polygenic signal capable of discriminating schizophrenia from bipolar disorder. In this context, it also merits attention that a study of relatives of high-density schizophrenia families in Ireland found molecular support for the concept of the schizophrenia spectrum and its genetic basis (Bigdeli et al., 2014).

Fourth, another challenge concerns the implications of the molecular genetic findings, i.e., how do we obtain scientific knowledge of the effects of the, e.g., now >100 susceptibility loci that have reached genome-wide significance and their possible involvement in the etiology of schizophrenia? Is an empirical, bottom-up approach, systematically eliciting the biological functions related to each risk locus at all a negotiable road in this case? The prospect of studying all identified loci, singly and in potential mutual interactions, could turn into an infinite task. Moreover, if common genetic variation implicates an intractable amount of genes of only very small individual effect alleles, we may find ourselves in a situation, where, as Goldstein (2009) put it, "in pointing at everything, genetics would point at nothing". Here, it seems that psychiatry may need assistance from systems biology to convert a multitude of genes of small effect alleles into a graspable and identifiable pathogenetic stream or field of study (Sauer et al., 2007; McCarthy et al., 2014b).

Fifth, some authors have used the apparent overlap of genetic susceptibility loci between schizophrenia and bipolar disorder as a lever to criticize the clinical validity of the Kraepelinian dichotomy (e.g., Owen et al., 2007; Lichtenstein et al., 2009; Doherty and Owen, 2014). The perpetual rebirth of the unitary view of psychosis is perhaps its clearest manifestation. Another expression of the dissatisfaction with the current psychiatric classification and the lack of etiological progress is found in the Research Domain Criteria (RDoC), which ultimately seeks to found psychiatric nosology on advances in genetics, neuroscience, behavioral sciences, etc., i.e., by disregarding the diagnostic categories of DSM-5 (American Psychiatric Association, 2013) and ICD-10 (World Health Organization, 1992). More generally, this criticism raises a crucial question, viz. what defines a mental disorder? Should we begin to understand psychosis on the basis of specific genetic profiles or on the basis of clinical phenotypes? Opting for a genetically (and biologically) informed remodeling of psychiatric nosology (e.g., as described by Insel and Cuthbert, 2015), founded upon i.a. our limited knowledge of certain susceptibility loci's potential involvement in the etiology of various mental disorders, appears self-defeating for a number of diagnostic, therapeutic and epistemological reasons. In our view, no diagnostic classification in psychiatry can remain indifferent to the relevant clinical phenotypes, i.e., the patients' suffering, experience and existence.

The final issue that we raise here is nosological and psychopathological in nature and it offers another perspective on how to key in on what is specific for schizophrenia, which also has relevance for genetic research. In this context, it merits attention that there are many schizophrenia definitions (Jansson and Parnas, 2007; Kendler, 2016) and most of these describe a relatively unspecific psychotic "end product" far away from the fundamental neurophysiological disturbances that assumingly are closer to the genetic basis of the disorder. In other words, psychiatric nosology carves phenotypes that have implications for research, and it is possible that the reification of the schizophrenia phenotype, which occurred with the so-called "operational revolution" in psychiatry in DSM-III (American Psychiatric Association, 1980), has in fact impeded rather than fostered research progress in schizophrenia (Parnas and Jansson, 2015). For example, the current schizophrenia concept in DSM-5 and ICD-10 defines the disorder as a primarily delusional-hallucinatory clinical phenotype—a definition that is remarkably different from Bleuler's original concept of schizophrenia. Bleuler (1950) famously distinguished between "fundamental" and "accessory" symptoms, arguing the former are essential to schizophrenia, whereas the latter are not. On his account, delusions and hallucinations were considered as accessory symptoms—these symptoms are typically episodic in nature, they can be entirely absent, and they may also be found in other disorders. By contrast, the fundamental symptoms exhibit a trait-like quality—"[they] are present in every case and at every period of the illness" (Bleuler, 1950, p. 13). The fundamental symptoms include disturbances of association (formal thought disorders), ambivalence, autism and experiential ego-disorders, etc. Keenly aware of the poly-symptomatology of schizophrenia, Bleuler argued that the decisive diagnostic factor, separating schizophrenia from manic or depressive psychosis, is the presence of fundamental symptoms (Bleuler, 1950, p. 304). With the exception of severe forms of formal thought disorders, Bleuler's fundamental symptoms and thus the core, trait-phenotypic features of schizophrenia were ignored in DSM-III and subsequent editions of the DSM as well as in ICD-10.

The theoretical and empirical research on anomalous self-experiences ("self-disorders") can to some extent be seen as a return to and a systematic succession of a Bleulerian approach to psychopathology, i.e., the research focus is once more directed towards certain specific, non-psychotic, trait-like features of schizophrenia. However, where Bleuler's (1950) fundamental symptoms largely were expressive features (signs), observable by the clinician, research on self-disorders elicits certain subjectively lived experiential anomalies (symptoms). For clinical descriptions of self-disorders in schizophrenia spectrum disorders, see Parnas and Handest (2003), Parnas et al. (2005a), Henriksen and Parnas (2012), and Henriksen and Nordgaard (2016). During the last two decades, empirical research on self-disorders consistently demonstrate: (i) that self-disorders hyper-aggregate in schizophrenia spectrum disorders but not in other mental disorders, including bipolar disorder (Parnas et al., 2003; Parnas et al., 2005b; Raballo et al., 2011; Haug et al., 2012; Raballo and Parnas, 2012; Nordgaard and Parnas, 2014), (ii) that self-disorders occur in genetically high-risk individuals (Raballo and Parnas, 2011), (iii) that self-disorders are temporarily stable over a 5-year period (Nordgaard et al., 2017); and finally (iv) prospective studies indicate that self-disorders predict transition to psychosis in an Ultra-High Risk for psychosis sample (Nelson et al., 2012) and that high baseline scores of self-disorders predict later transition to a schizophrenia spectrum diagnosis (Parnas et al., 2011, 2016)—for a review see Parnas and Henriksen (2014). Recently, self-disorders have been empirically explored as an intermediate phenotype of schizophrenia. Especially, discovering the neurophysiological correlates of self-disorders is already a topic of intense research. Several studies now point to a disturbance of emotional motor resonance and multisensory integration impairment as body-level correlates of self-disorders (e.g., Sestito et al., 2013, 2015a,b, 2017; Ebisch and Gallese, 2015). These studies show the potential of applying self-disorders as a target phenotype for neurobiological and also genetic research in schizophrenia.

CONCLUSION

Pre-molecular and molecular genetic studies have demonstrated that genetics form a strong risk factor for schizophrenia. Many findings from schizophrenia GWAS have been replicated and several of these findings have reached meta-analytic genome-wide significance. The robust associations between schizophrenia and the >100 susceptibility loci, the identified CNVs and SNVs, respectively, seem promising on a number of scores. Also, the importance of the thousands of common alleles of only a very small effect, which do not individually achieve significance but which collectively form a substantial polygenic component of schizophrenia risk, should not be underestimated. Hopefully, these results will pave the way to truly novel, actionable, therapeutic knowledge. However, we should not fail to also notice: (i) that associations between common (SNPs) or uncommon (CNVs, SNVs) genetic variants and schizophrenia, though statistical facts, are not necessarily indexes of causal pathways; and (ii) that many of the discovered associations are, in fact, non-specific to schizophrenia but indicative of a genetic vulnerability to several mental disorders. Overall, the details of the etiopathogenesis of schizophrenia and the genotype-environment interactions remain to large extent unknown, and therefore caution is still warranted when drawing conclusions about the size of the genetic contribution in the etiology of the disorder.

AUTHOR CONTRIBUTIONS

MGH, JN and LBJ planned the study collectively. All authors contributed to the design, analyses and discussion. MGH wrote the first draft and all authors participated in critical revisions of the draft. All authors approved the final version and made agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

Aberg, K. A., Liu, Y., Bukszar, J., McClay, J. L., Khachane, A. N., Andreassen, O. A., et al. (2013). A comprehensive family-based replication study of schizophrenia genes. *JAMA Psychiatry* 70, 573–581. doi: 10.1001/jamapsychiatry.2013.288

Andreasen, N. C. (1984). *The Broken Brain: The Biological Revolution in Psychiatry* New York, NY: Harper & Row.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders: DSM-III* Washington, DC: APA.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders. 5th Edn. DSM-5* Arlington, TX: APA.

Arnedo, J., Svrakic, D. M., Del Val, C., Romero-Zaliz, R., Hernández-Cuervo, H., Molecular Genetics of Schizophrenia Consortium, et al. (2015). Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies. *Am. J. Psychiatry* 172, 139–153. doi: 10.3410/f.718876350.793502752

Badner, J. A., and Gershon, E. S. (2002). Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Mol. Psychiatry* 7, 405–411. doi: 10.1038/sj.mp.4001012

Baron, M. (2001). Genetics of schizophrenia and the new millennium: progress and pitfalls. *Am. J. Hum. Genet.* 68, 299–312. doi: 10.1086/318212

Bigdeli, T. B., Bacanu, S. A., Webb, B. T., Walsh, D., O'Neill, F. A., Fanous, A. H., et al. (2014). Molecular validation of the schizophrenia spectrum. *Schizophr. Bull.* 40, 60–65. doi: 10.1093/schbul/sbt122

Bleuler, E. (1950). *Dementia Praecox or the Group of Schizophrenias* New York, NY: International Universities Press.

Bleuler, E., and Jung, C. (1908). Komplexe und Krankheitsursachen bei Dementia Praecox. *Zentralblatt für Nervenheilkunde und Psychiatrie* 31, 220–227.

Cardno, A. G., and Gottesman, I. I. (2000). Twin studies of schizophrenia: from bow-and-arrow concordances to star wars Mx and functional genomics. *Am. J. Med. Genet.* 97, 12–17. doi: 10.1002/(sici)1096-8628(200021)97:1<12::AID-AJMG3>3.0.co;2-u

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* 45, 984–994. doi: 10.1038/ng.2711

Chang, H., Li, L., Peng, T., Li, M., Gao, L., and Xiao, X. (2016). Replication analyses of four chromosomal deletions with schizophrenia via independent large-scale meta-analyses. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 171, 1161–1169. doi: 10.1002/ajmg.b.32502

Charney, E. (2012). Behavior genetics and postgenomics. *Behav. Brain Sci.* 35, 331–358. doi: 10.1017/S0140525X11002226

Doherty, J. L., and Owen, M. J. (2014). Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. *Genome Med.* 6:29. doi: 10.1186/gm546

Dudbridge, F. (2013). Power and predictive accuracy of polygenic risk scores. *PLoS Genet.* 9:e1003348. doi: 10.1371/journal.pgen.1003348

Ebisch, S.J.H., and Gallese, V. (2015). A neuroscientific perspective on the nature of altered self-other relationships in schizophrenia. *J. Conscious. Stud.* 22, 220–240.

Fischer, M. (1973). Genetic and environmental factors in schizophrenia. A study of schizophrenic twins and their families. *Acta Psychiatr. Scand. Suppl.* 238, 9–142.

Fromer, M., Pocklington, A. J., Kavanagh, D. H., Williams, H. J., Dwyer, S., Gormlet, P., et al. (2014). *De novo* mutations in schizophrenia implicate synaptic networks. *Nature* 506, 179–184. doi: 10.1038/nature12929

Gejman, P. V., Sanders, A. R., and Kendler, K. S. (2011). Genetics of schizophrenia: new findings and challenges. *Annu. Rev. Genomics Hum. Genet.* 12, 121–144. doi: 10.1146/annurev-genom-082410-101459

Glessner, J. T., Reilly, M. P., Kim, C. E., Takahashi, N., Albano, A., Hou, C., et al. (2010). Strong synaptic transmission impact by copy number variations in schizophrenia. *Proc. Natl. Acad. Sci. U S A* 107, 10584–10589. doi: 10.1073/pnas.1000274107

Goldstein, D. B. (2009). Common genetic variation and human traits. *N. Engl. J. Med.* 360, 1696–1698. doi: 10.1056/NEJMp0806284

Gottesman, I. I. (1991). *Schizophrenia Genesis: The Origins of Madness*. New York, NY: Freeman.

Gottesman, I. I., and Bertelsen, A. (1989). Confirming unexpressed genotypes for schizophrenia. Risks in the offspring of Fischer's danish identical and fraternal discordant twins. *Arch. Gen. Psychiatry* 46, 867–872. doi: 10.1001/archpsyc.1989.01810100009002

Gottesman, I. I., and Shields, J. (1967). A polygenic theory of schizophrenia. *Proc. Natl. Acad. Sci. U S A* 58, 199–205. doi: 10.1073/pnas.58.1.199

Haraldsson, H. M., Ettinger, U., and Sigurdsson, E. (2011). Developments in schizophrenia genetics: from linkage to microchips, deletions and duplications. *Nord. J. Psychiatry* 65, 82–88. doi: 10.3109/08039488.2011.552734

Haug, E., Lien, L., Raballo, A., Bratlien, U., Øie, M., Andreassen, O. A., et al. (2012). Selective aggregation of self-disorders in first-treatment DSM-IV schizophrenia spectrum disorders. *J. Nerv. Ment. Dis.* 200, 632–636. doi: 10.1097/nmd.0b013e31825bfd6f

Henriksen, M. G., and Nordgaard, J. (2016). "Self-disorders in schizophrenia," in *An Experiential Approach to Psychopathology. What is it Like to Suffer from Mental Disorders*, eds G. Stanghellini and M. Aragona (New York, NY: Springer), 265–280.

Henriksen, M. G., and Parnas, J. (2012). Clinical manifestations of self-disorders and the Gestalt of schizophrenia. *Schizophr. Bull.* 38, 657–660. doi: 10.1093/schbul/sbs033

Heston, L. L. (1966). Psychiatric disorders in foster home reared children of schizophrenic mothers. *Br. J. Psychiatry* 112, 819–825. doi: 10.1192/bjp.112.489.819

Higgins, J. (1976). Effects of child rearing by schizophrenic mothers: a follow-up. *J. Psychiatr. Res.* 13, 1–9. doi: 10.1016/0022-3956(76)90004-2

Holzman, P. S. (1989). The use of eye movement dysfunctions in exploring the genetic transmission of schizophrenia. *Eur. Arch. Psychiatry Neurol. Sci.* 239, 43–48. doi: 10.1007/bf01739743

Insel, T. R., and Cuthbert, B. N. (2015). Brain disorders? Precisely. *Science* 348, 499–500. doi: 10.1126/science.aab2358

International Schizophrenia Consortium. (2008). Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 455, 237–241. doi: 10.1038/nature07239

International Schizophrenia Consortium, Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., et al. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460, 748–752. doi: 10.3410/f.1161613.623171

Jansson, L., and Parnas, J. (2007). Competing definitions of schizophrenia: what can be learned from polydiagnostic studies? *Schizophr. Bull.* 33, 1178–1200. doi: 10.1093/schbul/sbl065

Kahn, E. (1923). *Studien uber Vererbung und Entstehung geistiger Stfrungen. IV. Schizoid und Schizophren im Erbgang*. Berlin: Springer-Verlag.

Kallmann, F. J. (1938). *The Genetics of Schizophrenia*. New York, NY: Augustin.

Kallmann, F. J. (1946). The genetic theory of schizophrenia; an analysis of 691 schizophrenic twin index families. *Am. J. Psychiatry* 103, 309–322. doi: 10.1176/ajp.103.3.309

Kendler, K. S. (2016). Phenomenology of schizophrenia and the representativeness of modern diagnostic criteria. *JAMA Psychiatry* 73, 1082–1092. doi: 10.1001/jamapsychiatry.2016.1976

Kendler, K. S., McGuire, M., Gruenberg, A. M., O'Hare, A., Spellman, M., and Walsh, D. (1993). The roscommon family study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch. Gen. Psychiatry* 50, 527–540. doi: 10.1001/archpsyc.1993.01820190029004

Kety, S. S., Rosenthal, D., Wender, P. H., Schulsinger, F., and Jacobsen, B. (1975). "Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: A preliminary report based on psychiatric interviews," in *Genetic Research in Psychiatry*, eds R. Fieve, D. Rosenthal and H. Brill. (Baltimore: John Hopkins University Press), 147–165.

Kety, S. S., Wender, P. H., Jacobsen, B., Ingraham, J. L., Jansson, L., Faber, B., et al. (1994). Mental illness in the biological and adoptive relatives of schizophrenic adoptees. Replication of the copenhagen study in the rest of Denmark. *Arch. Gen. Psychiatry* 51, 442–455. doi: 10.1001/archpsyc.1994.03950060006001

Kirov, G., Rujescu, D., Ingason, A., Collier, D. A., O'Donovan, M. C., and Owen, M. J. (2009). Neurexin 1 (*NRXN1*) deletions in schizophrenia. *Schizophr. Bull.* 35, 851–854. doi: 10.1093/schbul/sbp079

Kringlen, E. (1967). *Heredity and Environment in the Functional Psychoses*. London: Heinemann Medical Books.

Kringlen, E., and Cramer, G. (1989). Offspring of monozygotic twins discordant for schizophrenia. *Arch. Gen. Psychiatry* 46, 873–877. doi: 10.1001/archpsyc.1989.01810100015003

Lee, S. H., DeCandia, T. R., Ripke, S., Yang, J., Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ), International Schizophrenia Consortium (ISC), et al. (2012). Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nat. Genet.* 44, 247–250. doi: 10.1038/ng.1108

Lewis, C. M., Levinson, D. F., Wise, L. H., DeLisi, L. E., Straub, R. E., Hovatta, I., et al. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *Am. J. Hum. Genet.* 73, 34–48. doi: 10.3410/f.1010866.193265

Lichtenstein, P., Yip, B. H., Bjork, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., et al. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 373, 234–239. doi: 10.1016/S0140-6736(09)60072-6

Luxenburger, H. (1928). Vorläufiger Bericht über psychiatrische Serienuntersuchungen an Zwillingen. *Zeitschrift für die gesamte Neurologie und Psychiatrie* 116, 297–326.

Maier, W., Lichtermann, D., Minges, J., Hallmayer, J., Heun, R., Benkert, O., et al. (1993). Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. *Arch. Gen. Psychiatry* 50, 871–883. doi: 10.1001/archpsyc.1993.01820230041004

Malhotra, D., McCarthy, S., Michaelson, J. J., Vacic, V., Burdick, K. E., Yoon, S., et al. (2011). High frequencies of *de novo* CNVs in bipolar disorder and schizophrenia. *Neuron* 72, 951–963. doi: 10.1016/j.neuron.2011.12.008

McCarthy, N. S., Melton, P. E., Ward, S. V., Allan, S. M., Dragovic, M., Clark, M. L., et al. (2016). Exome array analysis suggests an increased variant burden in families with schizophrenia. *Schizophr. Res.* doi: 10.1016/j.schres.2016.12.007 [Epub ahead of print].

McCarthy, S. E., Gillis, J., Kramer, M., Lihm, J., Yoon, S., Berstein, Y., et al. (2014a). *De novo* mutations in schizophrenia implicate chromatin remodeling and support a genetic overlap with autism and intellectual disability. *Mol. Psychiatry* 19, 652–658. doi: 10.1038/mp.2014.29

McCarthy, S. E., McCombie, W. R., and Corvin, A. (2014b). Unlocking the treasure trove: from genes to schizophrenia biology. *Schizophr. Bull.* 40, 492–496. doi: 10.1093/schbul/sbu042

McClellan, J. M., Susser, E., and King, M. C. (2007). Schizophrenia: a common disease caused by multiple rare alleles. *Br. J. Psychiatry* 190, 194–199. doi: 10.1192/bjp.bp.106.025585

Mednick, S. A., Parnas, J., and Schulsinger, F. (1987). The copenhagen high-risk project, 1962–86. *Schizophr. Bull.* 13, 485–495. doi: 10.1093/schbul/13.3.485

Meehl, P. (1962). Schizotaxia, schizotypy, schizophrenia. *Am. Psychologist* 17, 827–838. doi: 10.1037/h0041029

Moskvina, V., Craddock, N., Holmans, P., Nikolov, I., Pahwa, J. S., Green, E., et al. (2009). Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. *Mol. Psychiatry* 14, 252–260. doi: 10.1038/mp.2008.133

Nelson, B., Thompson, A., and Yung, A. R. (2012). Basic self-disturbance predicts psychosis onset in the ultra high risk for psychosis 'prodromal' population. *Schizophr. Bull.* 38, 1277–1287. doi: 10.1016/s0920-9964(12)70144-5

Ng, M. Y., Levinson, D. F., Faraone, S. V., Suarez, B. K., DeLisi, L. E., Arinami, T., et al. (2009). Meta-analysis of 32 genome-wide linkage studies of schizophrenia. *Mol. Psychiatry* 14, 774–785.

Nordgaard, J., and Parnas, J. (2014). Self-disorders and schizophrenia-spectrum: A study of 100 first hospital admissions. *Schizophr. Bull.* 40, 1300–1307. doi: 10.1093/schbul/sbt239

Nordgaard, J., Handest, P., Vollmer-Larsen, A., Sæbye, D., Thejlade Pedersen, J., and Parnas, J. (2017). Temporal persistence of anomalous self-experience: A 5 years follow-up. *Schizophr. Res.* 179, 36–40. doi: 10.1016/j.schres.2016.10.001

Owen, M. J., Craddock, N., and Jablensky, A. (2007). The genetic deconstruction of psychosis. *Schizophr. Bull.* 33, 905–911. doi: 10.1093/schbul/sbm053

Parnas, J., Carter, J., and Nordgaard, J. (2016). Premorbid self-disorders and lifetime diagnosis in the schizophrenia spectrum: a prospective high-risk study. *Early Interv. Psychiatry* 10, 45–53. doi: 10.1111/eip.12140

Parnas, J., and Handest, P. (2003). Phenomenology of anomalous experiences in early schizophrenia. *Compr. Psychiatry* 44, 121–134. doi: 10.1053/comp.2003.50017

Parnas, J., Møller, P., Kircher, T., Thalbitzer, J., Jansson, L., Handest, P., et al. (2005a). EASE: Examination of anomalous self-experience. *Psychopathology* 38, 236–258. doi: 10.1159/000088441

Parnas, J., Handest, P., Jansson, L., and Sæbye, D. (2005b). Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology* 38, 259–267. doi: 10.1159/000088442

Parnas, J., Handest, P., Sæbye, D., and Jansson, L. (2003). Anomalies of subjective experience in schizophrenia and psychotic bipolar illness. *Acta Psychiatr. Scand.* 108, 126–133. doi: 10.1034/j.1600-0447.2003.00105.x

Parnas, J., and Henriksen, M. G. (2014). Disordered self in the schizophrenia spectrum: A clinical and research perspective. *Harv. Rev. Psychiatry* 22, 251–265. doi: 10.1097/hrp.0000000000000040

Parnas, J., and Jansson, L. (2015). Self-disorders: clinical and conceptual implications for the diagnostic concept of schizophrenia. *Psychopathology* 48, 332–338. doi: 10.1159/000437232

Parnas, J., Raballo, A., Handest, P., Jansson, L., Vollmer-Larsen, A., and Sæbye, D. (2011). Self-experience in the early phases of schizophrenia: 5-year follow-up of the copenhagen prodromal study. *World Psychiatry* 10, 200–204. doi: 10.1002/j.2051-5545.2011.tb00057.x

Parnas, J., Teasdale, T. W., and Schulsinger, H. (1985). Institutional rearing and diagnostic outcome in children of schizophrenic mothers. A prospective high-risk study. *Arch. Gen. Psychiatry* 42, 762–769. doi: 10.1001/archpsyc.1985.01790310024003

Purcell, S. M., Moran, J. L., Fromer, M., Ruderfer, D., Solovieff, N., Roussos, P., et al. (2014). A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* 506, 185–190. doi: 10.3410/f.718252264.793491785

Raballo, A., and Parnas, J. (2011). The silent side of the spectrum: schizotypy and the schizotaxic self. *Schizophr. Bull.* 37, 1017–1026. doi: 10.1093/schbul/sbq008

Raballo, A., and Parnas, J. (2012). Examination of anomalous self-experience: Initial study of the structure of self-disorders in schizophrenia spectrum. *J. Nerv. Ment. Dis.* 200, 577–583. doi: 10.1097/nmd.0b013e31825bfb41

Raballo, A., Sæbye, D., and Parnas, J. (2011). Looking at the schizophrenia spectrum through the prism of self-disorders: an empirical study. *Schizophr. Bull.* 37, 344–351. doi: 10.1093/schbul/sbp056

Rees, E., O'Donovan, M. C., and Owen, M. J. (2015). Genetics of schizophrenia. *Curr. Opin. Behav. Sci.* 2, 8–14. doi: 10.1016/j.cobeha.2014.07.001

Richards, A. L., Leonenko, G., and Walters, J. T. (2016). Exome arrays capture polygenic rare variant contributions to schizophrenia. *Hum. Mol. Genet.* 25, 1001–1007. doi: 10.1093/hmg/ddv620

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J. L., Kähler, A. K., Akterin, S., et al. (2013). Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat. Genet.* 45, 1150–1159. doi: 10.1038/ng.2742

Risch, N., and Baron, M. (1984). Segregation analysis of schizophrenia and related disorders. *Am. J. Hum. Genet.* 36, 1039–1059.

Risch, N., and Merikangas, K. (1996). The future of genetic studies of complex human diseases. *Science* 273, 1516–1517. doi: 10.1126/science.273.5281.1516

Rosenthal, D. (1959). Some factors associated with concordance and discordance with respect to schizophrenia in monozygotic twins. *J. Nerv. Ment. Dis.* 129, 1–10. doi: 10.1097/00005053-195907000-00001

Rosenthal, D. (1962). Problems of sampling and diagnosis in the major twin studies of schizophrenia. *J. Psychiatr. Res.* 1, 116–134. doi: 10.1016/0022-3956(62)90003-1

Rosenthal, D., Wender, P. H., Kety, S., Schulsinger, F., Welner, J., and Østergaard, L. (1968). "Schizophrenics' offspring in adoptive homes," in *The Transmission of Schizophrenia*, eds D. Rosenthal and S. Kety (Oxford: Pergamon Press), 377–391.

Ruderfer, D. M., Fanous, A. H., Ripke, S., McQuillin, A., Amdur, R. L., Schizophrenia 726 Working Group of Psychiatric Genomics Consortium, et al. (2014). Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Mol. Psychiatry* 19, 1017–1024. doi: 10.1038/mp.2013.138

Ruderfer, D. M., Hamamsy, T., Lek, K., Karczewski, K. J., Kavanagh, D., Samocha, K. E., et al. (2016). Patterns of genic intolerance of rare copy number variation in 59,898 human exomes. *Nat. Genet.* 48, 1107–1111. doi: 10.1038/ng.3638

Rüdin, E. (1916). *Zur Vererbung und Neuentstehung der Dementia Praecox*. Berlin: Springer.

Sauer, U., Heinemann, M., and Zamboni, N. (2007). Genetics. Getting closer to the whole picture. *Science* 316, 550–551. doi: 10.1126/science.1142502

Schulz, B. (1932). Zur Erbpathologie der Schizophrenic. *Zeitschrift für die gesamte Neurologie und Psychiatrie* 143, 175–293.

Sekar, A., Biales, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., et al. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature* 530, 177–183. doi: 10.1038/nature16549

Sestito, M., Parnas, J., Maggini, C., and Gallese, V. (2017). Sensing the worst: Neurophenomenological perspectives on neutral stimuli misperception in schizophrenia spectrum. *Front. Hum. Neurosci.* 11:269. doi: 10.3389/fnhum.2017.00269

Sestito, M., Raballo, A., Umiltà, M. A., Amore, M., Maggini, C., and Gallese, V. (2015a). Anomalous echo: Exploring abnormal experience correlates of emotional motor resonance in Schizophrenia Spectrum. *Psychiatry Res.* 229, 559–564. doi: 10.1016/j.psychres.2015.05.038

Sestito, M., Raballo, A., Umiltà, M. A., Leuci, E., and Tonna, M. (2015b). Mirroring the self: testing neurophysiological correlates of disturbed self-experience in schizophrenia spectrum. *Psychopathology* 48, 184–191. doi: 10.1159/000380884

Sestito, M., Umiltà, M. A., De Paola, G., Fortunati, R., Raballo, A., Leuci, E., et al. (2013). Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front. Hum. Neurosci.* 7:368. doi: 10.3389/fnhum.2013.00368

Shi, J., Levinson, D. F., Duan, J., Sanders, A. R., Zheng, Y., Pe'er, I., et al. (2009). Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 460, 753–757. doi: 10.1038/nature08192

Slater, E. (1953). Psychotic and neurotic illnesses in twins. *Spec. Rep. Ser. Med. Res. Counc. (G. B.)* 278, 1–385.

Sleiman, P., Wang, D., Glessner, J., Hadley, D., Gur, R. E., Cohen, N., et al. (2013). GWAS meta analysis identifies TSNARE1 as a novel schizophrenia/bipolar susceptibility locus. *Sci. Rep.* 3:3075. doi: 10.1038/srep03075

Schizophrenia Psychiatric Genome-Wide Association Study Consortium. (2011). Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* 43, 969–976. doi: 10.1038/ng.940

Stefansson, H., Ophoff, R. A., Steinberg, S., Andreassen, O. A., Cichon, S., Rujescu, D., et al. (2009). Common variants conferring risk of schizophrenia. *Nature* 460, 744–747. doi: 10.1038/nature08186

Sullivan, P. F., Kendler, K. S., and Neale, M. C. (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch. Gen. Psychiatry* 60, 1187–1192. doi: 10.1001/archpsyc.60.12.1187

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511, 421–427. doi: 10.1038/nature13595

Szatkiewicz, J. P., O'Dushlaine, C., Chen, G., Chambert, K., Moran, J. L., Neale, B. M., et al. (2014). Copy number variation in schizophrenia in sweden. *Mol. Psychiatry* 19, 762–773. doi: 10.1038/mp.2014.40

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K. E., Rönkkö, T., et al. (1985). The finnish adoptive family study of schizophrenia. *Yale J. Biol. Med.* 58, 227–237.

Tienari, P., Wynne, L. C., Sorri, A., Lahti, I., Läksy, K., Moring, J., et al. (2004). Genotype-environment interaction in schizophrenia-spectrum disorder. long-term follow-up study of finnish adoptees. *Br. J. Psychiatry* 184, 216–222. doi: 10.1192/bjp.184.3.216

Turkheimer, E., and Harden, K. P. (2014). "Behavior genetic resarch methods: testing quasi-causal hypotheses using multivariate twin data," in *Handbook of Research Methods in Social and Personality Psychology*, 2nd Edn. eds H. T. Reis and C. M. Judd (New York, NY: Cambridge University Press), 159–187.

Wender, P. H., Rosenthal, D., Kety, S. S., Schulsinger, F., and Welner, J. (1974). Crossfostering. a research strategy for clarifying the role of genetic and experiential factors in the etiology of schizophrenia. *Arch. Gen. Psychiatry* 30, 121–128. doi: 10.1001/archpsyc.1974.01760070097016

World Health Organization. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines*. Geneva: WHO.

Xiao, X., and Li, M. (2016). Replication of Han Chinese GWAS loci for schizophrenia via meta-analysis of four independent samples. *Schizophr. Res.* 172, 75–77. doi: 10.1016/j.schres.2016.02.019

Xu, B., Ionita-Laza, I., Roos, J. L., Boone, B., Woodrick, S., Sun, Y., et al. (2012). *De novo* gene mutations highlight patterns of genetic and neural complexity in schizophrenia. *Nat. Genet.* 44, 1365–1369. doi: 10.1038/ng.2446

Xu, B., Roos, J. L., Levy, S., van Rensburg, E. J., Gogos, J. A., and Karayiorgou, M. (2008). Strong association of *de novo* copy number mutations with sporadic schizophrenia. *Nat. Genet.* 40, 880–885. doi: 10.1038/ng.162

Yu, H., Yan, H., Li, J., Li, Z., Zhang, X., Ma, Y., et al. (2016). Common variants on 2p16.1, 6p22.1 and 10q24.32 are associated with schizophrenia in Han Chinese population. *Mol. Psychiatry* doi: 10.1038/mp.2016.212 [Epub ahead of print].

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Sensing the Worst: Neurophenomenological Perspectives on Neutral Stimuli Misperception in Schizophrenia Spectrum

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While investigating social cognitive impairments in schizophrenia, prominent evidence has been found that patients with schizophrenia show a tendency to misclassify neutral stimuli as negatively valenced. Within this population, patients presenting delusions are more prone to this phenomenon. In a previous study, Schizophrenia spectrum (SzSp) patients rated positive, negative and neutral stimuli that were multimodally presented, while assessed with a checklist exploring anomalous subjective experiences and evaluated for positive and negative symptomatology. In the present work, we aimed to further explore the relationship between neutral stimuli misperception, anomalous experiences and positive/negative symptoms in SzSp patients. To this end, we adopted a dimensional approach by reconstructing from available data: (1) four *a priori* scales representing essential dimensions of SzSp experiential pathology following Parnas et al. (2005); and (2) five clinically meaningful factors to describe illness severity derived by Toomey et al. (1997). Results showed that although overall patients correctly recognized the target emotions, those who misinterpreted neutral auditory cues as negatively valenced also presented higher scores in Perplexity (PY), Bizarre Delusions (BD) and Disorganization (Di) dimensions. Moreover, a positive association between BD and both PY and Self-Disorder (SD) dimensions emerged, suggesting that psychotic symptoms may be directly linked to patients' subjectivity. In an attempt to comprehensively capture the multilayered neutral stimuli misperception phenomenon in SzSp, we aimed at bridging phenomenology and neurobiology by connecting the levels of molecular neurochemistry (i.e., altered dopaminergic neurotransmission), system neuroscience (aberrant salience of perceptual details) and psychopathology (the chain involving hyper-reflexivity, self-disorders and the emergence of delusions).

Keywords: aberrant salience, affect recognition, delusions, hyper-reflexivity, emotion, neutral stimuli misperception, phenomenology, schizophrenia spectrum

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INTRODUCTION

Identifying neurobiologically rooted impairments in cognition has become an increasingly reliable way to detect endophenotypes of core components of schizophrenia. In the matter in question, disturbances in perhaps the most broadly studied domain of social cognition—emotion perception—held the promise of being a possible candidate as an early sign of the disease (Kee et al., 2004; Leppänen et al., 2008; Eack et al., 2010).

Previous research investigated the presence of social cognitive impairments in facial emotion recognition among patients with schizophrenia and populations at ultra-high risk for psychosis (Schneider et al., 2006; Sestito et al., 2013). The results reported that alongside a preserved sensitivity to detect the target emotions, they were more likely to overattribute emotions to neutral faces, predominantly misinterpreting such faces as negatively valenced (Kohler et al., 2003; Eack et al., 2010; van Rijn et al., 2011; Amminger et al., 2012a,b).

Biological theories of psychosis have accounted for the tendency to misinterpret benign or ambiguous social cues. In psychosis, increased dopamine is observed in the mesolimbic pathway, with dopamine being a key neurochemical determinant of the significance of environmental cues to human motivations. Abnormal increases in this neurotransmitter are proposed to influence the perceived salience of such environmental signs, leading to their *aberrant assignment of salience* (Kapur, 2003). This mechanism is thought to mediate the tendency to interpret neutral faces as emotionally meaningful (Kapur, 2003). Such negative misattribution bias has been shown to be a special trait of those individuals presenting positive symptoms (Holt et al., 2006; Eack et al., 2010). Also, the negative misattribution bias has been found to be more pronounced in patients with longer illness duration, indicating that while deficits are already present at early stages, they seem to progress along a chronic course (Habel et al., 2010). Prominent models of delusion formation further suggest that individuals with persecutory delusions and paranoia are more prone to mis-assigning emotional meaning to neutral information (Bentall et al., 2001). Recent findings showed elevated dopamine synthesis even in prodromal individuals, which is correlated with psychotic symptoms severity (Howes et al., 2009) and predicts later psychotic disorder transition (Howes et al., 2011; Allott et al., 2014).

Empirical evidence has been available since the dawn of schizophrenia research, suggesting that the onset of the illness may be predated or accompanied by characteristic qualitative changes of subjective experience (Berze, 1914; Berze and Gruhle, 1929; McGhie and Chapman, 1961; Huber, 1983; Clerambault, 1992; Janet, 1993). Such not-yet-psychotic—i.e., non-delusional, non-hallucinatory—manifestations may entail various forms of anomalies in the domains of perception, cognition and attention, body and movement awareness, as well as alarming alterations in the domain of self-awareness (Gross, 1989; Sass and Parnas, 2003; Schultze-Lutter, 2009). These anomalies are linked to profound alterations of self-experience such as impaired identity and demarcation, solipsistic detachment from common sense attunement to the world, and defective temporalization (Bovet and Parnas, 1993). According to Huber (1983), these so-called *basic symptoms* constitute an intermediate—i.e., transphenomenal—level between the basic biological processes and overt psychotic symptoms. These experiential anomalies indeed have been shown to aggregate selectively in patients with schizophrenia spectrum (SzSp), suggesting a basic phenomenological affinity of these disorders (Parnas et al., 2005; Nordgaard and Parnas, 2014). Basic symptoms in a more pragmatic clinical context may be potentially effective for early differential diagnosis (Klosterkötter et al., 2001; Parnas and Handest, 2003).

Within this framework, little is known about the degree to which the negative recognition bias is associated with manifestations of SzSp anomalous subjective experiences and their possible relationship with positive and negative symptoms. With the rationale to begin to address this matter, we considered behavioral and clinical data gathered from a previous study (Sestito et al., 2015), whereby SzSp patients were tested with a multimodal paradigm in order to investigate affect recognition. By embracing a *phenomenological leverage* (Nordgaard et al., 2008) in conceiving full-blown signs of schizophrenia, we intended to conduct an exploratory analysis in order to investigate whether possible connections are detectable between patients' psychotic symptoms and experiential dimensions. We considered such supplementary data acquired following this protocol to provide a useful way to begin to approach this inquiry, as patients were assessed with a checklist exploring anomalous subjective experiences and evaluated for positive and negative symptomatology.

MATERIALS AND METHODS

Participants

Nineteen outpatients (14 males, 5 females, mean age 34.11 years; SD ±6.73) were recruited at the Psychiatry Section of Parma University Department of Neuroscience. All of them were diagnosed with a Schizophrenia Spectrum (SzSp) disorder (i.e., schizophrenia (N = 15) or schizotypal personality disorder (N = 4) according to DSM-IV diagnostic criteria (American Psychiatric Association, 1994)) and were clinically stable at the time of the assessment. This clinical sample has been considered in a parallel study focusing on different inquiries than the one currently at stake (Sestito et al., 2015).

Patients suffering from organic brain disorders, brain injury, alcohol or substance abuse and mental retardation were excluded from the study. The Scales for the Assessment of Positive and Negative Symptoms (SAPS; SANS; Andreasen, 1984a,b) were coded and served as global measures of severity of the disorder. Disturbances of subjective experience were explored through the Italian version of the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Gross et al., 1992). The BSABS interviews were conducted by a senior psychiatrist (CM) with extensive research interview experience and principal translator of BSABS into Italian. Each patient was assessed in a semi-structured way about the anomalies of experience on a lifetime basis. A total amount of 103 items were rated for presence/absence (98 principal items plus five items exploring coping strategies).

Patients were all under psychopharmacologic treatment with antipsychotics, hence the cumulative measure of lifetime drug exposure was calculated following Andreasen et al. (2010). Demographic and psychopathological features of the sample are reported in **Table 1**.

All participants gave their written informed consent before entering the study, which was approved by the Ethics Committee of the University of Parma and carried out according with the ethical standards of the 2013 Declaration of Helsinki.

Experimental Paradigm: Stimuli and Procedure

The experimental paradigm herein used (Sestito et al., 2013) followed the subsequent procedure. Participants were presented with 2-s color video clips portraying two actors displaying positive (laugh), negative (cry) and neutral (control) facial expressions and sounds in visual (i.e., Video) and auditory (i.e., Audio) modalities. Video or Audio modalities were either in isolation (i.e., V or A alone), or combined (i.e., AV). AV combination were either congruent (Audio-Visual Congruent, AVC) i.e., A and V conveying the same emotion (e.g., Laugh) or incongruent (Audio-Visual Incongruent, AVI), i.e., A and V conveying contradictory information (for example, in AVI Cry, participants saw an actor laughing but heard crying, whereas in AVI Laugh, participants saw an actor crying but heard laughing). The neutral video clips showed actors making various faces associated with specific vocalizations that did not imply any particular emotional content. The sound associated to such stimuli were vocalizations similar to "ahh", "ohh", or "ehmm". Participants were asked to quantify the emotional value of the stimuli (see **Figure 1**) by verbally rating their intensity on a 7-point Likert scale ranging from −3 (very negative) to +3 (very positive), whereby 0 indicated lack of perceived emotional content. The validation of stimuli and experimental procedure employed have been reported in detail elsewhere (Sestito et al., 2013).

Data Analysis

Data Reduction

Participants' behavioral rating scores were analyzed following the same procedure defined in the validation protocol (Sestito et al., 2013). Following the specific aim of this study, only behavioral rates given to neutral stimuli have been taken into account, for those modalities which turned out to be informative as established statistically (see below).

In order to explore possible relations between behavioral evidence and phenomenological experiences believed to reflect a distinctive phenotype of the schizophrenia psychopathology, four *a priori* scales were constructed from the BSABS items following Parnas and colleagues (Parnas and Handest, 2003; Parnas et al., 2005). BSABS items were grouped into four rational

TABLE 1 | Demographic variables and psychopathological features of the Schizophrenia Spectrum (SzSp) sample and its constituent subgroups (Schizophrenia and Schizotypal personality disorder).

	SzSp sample (N = 19)			Schizophrenia subgroup (N = 15)			Schizotypal personality disorder subgroup (N = 4)		
	Mean	SD	Range (scale range)	Mean	SD	Range (scale range)	Mean	SD	Range (scale range)
Age (years)	34.11	6.73	25–49	32.180	6.55	25–49	39.00	5.60	32–44
Gender, F/M	5/14			5/14			0/4		
SAPS	24.01	16.26	1–58 (0–170)	26.61	16.17	1–58 (0–170)	14.25	14.36	2–35 (0–170)
SANS	46.34	17.63	15–83 (0–125)	48.16	17.64	17–83 (0–125)	39.5	18.27	15–58 (0–125)
BSABS	41.72	16.52	29–86 (0–103)	42.05	17.97	29–86 (0–103)	40.50	11.36	29–53 (0–103)
Length of illness (years)	11.06	4.84	2–24	11.21	5.03	2–24	10.50	4.65	6–17
Age at first recognized psychotic episode	24.06	4.30	19–34	22.87	2.59	19–28	28.5	6.81	20–34
Number of hospitalizations	3.35	1.82	0–7	3.78	1.47	2–7	1.75	2.36	0–5
Dose of typical and atypical antipsychotics[a]	26.41	19.54		31.13	19.32		8.71	4.52	
Dose of atypical antipsychotics[a]	20.01	15.64		23.51	15.67		6.86	5.59	
Dose of typical antipsychotics[a]	6.40	5.72		7.62	5.79		1.85	2.20	

[a] *Drugs are expressed as the cumulative value measured in dose-years in the form of (chlorpromazine equivalent in mg) × (time on dose measured in years; Andreasen et al., 2010).*

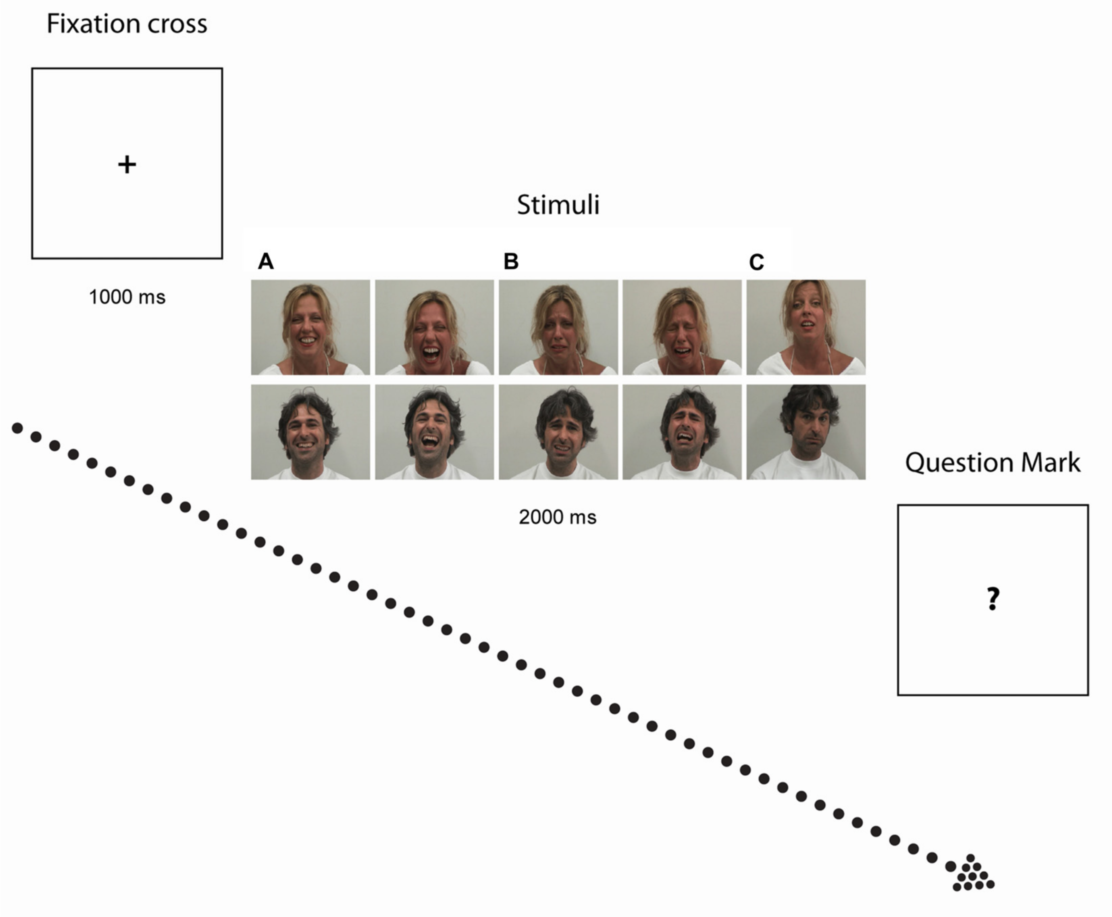

FIGURE 1 | Experimental paradigm. Photographs illustrate examples of stimuli depicting Laugh **(A)** Cry **(B)** and Neutral **(C)** stimuli. After exposure to each video clip, when the question mark symbol ("?") appeared on the screen, participants had to quantitatively rate the emotional value of the stimuli.

scales representing essential dimensions of SzSp experiential pathology: (1) *Perplexity* (PY), (2) *Perceptual Disorders* (PD), (3) *Self-Disorder* (SD) and (4) *Cenesthesias* (CEN). We herein choose to follow such a scale conformation adopted by Parnas et al. (2005) for many reasons. First, evidence has been previously provided demonstrating that individuals with schizophrenia and schizotypal disorders scored equally on such subjective dimensions (Parnas et al., 2005). Moreover, the SD scale here considered comprises some items usually considered to be "cognitive" (e.g., thought block and interference), in line with the view considering such anomalies of thinking as a facet of SD (Parnas and Handest, 2003).

Finally, scores derived from SANS and SAPS were arranged following Toomey et al. (1997). These Authors constructed, at item level, some clinically meaningful dimensions able to describe illness severity in a more informative way than the global scores themselves: (1) *Diminished Expression* (DE), (2) *Disorganization* (Di), (3) *Disordered Relating* (DR), (4) *Bizarre Delusions* (BD) and (5) *Auditory Hallucinations* (AH).

To ensure a good internal consistency, all scales were subjected to an item analysis, intended to maximize alpha coefficient (Cronbach, 1951). Only the scales reaching a satisfactory internal consistency ($\alpha > 0.50$) were retained in the subsequent analyses.

Statistical Analyses

First, normality of all variables was evaluated through visual inspection of histograms and the application of the Kolmogorov-Smirnov test. It turned out that assumptions for applying parametric tests were met for all variables.

The rating scores of each participant were averaged on the basis of modality and emotion and entered into a 4 (Modality: AVC, AVI, Audio, Video) $\times$ 3 (Emotion: Laugh, Cry, Control) repeated measures ANOVA, with Modality and Emotion as within-participants factors.

In checking for the assumptions for running the regression analysis, a preliminary check of the correlation matrix was done and those variables that showed a strong linear association (0.85 was used as cutoff) were not considered in the subsequent analysis.

A hierarchical regression analysis (forward stepping) was then conducted in order to determine the variance explained in the dependent variables (i.e., behavioral ratings), with Parnas' and Toomey's scales as predictors. As the sex variable was not balanced in our sample, it was included among predictors.

For all performed analyses, $p < 0.05$ was considered to be statistically significant.

RESULTS

Results of the analysis performed on behavioral rating scores showed that the Emotion factor was significant ($F_{(2,36)} = 60.58$, $p < 0.0001$; $\eta^2_p = 0.66$). *Post hoc* comparisons (Bonferroni corrected for multiple comparisons) revealed that Cry was rated by SzSp participants more negatively than Laugh, and Neutral stimuli were considered as devoid of any emotional content (Laugh vs. Cry; Neutral vs. Cry and Laugh all $p_s < 0.004$). Moreover, the Modality × Emotion interaction was significant ($F_{(6,108)} = 55.64$, $p < 0.0001$ $\eta^2_p = 0.76$), meaning that during AVI modality, SzSp participants based their ratings following the visual content of the stimuli—that is, cry in AVI Laugh condition (in which participants saw crying and heard laughing) and laugh in AVI Cry condition (in which participants saw laughing and heard crying; AVI Laugh vs. other modalities all $p_s < 0.0001$; AVI Cry vs. other modalities all $p_s < 0.0001$; **Figure 2**).

After a correlation matrix inspection (see Table A in the Supplementary Material Appendix), a strong linear correlation among behavioral ratings given in the AVC, AVI and V modalities emerged (AVC vs. AVI, V $p_s > 0.88$; AVI vs. AVC, V $p_s > 0.89$; V vs. AVC, AVI $p_s > 0.88$) so that they were excluded from the subsequent analyses. Finally, only the condition Audio Neutral (A Neutral) was retained as dependent variable, hence entered in the regression analysis.

After item analyses, all Toomey's scales and three out of the original four Parnas' *a priori* scales, i.e., (1) *Perplexity* (PY), (2) *Self-Disorders* (SD), (3) *Cenesthesias* (CEN) reached a satisfactorily internal consistency (alpha value ≥0.50) and were considered in the following analyses (for item composition and *alpha* coefficients for each scale, see Tables B and C in the Supplementary Material Appendix).

The hierarchical regression analysis (forward stepping) demonstrated that the behavioral rating given in the A Neutral condition was explained by the combination of four predictors: Bizarre Delusion (BD; $t = -1.85$ $\beta = -0.40$, $p < 0.09$ explaining the 24.23% of the variance), Perplexity (PY; $t = -1.62$ $\beta = -0.35$, $p < 0.2$ explaining the 21.82% of the variance), Sex ($t = -1.10$ $\beta = -0.21$, $p < 0.30$ explaining the 3.66% of the variance) and Disorganization (Di; $t = -1.00$ $\beta = -0.19$, $p < 0.4$ explaining the 0.58% of the variance) for which the overall regression model ($F_{(4,14)} = 3.52$, $p < 0.04$, $R = 0.71$, $R^2 = 0.50$) accounted for 50.17% of the variance. That is, the more participants rated neutral stimuli as negative, the higher the scores in Bizarre Delusion, Perplexity and Disorganization dimensions. Also the inclusion of Sex in the final model indicates males to be more prone to attribute a negative valence to neutral auditory stimuli. No other predictors were included in the regression model (**Figure 3**).

Pearsons' correlations between Parnas' and Toomey's scales disclosed a positive correlation between Bizarre Delusion (BD) and both Perplexity (PY; $r_{(19)} = 0.46$, $p < 0.05$) and Self-Disorder (SD; $r_{(19)} = 0.47$, $p < 0.05$) subscales (see **Table 2** and **Figure 4**). Given the exploratory nature of this study and the small sample size, we did not correct such correlations for multiple comparisons. Hence, the latter findings should be considered as suggestive of their generalizability to the general schizophrenia population.

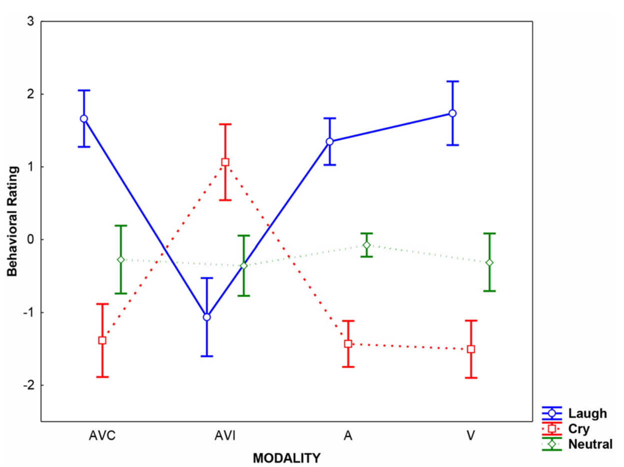

FIGURE 2 | Averaged rating scores detected for each modality (AVC: Audio-Video Congruent, AVI: Audio-Video Incongruent; A: Audio, V: Video) and emotion (Laugh, Cry, Neutral). Error bars represent the standard deviation (SD).

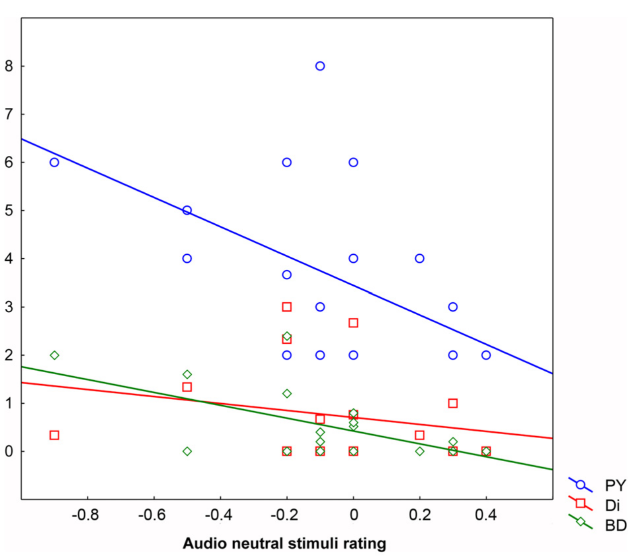

FIGURE 3 | Behavioral ratings in the Audio Neutral condition (*X* axis) as explained by scores obtained in the three predictors Perplexity (PY; *Y* axis), Disorganization (Di; *Y* axis) and Bizarre Delusions (BD; *Y* axis). Behavioral ratings given below "0" mean that stimuli are rated as negative, ratings given above "0" mean that stimuli are rated as positive, whereas "0" means lack of perceived emotional content.

TABLE 2 | Correlation matrix contrasting Parnas et al. (2005) scales (PY, Perplexity; SD, Self-Disorder; CEN, Cenesthesias) and Toomey et al. (1997) scales (DE, Diminished Expression; Di, Disorganization; DR, Disordered Relating; BD, Bizarre Delusions; AH, Auditory Hallucinations).

	PY	SD	CEN
DE	−0.142	0.140	−0.188
	$p = 0.561$	$p = 0.566$	$p = 0.442$
Di	0.074	0.008	−0.241
	$p = 0.763$	$p = 0.976$	$p = 0.320$
DR	−0.068	−0.071	0.013
	$p = 0.784$	$p = 0.772$	$p = 0.959$
BD	**0.461**	**0.466**	0.096
	p **= 0.047***	p **= 0.044***	$p = 0.696$
AH	−0.138	0.026	0.173
	$p = 0.572$	$p = 0.914$	$p = 0.479$

$p < 0.05$. Data in bold are statistically significant.

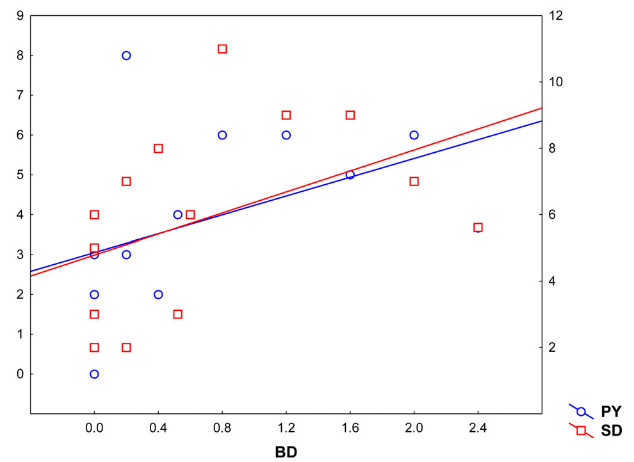

FIGURE 4 | Correlation between Toomey et al. (1997) Bizarre Delusions dimension (BD, *X* axis) and Parnas and colleagues' Perplexity and Self-Disorder scales (Perplexity, PY; *Y* left axis; Self-Disorder, SD; *Y* right axis).

DISCUSSION

In this exploratory study, by assuming a dimensional approach to the measurement of experiential anomalies and symptom severity, we aimed at furthering the relationship between neutral stimuli perception, anomalous subjective experiences and positive/negative symptoms in schizophrenia spectrum patients.

Notably, the prior correlation analysis carried out on behavioral ratings given in different modalities disclosed the auditory stimuli to be the most informative likely for their more equivocal nature, thus suitable for studying the ambiguous stimuli misperception phenomenon. The results showed that although overall patients correctly recognized positive, negative and neutral stimuli as such as previously reported (Sestito et al., 2013), those who misinterpreted neutral auditory cues as negatively valenced also presented higher scores in Perplexity (PY; Parnas et al., 2005), Bizarre Delusions (BD; Parnas et al., 2005) and Disorganization (Di; Toomey et al., 1997) dimensions. Also, the inclusion of sex in the final model indicates males to be more prone to this phenomenon. This is not surprising, as sex-related differences in the clinical expression and outcome of schizophrenia have long been recognized (Seeman, 1982). Males are reported to have an earlier onset of the disorder, more severe symptoms, prolonged period of untreated illness and poorer outcome with respect to females (Tandon et al., 2009; Cocchi et al., 2014). Multiple regression analysis demonstrated that the combination of these factors significantly accounted for the magnitude of the negative response bias given in the neutral auditory condition. It should be noted that the Auditory Hallucination (AH) dimension has not been included in the final regression model accounting for ratings given in the neutral auditory condition, confirming that neutral stimuli misreading doesn't herein merely characterize those patients presenting AH.

Further correlation analyses performed between experiential features (Parnas' *a priori* scales) and disease severity (Toomey's scales) showed a significant positive correlation between BD and both PY and SD dimensions in these individuals, suggesting that positive symptoms may be directly linked with patients' subjectivity.

The data herein reported are in concurrence with previous investigations employing similar emotion recognition paradigms, showing that patients with chronic schizophrenia presenting positive symptoms may also exhibit negative interpretations of neutral stimuli (Bentall et al., 2001; Holt et al., 2006; Eack et al., 2010). Delusions might stem from the misattribution of affective meaning to neutral or ambiguous information—an "affective misattribution bias". Our findings are consistent with an inappropriate activation of a *salience detector* (Kapur, 2003), as there is certainly enduring support for dopamine dysregulation as a final common pathway in psychosis, described as the *wind of the psychotic fire* (Laruelle et al., 1999). This might lead to the mis-assignment of emotional salience to ambiguous stimuli in the real world and ultimately, to the formation and maintenance of delusions.

Phenomenological psychiatry locates the disturbance of subjective experience in schizophrenia at the level of the pre-reflective and practical immersion of the self in the world, where the commonsense tie to natural reality is formed. Phenomenology describes this as the pre-conceptual intentional self-world relation (Blankenburg, 1971; Bovet and Parnas, 1993).

PY and SD dimensions jointly reflect a structural transformation of the *intentional arch* (Minkowski, 1927)—that is, the most basic relation between the self and the world. The PY scale signifies, in phenomenological terms, a difficulty in seeing the world as a familiar Gestalt, a difficulty in a natural grasp of meaning and hyper-reflexivity. Patients tend to perceive themselves or aspects of the environment as objects of intense reflection, preventing a smooth engagement in the interactions with the world. Isolated aspects of the environment, objects and situations, acquire an intrusive experiential quality, which indeterminately increase their significance. Such objects and situations may be experienced with enhanced emotional meaning. Included among PY scale items, (resulting) derealization (C.2.11 item) implies a change in the experience of the environment: the surrounding world appears somehow transformed, unreal, and strange. There is an increase or accentuation of the physiognomy (Gestalt meaning) of reality and of its isolated aspects, often occurring together with a captivation by details of perception (C.2.9 item) and de-automatization of common every day actions (C.3.3 item). Coherently with our results, derealization may be accompanied by more specific changes of perception, e.g., change in the quality of perceived sounds (Parnas et al., 2005).

The suggestion that the early stage of schizophrenia could be characterized by a breakdown of Gestalt perception was prominent in the work of Matussek (1952) and Conrad (1958). Matussek (1952) described a patient who reported no appreciation of the whole—he only saw details against a meaningless background (p. 92). Parnas et al. (1996) later defined this phenomenon as *impaired perceptual binding capacity*. Arieti (1962) reported in this regard, a patient who "*(..) could not look at the whole door. She could only look at the knob or some corner of the door. The wall was fragmented into parts*". Following a loosening of the perceptual context, attention may be captured by incidental details of the environment. Normally, such an aspect of the situation would not reach awareness; its detection however might prompt a search for reasons for its occurrence, which may take a delusional form. Insofar as people normally engage in causal reasoning to make sense of the world, an inappropriate, delusional frame of reference, may provide new elaborative contexts to understand the unexplained dislocated, overtly salient perceptual fragments. Notably on a clinical level, the most consistent clinical correlates of impaired perceptual organization in schizophrenia are the disorganized symptoms (e.g., thought disorders), found to be among the predictors interacting with BD and PY for neutral stimuli misperception in our study.

Notably, the above reported phenomenological descriptions characterizing the hyper-reflective status fit well with the aberrant salience hypothesis for delusions formation (Nelson et al., 2014), conferring an extraordinary richness in terms of experiential correlates upon Kapur's (2003) model. A comprehensive, plausible picture may thus be drawn by converging evidence related to phenomenology (PY) and psychotic symptoms (BD and Di) in explaining neutral stimuli misperception in SzSp.

As a second result (to be taken with precautions), a correlation has been found among BD and both PY and SD dimensions. The SD scale targets experiences in which the pre-reflective directedness toward the world in unity with the self, which is given prior to any specific act of reflection, becomes shattered and unstable. Under normal conditions, experience and self are not two distinct entities; rather the first person perspective is a medium through which the experience manifests itself (Parnas, 2000). Hyper-reflexivity entails a constant self-monitoring attitude whereby things that are matter of intense reflection are typically treated as "objects". This attitude creates a pervasive distance between self and experience. And when the self-experience bound becomes loose, then coherence breaks down, leading the delusional versions of the self, divorced from reality, to emerge. Notably in a previous study (Parnas et al., 2005), PY and SD turned out to be the scales that discriminated strongest between the SzSp and non-spectrum, a result confirming the diagnostic importance of such aberrations in the context of Schizophrenia.

Overall, these findings support some specificity of the negative misattribution bias to a combination of experiential features and positive symptoms, whose complex interplay and causality could be herein barely grasped given the exploratory nature of the study. This study indeed, is just a first attempt to comprehensively capture the multilayered turn of events that might characterize neutral stimuli misperception in schizophrenia. A possible movement from the levels of molecular neurochemistry (i.e., altered dopaminergic neurotransmission) to system neuroscience (aberrant salience of perceptual details and neutral cues) to psychopathology (the chain involving hyper-reflexivity, self-detachment and resulting delusional framing of isolated features to make sense of changed reality) may be herein tentatively postulated (Mishara and Fusar-Poli, 2013). Possible arguments aimed at bridging the phenomenological and neurobiological levels may hence be put forward and taken into account as a prompt for possible to-be-planned *ad hoc* studies on this issue, aimed at establishing the contribution of each psychopathological aspect considered.

In conclusion, this research calls for the need to adopt a more refined, emerging approach linking phenomenology, cognitive neuroscience and psychopathology. Such an effort would provide a burgeoning turf for mutual enrichment, and unique insights into vulnerability markers of psychosis (Mishara et al., 1998). Phenomenological accounts and their derived phenotypes can indeed provide the missing link in the chain between genetic or acquired biological vulnerability, the social environment, and the expression of individual positive symptoms. A complex interaction between experiential and full-blown psychotic symptoms might account for emerging problems in reading benign, emotionally un-laden cues adequately. These changes in processing neutral stimuli—primarily triggered by biologically-driven aberrant assignment of salience of perceptual details—seem to embody a peculiar experiential corollary accompanying psychotic symptoms, characterized by hyper-reflexivity and self-detachment.

Notwithstanding the exploratory nature of this study and its intrinsic limitations (the relatively small sample solely including chronic patients), we believe that these findings add important information in research on emotion processing disturbances reflecting possible trait markers of susceptibility to the disorder. However, given the relatively small sample size and the number of relevant variables taken into account, the results here reported should be interpreted with caution and further replication is needed.

Subsequent investigations would endeavor to elucidate the predictive strength of variegated psychopathological factors involved in negative emotion recognition bias for transition into full-fledged psychosis. Clinically, we hereby stress the need to integrate a phenomenological standpoint in the assessment of first-rank symptoms, as only such an approach may allow to grasp their organizing Gestalt (i.e., the altered consciousness of the patient) through the diagnostic process. Research from its side may integrate the rich phenomenological framework into its practice, creating a prolific field to formulate new, experimentally-testable empirical hypotheses strictly tied to patients' experiential dimension. Continued exploration of these deficits in high-risk populations employing longitudinal designs will be beneficial in the future investigations, thereby pointing to promising directions for early intervention and prevention programs for altering the deteriorative course of the disease.

AUTHOR CONTRIBUTIONS

MS: intellectual conceptualization, data collection and analyses, interpretation of data and manuscript drafting. JP: intellectual conceptualization. CM: intellectual conceptualization, data collection, interpretation of data. VG: intellectual conceptualization and interpretation of data. All the authors contributed to the final revision of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnhum.2017.00269/full#supplementary-material

REFERENCES

Allott, K. A., Schäfer, M. R., Thompson, A., Nelson, B., Bendall, S., Bartholomeusz, C. F., et al. (2014). Emotion recognition as a predictor of transition to a psychotic disorder in ultra-high risk participants. *Schizophr. Res.* 153, 25–31. doi: 10.1016/j.schres.2014.01.037

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edn. Washington DC: American Psychiatric Association.

Amminger, G. P., Schäfer, M. R., Klier, C. M., Schlögelhofer, M., Mossaheb, N., Thompson, A., et al. (2012a). Facial and vocal affect perception in people at ultra-high risk of psychosis, first-episode schizophrenia and healthy controls. *Early Interv. Psychiatry* 6, 450–454. doi: 10.1111/j.1751-7893.2012.00362.x

Amminger, G. P., Schäfer, M. R., Papageorgiou, K., Klier, C. M., Schlogelhofer, M., Mossaheb, N., et al. (2012b). Emotion recognition in individuals at clinical high-risk for schizophrenia. *Schizophr. Bull.* 38, 1030–1039. doi: 10.1093/schbul/sbr015

Andreasen, N. C. (1984a). *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa.

Andreasen, N. C. (1984b). *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City: University of Iowa.

Andreasen, N. C., Pressler, M., Nopoulos, P., Miller, D., and Ho, B.-C. (2010). Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol. Psychiatry* 67, 255–262. doi: 10.1016/j.biopsych.2009.08.040

Arieti, S. (1962). The microgeny of thought and perception: a psychiatric contribution. *Arch. Gen. Psychiatry* 6, 454–468. doi: 10.1001/archpsyc.1962.01710240050002

Bentall, R. P., Corcoran, R., Howard, R., Blackwood, N., and Kinderman, P. (2001). Persecutory delusions: a review and theoretical integration. *Clin. Psychol. Rev.* 21, 1143–1192. doi: 10.1016/S0272-7358(01)00106-4

Berze, J. (1914). *Die Primäre Insuffi Zienz der Psychischen Aktivität. ihr Wesen, ihre Erscheinungen und ihre Bedeutung als Grundstörungen der Dementia Praecox und der Hypophrenen überhaupt*. Leipzig: Franz Deuticke.

Berze, J., and Gruhle, H. W. (1929). *Psychologie der Schizophrenie*. Berlin: Springer.

Blankenburg, W. (1971). *The Loss of Natural Obviousness and Everyday Evidence. A Contribution to the Psychopathology of Patients with Symptom Impoverished Schizophrenia*. Enke: Stuttgart.

Bovet, P., and Parnas, J. (1993). Schizophrenic delusions: a phenomenological approach. *Schizophr. Bull.* 19, 579–597. doi: 10.1093/schbul/19.3.579

Clerambault, G. G. (1992). *L'automatisme Mental*. Paris: Les empêcheurs de penser en rond.

Cocchi, A., Lora, A., Meneghelli, A., La Greca, E., Pisano, A., Cascio, M. T., et al. (2014). Sex differences in first-episode psychosis and in people at ultra-high risk. *Psychiatry Res.* 215, 314–322. doi: 10.1016/j.psychres.2013.11.023

Conrad, K. (1958). *Die Beginnende Schizophrenie*. Stuttgart: G. Thieme.

Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrica* 16, 297–334. doi: 10.1007/bf02310555

Eack, S. M., Mermon, D. E., Montrose, D. M., Miewald, J., Gur, R. E., Gur, R. C., et al. (2010). Social cognition deficits among individuals at familial high risk for schizophrenia. *Schizophr. Bull.* 36, 1081–1088. doi: 10.1093/schbul/sbp026

Gross, G. (1989). The "basic" symptoms of schizophrenia. *Br. J. Psychiatry* 155, S21–S25.

Gross, G., Huber, G., Klosterkötter, J., and Linz, M. (1992). *Scala di Bonn per la valutazione dei Sintomi di Base (BSABS)*. Pisa: ETS.

Habel, U., Chechko, N., Pauly, K., Koch, K., Backes, V., Seiferth, N., et al. (2010). Neural correlates of emotion recognition in schizophrenia. *Schizophr. Res.* 122, 113–123. doi: 10.1016/j.schres.2010.06.009

Holt, D. J., Kunkel, L., Weiss, A. P., Goff, D. C., Wright, C. I., Shin, L. M., et al. (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr. Res.* 82, 153–162. doi: 10.1016/j.schres.2005.09.021

Howes, O. D., Bose, S. K., Turkheimer, F., Valli, I., Egerton, A., Valmaggia, L. R., et al. (2011). Dopamine synthesis capacity before onset of psychosis: a prospective ^{18}F-DOPA PET imaging study. *Am. J. Psychiatry* 168, 1311–1317. doi: 10.1176/appi.ajp.2011.11010160

Howes, O. D., Montgomery, A. J., Asselin, M. C., Murray, R. M., Valli, I., Tabraham, P., et al. (2009). Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch. Gen. Psychiatry* 66, 13–20. doi: 10.1001/archgenpsychiatry.2008.514

Huber, G. (1983). Das konzept substratnaher basissymptome und seine bedeutung für theorie und therapie schizophrener erkrankungen. *Nervenarzt* 54, 23–32.

Janet, P. (1993). Les délires d'influence et les sentiments sociaux. textes réunis par la société pierre janet. *Bull. Psychol.* 413, 1–3.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology and pharmacology in schizophrenia. *Am. J. Psychiatry* 160, 13–23. doi: 10.1176/appi.ajp.160.1.13

Kee, K. S., Horan, W. P., Mintz, J., and Green, M. F. (2004). Do the siblings of schizophrenia patients demonstrate affect perception deficits. *Schizophr. Res.* 67, 87–94. doi: 10.1016/s0920-9964(03)00217-2

Klosterkötter, J., Hellmich, M., Steinmeyer, E. M., and Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase. *Arch. Gen. Psychiatry* 58, 158–164. doi: 10.1001/archpsyc.58.2.158

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., et al. (2003). Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am. J. Psychiatry* 160, 1768–1774. doi: 10.1176/appi.ajp.160.10.1768

Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L., and Innis, R. (1999). Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol. Psychiatry* 46, 56–72. doi: 10.1016/s0006-3223(99)00067-0

Leppänen, J. M., Niehaus, D. J. H., Koen, L., Du, T. E., Schoeman, R., and Emsley, R. (2008). Deficits in facial affect recognition in unaffected siblings of xhosa schizophrenia patients: evidence for a neurocognitive endophenotype. *Schizophr. Res.* 99, 270–273. doi: 10.1016/j.schres.2007.11.003

Matussek, P. (1952). Studies in delusional perception. Psychiatrie und Zeitschrift. *Arch. Psychiatr. Nervenkr. Z Gesamte. Neurol. Psychiatr.* 189, 279–319.

McGhie, A., and Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *Br. J. Med. Psychol.* 34, 103–116. doi: 10.1111/j.2044-8341.1961.tb00936.x

Minkowski, E. (1927). *La schizophrénie. Psychopathologie des schizoïdes et des schizophrènes*. Paris: Payot La schizophrénie.

Mishara, A. L., and Fusar-Poli, P. (2013). The phenomenology and neurobiology of delusion formation during psychosis onset: jaspers, truman symptoms and aberrant salience. *Schizophr. Bull.* 39, 278–286. doi: 10.1093/schbul/sbs155

Mishara, A. L., Parnas, J., and Naudin, J. (1998). Forging the links between phenomenology, cognitive neuroscience and psychopathology: the emergence of a new discipline. *Curr. Op. Psychiatry* 11, 567–573. doi: 10.1097/00001504-199809000-00027

Nelson, B., Whitford, T. J., Lavoie, S., and Sass, L. A. (2014). What are the neurocognitive correlates of basic self-disturbance in schizophrenia? integrating phenomenology and neurocognition: part 2 (Aberrant salience). *Sch. Res.* 152, 20–27. doi: 10.1016/j.schres.2013.06.033

Nordgaard, J., Arnfred, S. M., Handest, P., and Parnas, J. (2008). The diagnostic status of first-rank symptoms. *Schizophr. Bull.* 34, 137–154. doi: 10.1093/schbul/sbm044

Nordgaard, J., and Parnas, J. (2014). Self-disorders and the schizophrenia spectrum: a study of 100 first hospital admissions. *Schizophr. Bull.* 40, 1300–1307. doi: 10.1093/schbul/sbt239

Parnas, J. (2000). "The self and intentionality in the pre-psychotic stages of schizophrenia," in *Exploring the Self: Philosophical and Psychopathological Perspectives on Self-Experience*, ed. D. Zahavi (Philadelphia, PA: John Benjamins), 115–147.

Parnas, J., Bovet, P., and Innocenti, G. M. (1996). Schizophrenic trait features, binding and corticocortical connectivity: a neurodevelopmental pathogenetic hypothesis. *Neurol. Psychiatry Brain Res.* 4, 185–196.

Parnas, J., and Handest, P. (2003). Phenomenology of anomalous self-experience in early schizophrenia. *Compr. Psychiatry* 44, 121–134. doi: 10.1053/comp.2003.50017

Parnas, J., Handest, P., Jansson, L., and Saebye, D. (2005). Anomalous subjective experience among first-admitted schizophrenia spectrum patients: empirical investigation. *Psychopathology* 38, 259–267. doi: 10.1159/000088442

Sass, L. A., and Parnas, J. (2003). Schizophrenia, consciousness and the self. *Schizophr. Bull.* 29, 427–444. doi: 10.1093/oxfordjournals.schbul.a007017

Schneider, F., Gur, R. C., Koch, K., Backes, V., Amunts, K., Shah, N. J., et al. (2006). Impairment in the specificity of emotion processing in schizophrenia. *Am. J. Psychiatry* 163, 442–447. doi: 10.1176/appi.ajp.163.3.442

Schultze-Lutter, F. (2009). Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophr. Bull.* 35, 5–8. doi: 10.1093/schbul/sbn139

Seeman, M. V. (1982). Gender differences in schizophrenia. *Can. J. Psychiatry* 27, 107–112.

Sestito, M., Umiltà, M. A., De Paola, G., Fortunati, R., Raballo, A., Leuci, E., et al. (2013). Facial reactions in response to dynamic emotional stimuli in different modalities in patients suffering from schizophrenia: a behavioral and EMG study. *Front. Hum. Neurosci.* 7:378. doi: 10.3389/fnhum.2013.00368

Sestito, M., Raballo, A., Umiltà, M. A., Amore, M., Maggini, C., and Gallese, V. (2015). Anomalous echo: exploring abnormal experience correlates of emotional motor resonance in schizophrenia spectrum. *Psych. Res.* 229, 559–564. doi: 10.1016/j.psychres.2015.05.038

Tandon, R., Nasrallah, H. A., and Keshavan, M. S. (2009). Schizophrenia,"just the facts" 4. clinical features and conceptualization. *Schizophr. Res.* 110, 1–23. doi: 10.1016/j.schres.2009.03.005

Toomey, R., Kremen, W. S., Simpson, J. C., Samson, J. A., Seidman, L. J., Lyons, M. J., et al. (1997). Revisiting the factor structure for positive and negative symptoms: evidence from a large heterogeneous group of psychiatric patients. *Am. J. Psychiatry* 154, 371–377. doi: 10.1176/ajp.154.3.371

van Rijn, S., Aleman, A., de Sonneville, L., Sprong, M., Ziermans, T., Schothorst, P., et al. (2011). Misattribution of facial expressions of emotion in adolescents at increased risk of psychosis: the role of inhibitory control. *Psychol. Med.* 41, 499–508. doi: 10.1017/s0033291710000929

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Agency and Anxiety: Delusions of Control and Loss of Control in Schizophrenia and Agoraphobia

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We review the distinction between sense of agency and sense of ownership, and then explore these concepts, and their reflective attributions, in schizophrenic symptoms and agoraphobia. We show how the underlying dynamics of these experiences are different across these disorders. We argue that these concepts are complex and cannot be reduced to neural mechanisms, but involve embodied and situated processes that include the physical and social environments. We conclude by arguing that the subjective and intersubjective dimensions of agency and ownership cannot be considered in isolation from one another, but instead form an interdependent pairing.

Keywords: sense of agency, sense of ownership, attribution of ownership, schizophrenia, agoraphobia

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INTRODUCTION

The sense of agency (SA) may be considered an experiential aspect of the embodied nature of self. One way to grasp the role played by SA is to situate it within the context of anomalous bodily experiences. Research on this theme has focused especially on cases of schizophrenia and depersonalization (e.g., Gallagher, 2005; David et al., 2008; Jeannerod, 2009; Sierra, 2009). In cases of schizophrenic delusions of control, according to some accounts, the sense of self-agency is disrupted; the patient at times experiences her thoughts, actions, and bodily movements as controlled by another agent. Importantly, the disruption of SA occurs not simply in an intra-psychic manner, even in the case of thought insertion, but involves relations to others and the world more broadly (Gallagher, 2012).

Alongside schizophrenia, agoraphobic anxiety offers another way in which disruptions in the experience of agency reveal the dynamic and relational structure of this phenomenon[1]. There are at least two points to consider. First, in terms of first-person experience, subjects with phobic anxiety tend to mistrust their own response to the world, feeling their bodies could give way at any point, thus positioning the locus of control outside of selfhood. Second, in cases of agoraphobic anxiety, loss of SA leads to a partial loss of the sense of bodily ownership. This can also be understood in the context of intersubjective relations. For the agoraphobic person, the encroachment of other

[1] We limit our discussion of anxiety to agoraphobia; this is a result of constraints of space and thematic scope. No doubt, social anxiety, and generalized anxiety each involve a specific and complex conceptualization of SA and ownership. Such anxieties are likely to have overlaps with that of agoraphobia, but nevertheless merit a separate investigation.

people into one's own space leads to anxiety, generating an experience of the body as both my own and not my own concurrently (Trigg, 2013a).

In this paper, after reviewing the distinction between SA and sense of ownership (SO), we explore these notions, and their reflective attributions, in schizophrenic symptoms and in agoraphobia. We show how the underlying dynamics of these experiences are different across these conditions. We conclude by arguing that the subjective and intersubjective dimensions of agency and ownership cannot be considered in isolation from one another, but instead form an interdependent pairing.

SENSE OF AGENCY AND SENSE OF OWNERSHIP

A number of theorists have defended clear phenomenological distinctions between experiences of agency and ownership (Graham and Stephens, 1994; Gallagher, 2000a,b, 2012; Stephens and Graham, 2000; Tsakiris et al., 2007; Synofzik et al., 2008). These distinctions have been made in regard to both pre-reflective and reflective consciousness. On the pre-reflective level of experience, SA is the sense that I originate and control my actions; SO is the sense that I am the one who is moving or undergoing an experience (Gallagher, 2000a). The case of involuntary action makes the distinction clear. For example, if someone pushes me from behind, my experience is that I am the one moving (I have SO for my bodily movement), but, at least in the first instant, I do not have SA for the movement since I was not the one who initiated the action. The phenomenological claim is that SA and SO are common features intrinsic to most pre-reflective agentive experience. This applies to thinking as well, insofar as thinking is considered to be an action.

Experimental studies have attempted to identify the neural correlates of SA and SO, which are thought to involve correlations between efferent signals (for SA) and afferent signals (for SO) (e.g., Tsakiris and Haggard, 2005), and may involve sensory integration in the anterior insula (e.g., Farrer and Frith, 2002). In a more recent study Tsakiris et al. (2010) found independent activations in midline cortical structures associated with SO, absent for SA; and activation in the pre-SMA linked to SA, but absent for SO. Although this finding supports an "independence" model, where SA and SO are understood to be two "qualitatively different experiences, triggered by different inputs, and recruiting distinct brain networks" (Ibid, 2740), there is behavioral and phenomenological evidence for a more integrative or "additive" model where SA and SO are strongly related (e.g., Caspar et al., 2015).

In addition to pre-reflective SA and SO, Stephens and Graham (2000) have proposed that one can attribute agency and ownership retrospectively based on a judgment of consistency between one's actions (or thoughts or beliefs) and one's self-narrative. They distinguish between the reflective attribution of agency (AA) and the reflective attribution of subjectivity or ownership (AO). They argue that with respect to agency, if an action I perform or a thought that I have are inconsistent with how I understand myself, my introspective sense that I am the agent may be less than if that action or thought is consistent with my self-understanding.

As Synofzik et al. (2008) indicate, AA and AO involve *judgments* of agency and ownership, the result of a second-order reflective consciousness, as distinct from a first-order pre-reflective *experience* of SA and SO. Graham and Stephens suggest that AA involves a process of comparing action (or belief) and narrative to test for consistency. It seems possible, however, that a second-order retrospective judgment about agency may be based directly on the first-order experience of SA (Bayne and Pacherie, 2007; Haggard and Tsakiris, 2009). That is, if I am asked whether I have engaged in a particular action, my reflective stance may simply discover that my pre-reflective experience of that action already involved SA. In that case AA may simply be a report on SA rather than a comparative judgment about one's action and one's self-narrative.

The phenomenological claim that SA and SO are common features intrinsic to most pre-reflective agentive experience has not gone unchallenged, however. Bermúdez (2011), for example, despite his contention that first-person bodily experience counts as a form of self-consciousness, argues that there is no evidence that SO is a feature of pre-reflective experience; he considers the SO to be a product of reflective judgment, which would make it equivalent to AO. Bermúdez interprets claims about SO to be claims about an aspect of experience separate and distinct from proprioception, kinaesthesia and other bodily sensations, and he denies that there is any such aspect. In contrast, we understand SO to be an implicit aspect of proprioception and other bodily sensations, rather than something separate from them (Gallagher, 2005; also see de Vignemont, 2007, 2013). In fact, this implicit self-experience (or ipseity) is precisely what makes first-person bodily (proprioceptive, kinaesthetic) awareness itself (i.e., prior to any judgment) a form of self-consciousness—it's what puts the "proprio" in proprioception. On this view such experiences are characterized by a "perspectival" SO (Albahari, 2006), i.e., an intrinsic SO directly tied to a first-person perspective.

With respect to SA, Grünbaum (2015) offers a more detailed critique that draws a conclusion similar and parallel to Bermúdez's conclusion about SO, namely that there is no separate and distinct pre-reflective SA that acts as the basis for a judgment about agency (AA). Grünbaum focuses on the particular account of SA that considers it the product of comparator mechanisms involved in motor control. He doesn't deny that a comparator mechanism may be involved in motor control, but he challenges the idea that comparator processes generate a distinct experience of agency. He views the claim that SA is generated by such mechanisms to mean that SA is intention-free. By "intention-free" we take him to mean that, on such accounts, SA is generated even if the agent has not formulated a prior, personal-level intention to act in a certain way. Reaching for my cup of tea as I work on my computer does not require that I consciously deliberate and form a plan to do so. Still, it counts as an intentional action and may involve a present intention-in-action, and motor intentions (Pacherie, 2006, 2008). Moreover, at least some comparator models include the idea that there is some functional element in the system that counts as an intention, and that this intention is compared to efference copy or sensory input from the movement to facilitate motor control (e.g., Frith, 1992; Wolpert and Flanagan, 2001). In this respect it's not clear that SA can be characterized as intention-free.

Grünbaum also points to an important qualification involved in a number of experiments on SA. For example, in an action-recognition experiment, Daprati et al. (1997) ask subjects to perform a hand movement and monitor it on a computer screen, which shows either their own hand movement, or a hand movement made by someone else. They are then asked whether what they saw was their action or not. Typically subjects mistook the actions of the other's hand as their own in about 30% of the cases; schizophrenic subjects who had a history of delusions of control and/or hallucinations misjudged 50–77% of the cases. The problem, as Grünbaum notes, is that on each trial the subject is in fact engaging in the action of moving his own hand. The same objection can be raised in regard to other experiments. For example, Farrer and Frith (2002) use a similar experimental design and claim that this allows for the dissociation between SO and SA. SO for the movement, they contend, was kept constant because the subject moved on each trial; but SA varied depending on whether subjects felt they were in control of what was happening on the computer screen.

With respect to the Daprati et al. experiment, Grünbaum concludes that rather than reporting SA based on comparator processes (since hypothetically that would also remain constant across all trials), subjects were simply reporting differences in what they were monitoring on the screen. An alternative conclusion, however, is that the pre-reflective SA is more complex than an experience that is generated by comparator processes. The idea that SA involves at least two aspects—one having to do with the control of bodily movement in action, and one having to do with the intentional aspect of the action, i.e., what the action accomplishes in the world—has been either assumed (as in Farrer and Frith, 2002) or explicitly stated (Gallagher, 2005, 2012; Haggard, 2005). Even if Grünbaum were right about comparator mechanisms not generating SA, SA may still be generated in our perceptual monitoring of what our actions are accomplishing in the world. Langland-Hassan (2008) raises similar worries about the positive phenomenology of SA, but concludes that the phenomenology of agency is "one that is embedded in all first order sensory and proprioceptive phenomenology as diachronic, action-sensitive patterns of information; it does not stand apart from them as an inscrutable emotion" (p. 392).

Although we cannot respond to all of Grünbaum's detailed arguments here, we do want to indicate that we take SA to be a more complex phenomenon than just a simple phenomenal experience generated by a subpersonal comparator mechanism. Indeed, there are reasons to question whether comparator models of motor control offer the best explanation (see, e.g., Synofzik et al., 2008; Friston, 2011). That issue aside, however, the pre-reflective SA may be constituted by a number of contributories, including reflective processes that involve prior or distal intentions, long-term intentions, and retrospective attribution (Pacherie, 2006, 2008; Gallagher, 2012; Vinding et al., 2013).

It may sound strange to suggest that reflective processes that involve prior intention formation may contribute to a pre-reflective experience of agency. The idea is simply that if I deliberate and create an action plan or prior intention to do something (for example, to buy a new car next week), when the time comes and I put that intention into action, the fact that I had planned it out and am not acting in a completely spontaneous way should enhance my sense of control over my action. If, in contrast, I found myself in the car dealership due to a spontaneous desire for a red Mustang convertible that I spotted on the lot, I might in fact feel a little out of control, and this feeling of lack of control (or decreased SA) may be reinforced when I start to evaluate my action in terms of my self-narrative or in terms of a violation of my long-term intention to reduce my dependency on fossil fuels. In this respect, a lack of deliberative reflection or a modulation in AA, the judgment or AA that I make about my action, may in fact have an effect on my ongoing pre-reflective SA for the action[2].

On this view we can identify several different contributories to a complex SA connected with any particular action, and we can think of these contributories as forming a dynamical, relational gestalt of factors, changes in any one of which can modulate the experience of SA.

- Formation of prior intentions, often involving a prospective reflective deliberation or planning that precedes some actions.
- Pre-reflective perceptual monitoring of the effect of my action on the world in terms of specific intentional or means-ends relations in specific situations.
- Basic efferent motor-control processes that generate a first-order experience linked to bodily movement in and toward an environment.
- The retrospective AA that follows action.

We want to go even further in identifying contributories to SA, although we won't be able to lay out the entire argument here. We contend that the experience of agency is not reducible to neural comparator mechanisms, even if these mechanisms are involved in motor control, or even to the purely internal processes described above. Rather, we suggest that agency, and the SA that accompanies it, are fully embodied and situated (Buhrmann and Di Paolo, 2015). That it is embodied should be obvious since it involves bodily action, the peripheral nervous system (proprioception, kinaesthesia), autonomic and vestibular processes, affective and emotional aspects[3] and so on (and on embodied cognition views, even thinking involves bodily processes). That it is situated means that our agency, and our experience of it, can be modulated—increased or decreased—by physical and spatial features of environments as well as social environments that include, not only other people, but also normative, social, and institutional practices (Gallagher, 2012, 2014). Consider that even large social structures (e.g., institutions of apartheid and slavery) can literally rob individuals of their agency and make them feel that they have no control over

[2] We're assuming that neither the action nor SA is a momentary phenomenon but extends over time.

[3] Christensen et al. (2016) have shown that fear and anger can reduce an implicit measure (action binding) for SA.

their own lives (Gallagher, 2011, 2012). Just as spontaneous decisions (e.g., the lack of reflective deliberation, as in the case of spontaneously deciding to buy a car) can diminish one's feeling of self-control and SA as one engages in a particular action, so also a social structure (or intersubjective relation) that takes away the possibility of making one's own decision can have an effect on one's agentive experience in so far as actions may be prevented (by psychologically undermining motivation) or forced (by physical discipline)[4].

If SA may be modulated by changes in varied factors that involve, most centrally, pre-reflective perceptual monitoring of the effects of action, and basic motor-control processes, but also reflective deliberation, retrospective judgments, environmental, intersubjective, socio-normative, and even cultural and political arrangements, then a disruption in any of these factors may generate nuanced and in some cases, pathological differences in SA of different sorts [as well as in SO, and the attributions of agency (AA) and ownership (AO) in so far as these are related to SA]. That is, we should expect that in different pathologies, SA may be changed or undermined in different ways, depending on what factors may be involved. Accordingly, we turn now to examine changes in SA in two different disorders, schizophrenia and agoraphobia, to discover both what is common and what is different in these disorders with respect to SA.

DELUSIONS OF CONTROL IN SCHIZOPHRENIA

In typical cases of involuntary movement, efferent signals are missing and, in some situations, so is SA; but SO for the movement is maintained because of the presence of afferent sensory feedback. In such cases, my experience is that I am moving, but I did not initiate the movement. The same logic may explain some aspects of schizophrenic delusions of control. If there are neurological problems with efference copy (understood as a signal sent to a forward comparator involved in motor control) it may result in a loss of SA for the action (Frith, 1992). Consider the following report by a patient suffering from delusions of control.

> They inserted a computer in my brain. It makes me turn to the left or right. It's just as if I were being steered around, by whom or what I don't know. (Cited in Frith et al., 2000, p. 358).

The patient expresses no question about who is being turned or steered (he has an intact SO—it is he who is moving); but his experience is of something (or someone) else controlling his movement (he has no SA or sense of self-agency for that movement). This suggests a bottom-up, empiricist account of one aspect involved in delusions of control; something goes wrong at a neural level that has an anomalous effect at the level of awareness.

With respect to the schizophrenic symptom of thought insertion, however, it's not clear that (or how) efference or a comparator model could be involved in thinking, and accordingly, it's not clear that thought insertion can be explained in the same way as delusions that involve bodily movement (Gallagher, 2004). There may be a more general or basic disruption of neuronal processes that affect not just SA for motor action, but also for cognitive processes, resulting in symptoms of thought insertion. SA for higher-order cognitive processes may depend on the anticipatory aspect of working memory (Gallagher, 2000b, 2004), something that may also malfunction in schizophrenic subjects with delusions of control (see Singh et al., 1992; Daprati et al., 1997; Vogeley et al., 1999). Moreover, as we indicated in the previous section, multiple factors may be involved in generating and maintaining SA, and some of these may still remain in effect.

In addition, the absence of efference copy does not explain the full phenomenon of delusions of control since the anomalous experience may also feel alien and there is usually an AA to another person or object. Billon and Kriegel (2014) suggest that rather than there being "something missing" (i.e., SA), delusions of control and thought insertion really involve "something added"—namely a phenomenology of alienation, which is reflected in the subject's claim that someone or something else is making his thoughts. One possible explanation for the alien feeling is that a disruption in the integration of somatosensory signals, visual and auditory signals, and efference (corollary discharge), or some other kind of malfunction in the anterior insula or the right inferior parietal cortex (Farrer and Frith, 2002), or in mechanisms that allows for the proper discrimination between self and non-self (Georgieff and Jeannerod, 1998), may generate a sense of alien control at the level of first-order experience (de Vignemont and Fourneret, 2004; Gallagher, 2004; Pacherie et al., 2006).

On phenomenological approaches to schizophrenia, delusions of control are considered disorders of basic self-experiences. Parnas and Sass (2011) refer to this as a form of *ipseity-disturbance*. Ipseity "refers to the most basic sense of selfhood or self-presence: A crucial sense of self-sameness, fundamental (thus nearly indescribable) sense of existing as a vital and self-identical *subject* of experience or *agent* of action" (Sass, 2014, p. 6). Sass, for example, argues that in cases of ipseity disturbance in schizophrenia, first-person experience is disrupted in two central ways. First, the patient engages in "hyper-reflexivity," which is marked by an amplified self-consciousness of processes and phenomena that would normally be tacit, or "inhabited" as part of oneself (Sass, 2014, p. 6). Such self-consciousness, Sass notes, is neither introspective nor reflective in nature, but instead functions in a perception-like way. Second, a "diminished self-affection" emerges, such that the patient undergoes a diminished "sense of existing as a subject of awareness or agent of action" (p. 6) and a feeling of alienation. According to this model, an initial heightened self-awareness leads to a diminished self-awareness and alien feeling, similar to the way in which if you stare at the back of your hand long enough it starts to feel as if you are staring at something that is not you[5]. The

[4]A study by Caspar et al. (2016), for example, shows that SA, measured by implicit intentional binding, decreases when agents act under orders.

[5]It may be that in delusions of control the schizophrenic starts to experience what Merleau-Ponty has called the impersonal that subtends our personal life: "if I wanted to express perceptual experience with precision, I would have to say that one perceives in me, and not that I perceive. Every sensation includes a seed of dream or depersonalization, as we experience through this sort of stupor into

ipseity-disturbance model is grounded in the broader distinction between a minimal or prereflective sense of self-experience and a second-order, reflective level involving the narrative of autobiographical self (Sass, 2014, p. 7; Gallagher, 2011). The disturbance at stake in schizophrenia is a disturbance leveled precisely at the prereflective or minimal self, rather than the narrative self (Parnas and Sass, 2011). What is at stake, therefore, are the experiential aspects of SA and SO.

In contrast to empiricist and phenomenological explanations, Graham and Stephens (1994) and Stephens and Graham (2000) propose that in cases of schizophrenic delusions of control or thought insertion the problem is with AA. The subject fails to attribute agency to his actions or thoughts because they seem radically inconsistent with his self-narrative. In such cases the important change is in the reflective judgment of agency. According to Graham and Stephens, there is no change in AO, however; the subject does not deny that the action is being carried out by his own bodily movement, or that the thought is occurring as part of his own experience. Indeed, that is precisely his complaint—that this action or thought involves his body or his thinking, but does not seem consistent with his beliefs or self-conceptions. Again, although this top-down, rationalist account may be more consistent with the view that a delusion is "a false belief based on incorrect inference" (as it had been controversially defined by the DSM-4), it doesn't provide a full explanation since it's not clear why an inconsistency between action and narrative would prevent an attribution of self-agency rather than, for example, a sense that one has made a mistake or was simply inconsistent in one's actions, or why it would motivate a misattribution of agency to someone else. In addition, top-down accounts don't address a puzzle raised by Bayne and Pacherie (2004,p. 8): "We are also puzzled by the question of how a top-down account of delusions could explain the damage to the autonomic system that one finds in the Capgras and Cotard delusions. Is this caused by the delusional belief? That seems unlikely." More generally, top-down accounts don't provide a clear picture of how organic malfunction is related to the cognitive mechanisms that purportedly generate delusions.

Furthermore, if introspective or narrative capabilities are in some way undermined by organic damage, as Graham and Stephens would have it (also Campbell, 2002), it is not clear why the subject's delusions would be selectively about certain topics and not others—that is, why the subject is not delusional about everything he believes, or why some actions or thoughts are considered alien, but not others. This has been called the problem of specificity (Gallagher, 2004, 2007). Pacherie et al. (2006, p. 575) suggest that it remains unsolved. This also seems a problem for those empiricist (bottom-up) accounts that would explain the loss of SA solely in terms of a faulty comparator. It may be that the specificity of delusions depends on a kind of internal logic that involves the integration or disintegration of selfhood; and a solution may also depend on conceiving of SA as constituted by a plurality of factors that include physical and social environmental elements.

A more hybrid explanation may also address some of these issues. Two-factor models of delusion combine top-down and bottom-up accounts and suggest a more central role for neurological problems. The first factor consists of an anomalous experience, such as an odd feeling (or lack of appropriate feeling), anomalous perception, or hallucination caused by some neurological dysfunction that interferes with SA or with some emotional aspect of experience; the second factor consists of an attempt to explain or rationalize the anomalous experience, leading to what the DSM-5 defines as "fixed beliefs that are not amenable to change in light of conflicting evidence" (see, e.g., Ellis and Young, 1990; Davies et al., 2001; Garety et al., 2001). On some views, experience itself is considered delusional, while higher-order cognition simply reports (endorses and, as things develop, perhaps enhances) the delusion (see e.g., Hohwy and Rosenberg, 2005; Mundale and Gallagher, 2009).

Not everyone agrees, however, that the experience or judgment about agency is the thing at stake in delusions of control and thought insertion. Bortolotti and Broome (2009), for example, deny that delusions of control and thought insertion involve problems of SA or AA. Rather, they propose that such delusions involve problems with AO, attributions of ownership. They view this as a "more demanding notion of ownership" that involves a self-ascription condition by which a subject acknowledges an action or thought as her own and ascribes it to herself on the basis of introspection, or her reasons (or lack of reasons) for acting or thinking in that way. That there may be a problem with AO in such cases, however, does not rule out the possibility that the primary problem is still a problem with SA. If we ask why the subject reflectively disowns the action or the thought, two answers still seem possible. Either (1) the thought doesn't fit with her self-narrative (as suggested by Graham and Stephens), and is not "endorsed" by the subject since she is not able to provide reasons for it (as suggested by Bortolotti and Broome), or, (2) the action or thought actually feels or is experienced as alien—a first-order experience that may have initially motivated the second-order reflection. This type of first-order experience, even in the case of thought insertion may involve bodily and spatial aspects, as when patients describe thoughts entering into their heads literally at certain locations on their skulls (e.g., Cahill and Frith, 1996). Moreover, this first-order feeling of alienation may result from, or may result in, a modulation or displacement of SA for that action or thought. So, even if Bortolotti and Broome are right that the person's second-order, retrospective report indicates a problem with AO, this problem may be due to a first-order, experiential problem with SA and/or feeling of alienation (Gallagher, 2015).

Billon (2013), who also thinks that thought insertion involves problems with AO, provides a different argument against the

which it puts us when we truly live at the level of sensation" (Merleau-Ponty, 2012, p. 249/223). We typically do not live at the level of sensation, however; we are typically perceivers and agents living in the world. In schizophrenia, this natural attitude can be disrupted. As Merleau-Ponty suggests, one may find a similar movement toward the impersonal or pure sensibility in art. Levinas suggests something similar. Art leaves "the level of perception so as to reinstate sensation" (Levinas, 2001, p. 85/47); it allows us to "wander about in sensation" and to return to the "impersonality of the elements" (Levinas, 2001, p. 85–86/47). Merleau-Ponty attributes these kinds of experiences to Cézanne, who he describes as schizothymic. Cézanne's paintings reveal the "base of inhuman nature" that our human agency hides from us (Merleau-Ponty, 1964, p. 76)—an "unfamiliar" world the experience of which may lead to an uncomfortable anxiety.

SA explanation. He argues that the subject doesn't actually have a first-order experience of the thought. Rather, the inserted thought is generated and inserted by the second-order reflection. Such thoughts lack first-order (pre-reflective) phenomenality and therefore there can't be a first-order SA or SO for the thought.

Even if one were to accept this account, however, the problem is still one that involves SA. What does it mean to be able to come upon a thought that is in itself unconscious (without phenomenal properties) and for that reason, seemingly not mine? Billon's analogy is that the inserted thought is "akin" to a sentence uttered by someone else, or in a text that one is reading. I may have reflective access to the thought in a way that is akin to my perceptual awareness of a sentence on the page or of the sentence you just uttered. There may be something it is like to have that reflective access, or to perceive the sentence, but the sentence, does not have anything like a thought-like phenomenal character. I come upon a certain intentional content, a certain thought-meaning that seems independent of any process of thinking that would bestow on it a phenomenal feeling such that it would feel like I was the one thinking it. In that case it's a thought that I seemingly did not think—something that did not get generated in my thinking process. But if what's missing is the sense that I am the one generating the thought in a process of thinking, then what's missing is precisely the sense of self-agency—the pre-reflective SA which just is the sense that I am the generator of the thought or action.

The analyses of Bortolotti and Broome and Billon suggest again the complexity and ambiguity involved in these issues—that is, the complexity and ambiguity involved in the actual relations that exist among SA, SO, AA, and AO. It's possible that SA and SO are closely related on the prereflective experiential level of ipseity (consistent with an *ipseity-disturbance* model—Parnas and Sass, 2011; Sass, 2014) even if they are not correlated to the same neural activations (Tsakiris et al., 2010); and it's also possible that there are reciprocal relations between SA/SO and reflective judgments (AA and AO) about agency and ownership so that modulations run in both directions. If, for example, SA is disrupted by neural or extra-neural factors, both AO and AA may be affected such that I am led to judge an action or thought as not mine or as not under my control. This ambiguity is reflected in the various explanations of schizophrenic delusions of control and thought insertion.

LOSS OF CONTROL IN AGORAPHOBIC ANXIETY

The experience of agoraphobic anxiety presents us with an interesting counterpart to that of schizophrenia. If schizophrenia tends to involve a disruption in SA, which may also involve a disruption in AO, such that one experiences "a disturbance in the ownership of one's body, thoughts and actions, accompanied by faulty self-monitoring" (Park and Nasrallah, 2014, p. 1), then in the case of anxiety, the disruption in agency may play a different role. Unlike schizophrenia, which can entail a "severe erosion of minimal self-experience or real confusion of self and other" (Sass, 2014, p. 5), in cases of agoraphobic anxiety, the boundary between self and other tends to be retained. Indeed, it is precisely because this boundary is retained rather than destroyed that anxiety and a loss of control emerges. In this section, we attend to this loss of control in and through the experience of the anxiety as it relates to agoraphobia. Our intention in this section is to further underscore our view that dimensions of agency and ownership are intertwined, and always situated within both a subjective and intersubjective context. Our secondary aim is to consider the points of convergence and divergence between agoraphobic anxiety and schizophrenia.

Agoraphobia presents us with an especially clear (and often striking) sense of how a disruption in agency can lead to a disruption in a sense of self more broadly. This is clear in at least two ways. In the first case, the anxiety specific to agoraphobia often involves a disturbance in bodily motricity, such that sensations of anxiety, including the inability to move or the sudden urge to move, is felt as if it comes from nowhere. In the second case, the body of the agoraphobic person is often presented as a distinct *thing* in the world rather than a center of agentive selfhood or a body-as-subject, thus disturbing SO, or more precisely, the felt sense of bodily ownership. Together, we consolidate these aspects under the heading of the *bodily-inhibition model of anxiety*. Such a model allows us to see that what is at stake in agoraphobic anxiety is not simply the discomfort of physical sensations or symptoms, but instead the threat these symptoms pose to the integrity of self and self-agency. To defend this claim, we begin by detailing the agoraphobic condition before considering its conceptual implications for an understanding of agency.

In clinical terms, agoraphobia tends to be characterized by symptoms such as heart palpations, trembling of the legs, nausea, social discomfort, fear of losing control, a sense of impending doom, and an alienation from the body. Etymologically, agoraphobia is situated in relation to public spaces the word stems from *agora* (Greek for marketplace) and *phobia* (from the Greek word *phobos* meaning flight or terror) (Goldstein and Chambless, 1982). According to Carl Westphal, the originator of the term "agoraphobia," the anxiety experienced during an attack of agoraphobia was often alleviated when the agoraphobic person was accompanied by a trusted companion, was slightly intoxicated, or was able to use a "prop" to move around the world, such as a stick or an umbrella (Knapp, 1988).

In causal terms, Westphal accented a fault in thinking, remarking that, the problem is "more in the head than in the area of the heart" (p. 60). From the perspective of a cognitive model, the idea is that our thinking is at fault, specifically thinking orientated toward dangers in the surrounding world. According to this model, three stages can be mapped out, each of which delineates the development of agoraphobia (Clark, 1988). In the first stage, a subject perceives a threat in the environment, which seems more dangerous than it actually is in objective terms. This environmental danger can also be reflected in bodily sensations. Thus, where panic based agoraphobia is concerned, the tendency to perceive threats in the environment is transferred to a "misinterpretation" of specific bodily sensations, in which those sensations are regarded as signals of impending disaster (Clark, 1988). Such sensations include the sense of impending collapse, a loss of control, an anxiety over passing out, and a more generalized anxiety over "losing one's mind" (Barlow, 2002, p. 107). In the second stage, once these sensations become marked as a focal point in a subject's experience, an adjoining coping and behavioral mechanism forms, which is orientated toward the avoidance of places that arouse undesirable sensations. Thereafter, a vigilant mode of anticipating both the onset of anxiety and possible "threats" becomes a defining feature of the agoraphobic person's world. In the final stage, to counter these threats, avoidance behavior becomes habitual, a way of organizing both the social and spatial dimensions of a subject's world, such that the chance of experiencing panic or anxiety is minimized. Of course, this "mastery" over anxiety comes at the expense of the subject's freedom and an experienced loss of SA. In this respect, Isaac Marks provides a succinct account of the development of agoraphobia: "Once she cannot get off an express train, as soon as anxiety starts she will restrict herself to local trains; when these, too, become the setting for anxiety she retreats to buses, then to walking, then to going only a few yards from home, until finally she becomes unable to proceed beyond the front gate without a companion" (Marks, 1987, p. 336). What starts out as taking action to restrict one's actions in certain places and contexts, ends up in a feeling that one cannot take action at all in those places and contexts.

Prima facie this cognitive model of the development of agoraphobia suggests that it can be efficiently treated by cognitive oriented behavioral therapy (CBT) (Meyer and Gelder, 1963, p. 19). One reason for the relevance of CBT is that symptoms of agoraphobia present themselves as discrete events in what is often otherwise a functional existence. Using CBT, patients are educated about the physiological processes that give rise to an acute sense of anxiety. Once the subject "accepts" that their anxiety is a misinterpretation of perceived danger, "the secretion of adrenaline" is diminished thanks to a "cognitive restructuring" (Aslam, 2012)[6]. This suggests that, in contrast to schizophrenia, the subject may be able to reflectively alter his belief structure and adjust his behavior. The person with schizophrenic delusions, according to the DSM, holds fixed beliefs that are not amenable to change in light of reflectively considering evidence to the contrary. CBT treatment of agoraphobia is often implemented alongside exposure therapy, where the patient is encouraged to desensitize themselves to places and situations that are liable to invoke and provoke anxiety (Edelman and Chambless, 1993). Patients are then asked to repeat the procedure in order to facilitate and expedite the desensitization process, until the patient is entirely acclimatized to the fact that the places originally thought of as terrifying are, in reality, devoid of danger. As a result, the patient is able to inhabit the world without the sense of impending collapse previously associated with venturing outside the home.

Recent studies have focused on identifying the neural correlates of agoraphobia with the intention of predicting treatment response to CBT (e.g., Lueken et al., 2013; Hahn et al., 2015). In contrast to clinical descriptions of a dynamic development of symptoms over time, involving space perception, specific bodily sensations, loss of control, avoidance of certain environments, and the forming of behavioral habits, however, neuroscientific approaches offer snapshot pictures (literally showing photos of typical agoraphobic situations to patients in fMRI) of neural activations, namely hyperactivation of the ventral striatum, insula, amygdala, and hippocampal areas (Wittmann et al., 2011, 2014).

Although contributing to treatment and an explanation of agoraphobia, CBT, along with the correlated neuroscience tend to treat the subject and her surroundings in purely mechanical-causal terms. This is problematic in at least two respects. First, no attention is given to the way in which (inter)subjectivity and spatiality are co-constitutively organized and formed in a meaningful fashion. To the contrary, spatiality is thought of as being a largely neutral canvas, an already formed container, against which the agoraphobic person needs to restructure their way of thinking (Martin and Dahlen, 2005). Second, the lack of attention to the lived experience of spatiality fails to capture the pervasive importance a loss of SA and SO plays in the development of agoraphobic anxiety. Spatiality, for example, is understood as a mere background, which provokes and stimulates an anxiety and sense of panic that ultimately derives from the subject's misinterpretation of the world (Gloster et al., 2013). This overlooks both the rich and relational way in which anxiety is formed, and also fails to consider that the "disorder" involved in agoraphobia involves as much a disorder in spatial experience (or the experience of space as an action space), as a disorder in the SA.

A phenomenological approach to agoraphobic anxiety is helpful here in attending to these oversights (Trigg, 2013a,b, 2016a, in press). As is evident in the preceding analysis of schizophrenia, a phenomenological perspective on anomalous experience reveals not only that SA and SO are integral to a sense of self, but also that a disruption in both SA and AO is not simply an intra-corporeal or intra-psychic occurrence, but instead involves a certain dynamical structure that includes brain, body, and physical and social environments. As such, disruption in SA is not a localized event, but is instead taken up in a disturbance of selfhood more broadly. In the section that follows, we will frame this understanding in terms of the *bodily-inhibition* model of anxiety.

In non-pathological experiences of subjectivity, we experience ourselves for the most part as unified agents. That is to say, we have a prereflective sense of ourselves as both the cause of our bodily movement and also a prereflective sense of being the subject of those movements. Furthermore, in everyday existence SA and SO cohere. As we have seen in the case of schizophrenia, this coincidence of agency and ownership is not absolute. Agoraphobic anxiety affords us another inroad to see SA and SO as integral to understanding both a loss of control and the related disturbance of selfhood. Indeed, in the clinical literature, disturbances of agency, selfhood, and control are presented as being interdependently related. "Agoraphobia," so Capps and Ochs writes, "is intimately tied to a deep sense of the absence of

[6]The idea that this is a cognitive restructuring which involves a change in beliefs may suggest a response to Bayne and Pacherie's (2007) question about how a belief might be related to changes in ANS. This, as well as the exposure therapy mentioned below, suggests that the C and the B in CBT are not separable, but, at the very least, and consistent with concepts of embodied cognition, integrated.

control over one's feelings and actions" (Capps and Ochs, 1997, p. 152). Likewise, Barlow writes of the "core of anxiety" as involving "the sense of a lack of control" (Barlow, 2002, p. xiii). This loss of control in cases of agoraphobic anxiety is evident in at least two ways: Bodily motricity and bodily objectification.

"Bodily motricity" refers to the body's action-oriented power to project intention into the world in a movement of spontaneity and possibility (Merleau-Ponty, 2012). In this regard it is, from a phenomenological perspective, the general source of SA. Normally we move through the world without significant obstruction. Our bodily experiences and our sense of self cohere, such that we have a prereflective sense that the body as agentive, rather than as "an assemblage of organs juxtaposed in space." This agentive body is an "indivisible possession," united and integrated (Merleau-Ponty, 2012,p. 100). In most cases, this capacity of our bodily existence allows us to be situated in the world without the need for reflective or abstract thought. Moreover, in normal instances of bodily action, the spatiality of the world is not divided and dissected into fragmented parts, but instead unfolds in uniform with the synthesis of the body; that is, as a whole. In this respect, background and foreground do not form a binary division, but instead unfold and overlap with one another (p. 113). The result of the body's motricity is that our body operates according to a certain logic, which, whilst not always available to us in reflection, nevertheless serves to underscore a temporal and spatial unity operational "beneath intelligence and perception" (p. 137).

In its everyday motricity the body tends to efface itself, remaining tacitly in the background (Gallagher, 1986; Leder, 1990). This is not an indication of its insignificance, but a marker of its irreducible cohesion and integrity. At the same time the body is an object that we can reflect upon. At times, this reflective stance on the body is employed in a self-conscious manner, such as when I am injured and assess the wound in a critical manner (Legrand, 2007). At other times, my body becomes an object for me against my own volition, such as when I am ill and feel my body as an impediment to my existence. On other occasions, I might experience a broader alienation from my body, such as when I see a photo of myself and fail to identify with the subject captured in the frame. In these moments, we may well have an experience of the body as somehow distinct, other, or *thinglike* (Merleau-Ponty, 1965, p. 209). That the body appears for me as different or even alien does not, of course, attest to substance dualism. Rather, the body's apparent distinction is maintained as a certain affective relation I have to my body. In general, these movements of self-alienation and bodily objectification are brief, and are often consolidated into a unified and relatively coherent sense of self that includes SA and SO, which accompanies us throughout the contingences and ambiguities of our perceptual existence.

Agoraphobia provides us with a different story of the motricity and objectification of the body. In distinction to the normal experience of spatiality and SA, where the body provides a forward-looking *I can*, a trustworthy center of orientation actively engaged with the affordances that surround it, the agoraphobic person's bodily experience of space and agency is marked by hesitancy, disquiet, and a lack of trust in how he or she will respond to an unpredictable or unfamiliar situation (Trigg, 2016a). If the subject is able to move in the world, then it is thanks only to the construction of a rigidly established set of habits and patterns. By way of an illustration, consider several of the motifs appearing in Westphal's case studies: "He cannot visit the zoo in Charlottenburg, because there are no houses" (Knapp, 1988, p. 60); "When in the company of a friend—he then experiences no fear of crossing spaces ... The crossing of spaces becomes easier when he stays next to a moving vehicle" (p. 66); "A cane or umbrella in his hand often makes the crossing easier" (p. 70). These examples reveal the highly structured and always conditional way in which people prone to agoraphobia move through the world. Lacking the freedom and agency often taken for granted in bodily existence, the subject has a tendency to rely on a proximity to familiar objects (the home), a means of escape (the car), or a prop employed to forge a spatiality of his or her own (the cane). In each case, the inevitable failure to maintain this tightly woven yet precarious grip on control leads to anxiety. When anxiety emerges, then it does so in the form of what we are calling *bodily inhibition*, and with it a diminished SA.

THE BODILY-INHIBITION MODEL OF ANXIETY

In the notion of *bodily inhibition*, we include two components central to agoraphobic anxiety: A diminishment or disruption in SA and a partial disruption in SO. We maintain that each of these components leads to a broader destabilization in the integrity of selfhood. Moreover, there is evidently a circular relation between (i) anxiety causing a disruption in SA and SO, and (ii) further anxiety being provoked by the loss of SA.

In cases of agoraphobia, anxiety not only causes disruptions in SA and SO, but also exacerbates existing anxiety conditions. This is clear in at least two ways. First, the disruption in SA is related to a shift in bodily motricity. The agoraphobic person's hesitant or inhibited movement in the world often involves an adjoining awareness that anxious sensations and movements originate less from the agent as an integral and unified subject, and more from the body as an autonomous thing (which involves a modulation of SO). As a result, the subject experiences the onset of anxiety (and thus the inhibition of the body) as if coming from nowhere and without any apparent rationale, as Westphal reports on one case study: "He is absolutely unable to offer a specific reason for his feeling of anxiety; it is just there despite all reasoning" (p. 66). Westphal goes on to mention that in all cases "[the patients] absolutely do not know the reasons for this fear. It comes by itself; a sudden occurring, strange thing" (p. 73). The absence of reason explaining the behavior of the agoraphobic person has a critical outcome: She or he experiences the inhibition of movement as being caused by the body as a *thing* rather than as an agentive center of subjectivity. A pattern can be mapped accordingly: (i) sensations of anxiety are experienced as if deriving from nowhere, disrupting agentive self-identification; (ii) the resultant consequence is that patients experience the affected body as not entirely their own; (iii) finally, this partial (but never absolute) loss of SO entails a more generalized disturbance in selfhood.

In such cases, as a thing divorced from self-experience (lacking SO), the body is often presented as having a certain degree of autonomy. Such a body can only be "trusted" in certain situations, and it is for this reason that subjects who often speak of an anxiety over loss of control [as when they fear "becom(ing) crazed and, in panic, jump(ing) over the rail" to a drop below] often invoke the body as having autonomy from the self (Goldstein and Chambless, 1982, p. 131). The American composer and sufferer of agoraphobia Allen Shawn writes as follows of the experience of coming to a standstill when faced with an open space: "If you are very attuned to sensations in your legs, you will notice that they seem to have a mind of their own.... The flight impulse is felt keenly in the legs; it feels almost as if your very limbs were demanding that you run" (Shawn, 2008, p. 119). Here, we have a striking example of the concordance between a lack of bodily motricity (disruption in SA) and bodily objectification (disruption in SO), such that inhibition in movement results in an alienation from the body and the body's potential action. In cases of agoraphobic anxiety, it is not that *I* am the one running from danger, but rather it is *the* legs that are instructing *me* to run. In coming to standstill on a road exposed to wide fields, the legs present themselves as discernible "things" in the world, impeding the experience of the body as "one's own." In this case the SO for the legs and for the resulting action is disturbed. As bodily motricity ceases to be an *I can* and instead becomes an *I cannot*, so the body becomes partially distinct from the self.

The body that is inhibited by anxiety is a body that renders SO ambiguous. Whilst there is no doubt that it is I who am undergoing and enduring the experience of agoraphobic anxiety, there is nevertheless a parallel uncertainty as to what extent the body and its actions are irreducibly *mine*. In the case of Shawn's illustration, if the body as a whole remains constitutive of his sense of self, then the legs simultaneously contest this sense; neither entirely disowned nor owned; individual body parts instead assume an uncanny quality reflective of a broader disintegration of self during anxiety (Trigg, 2014).

ANXIETY, INTERSUBJECTIVITY, AND SENSE OF SELF

The phenomenological analysis of schizophrenic self-experience—the conception of *ipseity-disturbance* as central to the schizoid pathologies—is instructive in shedding light on disturbances in agoraphobic anxiety In effect, there are close parallels to be drawn between the *ipseity-disturbance* model of schizophrenia and what we are calling the *bodily-inhibition* model of anxiety. Both models involve a heightened self-reflexivity (hyperreflexivity), in which things that are normally taken-for-granted—not least the body's physiological processes—become focal points of attention. In cases of agoraphobic anxiety, this self-reflexivity can be framed as a constant vigilance toward unfamiliar bodily sensations (Trigg, 2016a).

For the sake of the present paper, we are focusing on similarities between schizophrenia and agoraphobic anxiety. Nevertheless, there are also clear qualitative differences between these models. One such difference concerns the temporal structure of these disorders. As understood from the *ipseity-disturbance* model, the difference between cases of schizophrenia and agoraphobic anxiety concerns the temporality involved in the diminishment of self-awareness. If schizophrenia involves the sustained diminishment of a "sense of basic self-presence, the implicit sense of existing as a vital and self-possessed subject of awareness" (Sass and Parnas, 2003, p. 428), in cases of agoraphobic anxiety, this diminishment in self-presence is momentary. The rhythm of agoraphobia is neither homogenous nor uniform, but instead punctuated by moments of bodily integrity, spatial coherence, and self-presence alongside moments of bodily disintegration, spatial incoherence, and self-alienation. Indeed, it is precisely for these reasons that the agoraphobic person divides space into safe/danger and familiar/unfamiliar regions. So long as dangerous and unfamiliar spaces can be avoided, the subject can function in a "normal" fashion.

The idea that the "normal" or healthy self is contemporary with the agoraphobic self is instructive. Of one patient, Westphal notes, "with the exception of (being unable to cross open spaces without anxiety), he likes to believe he is healthy" (Knapp, 1988, p. 63). Likewise, speaking of being in "secure surroundings," Shawn reflects on how he feels himself to be "normal": "I even pretend to myself that my 'personality' is somehow incompatible with agoraphobia.... Agoraphobia *is* at odds with the tone of some of what I do. I am not wary in every domain" (p. 119–120). Shawn's "normal" personality is the one able to assume the role of a performing pianist, able to face a "hostile audience," courageous enough to posit a "minority view" at a faculty meeting, and tolerant of "good and bad reviews" of his work (p. 120). Moreover, the "normal" articulation of selfhood is one that is able to circumnavigate the dense but familiar streets of Manhattan without the incursion of anxiety. This "normal" self, then, is precisely defined by a strong sense of being both the originator and controller of bodily movement (SA) coupled with a tacit sense that it is *I* who am undergoing that movement (SO). Agoraphobia is thus patently at odds with this self-presentation of agency and ownership given that the condition is marked by a self-alienation from the body (and thus the world) brought about by a doubt over who/what is inhibiting movement.

With this in mind, we can begin to see how the onset of agoraphobic symptoms marks a broader disturbance in bodily selfhood. If the spatiality of the world is cut up into different regions, then something similar in the index of temporality is true of the body. A person suffering from agoraphobia tends to treat their body as either *owned* when movement is experienced as deriving from the self, or otherwise partially *disowned* when movement feels as though it is inhibited or caused by the autonomy of the body itself.

Notably, the dissection of the body and the world into normal/anxious, owned/disowned, and safe/dangerous categories extends to intersubjectivity, too. Other people are present not as innocuous bystanders or incidental aspects within the world of the agoraphobia, but as constituents in a sense of self and contributors to a loss of self. In the case of the former, the role of the "trusted person" assumes a defining importance in the subject's ability to traverse space without anxiety. In the company of the trusted person, there is an increase in SA. Allen Shawn's ability to cross a wide-open space is assisted not simply by the presence of "safety items" (Xanax, ginger all, and a cell phone) but also by the presence of his companion, who "coaxes" him with the offer of a kiss as a "reward" (Shawn, 2008, p. 118). In the same way that the car, umbrella, and proximity to home serve as "escape routes," so the same is true of the trusted person who accompanies the agoraphobic person in their anxiety. Their presence signals a familiarity, constancy, and understanding lacking in an otherwise precarious experience of the world (Trigg, 2013a). Barlow describes a "safe person" in the following respect: "A safe person is commonly a significant other whose company enables the patient to feel more comfortable going places than he or she can be either alone or with other people. Usually, this person is considered "safe" because he or she knows about the panic attacks" (Barlow, 2002, p. 343). Having knowledge of the patient's panic attacks not only disarms the efficacy of the panic attack but also provides a legitimate context to manage anxiety should the subject be "incapacitated by panic" (p. 343). As a result, in the company of the trusted other, the agoraphobic person is able to maintain a stronger SA, and an intact SO, than if he or she were alone.

Other people do not always assuage the experience of anxiety; they can also amplify and reinforce an already existing anxiety and rob the subject of the SO (through a process of objectification) and thence of SA. Clinical research on the role of other people in the development of agoraphobic anxiety suggests that the gaze of other people is a significant factor in precipitating the onset of panic (cf. Davidson, 2002). Indeed, a heightened self-consciousness concerning how other people perceive the subject is consistent with the ongoing desire to maintain the self-presentation of being a "normal" and "healthy" individual both to oneself and to others (Vincent, 1919). In this respect, other people are a critical problem for agoraphobic people. Whereas, spatial routes and bodily habits can be controlled to some extent by developing a set of habitual patterns that render perceptual experience predictable, exerting control over how other people perceive us remains impossible. In this respect, the very centrality of the home as the safe place *par excellence* is predicated on its function as concealing the look of the other, as Joyce Davidson notes, "[s]ufferers' homes are frequently organized to minimize the fear of the look" (Davidson, 2003, p. 84). Unlike inanimate props such as cars and umbrellas, other people are not simply objects for our own use, but also perceive us as objects in the world (Sartre, 1998). As objectified by the look of the other, the attempt at maintaining a presentation of being "normal" for the subject proves contentious. Through the look of the other, the attempt at concealing anxiety through adhering to a ritualized and regulated life risks being detected, and in being detected, the very anxiety that the subject seeks to mask from the world in turn becomes an object of interrogation for the other person.

CONCLUSION

In this paper we have explicated the distinctions and connections between the prereflective experience and the reflective AA and ownership, within the context of anomalous bodily experiences in schizophrenia and agoraphobia. We've shown that these phenomena are more complex and ambiguous than usually thought, both in terms of their neuronal bases and in terms of their relations with extra-neural factors. We suggested that in cases of schizophrenic delusions of control, disruptions in SA at the level of first-order experience may lead to problems with the reflective attributions of both agency and ownership. Those who suffer from such delusions at times experience their thoughts, actions, and bodily movements as alien and controlled by another agent.

In the case of agoraphobia, disruptions in SA reveal the dynamic and relational structure of this condition. In terms of first-person experience, subjects with phobic anxiety tend to mistrust their own response to the world, feeling their bodies could give way at any point, thus positioning the locus of control outside of selfhood. In such cases, loss of SA leads to a partial loss of SO for body and bodily action. In the context of intersubjective relations, for people suffering from agoraphobia, the encroachment of other people into one's own space leads to anxiety, generating an experience of the body as both my own and not my own concurrently.

The underlying dynamics of these disorders with respect to SA and SO and how they fit into the pattern of self-experience and its disruption are different. It's clear, however, that in both disorders SA and SO cannot be considered in isolation from one another, but instead form an interdependent pairing.

We also hope to have shown the relevance of phenomenological accounts of schizophrenia and agoraphobia, and that purely causal-mechanistic explanations may not be able to capture everything of importance in these disorders. In focusing on disruptions in SA and SO, we have not said enough about the responses to the significantly alien character of the experiences. To such experiences there are at least two possible responses corresponding to the two conditions that we have discussed: (1) anxiety and a retreating reaction against the alien nature of the experience, generating temporally intermittent variations in experience, and in some cases the possibility of a reflective management; or (2) a response that continues and builds contact with the alien experience—a following along in which the subject is drawn into a more permanent delusional withdrawal of meaning even as he continues to try to make sense of it.

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All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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REFERENCES

Albahari, M. (2006). *Analytic Buddhism: The Two-tiered Illusion of Self*. New York, NY: Palgrave Macmillan.

Aslam, N. (2012). Management of panic anxiety with agoraphobia by using cognitive behavior therapy. *Indian J. Psychol. Med.* 34, 79–81. doi: 10.4103/0253-7176.96166

Barlow, D. (2002). *Anxiety and its Disorders*. New York, NY: Guilford Press.

Bayne, T., and Pacherie, E. (2004). Bottom-up or top-down: campbell's rationalist account of monothematic delusions. *Philos. Psychiatry Psychol.* 11, 1–11. doi: 10.1353/ppp.2004.0033

Bayne, T., and Pacherie, E. (2007). Narrators and comparators: the architecture of agentive self-awareness. *Synthese* 15, 475–491. doi: 10.1007/s11229-007-9239-9

Bermúdez, J. L. (2011). "Bodily awareness and self-consciousness," in *The Oxford Handbook of the Self,* ed S. Gallagher (Oxford: Oxford University Press), 157–179.

Billon, A. (2013). Does consciousness entail subjectivity? The puzzle of thought insertion. *Philos. Psychol.* 26, 291–314. doi: 10.1080/09515089.2011.625117

Billon, A., and Kriegel, U. (2014). "Jaspers' dilemma: the psychopathological challenge to subjectivity theories of consciousness," in *Disturbed Consciousness*, ed R. Gennaro (Cambridge, MA: MIT Press), 29–54.

Bortolotti, L., and Broome, M. (2009). A role for ownership and authorship in the analysis of thought insertion. *Phenomenol. Cogn. Sci.* 8, 205–224. doi: 10.1007/s11097-008-9109-z

Buhrmann, T., and Di Paolo, E. (2015). The sense of agency–a phenomenological consequence of enacting sensorimotor schemes. *Phenomenol. Cogn. Sci.* doi: 10.1007/s11097-015-9446-7. [Epub ahead of print].

Cahill, C., and Frith, C. (1996). "False perceptions or false beliefs? Hallucinations and delusions in schizophrenia," in *Method In Madness: Case Studies In Cognitive Neuropsychiatry*, eds P. W. Halligan and J. C. Marshall (Hove: Psychology Press), 267–291.

Campbell, J. (2002). The ownership of thoughts. *Philos. Psychol. Psychiatry* 9, 35–39. doi: 10.1353/ppp.2003.0001

Capps, L., and Ochs, E. (1997). *Constructing Panic: The Discourse of Agoraphobia*. Boston, MA: Harvard University Press.

Caspar, E. A., Christensen, J. F., Cleeremans, A., and Haggard, P. (2016). Coercion changes the sense of agency in the human brain. *Curr. Biol.* 26, 585–592. doi: 10.1016/j.cub.2015.12.067

Caspar, E. A., De Beir, A., Magalhaes De Saldanha Da Gama, P. A., Yernaux, F., Cleeremans, A., and Vanderborght, B. (2015). New frontiers in the rubber hand experiment: when a robotic hand becomes one's own. *Behav. Res. Methods* 47, 744–755. doi: 10.3758/s13428-014-0498-3

Christensen, J. F., Yoshie, M., Di Costa, S., and Haggard, P. (2016). Emotional valence, sense of agency and responsibility: a study using intentional binding. *Conscious. Cogn.* 43, 1–10. doi: 10.1016/j.concog.2016.02.016

Clark, D. M. (1988). "A cognitive model of panic attacks," in *Panic: Psychological Perspectives,* eds S. Rachman and J. D. Maser (Hillsdale, NJ: Erblaum), 71–90.

Daprati, E., Franck, N., Georgieff, N., Proust, J., Pacherie, E., Dalery, J., et al. (1997). Looking for the agent: an investigation into consciousness of action and self-consciousness in schizophrenic patients. *Cognition* 65, 71–86. doi: 10.1016/S0010-0277(97)00039-5

David, N., Newen, A., and Vogeley, K. (2008). The "sense of agency" and its underlying cognitive and neural mechanisms. *Conscious. Cogn.* 17, 523–534. doi: 10.1016/j.concog.2008.03.004

Davidson, J. (2002). 'Putting on a face': sartre, goffman, and agoraphobic anxiety in social space. *Environ. Planning D* 21, 107–122. doi: 10.1068/d45j

Davidson, J. (2003). *Phobic Geographies: The Phenomenology of Spatial Identity*. London: Ashgate Press.

Davies, M., Coltheart, M., Langdon, R., and Breen, N. (2001). Monothematic delusions: towards a two-factor account. *Philos. Psychiatry Psychol.* 8, 133–158. doi: 10.1353/ppp.2001.0007

de Vignemont, F. (2007). Habeas corpus: the sense of ownership of one's own body. *Mind Lang.* 22, 427–449. doi: 10.1111/j.1468-0017.2007.00315.x

de Vignemont, F. (2013). The mark of bodily ownership. *Analysis* 73, 643–651.

de Vignemont, F., and Fourneret, P. (2004). The sense of agency: a philosophical and empirical review of the "Who" system. *Conscious. Cogn.* 3, 1–19. doi: 10.1057/9780230800540

Edelman, R. E., and Chambless, D. L. (1993). Compliance during sessions and homework in exposure-based treatment of agoraphobia. *Behav. Res. Ther.* 31, 767–773. doi: 10.1016/0005-7967(93)90007-H

Ellis, H. D., and Young, A. W. (1990). Accounting for delusional misidentifications. *Br. J. Psychiatry* 157, 239–248. doi: 10.1192/bjp.157.2.239

Farrer, C., and Frith, C. D. (2002). Experiencing oneself vs. another person as being the cause of an action: the neural correlates of the experience of agency. *NeuroImage* 15, 596–603. doi: 10.1006/nimg.2001.1009

Friston, K. (2011). What is optimal about motor control? *Neuron* 72, 488–498. doi: 10.1016/j.neuron.2011.10.018

Frith, C. D. (1992). *The Cognitive Neuropsychology of Schizophrenia*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Frith, C. D., Blakemore, S., and Wolpert, D. (2000). Abnormalities in the awareness and control of action. *Philos. Trans. Roy. Soc. Lond.* 355, 1771–1788. doi: 10.1098/rstb.2000.0734

Gallagher, S. (1986). Lived body and environment. *Res. Phenomenol.* 16, 139–170. doi: 10.1163/156916486X00103

Gallagher, S. (2000a). Philosophical conceptions of the self: implications for cognitive science. *Trends Cogn. Sci.* 4, 14–21. doi: 10.1016/S1364-6613(99)01417-5

Gallagher, S. (2000b). "Self-reference and schizophrenia: a cognitive model of immunity to error through misidentification," in *Exploring the Self: Philosophical and Psychopathological Perspectives on Self-experience*, ed D. Zahavi (Amsterdam; Philadelphia, PA: John Benjamins), 203–239.

Gallagher, S. (2004). Neurocognitive models of schizophrenia: a neurophenomenological critique. *Psychopathology* 37, 8–19. doi: 10.1159/000077014

Gallagher, S. (2005). *How the Body Shapes the Mind*. Oxford: Oxford University Press.

Gallagher, S. (2007). Sense of agency and higher-order cognition: levels of explanation for schizophrenia. *Cogn. Semiotics* 0, 32–48.

Gallagher, S. (2011). "Time in action," in *Oxford Handbook on Time,* ed C. Callender (Oxford: Oxford University Press), 419–437.

Gallagher, S. (2012). Multiple aspects in the sense of agency. *N. Ideas Psychol.* 30, 15–31. doi: 10.1016/j.newideapsych.2010.03.003

Gallagher, S. (2014). The cruel and unusual phenomenology of solitary confinement. *Front. Psychol.* 5:585. doi: 10.3389/fpsyg.2014.00585

Gallagher, S. (2015). Relations between agency and ownership in the case of schizophrenic thought insertion. *Rev. Philos. Psychol.* 6, 865–879. doi: 10.1007/s13164-014-0222-3

Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., and Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. *Psychol. Med.* 31, 189–195. doi: 10.1017/S0033291701003312

Georgieff, N., and Jeannerod, M. (1998). Beyond consciousness of external events: a 'who' system for consciousness of action and self-consciousness. *Conscious. Cogn.* 7, 465–477. doi: 10.1006/ccog.1998.0367

Gloster, A. T., Hauke, C., Höfler, M., Einsle, F., Fydrich, T., Hamm, A., et al. (2013). Long-term stability of cognitive behavioral therapy effects for panic disorder with agoraphobia: a two-year follow-up study. *Behav. Res. Ther.* 51, 830–839. doi: 10.1016/j.brat.2013.09.009

Goldstein, A., and Chambless, D. (1982). *Agoraphobia: Multiple Perspectives on Theory and Treatment*. Chichester: Wiley and Sons.

Graham, G., and Stephens, G. L. (eds.). (1994). "Mind and mine," in *Philosophical Psychopathology*, (Cambridge, MA: MIT Press), 91–109.

Grünbaum, T. (2015). The feeling of agency hypothesis: a critique. *Synthese* 192, 3313–3337. doi: 10.1007/s11229-015-0704-6

Haggard, P. (2005). Conscious intention and motor cognition. *Trends Cogn. Sci.* 9, 290–95. doi: 10.1016/j.tics.2005.04.012

Haggard, P., and Tsakiris, M. (2009). The experience of agency feelings, judgments, and responsibility. *Curr. Dir. Psychol. Sci.* 18, 242–246. doi: 10.1111/j.1467-8721.2009.01644.x

Hahn, T., Kircher, T., Straube, B., Wittchen, H. U., Konrad, C., Ströhle, A., et al. (2015). Predicting treatment response to cognitive behavioral therapy in panic disorder with agoraphobia by integrating local neural information. *JAMA Psychiatry* 72, 68–74. doi: 10.1001/jamapsychiatry.2014.1741

Hohwy, J., and Rosenberg, R. (2005). Unusual experiences, reality testing and delusions of alien control. *Mind Lang.* 20, 141–162. doi: 10.1111/j.0268-1064.2005.00280.x

Jeannerod, M. (2009). The sense of agency and its disturbances in schizophrenia: a reappraisal. *Exp. Brain Res.* 192, 527–532. doi: 10.1007/s00221-008-1533-3

Knapp, T. (1988). *Westphal's "Die Agoraphobie" with Commentary: The Beginnings of Agoraphobia*. Lanham: University Press of America.

Langland-Hassan, P. (2008). Fractured phenomenologies: thought insertion, inner speech, and the puzzle of extraneity. *Mind Lang.* 23, 369–401. doi: 10.1111/j.1468-0017.2008.00348.x

Leder, D. (1990). *The Absent Body*. Chicago, IL; London: University of Chicago Press.

Legrand, D. (2007). Pre-reflective self-consciousness: on being bodily in the world. *Janus Head*. 9, 493–519. doi: 10.1016/j.concog.2007.04.002

Levinas, E. (2001). *Existence and Existents, Trans. A. Lingis*. Pittsburgh: Duquesne University Press.

Lueken, U., Straube, B., Konrad, C., Wittchen, H. U., Ströhle, A., Wittmann, A., et al. (2013). Neural substrates of treatment response to cognitive-behavioral therapy in panic disorder with agoraphobia. *Am. J. Psychiatry* 170, 1345–1355. doi: 10.1176/appi.ajp.2013.12111484

Marks, I. (1987). *Fears, Phobias, and Rituals: Panic, Anxiety, and their Disorders*. Oxford: Oxford University Press.

Martin, R., and Dahlen, E. (2005). Cognitive emotion regulation in the prediction of depression, anxiety, stress, and anger. *Pers. Indiv. Dif.* 39, 1249–1260. doi: 10.1016/j.paid.2005.06.004

Merleau-Ponty, M. (1964). *Sense and Non-sense*. Evanston, IL: Northwestern University Press.

Merleau-Ponty, M. (1965). *The Structure of Behavior. Trans. Alden Fisher*. Boston, MA: Beacon Press.

Merleau-Ponty, M. (2012). *Phenomenology of Perception. Trans. Donald Landes.* New York, NY; London: Routledge.

Meyer, V., and Gelder, M. G. (1963). Behaviour therapy and phobic disorders. *Br. J. Psychiatry* 109, 19–28. doi: 10.1192/bjp.109.458.19

Mundale, J., and Gallagher, S. (2009). "Delusional experience," in *Oxford Handbook of Philosophy and Neuroscience*, ed J. Bickle (Oxford: Oxford University Press), 513–521.

Pacherie, E. (2006). "Towards a dynamic theory of intentions," in *Does Consciousness Cause Behavior? An Investigation of the Nature of Volition*, eds S. Pockett, W. P. Banks, and S. Gallagher (Cambridge, MA: MIT Press), 145–167.

Pacherie, E. (2008). The phenomenology of action: a conceptual framework. *Cognition* 107, 179–217. doi: 10.1016/j.cognition.2007.09.003

Pacherie, E., Green, M., and Bayne, T. (2006). Phenomenology and delusions: who put the 'alien' in alien control? *Conscious. Cogn.* 15, 566–577. doi: 10.1016/j.concog.2005.11.008

Park, S., and Nasrallah, H. (2014). The varieties of anomalous self experiences in schizophrenia: splitting of the mind at a crossroad. *Schizophr. Res.* 152, 1–4. doi: 10.1016/j.schres.2013.11.036

Parnas, J., and Sass, L. (2011). "The structure of self-consciousness in schizophrenia," in *The Oxford Handbook of the Self*, ed S. Gallagher (Oxford: Oxford University Press), 521–546.

Sartre, J. P. (1998). *Being and Nothingness. Trans. Hazel Barnes*. London; New York, NY: Routledge.

Sass, L. (2014). Self-disturbance and schizophrenia: structure, specificity, pathogenesis. *Schizophr. Res.* 152, 5–11. doi: 10.1016/j.schres.2013.05.017

Sass, L., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr. Bull.* 29, 427–444. doi: 10.1093/oxfordjournals.schbul.a007017

Shawn, A. (2008). *Wish I Could Be There: Notes from a Phobic Life*. New York, NY: Penguin.

Sierra, M. (2009). *Depersonalization: A New Look at a Neglected Syndrome*. Cambridge: Cambridge University Press.

Singh, J. R., Knight, T., Rosenlicht, N., Kotun, J. M., Beckley, D. J., and Woods, D. L. (1992). Abnormal premovement brain potentials in schizophrenia. *Schizophr. Res.* 8, 31–41. doi: 10.1016/0920-9964(92)90058-D

Stephens, G. L., and Graham, G. (2000). *When Self-Consciousness Breaks: Alien Voices and Inserted Thoughts*. Cambridge MA: MIT Press.

Synofzik, M., Vosgerau, G., and Newen, A. (2008). Beyond the comparator model: a multifactorial two-step account of agency. *Conscious. Cogn.* 17, 219–239. doi: 10.1016/j.concog.2007.03.010

Trigg, D. (2013a). The body of the other: intercorporeality and the phenomenology of agoraphobia. *Cont. Philos. Rev.* 46, 413–429. doi: 10.1007/s11007-013-9270-0

Trigg, D. (2013b). "Bodily moods and unhomely environments: the hermeneutics of agoraphobia," in *Interpreting Nature: The Emerging Field of Environmental Hermeneutics*, eds F. Clingerman, B. Treanor, M. Drenthen, and D. Ulster (New York, NY: Fordham University Press), 160–177.

Trigg, D. (2014). *The Thing: a Phenomenology of Horror*. Washington, DC: Zero Books.

Trigg, D. (2016a). *Topophobia: a Phenomenology of Anxiety*. London: Bloomsbury.

Trigg, D. (in press). "Agoraphobia, Sartre, and the Spatiality of the Other's Look," in *Body/Self/Other: Phenomenology of Social Encounters*. eds L. Dolezal and D. Petherbridge (New York, NY: SUNY).

Tsakiris, M., Bosbach, S., and Gallagher, S. (2007). On agency and body-ownership: phenomenological and neuroscientific reflections. *Conscious. Cogn.* 16, 645–660. doi: 10.1016/j.concog.2007.05.012

Tsakiris, M., and Haggard, P. (2005). Experimenting with the acting self. *Cogn. Neuropsychol.* 22, 387–407. doi: 10.1080/02643290442000158

Tsakiris, M., Longo, M. R., and Haggard, P. (2010). Having a body versus moving your body: neural signatures of agency and body-ownership. *Neuropsychologia* 48, 2740–2749. doi: 10.1016/j.neuropsychologia.2010.05.021

Vincent (1919). Confessions of an agoraphobic victim. *Am. J. Psychol.* 30, 295–299.

Vinding, M. C., Pedersen, M. N., and Overgaard, M. (2013). Unravelling intention: distal intentions increase the subjective sense of agency. *Conscious. Cogn.* 22, 810–815. doi: 10.1016/j.concog.2013.05.003

Vogeley, K., Kurthen, M., Falkai, P., and Maier, W. (1999). Essential functions of the human self model are implemented in the prefrontal cortex. *Conscious. Cogn.* 8(3), 343–363. doi: 10.1006/ccog.1999.0394

Wittmann, A., Schlagenhauf, F., Guhn, A., Lueken, U., Gaehlsdorf, C., Stoy, M., et al. (2014). Anticipating agoraphobic situations: the neural correlates of panic disorder with agoraphobia. *Psychol. Med.* 44, 2385–2396. doi: 10.1017/S0033291713003085

Wittmann, A., Schlagenhauf, F., John, T., Guhn, A., Rehbein, H., Siegmund, A., et al. (2011). A new paradigm (Westphal-Paradigm) to study the neural correlates of panic disorder with agoraphobia. *Eur. Arch. Psychiatry Clin. Neurosci.* 261, 185–194. doi: 10.1007/s00406-010-0167-1

Wolpert, D. M., and Flanagan, J. R. (2001). Motor prediction. *Curr. Biol.* 11, R729–R732. doi: 10.1016/S0960-9822(01)00432-8

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The Association between Anomalous Self-experiences, Self-esteem and Depressive Symptoms in First Episode Schizophrenia

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Background: Anomalous self-experiences (ASEs) aggregate in schizophrenia spectrum disorders, but the relationship between ASEs, and depression has been studied to a limited extent. Lower self-esteem has been shown to be associated with depression in early psychosis. Our hypothesis is that ASEs in early phases of schizophrenia are linked to lower levels of self-esteem, which in turn is associated with depression.

Aim: The aim is to examine the relationship between ASEs, self-esteem and depression in first-episode schizophrenia spectrum disorders.

Method: ASEs were assessed in 55 patients with first-episode schizophrenia by means of the Examination of anomalous Self-Experience (EASE) instrument. Assessment of depression was based on the Calgary Depression Scale for Schizophrenia (CDSS). Self-esteem was measured using the Rosenberg Self-Esteem Scale (RSES). Symptom severity was assessed using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS). Substance misuse was measured with the Drug Use Disorder Identification Test (DUDIT), and alcohol use was measured with the Alcohol Use Disorder Identification Test (AUDIT). Data on childhood adjustment were collected using the Premorbid Adjustment Scale (PAS). Data on childhood trauma were collected using the Norwegian version of the Childhood Trauma Questionnaire, short form (CTQ-SF).

Results: Analyses detected a significant association between current depression and ASEs as measured by the EASE in women, but not in men. The effect of ASEs on depression appeared to be mediated by self-esteem. No other characteristics associated with depression influenced the relationship between depression, self-esteem and ASEs.

Conclusion: Evaluating ASEs can assist clinicians in understanding patients' experience of self-esteem and depressive symptoms. The complex interaction between ASEs, self-esteem, depression and suicidality could be a clinical target for the prevention of suicidality in this patient group.

Keywords: schizophrenia, anomalous self-experiences, depression, self-esteem, first episode psychosis, childhood trauma, gender differences

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INTRODUCTION

Schizophrenia and Anomalous Self-experience

Studies show that anomalous self-experiences (ASEs) aggregate in schizophrenia spectrum disorders (Haug et al., 2012a; Nelson et al., 2013; Nordgaard and Parnas, 2014), and precede their onset (Parnas et al., 1998; Møller and Husby, 2000; Nelson et al., 2012). The sense of self (identity feeling) can be described on three hierarchical but interconnected levels: the narrative, the reflective, and the prereflective identity level (Sass and Parnas, 2003). The narrative- or social self refers to certain explicit characteristics, like personality traits and the overt narratives of the person; whereas the reflective self is the awareness of a stable "I" over time and situations. The prereflective self is the most basic level of self-awareness, implicit, preverbal, and inseparable from subjective experience *per se*. This prereflective self-awareness, also described as the basic self, is a necessary basis for the other two levels.

ASEs are subtle disturbances of the prereflective self, affecting the person's deepest sense of being, the experience of him- or herself as a vital subject, naturally immersed in the world, and the sense of continuity and coherence in self-experience (Sass and Parnas, 2003). ASEs include certain and subtle forms of depersonalization, anomalous experiences of cognition and stream of consciousness, self-alienation, pervasive difficulties in grasping familiar and taken-for-granted meanings, unusual bodily feelings and existential reorientation (Parnas et al., 2005). In schizophrenia, ASEs are believed to underpin and generate several symptom dimensions such as positive, negative, and disorganized psychotic symptoms (Sass and Parnas, 2003). An earlier study also found a link between ASEs and suicidality among patients with schizophrenia (Skodlar and Parnas, 2010), and we have in previous reports from the current study also shown that ASEs are linked to suicidality (Haug et al., 2012b) in addition to a longer duration of untreated psychosis (DUP) (Haug et al., 2015b), social dysfunction (Haug et al., 2014) and childhood trauma, the latter however only in women (Haug et al., 2015a). We have here observed an association between ASEs and depressive symptoms (Haug et al., 2012b, 2015a).

Schizophrenia and Depressive Symptoms

Depressive symptoms are common in patients with schizophrenia spectrum disorders (Birchwood et al., 2000) and is particularly prevalent in first episode psychosis (Romm et al., 2010). There are several possible pathways to depressive symptoms in schizophrenia (Birchwood, 2003; Skodlar, 2009). The first possibility is that depressive and psychotic symptoms are parts of two different disorders that co-occur due to overlapping risk factors (such as social difficulties and childhood maltreatment). Another possibility is that it is a psychological reaction to the psychosis, either through its implications for social status (Birchwood, 2003) or as a reaction to the experience of psychological deficits (Liddle et al., 1993). Difficult childhood experiences, such as childhood loss and social marginalization could also contribute to a cognitive vulnerability that is accompanied by a negative view of the person him/herself and toward others (Greenberg et al., 1992; Garety et al., 2001; Birchwood, 2003). Finally, it could be a core dimension of the psychosis in line with negative symptoms (Upthegrove et al., 2016)

Anomalous Self-experience and Depressive Symptoms

The relationship between disturbances in basic self-awareness, i.e., ASEs, and depressive symptoms has been studied to a limited extent. Yon and colleagues found that subjective experience, measured by the Frankfurt Complaint Questionnaire, was separate and distinct from the objective symptomatology in schizophrenia (Yon et al., 2005). Another study found that depressed patients with schizophrenia showed significantly higher levels of basic symptoms as measured by Bonn Scale for the Assessment of Basic Symptoms, a concept related to ASEs (Maggini and Raballo, 2006). The aim of the current study is to explore this association in more detail. Skodlar suggested that feelings of inferiority could serve as link between ASEs and suicidality; i.e., a version of the reaction hypothesis. In line with this, we chose to examine if self-esteem mediated the association between ASEs and depressive symptoms.

Broadening the Scope with Self-esteem

Self-esteem was introduced in this study to shed a broader light on this symptom complex. Self-esteem reflects a person's overall subjective emotional evaluation of his or her own worth and is the positive or negative evaluations of the self, while the self-concept is what we think about the self (Smith and Mackie, 2007). Maslow included positive self-esteem in his hierarchy of human needs. He described two variants of "esteem": the need for respect from others, and the need for self-respect (Maslow, 1987). People need both these forms of "esteem" to grow as a person and achieve self-actualization (Maslow, 1987). There are different factors that can influence self-esteem. Self-esteem is usually regarded as an enduring personality characteristic. Genetic factors that help shape overall personality can play a role, but it is often our life experiences that form the basis of overall self-esteem. Models of global self-esteem suggest that it is both a trait and a state measure (Crocker and Wolfe, 2001). Rosenberg made distinctions between *baseline* instability, i.e., long- term fluctuations in self-esteem that gradually changes over a longer period of time, and *barometric* instability, which reflects the short term fluctuations in ones contextually based global self-esteem (Rosenberg, 1986). It is the person's interpretation of the event or circumstance, and its relevance to his or her contingencies of self-worth, that determines both if and how strongly it will affect state self-esteem (McFarl and Ross, 1982; Crocker and Wolfe, 2001).

Lower self-esteem has repeatedly been shown to be associated with depressive symptoms, also in patients with early psychosis (Karatzias et al., 2007) where it is viewed as both a possible cause—and a possible consequence of psychotic symptoms (Karatzias et al., 2007; Romm et al., 2011). The two concepts of self-esteem and self-disturbances are based in very different theoretical frameworks. Self-esteem can however be seen as related to the narrative- or social level of selfhood.

Our hypothesis for the current study is thus that ASEs in early phases of schizophrenia are linked to poor self-esteem, which in turn is associated with depressive symptoms. The inclusion of self-esteem may contribute to more knowledge about the phenomenology of depressive symptoms in schizophrenia, and may thus have implications for therapeutic approaches to a condition that is accompanied with considerable suffering and risk of suicide.

In previous studies men have been showing lower levels of depression and higher levels of self-esteem than women (Thorup et al., 2007; Romm et al., 2011), and in previous reports from the current study we have shown that ASEs are linked childhood trauma only in women (Haug et al., 2015a). Thus, there is a possibility of real gender difference in this area.

MATERIALS AND METHODS

Design and Sample

The current study is part of the Norwegian Thematically Organized Psychosis (TOP) study (Romm et al., 2010). Inclusion criteria were age 18–65 years, and being consecutive in- or outpatient referred to first adequate treatment for a psychotic disorder that is a DSM-IV diagnosis of schizophrenia (schizophrenia, schizophreniform disorder, and schizoaffective disorder). Exclusion criteria were the presence of brain injury, neurodegenerative disorder, or mental retardation. The patients were required not be so overtly psychotic that they had problems participating in a lengthy interview. Patients with concurrent substance use disorders were not excluded, but had to demonstrate at least 1 month without substance use, or clear signs that the psychotic disorder had started before the onset of significant substance use (i.e., did not meet the criteria for substance induced psychotic disorder). The sample includes all consecutively identified first episode patients from all treatment facilities in two Norwegian counties (Hedmark and Oppland) with a county-wide population of 375,000 people. During 2008 and 2009 a total of 44 patients with schizophrenia spectrum disorders were coming to their first adequate treatment (i.e., not having previously received adequate antipsychotic medication in adequate doses for 12 weeks, or until remission); some had not initiated treatment at first evaluation. To enhance statistical power we additionally included 11 patients enrolled in a related study of young patients with psychosis born in 1985/86 (Bratlien et al., 2014, 2015). They were in the early phases of treatment, with an even shorter DUP than the strict first treatment patients, and met the same inclusion and exclusion criteria, except for the strict definition of first treatment.

All participants gave written, informed consent to participate in accordance with the Declaration of Helsinki. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Clinical Assessments

Diagnoses were ascertained by two researchers who were also experienced psychiatrists (EH and UB) using the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (SCID-IV) (Amercan Psychiatric Association, 1994).

ASEs were assessed using the Examination of Anomalous Self-Experience (EASE) manual (Parnas et al., 2005), a 30–90 min interview comprising five domains: (1) Cognition and stream of consciousness. (2) Self-awareness and presence. (3) Bodily experiences. (4) Demarcation/transitivism. (5) Existential reorientation. This represents a wide variety of ASEs condensed into 57 main items and scored on a 5-point Likert scale (0–4), in which 0 = absent; 1 = questionably present; 2 = definitely present, mild; 3 = definitely present, moderate; 4 = definitely present, severe. For the purpose of the analyses, the resulting scores were dichotomized into 0 (absent or questionably present) and 1 (definitely present, all severity levels). ASEs are not considered to be discrete symptoms but rather interconnected aspects of a full gestalt. There are thus considerable overlap between single items and domains, and both items and domains are statistically highly inter-correlated. We have thus used the total EASE score in the analyses. The questions about ASEs in the EASE are not focused on a specific time period but capture life-time experiences of ASEs. EH was trained by one of the main authors of the EASE (PM) and conducted all the interviews. The inter-rater reliability (IRR) of the EASE, including in the current study, has been found to be very good (Møller et al., 2011; Nelson et al., 2012; Raballo and Parnas, 2012).

Assessment of depressive symptoms was based on the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). Self-esteem was measured using the Rosenberg Self-Esteem Scale (RSES) (Rosenberg, 1965). This is a 10 item self-administered questionnaire with a 4-point Likert-type response set, ranging from strongly disagree to strongly agree on statements about their self-esteem and self-deprecation. RSES is validated and used in several studies with psychotic patients (Torrey et al., 2000). Symptom severity was assessed using the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) (Kay et al., 1987). We have in our analyses used the Wallwork/Fortgang five-factor model for PANSS (Wallwork et al., 2012), which is recommended for describing symptoms in patients with first episode psychosis. Insight was assessed by PANSS item G 12 (insight). G12 is a global measure of insight used in many studies of psychotic patients. Substance misuse was measured with the Drug Use Disorder Identification Test (DUDIT) (Berman et al., 2007), and alcohol use was measured with the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993). Data on childhood adjustment were collected using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Data on childhood trauma were collected using the Norwegian version of the Childhood Trauma Questionnaire, short form (CTQ-SF) (Bernstein et al., 2003). This is a 28-item self-report inventory, developed and validated based on the original 70-item version (Bernstein et al., 1997), that provides a relatively short screening of maltreatment experiences before the age of 18. It comprises 28 items, yielding scores on five subscales of trauma: physical abuse, sexual abuse, emotional abuse, emotional neglect, and physical neglect.

Both researchers involved in the clinical assessments (EH and UB) completed the TOP study group's training and reliability program with SCID training based on- and supervised by the UCLA training program (Ventura et al., 1998). For DSM-IV diagnostics, mean overall kappa for the standard diagnosis of training videos for the study as a whole was 0.77, and mean overall kappa for a randomly drawn subset of study patients was also 0.77 (95% CI 0.60–0.94). Intra Class Coefficients (ICC 1.1) for the other scales were: PANSS positive subscale 0.82 (95% CI 0.66–0.94), PANSS negative subscale 0.76 (95% CI 0.58–0.93), and PANSS general subscale 0.73 (95% CI 0.54–0.90).

Statistical Analysis

All analyses were performed with the statistical package SPSS, version 21.0 (SPSS, Chicago, IL). Mean and standard deviations are reported for continuous variables and percentages for categorical variables. Since DUP had a markedly skewed distribution, median, and range values are reported and a transformation into its natural logarithm was used in parametric analyses. We first examined bivariate associations between depressive symptoms, ASEs and self-esteem, respectively using Pearson correlations, and then the association between depressive symptoms and ASEs after controlling for levels of self-esteem, using multiple linear regression analysis. We used the Sobel test to evaluate mediation. We then went on to examine possible confounders of these associations using a series of multiple linear regression analyses, correcting for patient characteristics associated with depressive symptoms one at a time (since the sample size did not allow for more than four to five variables in the equation). There were no interaction effects.

TABLE 1 | Demographic and clinical characteristics.

Number of patients	55
DEMOGRAPHICS	
Male gender, n (%)	28 (51)
Age years, mean (SD)	25.2 (7.3)
DUP[a] weeks, median (range)	122 (2–1560)
PREMOBID ADJUSTMENT[b]	
Childhood, mean (SD)	0.3 (0.2)
Early adulthood, mean (SD)	0.4 (0.2)
SUBSTANCE USE	
Alchohol[c], mean (SD)	9.1 (8.8)
Drugs[d], mean (SD)	2.9 (7.8)
SYMPTOMS	
Depressive symptoms[e], mean (SD)	9.1 (6.0)
ASEs[f], mean (SD)	25.5 (9.7)
Self-esteem[g], mean (SD)	21.4 (6.2)
PANSS[h]	
Positive symptoms, mean (SD)	13.9 (5.6)
Negative symptoms, mean (SD)	14.1 (6.7)
Disorganization symptoms, mean (SD)	6.6 (3.2)
Depressive symptoms, mean (SD)	9.7 (3.3)
Excitement symptoms, mean (SD)	6.4 (2.1)
Childhood trauma[i], mean (SD)	47.2 (18.8)

[a] *Duration of Untreated Psychosis.*
[b] *PAS (Premorbid Adjustment Scale).*
[c] *AUDIT (Alcohol Use Disorder Identification Test) total score.*
[d] *DUDIT (Drug Use Disorder Identification Test) total score.*
[e] *CDSS (Calgary Depression Scale for Schizophrenia) total score.*
[f] *EASE (Examination of Anomalous Self-Experience) total score.*
[g] *RSES (Rosenberg Self-Esteem Scale) total score.*
[h] *Wallwork/Fortgang five-factor model for PANSS (Positive and Negative Syndrome Scale).*
[i] *CTQ (Childhood Trauma Questionnaire) total score.*

RESULTS

Table 1 presents the sociodemografic and clinical features of the sample. The mean EASE total score was 25.5, which is at the same level as other studies of ASEs in schizophrenia. The mean CDSS score was 9.1, indicating high levels of depressive symptoms. We found a statistically significant positive association between ASEs (EASE total score) and depressive symptoms ($r = 0.356$ $p = 0.008$) and a negative association with self-esteem ($r = -0.361$ $p = 0.007$), indicating that high levels of ASEs were associated with high levels of depressive symptoms and low self-esteem. EASE domain 1, 3, and 4 were significantly correlated with depressive symptoms, while EASE domain 1, 2, and 3, were significantly correlated with self-esteem (data not shown). The main analyses of the current paper focus on the EASE total score. As expected, we also found a strong and significant negative association between depressive symptoms and self-esteem ($r = -0.761$, $p < 0.0001$). In a multiple linear regression analysis the effect of ASEs on depressive symptoms was no longer significant after correcting for levels of self-esteem, indicative of a mediation effect (**Table 2**). This was supported by a significant positive Sobel test ($p = 0.01$).

We then examined the association to other variables with a putative effect on depressive symptoms. We found a statistically significant association between depressive symptoms and childhood trauma, the PANSS negative- and disorganized sub scales, drug use and female gender; but not with other PANSS sub scales, insight, DUP, premorbid adjustment or alcohol use (**Table 3**). In the ensuing multiple linear regression analysis, we explored if the characteristics associated with depressive symptoms influenced the relationship between depressive symptoms, self-esteem and ASEs. Of these variables the scores on the PANSS negative- and disorganized sub scales and the childhood trauma had an independent effect on depressive symptoms when entered in the multiple linear regression analyses; but without influencing the relationship between depressive symptoms, self-esteem and ASEs.

Investigating males and females separately we found a strong and significant negative association between depressive symptoms and self-esteem in both men and women (data not shown). Further we found that women had more depressive symptoms and lower levels of self-esteem than men, with a highly statistically significant association between ASEs, self-esteem ($r = -0.481$, $p = 0.011$) and depressive symptoms ($r = 0.488$, $p = 0.010$) in women, but not in men. In a multiple linear regression analysis the effect of ASEs on depressive symptoms in women was no longer significant after correcting for levels of self-esteem, indicative of a mediation effect (**Table 4**). This was supported by a significant positive Sobel test ($p = 0.01$). We then examined the association to

TABLE 2 | Hierarchical regression analysis with depressive symptoms as the dependent variable and ASEs and self-esteem as independent variables, demonstrating mediating effects of self-esteem.

Dependent variable: Depressive symptoms[a]	B	p	95% CI
ASEs[b]	0.356*	0.008	0.060 to 0.377
Dependent variable: Depressive symptoms[a]	**B**	***p***	**95% CI**
Self-esteem[c]	−0.761**	< 0.001	−0.896 to −0.555
Dependent variable: Depressive symptoms[a]	**B**	***p***	**95% CI**
Self-esteem[c]	−0.727**	< 0.001	−0.876 to −0.510
ASEs[b]	0.093	0.337	−0.061 to 0.175

[a] *CDSS (Calgary Depression Scale for Schizophrenia) total score.*
[b] *EASE (Examination of Anomalous Self-Experiences) total score.*
[c] *RSES (Rosenberg Self-Esteem Scale) total score.*
* *Correlation is significant at the 0.05 level (2-tailed).*
** *Correlation is significant at the 0.001 level (2-tailed).*

TABLE 3 | Correlations.

	Depressive symptoms[a]
Gender	
Pearson correlation	0.333*
Sig. (2-tailed)	0.013
Duration of untreated psychosis[b]	
Pearson correlation	0.102
Sig. (2-tailed)	0.460
Premorbid adjustment[c]	
Childhood	
Pearson correlation	0.128
Sig. (2-tailed)	0.350
Early adulthood	
Pearson correlation	−0.054
Sig. (2-tailed)	0.69
Alcohol use[d]	
Pearson correlation	0.105
Sig. (2-tailed)	0.447
Drug use[e]	
Pearson correlation	0.286*
Sig. (2-tailed)	0.034
PANSS[f]	
Positive symptoms	
Pearson correlation	0.168
Sig. (2-tailed)	0.219
Negative symptoms	
Pearson correlation	−0.289*
Sig. (2-tailed)	0.032
Disorganization symptoms	
Pearson correlation	−0.343*
Sig. (2-tailed)	0.010
Depressive symptoms	
Pearson correlation	0.634**
Sig. (2-tailed)	0.000
Excitement symptoms	
Pearson correlation	0.102
Sig. (2-tailed)	0.459
Insight[g]	
Pearson correlation	−0.154
Sig. (2-tailed)	0.262
Childhood trauma[h]	
Pearson correlation	0.568**
Sig. (2-tailed)	< 0.001

[a] *CDSS (Calgary Depression Scale for Schizophrenia) total score.*
[b] *Ln DUP.*
[c] *PAS (Premorbid Adjustment Scale).*
[d] *AUDIT (Alcohol Use Disorder Identification Test) total score.*
[e] *DUDIT (Drug Use Disorder Identification Test) total score[f] Wallwork/Fortgang five-factor model for PANSS (Positive and Negative Symptom Scale).*
[f] *Wallwork/Fortgang five-factor model for PANSS (Positive and Negative Syndrome Scale).*
[g] *PANSS item g12.*
[h] *CTQ (Childhood Trauma Questionnaire) total score.*
* *Correlation is significant at the 0.05 level (2-tailed).*
** *Correlation is significant at the 0.001 level (2-tailed).*

other variables with a putative effect on depressive symptoms in women. We found a statistically significant association between depressive symptoms and childhood trauma, the PANSS negative- and disorganized sub scales, DUP, and premorbid childhood adjustment (data not shown). Of these variables only the scores on the childhood trauma score had an independent effect on depressive symptoms when entered in the multiple linear regression analyses; but without influencing the relationship between depressive symptoms, self-esteem and ASEs.

DISCUSSION

Our main finding in the present study is that the association between ASEs and depressive symptoms in women appears to be mediated by self-esteem. We have previously reported an association between ASEs and depressive symptoms (Haug et al., 2012b). This is in line with an earlier study that found that depressed patients showed significantly higher levels of basic symptoms measured by BSABS (Gross et al., 1987) a construct that is related to ASEs (Maggini and Raballo, 2006). As far as we know, our current study is the first study on the association between ASEs and self-esteem. These results are however in line with the hypothesis presented by Skodlar and associates (Skodlar et al., 2008; Skodlar and Parnas, 2010), where the authors suggested that the effect of ASEs on depressive symptoms and suicidality was mediated by specific feelings of inferiority that could be an aspect of low self-esteem. ASEs also include disturbances of the basic self, to the extreme extent that the person feels as if not existing or not being human. These are obviously experiences that accelerate the feeling of worthlessness. It is also in line with observations from Liddle and colleagues, that experience of psychological deficits in schizophrenia was associated with depression (Liddle et al., 1993), where ASEs in this context could be experienced as- or resemble psychological deficits. The results thus primarily support the hypothesis that depression is a reaction to the psychotic illness. The independent effect of childhood trauma also supports the notion of common predictors to depression and to psychosis.

TABLE 4 | Women: Hierarchical regression analysis with depressive symptoms as the dependent variable and ASEs and self-esteem as independent variables, demonstrating mediating effects of self-esteem in women.

Dependent variable: Depressive symptoms[a]	*B*	*p*	95% CI
ASEs[b]	0.327*	0.010	0.086 to 0.569
Dependent variable: Depressive symptoms[a]	***B***	***p***	**95% CI**
Self-esteem[c]	−0.790**	< 0.001	−1.035 to −0.544
Dependent variable: Depressive symptoms[a]	***B***	***p***	**95% CI**
Self-esteem[c]	−0.725**	< 0.001	−1.006 to −0.444
ASEs[b]	0.091	0.334	−0.099 to 0.281

[a] CDSS (Calgary Depression Scale for Schizophrenia) total score.
[b] EASE (Examination of Anomalous Self-Experiences) total score.
[c] RSES (Rosenberg Self-Esteem Scale) total score.
** Correlation is significant at the 0.05 level (2-tailed).*
*** Correlation is significant at the 0.001 level (2-tailed).*

The current study is cross-sectional and can thus not say anything directly about the direction of association. However, the ASEs are subtle and relatively stable disturbances of the most basic level of self-awareness, depressive symptoms are more fluid and state-like phenomena while self-esteem can be viewed as both a trait and a state phenomenon (Crocker and Wolfe, 2001). Our interpretation of the findings is thus that ASEs contribute to lower self-esteem, which in turn increases the risk of depressive symptoms.

The association between ASEs, self-esteem and depression appeared to be carried by the female part of the sample. Men showed lower levels of depression and higher levels of self-esteem than women in line with previous studies (Thorup et al., 2007; Romm et al., 2011), while the direction of associations were the same for both genders with no interaction effects. We thus interpret the differences in statistically significant associations as mainly based in lower statistical power in the male part of the sample. The possibility of real gender differences in this area should however be kept in mind and included in further investigations.

In addition to high levels of depressive symptoms, the current sample was also characterized by a long median DUP. Long DUP has previously been shown to be associated with depressive symptoms (Marshall et al., 2005). However, in the current study we did find significant correlations between DUP and depressive symptoms only in women, but it does not appear as if the association between ASEs and depressive symptoms was mediated by DUP. The presence of childhood trauma was associated with both ASEs and depressive symptoms, but did not appear to mediate the relationship.

The current findings suggest that evaluating ASEs can assist clinicians in understanding patients' experience of self-esteem and depressive symptoms. The ASE perspective has turned out to be fruitful in clinical settings, and for therapeutic interventions; as it gives an experience of comprehension and meaning back to the patients by making bizarre experiences subjectively understandable and thus possible to communicate to others. Suicidality is a major complication in the early phases of schizophrenia and is associated with both ASEs and depressive symptoms (Haug et al., 2012b). Thus, the complex interaction between ASEs, self-esteem, depressive symptoms, and suicidality could be a clinical target for the prevention of suicidality in this patient group.

More knowledge about this may also have implications for other treatment approaches, including CBT schema therapy targeting depressive symptoms. Birchwood postulated that childhood trauma and psychosis-like experiences in early adolescence, ASEs associated phenomena, may contribute to cognitive schemas characterized by negative self-evaluation that predispose to depressive symptoms as a reaction to psychosis (Birchwood, 2003). This is in line with our previously reported association between childhood trauma and ASEs in women (Haug et al., 2015a). The current findings however indicate that childhood trauma also influence depressive symptoms through other pathways than ASEs and self-esteem.

Strengths

We included patients in the early phase of the treated course of the disorder, thereby minimizing potential confounding effects such as selection of non-responders and chronicity that might impact on the assessment of ASEs, self-esteem, and depressive symptoms. The Norwegian mental health care offers public mental health care to all individuals with mental illness within a given catchment area. Because of the next-to absence of private mental health care in Norway, the sample is not biased for socioeconomic class. The study included all consecutive in- or outpatients referred to treatment for a psychotic disorder in two neighboring Norwegian counties in a defined time period, and the participants are thus highly representative of the patient group.

Limitations

The correlational nature of this study gives neither firm conclusions about the direction of associations, nor about causality. High levels of ASEs and low levels of self-esteem could also be influenced by recall bias among patients with high levels of depressive symptoms. Previous studies of the temporal relationship between these factors however indicate that the subjective experience of psychological deficits in schizophrenia patients with depressive episodes is high, even when they are not depressed (Liddle et al., 1993). The size of the study sample imposes limits on statistical approaches to study complex interactions. To combine data intended to tap different levels of the self/ (self-esteem and self-disturbance) raises conceptual dilemmas. Self-esteem is mainly conceived as a fully conscious social/narrative level, whereas self-disturbance in the present context refers to a pre-reflective, pre-conscious level. While the scale used to measure self-esteem is validated in groups with psychotic disorders, it is not fully clear if the instrument take sufficiently into account the structural distinctiveness of psychotic consciousness in persons with severe self-disorders. Results should thus be interpreted with caution.

AUTHOR CONTRIBUTIONS

EH, IM, MØ, and PM planned the current study, and OA and KR contributed to the study design. EH and UB contributed to data collection. EH conducted the statistical analyses and also wrote the first draft of the manuscript, while IM contributed to the analyses. All the authors contributed to the interpretation of the data and participated in critical revision of manuscript drafts, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

Addington, D., Addington, J., and Schissel, B. (1990). A depression rating scale for schizophrenics. *Schizophr. Res.* 3, 247–251. doi: 10.1016/0920-9964(90)90005-R

Amercan Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edn. (DSM-IV)*. Washington, DC: American Psychiatric Association.

Berman, A. H., Palmstierna, T., Källmén, H., and Bergman, H. (2007). The self-report drug use disorders identification test: extended (DUDIT-E): reliability, validity, and motivational index. *J. Subst. Abuse Treat.* 32, 357–369. doi: 10.1016/j.jsat.2006.10.001

Bernstein, D. P., Ahluvalia, T., Pogge, D., and Handelsman, L. (1997). Validity of the childhood trauma questionnaire in an adolescent psychiatric population. *J. Am. Acad. Child Adolesc. Psychiatry* 36, 340–348. doi: 10.1097/00004583-199703000-00012

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., et al. (2003). Development and validation of a brief screening version of the childhood trauma questionnaire. *Child Abuse Negl.* 27, 169–190. doi: 10.1016/S0145-2134(02)00541-0

Birchwood, M. (2003). Pathways to emotional dysfunction in first-episode psychosis. *Br. J. Psychiatry* 182, 373–375. doi: 10.1192/bjp.182.5.373

Birchwood, M., Iqbal, Z., Chadwick, P., and Trower, P. (2000). Cognitive approach to depression and suicidal thinking in psychosis. 1. Ontogeny of post-psychotic depression. *Br. J. Psychiatry* 177, 516–521. doi: 10.1192/bjp.177.6.516

Bratlien, U., Øie, M., Haug, E., Moller, P., Andreassen, O. A., Lien, L., et al. (2014). Environmental factors during adolescence associated with later development of psychotic disorders - a nested case-control study. *Psychiatry Res.* 215, 579–585. doi: 10.1016/j.psychres.2013.12.048

Bratlien, U., Øie, M., Haug, E., Moller, P., Andreassen, O. A., Lien, L., et al. (2015). Self-reported symptoms and health service use in adolescence in persons who later develop psychotic disorders: a prospective case-control study. *Early Interv. Psychiatry* 9, 221–227. doi: 10.1111/eip.12102

Cannon-Spoor, H. E., Potkin, S. G., and Wyatt, R. J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr. Bull.* 8, 470–484. doi: 10.1093/schbul/8.3.470

Crocker, J., and Wolfe, C. T. (2001). Contingencies of self-worth. *Psychol. Rev.* 108, 593–623. doi: 10.1037/0033-295X.108.3.593

Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., and Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. *Psychol. Med.* 31, 189–195. doi: 10.1017/S0033291701003312

Greenberg, J., Solomon, S., Pyszczynski, T., Rosenblatt, A., Burling, J., Lyon, D., et al. (1992). Why do people need self-esteem? Converging evidence that self-esteem serves an anxiety-buffering function. *J. Pers. Soc. Psychol.* 63, 913–922. doi: 10.1037/0022-3514.63.6.913

Gross, G., Huber, G., Klosterkötter, J., and Linz, M. (1987). *Bonner Skala für die Beurteilung von Basissymptomen*. Berlin: Springer.

Haug, E., Lien, L., Raballo, A., Bratlien, U., Oie, M., Andreassen, O. A., et al. (2012a). Selective aggregation of self-disorders in first-treatment DSM-IV schizophrenia spectrum disorders. *J. Nerv. Ment. Dis.* 200, 632–636. doi: 10.1097/NMD.0b013e31825bfd6f

Haug, E., Melle, I., Andreassen, O. A., Raballo, A., Bratlien, U., Oie, M., et al. (2012b). The association between anomalous self-experience and suicidality in first-episode schizophrenia seems mediated by depression. *Compr. Psychiatry* 53, 456–460. doi: 10.1016/j.comppsych.2011.07.005

Haug, E., Øie, M., Andreassen, O. A., Bratlien, U., Nelson, B., Aas, M., et al. (2015a). Anomalous self-experience and childhood trauma in first-episode schizophrenia. *Compr. Psychiatry* 56, 35–41. doi: 10.1016/j.comppsych.2014.10.005

Haug, E., Øie, M., Andreassen, O. A., Bratlien, U., Nelson, B., Melle, I., et al. (2015b). High levels of anomalous self-experience are associated with longer duration of untreated psychosis. *Early Interv. Psychiatry*. doi: 10.1111/eip.12220. [Epub ahead of print].

Haug, E., Øie, M., Andreassen, O. A., Bratlien, U., Raballo, A., Nelson, B., et al. (2014). Anomalous self-experiences contribute independently to social dysfunction in the early phases of schizophrenia and psychotic bipolar disorder. *Compr. Psychiatry* 55, 475–482. doi: 10.1016/j.comppsych.2013.11.010

Karatzias, T., Gumley, A., Power, K., and O'Grady, M. (2007). Illness appraisals and self-esteem as correlates of anxiety and affective comorbid disorders in schizophrenia. *Compr. Psychiatry* 48, 371–375. doi: 10.1016/j.comppsych.2007.02.005

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276. doi: 10.1093/schbul/13.2.261

Liddle, P. F., Barnes, T. R., Curson, D. A., and Patel, M. (1993). Depression and the experience of psychological deficits in schizophrenia. *Acta Psychiatr. Scand.* 88, 243–247. doi: 10.1111/j.1600-0447.1993.tb03450.x

Maggini, C., and Raballo, A. (2006). Exploring depression in schizophrenia. *Eur. Psychiatry* 21, 227–232. doi: 10.1016/j.eurpsy.2005.07.001

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., and Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch. Gen. Psychiatry* 62, 975–983. doi: 10.1001/archpsyc.62.9.975

Maslow, A. H. I. (1987). *Motivation and Personality,* 3rd *Edn.* New York, NY: Harper & Row.

McFarland, C. and Ross, M. (1982). Impact of causal attributions on affective reactions to success and failure. *J. Pers. Soc. Psychol.* 43, 937–946. doi: 10.1037/0022-3514.43.5.937

Møller, P., and Husby, R. (2000). The initial prodrome in schizophrenia: searching for naturalistic core dimensions of experience and behavior. *Schizophr. Bull.* 26, 217–232. doi: 10.1093/oxfordjournals.schbul.a033442

Møller, P., Haug, E., Raballo, A., Parnas, J., and Melle, I. (2011). Examination of anomalous self-experience in first-episode psychosis: interrater reliability. *Psychopathology* 44, 386–390. doi: 10.1159/000325173

Nelson, B., Thompson, A., and Yung, A. R. (2012). Basic self-disturbance predicts psychosis onset in the ultra high risk for psychosis "prodromal" population. *Schizophr. Bull.* 38, 1277–1287. doi: 10.1093/schbul/sbs007

Nelson, B., Thompson, A., and Yung, A. R. (2013). Not all first-episode psychosis is the same: preliminary evidence of greater basic self-disturbance in schizophrenia spectrum cases. *Early Interv. Psychiatry* 7, 200–204. doi: 10.1111/j.1751-7893.2012.00381.x

Nordgaard, J., and Parnas, J. (2014). Self-disorders and the schizophrenia spectrum: a study of 100 first hospital admissions. *Schizophr. Bull.* 40, 1300–1307. doi: 10.1093/schbul/sbt239

Parnas, J., Jansson, L., and Handest, P. (1998). Self-experience in the prodromal phases of schizophrenia: a pilot study of first admissions. *Neurol. Psychiat. Brain Res.* 6, 107–116.

Parnas, J., Moller, P., Kircher, T., Thalbitzer, J., Jansson, L., Handest, P., et al. (2005). EASE: examination of anomalous self-experience. *Psychopathology* 38, 236–258. doi: 10.1159/000088441

Raballo, A., and Parnas, J. (2012). Examination of anomalous self-experience: initial study of the structure of self-disorders in schizophrenia spectrum. *J. Nerv. Ment. Dis.* 200, 577–583. doi: 10.1097/NMD.0b013e31825bfb41

Romm, K. L., Rossberg, J. I., Berg, A. O., Barrett, E. A., Faerden, A., Agartz, I., et al. (2010). Depression and depressive symptoms in first episode psychosis. *J. Nerv. Ment. Dis.* 198, 67–71. doi: 10.1097/NMD.0b013e3181c81fc0

Romm, K. L., Rossberg, J. I., Hansen, C. F., Haug, E., Andreassen, O. A., and Melle, I. (2011). Self-esteem is associated with premorbid adjustment and positive psychotic symptoms in early psychosis. *BMC Psychiatry* 11:136. doi: 10.1186/1471-244X-11-136

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*. Princeton, NJ: Princeton University Press.

Rosenberg, M. (1986). *The Development of the Self. Self-consept from Middle Childhood through Adolescence*. Hillsdale, NJ: Erlbaum.

Sass, L. A., and Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophr. Bull.* 29, 427–444. doi: 10.1093/oxfordjournals.schbul.a007017

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., and Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction* 88, 791–804. doi: 10.1111/j.1360-0443.1993.tb02093.x

Skodlar, B. (2009). Three different meanings of depression in schizophrenia. A phenomenological perspective. *Psychiatr. Danub.* 21(Suppl. 1), 88–92.

Skodlar, B., and Parnas, J. (2010). Self-disorder and subjective dimensions of suicidality in schizophrenia. *Compr. Psychiatry* 51, 363–366. doi: 10.1016/j.comppsych.2009.11.004

Skodlar, B., Tomori, M., and Parnas, J. (2008). Subjective experience and suicidal ideation in schizophrenia. *Compr. Psychiatry* 49, 482–488. doi: 10.1016/j.comppsych.2008.02.008

Smith, E. R. and Mackie, D. M. (2007). *Social Psychology,* 3rd Edn. Hove: Psychology Press.

Thorup, A., Petersen, L., Jeppesen, P., Ohlenschlaeger, J., Christensen, T., Krarup, G., et al. (2007). Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. *J. Nerv. Ment. Dis.* 195, 396–405. doi: 10.1097/01.nmd.0000253784.59708.dd

Torrey, W. C., Mueser, K. T., McHugo, G. H., and Drake, R. E. (2000). Self-esteem as an outcome measure in studies of vocational rehabilitation for adults with severe mental illness. *Psychiatr. Serv.* 51, 229–233. doi: 10.1176/appi.ps.51.2.229

Upthegrove, R., Marwaha, S., and Birchwood, M. (2016). Depression and schizophrenia: cause, consequence or trans-diagnostic issue? *Schizophr. Bull.* doi: 10.1093/schbul/sbw097. [Epub ahead of print].

Ventura, J., Liberman, R. P., Green, M. F., Shaner, A., and Mintz, J. (1998). Training and quality assurance with the structured clinical interview for DSM-IV (SCID-I/P). *Psychiatry Res.* 79, 163–173. doi: 10.1016/S0165-1781(98)00038-9

Wallwork, R. S., Fortgang, R., Hashimoto, R., Weinberger, D. R., and Dickinson, D. (2012). Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. *Schizophr. Res.* 137, 246–250. doi: 10.1016/j.schres.2012.01.031

Yon, V., Loas, G., and Brien, D. (2005). Subjective experiences and the psychopathological dimensions in schizophrenia. *Psychiatry Res.* 137, 93–102. doi: 10.1016/j.psychres.2004.11.010

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OPINION
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Toward a Unified Social Motor Cognition Theory of Understanding Mirror-Touch Synaesthesia

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Keywords: mirror-touch synaesthsia, mirror neuron system, mentalizing system, social motor cognition, predictive coding, common coding theory

Mirror-touch synaesthesia (MTS) is a conscious tactile sensation in the observer when watching somebody else being touched. Two disparate theories have been suggested to explain MTS. The threshold theory links MTS to hyper-activity in the parietal-frontal mirror neuron system, while the self-other theory attributes MTS to impaired self-other representations in temporal-parietal junction (TPJ) and medial prefrontal cortex (mPFC). Here, I propose that these two theories can be synthesized under a unified social motor cognition theory which states that action observation engages two complementary levels of cognitive processing: a lower-level, physical process regarding basic sensory-motor aspects of the action, which supports motor imitation and goal understanding, and an abstract mental level concerning attribution of mental states, which supports inferring others' minds and self-other distinctions. While the physical process preferentially recruits the mirror neuron system, the mental process depends critically on the mentalizing network comprised of TPJ and mPFC. Importantly, despite of these anatomical and functional dissimilarities, the mirroring and mentalizing processes involve shared predictive coding, which is a general computational principle for a wide range of prominent concepts in motor cognition.

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INTRODUCTION

Mirror-touch synaesthesia (MTS) is a special kind of tactile sensation in one's own body when seeing someone else being touched (Blakemore et al., 2005). While MTS people constitute only a minority (1.6%), studying the neural underpinnings of MTS provides important insights into the mechanisms of sensory, motor, and social cognitive functions in the brain. Although MTS has drawn increasing attention from the field of psychology and neuroscience in recent years, the underlying mechanisms remain largely controversial. As summarized recently in Ward and Banissy (2015), two different theories have been put forward to account for MTS. The threshold theory posits that MTS synaesthetes exhibit hyper-activity in the mirror neuron system, which leads to heightened somatosensory activation crossing certain perceptual threshold (Blakemore et al., 2005; Bolognini et al., 2013). The self-other theory claims that MTS is associated with impaired ability to distinguish self from others in temporal-parietal junction (TPJ) and medial prefrontal cortex (mPFC) (Banissy and Ward, 2013; Holle et al., 2013).

As mentioned in passing by Ward and Banissy (2015), the two theories are not necessarily mutually exclusive. Yet, it fails to offer specific explanations and/or speculations as to how the two disparate theories might be related. Here, I propose a unified social motor cognition theory which not only conceptually incorporates these two theories, but also potentially serves as a coherent, parsimonious interpretation for a broader range of prominent action cognition concepts that are closely related to MTS. Below, I will first address the concept that the threshold theory and the self-other theory reflect nothing but two complementary levels of cognitive processing during action observation. I will then elaborate and discuss the shared neural codes and computational principles between these two cognitive processes.

COMPLEMENTARY PROCESSING DURING ACTION OBSERVATION: MIRRORING AND MENTALIZING

Contemporary view in social motor cognition holds that action observation triggers two different levels of cognitive processing which are supported by distinct brain systems (De Lange et al., 2008; Van Overwalle and Baetens, 2009). The lower-level, physical processing concerns basic sensory-motor and kinematic representations, which are good for motor imitation and for prediction of sensory outcome of an observed action to facilitate goal understanding (Rizzolatti and Sinigaglia, 2010). It is generally accepted that the physical mirroring aspects of action recognition are supported by the mirror neuron system, located primarily in the frontal-parietal circuits comprised of ventral premotor cortex, dorsal premotor cortex, and anterior intraparietal sulcus (Gallese and Goldman, 1998). In contrast, the higher-level, abstract mentalizing process involves attributing mental states (thoughts, desires, intention, etc) to oneself and to others, which supports inferring others' minds, self-awareness, and self-other distinctions (Frith and Frith, 2006; Lieberman, 2007). The mentalizing process engages a distinct set of brain networks mainly including area TPJ, area mPFC, and posterior superior temporal sulcus (Amodio and Frith, 2006; Van Overwalle and Baetens, 2009). The mirroring and mentalizing systems are two anatomically distinct yet functionally complementary aspects of action recognition during social interactions (Mainieri et al., 2013; Spunt and Lieberman, 2013; Ciaramidaro et al., 2014; Sperduti et al., 2014).

The mirroring and mentalizing systems are often differentially recruited, depending on specific task demands and social-cognitive contexts. For instance, it has been shown that participants show increased activations in the mentalizing system when thinking about why an action in a video clip was performed, comparing to thinking about what the action was and how the action was performed (Spunt et al., 2011). Similarly, observations of familiar actions that have pre-existing sensory and motor repertoires preferentially activate the mirroring neuron system (Calvo-Merino et al., 2005), while observations of unfamiliar actions more strongly recruit the mentalizing network, probably reflecting the increased demand of mental inferences in order to make sense of novel actions (Brass et al., 2007). As such, the threshold theory for MTS likely reflects abnormal processing at a mirroring level, while the self-other theory corresponds to atypical representations at a mental level. In this way, the two competing theories are not separate theories for explaining MTS. Instead, they should be viewed as reflecting two complementary aspects of cognitive processes during touch observation, which work synergistically to ensure appropriate social interactions in a given behavioral context.

The dichotomy between the mirroring and mentalizing processes captures not only the threshold theory and the self-other theory, but also may explain a few additional concepts associated with MTS. For instance, the dichotomy suggests that self-other distinction should operate at both the mental and physical levels: the former refers to psychologically separating oneself from others and plays a role in self-awareness (Jenkins and Mitchell, 2011) and empathy (Decety and Jackson, 2004), while the latter supports several aspects of bodily self-consciousness (Ionta et al., 2011a; Blanke et al., 2014), which includes senses of body ownership (Tsakiris et al., 2007), sense of agency (Jeannerod, 2003; Jackson and Decety, 2004), as well as processing related to self-location and first-person perspective (Ionta et al., 2011b). Interestingly, people with MTS often exhibit various aspects of these anomalous self-experience at both the mental and physical body levels (Ward and Banissy, 2015), which can be parsimoniously interpreted as aberrant representations in the mirroring and mentalizing systems during touch observation.

SHARED CODING PRINCIPLES BETWEEN MIRRORING AND MENTALIZING: PREDICTIVE CODING

The mirroring and mentalizing systems might have shared predictive coding principle. First, at the physical mirroring level, goal understanding, sense of agency, and bodily self awareness are each associated with predictive processing. Goal understanding hinges on the ability to make predictions about the consequence and sensory outcome of an observed action (Kilner et al., 2007). This prediction is thought to be based on efference copies of the mapped motor representations in the observer during action observation (Gallese and Goldman, 1998; Rizzolatti and Sinigaglia, 2010). Sense of agency depends critically on the congruency between the predicted sensory outcome and the actual sensory feedback associated with an action (Tsakiris et al., 2007). In a similar vein, a predictive coding account of bodily self awareness (Apps and Tsakiris, 2014) proposes that, recognizing one's self is a probabilistic process of multimodal integration between the actual sensory states (re-afference) and other bodily related information including predictions based on corollary discharge (efference). Second, at the abstract mentalizing level, theory of mind engages simulations of one's own intentions, desires, and beliefs to predict the mental states of others. This allows an individual to understand and empathize with others (Decety and Jackson, 2004). Our brain may be constantly making predictions at distinct levels during action observation, and deficits in these predictive processing will result in social-cognitive abnormalities such as MTS and neuropsychiatric symptoms including autism spectrum disorders (Van Boxtel and Lu, 2013) and schizophrenia (Biedermann et al., 2012).

Predictive coding is not restricted to social-cognitive processing. Instead, it is considered to be a general coding principle which underlies a wide variety of perceptual and motor functions (Brown and Brune, 2012). Take the field of motor cognition as an example, predictive coding has been well-established as the core principle for several prominent concepts. For instance, it serves as the underlying mechanism for adaptive motor control (Shadmehr et al., 2010; Franklin and Wolpert, 2011) and motor awareness (Blakemore and Frith, 2003; Desmurget and Sirigu, 2009), both of which involve internal forward predictions of sensory consequence of executed actions. It should be noted that, while forward models of action are framed in a predictive scheme, the underlying mechanisms involve neural computations specifically related to efference copy signals (or "corollary discharge"), which are different from predictive computations implemented in other brain functions such as visual processing (Rao and Ballard, 1999), associative learning (Schultz and Dickinson, 2000), and decision making (Rushworth et al., 2009). In addition to action execution, predictive coding has also been linked to concepts related to action selection and planning in a recent neurophysiology study (Kuang et al., 2016). It is shown that when monkeys are planning an arm movement, neurons in posterior parietal cortex encode not only the intended physical movement but also the visual sensory anticipation of the planned movement. These predictive coding of planned action support the longstanding ideomotor theory in cognitive psychology, which states that actions are planned and selected with respect to their perceptual consequences (Shin et al., 2010; Waszak et al., 2012). More broadly, the co-existence of physical and visual predictive representations in the same brain area is very reminiscent of the idea of common coding theory which posits a tight bi-directional link between action and perception systems (Prinz, 1987; Hommel et al., 2001).

CONCLUSION

In summary, this paper provides a synthetic view for understanding MTS from the perspective of a unified social motor cognition theory. Instead of two competing, disparate theories, I propose that MTS is attributable to the disturbed mirroring and mentalizing functions, which represent the dual complementary aspects of cognitive processing with shared predictive coding during touch observation. Thus, the current unified viewpoint may serve as a coherent guiding principle for explaining diverse aspects of bodily and mentally abnormal phenomena in MTS populations.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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REFERENCES

Amodio, D. M., and Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nat. Rev. Neurosci.* 7, 268–277. doi: 10.1038/nrn1884

Apps, M. A., and Tsakiris, M. (2014). The free-energy self: a predictive coding account of self-recognition. *Neurosci. Biobehav. Rev.* 41, 85–97. doi: 10.1016/j.neubiorev.2013.01.029

Banissy, M. J., and Ward, J. (2013). Mechanisms of self-other representations and vicarious experiences of touch in mirror-touch synesthesia. *Front. Hum. Neurosci.* 7:112. doi: 10.3389/fnhum.2013.00112

Biedermann, F., Frajo-Apor, B., and Hofer, A. (2012). Theory of mind and its relevance in schizophrenia. *Curr. Opin. Psychiatry* 25, 71–75. doi: 10.1097/YCO.0b013e3283503624

Blakemore, S. J., Bristow, D., Bird, G., Frith, C., and Ward, J. (2005). Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia. *Brain* 128, 1571–1583. doi: 10.1093/brain/awh500

Blakemore, S. J., and Frith, C. (2003). Self-awareness and action. *Curr. Opin. Neurobiol.* 13, 219–224. doi: 10.1016/S0959-4388(03)00043-6

Blanke, O., Pozeg, P., Hara, M., Heydrich, L., Serino, A., Yamamoto, A., et al. (2014). Neurological and robot-controlled induction of an apparition. *Curr. Biol.* 24, 2681–2686. doi: 10.1016/j.cub.2014.09.049

Bolognini, N., Miniussi, C., Gallo, S., and Vallar, G. (2013). Induction of mirror-touch synaesthesia by increasing somatosensory cortical excitability. *Curr. Biol.* 23, R436–R437. doi: 10.1016/j.cub.2013.03.036

Brass, M., Schmitt, R. M., Spengler, S., and Gergely, G. (2007). Investigating action understanding: inferential processes versus action simulation. *Curr. Biol.* 17, 2117–2121. doi: 10.1016/j.cub.2007.11.057

Brown, E. C., and Brune, M. (2012). The role of prediction in social neuroscience. *Front. Hum. Neurosci.* 6:147. doi: 10.3389/fnhum.2012.00147

Calvo-Merino, B., Glaser, D. E., Grezes, J., Passingham, R. E., and Haggard, P. (2005). Action observation and acquired motor skills: an FMRI study with expert dancers. *Cereb. Cortex* 15, 1243–1249. doi: 10.1093/cercor/bhi007

Ciaramidaro, A., Becchio, C., Colle, L., Bara, B. G., and Walter, H. (2014). Do you mean me? Communicative intentions recruit the mirror and the mentalizing system. *Soc. Cogn. Affect. Neurosci.* 9, 909–916. doi: 10.1093/scan/nst062

Decety, J., and Jackson, P. L. (2004). The functional architecture of human empathy. *Behav. Cogn. Neurosci. Rev.* 3, 71–100. doi: 10.1177/1534582304267187

De Lange, F. P., Spronk, M., Willems, R. M., Toni, I., and Bekkering, H. (2008). Complementary systems for understanding action intentions. *Curr. Biol.* 18, 454–457. doi: 10.1016/j.cub.2008.02.057

Desmurget, M., and Sirigu, A. (2009). A parietal-premotor network for movement intention and motor awareness. *Trends Cogn. Sci.* 13, 411–419. doi: 10.1016/j.tics.2009.08.001

Franklin, D. W., and Wolpert, D. M. (2011). Computational mechanisms of sensorimotor control. *Neuron* 72, 425–442. doi: 10.1016/j.neuron.2011.10.006

Frith, C. D., and Frith, U. (2006). The neural basis of mentalizing. *Neuron* 50, 531–534. doi: 10.1016/j.neuron.2006.05.001

Gallese, V., and Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. *Trends Cogn. Sci.* 2, 493–501. doi: 10.1016/S1364-6613(98)01262-5

Holle, H., Banissy, M. J., and Ward, J. (2013). Functional and structural brain differences associated with mirror-touch synaesthesia. *Neuroimage* 83, 1041–1050. doi: 10.1016/j.neuroimage.2013.07.073

Hommel, B., Musseler, J., Aschersleben, G., and Prinz, W. (2001). The Theory of Event Coding (TEC): a framework for perception and action planning. *Behav Brain Sci.* 24, 849-878; discussion 878–937. doi: 10.1017/s0140525x01000103

Ionta, S., Gassert, R., and Blanke, O. (2011a). Multi-sensory and sensorimotor foundation of bodily self-consciousness - an interdisciplinary approach. *Front. Psychol.* 2:383. doi: 10.3389/fpsyg.2011.00383

Ionta, S., Heydrich, L., Lenggenhager, B., Mouthon, M., Fornari, E., Chapuis, D., et al. (2011b). Multisensory mechanisms in temporo-parietal cortex support self-location and first-person perspective. *Neuron* 70, 363–374. doi: 10.1016/j.neuron.2011.03.009

Jackson, P. L., and Decety, J. (2004). Motor cognition: a new paradigm to study self-other interactions. *Curr. Opin. Neurobiol.* 14, 259–263. doi: 10.1016/j.conb.2004.01.020

Jeannerod, M. (2003). The mechanism of self-recognition in humans. *Behav. Brain Res.* 142, 1–15. doi: 10.1016/S0166-4328(02)00384-4

Jenkins, A. C., and Mitchell, J. P. (2011). Medial prefrontal cortex subserves diverse forms of self-reflection. *Soc. Neurosci.* 6, 211–218. doi: 10.1080/17470919.2010.507948

Kilner, J. M., Friston, K. J., and Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. *Cogn. Process.* 8, 159–166. doi: 10.1007/s10339-007-0170-2

Kuang, S., Morel, P., and Gail, A. (2016). Planning movements in visual and physical space in monkey posterior parietal cortex. *Cereb. Cortex* 26, 731–747. doi: 10.1093/cercor/bhu312

Lieberman, M. D. (2007). Social cognitive neuroscience: a review of core processes. *Annu. Rev. Psychol.* 58, 259–289. doi: 10.1146/annurev.psych.58.110405.085654

Mainieri, A. G., Heim, S., Straube, B., Binkofski, F., and Kircher, T. (2013). Differential role of the Mentalizing and the Mirror Neuron system in the imitation of communicative gestures. *Neuroimage* 81, 294–305. doi: 10.1016/j.neuroimage.2013.05.021

Prinz, W. (1987). "Ideo-motor action," in *Perspectives on Perception and Action,* eds H. Heuer and A. F. Sanders (Hillsdale, NJ: Erlbaum), 47–76.

Rao, R. P., and Ballard, D. H. (1999). Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat. Neurosci.* 2, 79–87. doi: 10.1038/4580

Rizzolatti, G., and Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nat. Rev. Neurosci.* 11, 264–274. doi: 10.1038/nrn2805

Rushworth, M. F., Mars, R. B., and Summerfield, C. (2009). General mechanisms for making decisions? *Curr. Opin. Neurobiol.* 19, 75–83. doi: 10.1016/j.conb.2009.02.005

Schultz, W., and Dickinson, A. (2000). Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500. doi: 10.1146/annurev.neuro.23.1.473

Shadmehr, R., Smith, M. A., and Krakauer, J. W. (2010). Error correction, sensory prediction, and adaptation in motor control. *Annu. Rev. Neurosci.* 33, 89–108. doi: 10.1146/annurev-neuro-060909-153135

Shin, Y. K., Proctor, R. W., and Capaldi, E. J. (2010). A review of contemporary ideomotor theory. *Psychol. Bull.* 136, 943–974. doi: 10.1037/a0020541

Sperduti, M., Guionnet, S., Fossati, P., and Nadel, J. (2014). Mirror Neuron System and Mentalizing System connect during online social interaction. *Cogn. Process.* 15, 307–316. doi: 10.1007/s10339-014-0600-x

Spunt, R. P., and Lieberman, M. D. (2013). The busy social brain: evidence for automaticity and control in the neural systems supporting social cognition and action understanding. *Psychol. Sci.* 24, 80–86. doi: 10.1177/0956797612450884

Spunt, R. P., Satpute, A. B., and Lieberman, M. D. (2011). Identifying the what, why, and how of an observed action: an fMRI study of mentalizing and mechanizing during action observation. *J. Cogn. Neurosci.* 23, 63–74. doi: 10.1162/jocn.2010.21446

Tsakiris, M., Schutz-Bosbach, S., and Gallagher, S. (2007). On agency and body-ownership: phenomenological and neurocognitive reflections. *Conscious. Cogn.* 16, 645–660. doi: 10.1016/j.concog.2007.05.012

Van Boxtel, J. J., and Lu, H. (2013). A predictive coding perspective on autism spectrum disorders. *Front. Psychol.* 4, 19. doi: 10.3389/fpsyg.2013.00019

Van Overwalle, F., and Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *Neuroimage* 48, 564–584. doi: 10.1016/j.neuroimage.2009.06.009

Ward, J., and Banissy, M. J. (2015). Explaining mirror-touch synesthesia. *Cogn. Neurosci.* 6, 118–133. doi: 10.1080/17588928.2015.1042444

Waszak, F., Cardoso-Leite, P., and Hughes, G. (2012). Action effect anticipation: neurophysiological basis and functional consequences. *Neurosci. Biobehav. Rev.* 36, 943–959. doi: 10.1016/j.neubiorev.2011.11.004

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Sleep Paralysis, "The Ghostly Bedroom Intruder" and Out-of-Body Experiences: The Role of Mirror Neurons

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Rapid eye movement (REM) sleep—for good reasons—is referred to as *paradoxical sleep*: our blood pressure, heart rate, and breathing become elevated. And electroencephalography (EEG) recordings show a peculiar, lower voltage, and mixed frequency pattern (La Berge et al., 1981; Horne, 2013). In fact, the firing pattern of most neurons during REM sleep resemble those of wakefulness—and in some cases neurons fire in even more intense bursts (e.g., in the pons, lateral geniculate nucleus, and occipital cortex), than when we're awake (Kandel et al., 2000). This is not all too surprising, as we have our most vivid and emotionally-charged dreams during REM sleep, often involving a complex story plot. In order for us not to act out these dreams—and potentially hurt ourselves—our brain has an ingenious solution: it leaves us temporarily paralyzed from head to toe. This paralysis (postural atonia) is triggered by the pons (including the pontine reticular formation) and ventromedial medulla that suppress skeletal muscle tone during REM sleep—via inhibition of motor neurons in the spinal cord; through neurotransmitters GABA and glycine (Brooks and Peever, 2012; Jalal and Hinton, 2013).

Occasionally, perceptual activation occurs (we start to wake up mentally), while under the "spell" of REM paralysis. The result is a curious condition called sleep paralysis (SP), where the person is left "trapped"—unable to move or speak upon falling asleep or upon awakening (Hobson, 1995; Jalal et al., 2014a). Intriguingly during SP, the sensory system is clear, and ocular, and respiratory movements remain intact, culminating in a state of semi-consciousness coupled with bodily paralysis (Jalal and Hinton, 2013). While once thought to only arise in the context of narcolepsy—a rare autoimmune sleep disorder affecting <1% of the population (Jalal, 2016)—we now know that 20% of the general population have SP episodes (Sharpless and Barber, 2011; Jalal and Hinton, 2013).

During SP, the vivid—and sometimes terrifying—dreams of REM sleep (REM mentation) can spill over into emerging wakefulness (Jalal and Hinton, 2015). Hypnogogic or hypnopompic hallucinations occur in all sensory modalities, and include out-of-body experiences (OBE), and sensing and seeing the presence of menacing intruders in one's bedroom (Jalal and Hinton, 2013; Jalal and Ramachandran, 2014; Jalal et al., 2014b, 2015).

We have proposed that a functional disturbance of the (right) parietal cortex may give rise to the common "bedroom intruder" hallucination seen during SP (Jalal and Ramachandran, 2014).

As described, the absence of afferent sensory signals might cause this disturbance of "body image"; implicating regions such as the right superior parietal lobule (SPL) and the temporoparietal junction (TPJ)—critical for the construction of a neural representation of the body. Essential to this hypothesis, is the hallucinated projection of a genetically hardwired body-map (homunculus) due to conflicting (efferent and afferent) neural conduction. This hypothesis is broadly consistent with the finding that disrupting the TPJ using focal electrical stimulation can induce the feeling of an illusory "other" shadow-like person mimicking one's body postures (Arzy et al., 2006); and that hyperactivity in the temporoparietal cortex of schizophrenics can lead to the misattribution of their own actions to others (Farrer et al., 2004).

We further evoke the mirror neuron system (MNS) as crucial in giving rise to this "intruder" hallucination. Neurons in area V5 of the premotor cortex fire when you make volitional movements. Intriguingly, a subset of them (10%), fire even when you merely watch another person performing the action. These neurons—dubbed mirror neurons—allow higher centers to say in effect "the same cells are firing as would fire if I were about to reach out for the peanut—so that's what the other person is *intending* to do" (Rizzolatti et al., 1996, 2001). Circuits performing analogous computations may be involved in reading the higher order intentions that are required for constructing a *theory of mind* (ToM), but this is still a matter of some debate.

The MNS allows you to temporarily detach yourself from your body and "see" the world from another person's vantage point. In other primates, this requires the physical presence of another individual—whereas, in humans, it might be that the MNS is sufficiently well connected that it allows you a virtual point of view (i.e., imagine what you would be seeing if you were in the other person's place). However, even though you temporarily see the world from another's location—you don't literally leave your body (i.e., you don't have an out-of-body experience [OBE]). This is because the MNS has multiple outputs, which are powerfully modulated by two sources. First, sensory afferents from the body—and, second—prefrontal cortex. The triadic interaction between MNS, prefrontal cortex (anterior to V5), and sensory feedback results in a dual representation—a feeling that you are "out there" looking at someone else's actions—while at the same time being fully anchored, here, and now in your own body (Ramachandran, 2012).

This interaction involves a convergence of inputs in the right SPL, and their target zones in V5. Not surprisingly, damage to the prefrontal cortex sometimes results in echopraxia—i.e., miming what somebody near is doing. Analogously, the massive deafferentation of sensory input during SP would lead to a similar disinhibition of the MNS and its propensity to project its body into another individual—if you are a chimp—or another virtual body, if you are a human. A disturbance of these interactions would lead to the more florid manifestations of an alien abductor, bedroom intruder, or mysterious other—seen so frequently during SP. In addition, we suggest that OBEs during SP, likewise result from the massive deafferentation that occurs during REM sleep paralysis. These ideas could be explored using neuroimaging, to examine the selective activation of brain regions associated with mirror neuron activity, when the individual is hallucinating an intruder or having an OBE during SP.

AUTHOR CONTRIBUTIONS

BJ and VR came up with the intellectual content of the article, and wrote up the article.

REFERENCES

Arzy, S., Seeck, M., Ortigue, S., Spinelli, L., and Blanke, O. (2006). Induction of an illusory shadow person. *Nature* 443, 287–287. doi: 10.1038/443287a

Brooks, P. L., and Peever, J. H. (2012). Identification of the transmitter and receptor mechanisms responsible for REM sleep paralysis. *J. Neurosci.* 32, 9785–9795. doi: 10.1523/JNEUROSCI.0482-12.2012

Farrer, C., Franck, N., Frith, C. D., Decety, J., Georgieff, N., d'Amato, T., et al. (2004). Neural correlates of action attribution in schizophrenia. *Psychiatry Res. Neuroimaging* 131, 31–44. doi: 10.1016/j.pscychresns.2004.02.004

Hobson, J. A. (1995). *Sleep*. New York, NY: Scientific American Library.

Horne, J. (2013). Why REM sleep? Clues beyond the laboratory in a more challenging world. *Biol. Psychol.* 92, 152–168. doi: 10.1016/j.biopsycho.2012.10.010

Jalal, B. (2016). How to make the ghosts in my bedroom disappear? Focused-attention meditation combined with muscle relaxation (MR therapy)—a direct treatment intervention for sleep paralysis. *Front. Psychol.* 7:28. doi: 10.3389/fpsyg.2016.00028

Jalal, B., and Hinton, D. E. (2013). Rates and characteristics of sleep paralysis in the general population of Denmark and Egypt. *Cult. Med. Psychiatry* 37, 534–548. doi: 10.1007/s11013-013-9327-x

Jalal, B., and Hinton, D. E. (2015). Sleep Paralysis among Egyptian college students: a. association with anxiety symptoms (PTSD, trait anxiety, pathological worry). *J. Nerv. Ment. Dis.* 203, 871–875. doi: 10.1097/NMD.0000000000000382

Jalal, B., and Ramachandran, V. S. (2014). Sleep paralysis and "the bedroom intruder": the role of a. the right superior parietal, phantom pain and body image projection. *Med. Hypotheses* 83, 755–757. doi: 10.1016/j.mehy.2014.10.002

Jalal, B., Romanelli, A., and Hinton, D. E. (2015). Cultural explanations of sleep paralysis in a. Italy: the pandafeche attack and associated supernatural beliefs. *Cult. Med. Psychiatry* 39, 651–664. doi: 10.1007/s11013-015-9442-y

Jalal, B., Simons-Rudolph, J., Jalal, B., and Hinton, D. E. (2014b). Explanations of a. sleep Paralysis among Egyptian college students and the general population in Egypt and Denmark. *Transcult. Psychiatry* 51, 158–175. doi: 10.1177/1363461513503378

Jalal, B., Taylor, C. T., and Hinton, D. E. (2014a). A comparison of self-report and interview methods for assessing sleep paralysis: a pilot investigation in Denmark and the United States. *J. Sleep Disord.* 3, 9–13. doi: 10.4172/2325-9639.1000131

Kandel, E. R., Schwartz, J. H., and Jessell, T. M. (2000). *Principles of Neural Science, 4th Edn*. New York, NY: McGraw-Hill.

La Berge, S. P., Nagel, L. E., Dement, W. C., and Zarcone, V. P. (1981). Lucid dreaming verified by volitional communication during REM sleep. *Percept. Mot. Skills* 52, 727–732. doi: 10.2466/pms.1981.52.3.727

Ramachandran, V. S. (2012). *The Tell-Tale Brain: Unlocking the Mystery of Human Nature*. London: Windmill Books.

Rizzolatti, G., Fadiga, L., Gallese, V., and Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cogn. Brain Res.* 3, 131–141. doi: 10.1016/0926-6410(95)00038-0

Rizzolatti, G., Fogassi, L., and Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat. Rev. Neurosci.* 2, 661–670. doi: 10.1038/35090060

Sharpless, B. A., and Barber, J. P. (2011). Lifetime prevalence rates of sleep paralysis: a systematic review. *Sleep Med. Rev.* 15, 311–315. doi: 10.1016/j.smrv.2011.01.007

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