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Review article

Neuropharmacological modulation of the aberrant bodily self through psychedelics

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ABSTRACT

As a continual source of sensory input and fundamental component of self-referential processing, the body holds an integral modulatory role in cognition. In a healthy state, predictive coding of multisensory integration promotes the construction of a coherent self. However, several psychiatric disorders comprise aberrant perceptions of the bodily self that are purported to involve discrepancies in the integration and updating of multisensory systems. Changes in functional connectivity of somatomotor and high-level association networks in these disorders could be successfully remediated through 5-HT_{2A} receptor agonism via psychedelics. Reported alterations of bodily self-awareness during psychedelic experiences allude to a potentially central role of the bodily self. In this article, we bridge the domains of (aberrant) bodily self-awareness and psychedelics by discussing the predictive coding mechanisms underlying the bodily self and psychedelics. Furthermore, we propose that psychedelically-induced desynchronization of predictive coding might involve modulation of somatomotor, sensorimotor, and high-level association networks that could remediate aberrant perceptions of the bodily self.

1. Introduction

Embodied cognition has permeated the fields of psychology, neuroscience, and cognitive science by highlighting the intricate connection between bodily structures, dynamic interoceptive and sensorimotor states, and their neural and computational representations and awareness (e.g., Bechara and Damasio, 2005). In a healthy state, the self[1] is continuously and actively constructed by contrasting predictions, based on slowly changing priors, with incoming multisensory signals (Apps and Tsakiris, 2014). However, when these systems are no longer appropriately integrated and updated, aberrations in bodily self-awareness might manifest, which are core to several psychiatric disorders, such as anorexia nervosa (Gadsby and Hohwy, 2019), body dysmorphic disorder (Hrabosky et al., 2009), or depression (Fuchs and Schlimme, 2009).

Therapy of such pathologies remains challenging, and conventional psychopharmacological treatment using selective serotonin reuptake inhibitors (SSRIs) does not consistently improve the clinical manifestations in all patients (Rush et al., 2006). Consideration of alternative neuropharmacological mechanisms could thus prove informative not only for further elucidating the role of serotonin in the intricate connection between the bodily self and cognition, but also hold potential relevance for clinical practice. Several clinical trials using psychedelics and other psychotropic substances (Carhart-Harris et al., 2016a, 2016b; Stocker et al., 2019) have evinced impressive and often persistent improvements in mental disorders that are characterized by aberrant forms of the bodily self (Fuchs and Schlimme, 2009). Yet, despite the frequently reported alterations in bodily self-awareness through psychedelics, and their profound ability to alter cognition, the description of this interrelationship in pathological conditions remains scarce.

In contrast to SSRIs targeting the serotonin transporter SERT, psychedelics exert their psychotropic effects via direct stimulation of specific receptors, in particular agonistic activity on the 5-HT_{2A} receptor (psilocybin: Kometer et al., 2013; LSD: Preller et al., 2018a, 2018b, 2017; DMT: Valle et al., 2016) and/or sigma-1 receptors (DMT: Palhano-Fontes et al., 2015). Preliminary evidence in human studies supports significant symptom alleviation through psychedelic substances in various psychiatric disorders, including depression (Carhart-

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[1] The metaphysics of the self are still very controversially discussed; however, for the sake of this article, we use the term 'self' referring to a self-model (Hohwy and Michael, 2018) that is created through integration of low-level multisensory information that is contrasted against top down priors in a predictive coding manner. The 'bodily self', by our definition, entails subconscious monitoring of the body, but can also involve conscious bodily self-awareness.

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Harris et al., 2016a, 2016b; Watts et al., 2017), obsessive-compulsive disorder (Moreno et al., 2006; Wilcox, 2014), body dysmorphic disorder (Hanes, 1996), and eating disorders (Mills et al., 1998; Renelli et al., 2018). Subjective reports often include psychedelically-induced embodiment of emotions, disembodiment, manifestations of somatic symptoms following physical sensations, or other alterations of the bodily self (Belser et al., 2017; Watts et al., 2017).

Research focusing on the bodily self during psychedelic experiences and its relation to self-referential processing could therefore uncover a potentially modulatory role in symptom alleviation of psychiatric disorders. This article thus adopts a hybrid approach: we first review the rich literature on the bodily self, embodied cognition, and predictive coding accounts of the self, and how these aspects might be altered in disorders. We subsequently focus on the neuropharmacology of psychedelic substances, particularly classical serotonergic psychedelics, and consequently move towards a more speculative approach by generating a hypothetical model explicating how psychedelics, via 5-HT_{2A} receptor agonism, could lead to remediation of disorders of the bodily self.

2. Phenomenology of the bodily self

To better understand the role of embodied processes in mental disorders, we must first delve into the phenomenology of (bodily) self-awareness, as well as the diversely employed related terminology in the literature. The bodily self is comprised by a first-person perspective of our body and surroundings, and our actions as agents within such environments (Wilson, 2002). We will refer to this experience of ourselves as an embodied agent from a first-person perspective as "bodily self"(Apps and Tsakiris, 2014; Brugger and Lenggenhager, 2014).

The existence of a self has been extensively debated in philosophy, neuroscience, and psychology: while some maintain that there is no existence of a 'self' (i.e., the no-self position: Metzinger, 2003, 2009), others maintain a realism of the self (Hohwy and Michael, 2018), and approach the overarching 'self' by distinguishing between different types of selves that purportedly exist (Gallagher, 2000). A common and established distinction surrounds the sense of "being a self" or "subject" (i.e., being the subject of conscious experience in a first-person perspective) versus "being self-aware" or "object", which involves conscious reflection about oneself, as well as the way we are perceived by others (Millière, 2017; Musholt, 2013). The former is seen as "a basic notion of the self as the first-personal aspect of normal conscious experience implemented by low-level bodily processes" (pre-reflective self), while the latter refers to "a more sophisticated conception of the self as constituted by high-level reflective processes involving introspection, self-evaluation, and autobiographical memory retrieval" (narrative self) (Millière, 2017, p. 10-11). These conceptual distinctions are also applied to psychopathological disorders: for example, schizophrenia and depression relate to disruptions of the pre-reflective self, whereas anorexia nervosa or body dysmorphic disorder presumably connect to higher order self-referential processing mechanisms underlying reflective self-awareness of the narrative self (Fuchs and Schlimme, 2009; for a review of disorders of bodily awareness, see de Vignemont, 2010).

3. Predictive coding accounts of the self

Predictive coding presents a plausible account to better understand not only the potential underlying mechanisms of the bodily self and its disorders, but also how they may be modulated by psychedelics. The self is believed to be an "inferred model of endogenous, deeply hidden causes of behavior" and theorized to result from prediction error minimization in the brain (Hohwy and Michael, 2018, p. 363). Several related theoretical frameworks have formalized the mechanisms of these self-specifying processes, of which the most universal three are the predictive coding framework, Bayesian inference, and the free energy principle model. Predictive coding refers to the conception that instead of representing input directly, our brain rather computes a prediction error (i.e., actual outcome – predicted outcome) to improve efficiency (Aitchison and Lengyel, 2017), and generates hierarchical probabilistic representations to account for bottom-up prediction errors. Applying these concepts to the self, Apps and Tsakiris (2014) posit that the recognition and representation of one's self results from a dynamic optimization process, where discrepancies between predicted sensory outcomes and actual sensory events (prediction errors) are updated in a Bayesian inference manner to generate the most probabilistic version of the self.

Although both predictive coding and Bayesian inference combine external inputs with internal signals (predictions or priors), predictive coding represents the neural representations, whereas Bayesian inference specifies the implicated computational algorithm and resultant behavior. The free-energy principle constitutes a recent application of Bayesian predictive coding, in which the brain attempts to maintain a low level of entropy (a highly predictable environment) by minimizing the amount of free-energy ('surprise' or improbable outcomes) in sensory systems and making predictions about the type of sensorial consequences expected based on Bayesian optimized probabilities (Friston, 2005). High level priors generally represent abstract multimodal beliefs that are learned through associations between congruent low-level sensory events from different systems, and there must be a high-level representation of the self that elaborates descending predictions to produce these parallel multimodal predictions. Therefore, the self is posited to arise from the integration of information from lower-level unimodal systems, which are systematically explained away by higher-level multimodal areas in an attempt to minimize free energy. These optimization processes occur through the dynamic updating of Bayesian sensory predictions in an attempt to reduce the discrepancy between a predicted sensory outcome and the actual sensory event (prediction errors), with resultant body and self representations that can be highly plastic and modulated by contextual information (Apps and Tsakiris, 2014).

Riva (2018a, 2018b) recently proposed a multilayered developmental "body matrix" that is dichotomously differentiated by the pre-reflective experience of the body ("body schema") and the later maturation of the narrative self, which embodies the knowledge, beliefs, and attitudes encompassing body image. The emergence of the narrative self is contingent on the maturation of the hippocampus and the development of allocentric spatial memories (Ribordy et al., 2013; Riva, 2018b). Subsequently, autobiographical components, which are grounded in a system of temporal, spatial, and self-referential retrieval, can emerge (Damasio, 2008). Our body image thus constitutes a multidimensional construct comprised of affective, cognitive, and perceptive components (De Vignemont, 2014; Riva, 2018b), in which spatial experiences are organized around schematic (allocentric) and perceptual (egocentric) frameworks that interact to form the beliefs and knowledge of our bodily and narrative self (Galati et al., 2010; Riva, 2014). Based on a predictive coding approach, a hierarchical organization structures our bodily self (Seth, 2014): lower level, intero- and exteroceptive sensorimotor bodily signals within an egocentric reference frame are progressively integrated before being recalibrated by higher level contextual and allocentric representation to continually update our body image (Riva, 2018a).

3.1. Interoceptive predictive coding

Self-related predictive coding engages multiple representations of the pre-reflective self, including the integrity of the body, physical location, but also physiological homeostasis. One account within the predictive coding framework thus places emphasis on the role of interoception (i.e., the primary internal representation of the body's physiological states) in the representation and maintenance of the bodily self (Seth et al., 2011). The account posits the (bodily) self to be modulated by multisensory integration of precision-weighted interoceptive and exteroceptive signals through mediation of the anterior insula (AI) (Seth, 2014). Afferent input from the anterior insula and the efferently-driven responses from the anterior cingulate cortex (ACC) anchor the salience network (SN) and guide individuals' actions and decisions (Craig, 2002). It has been recently shown that interoception is related to insular functional connectivity in the SN at rest, demonstrating that greater connectivity between these regions correlates with enhanced processing, integration, and representation of internal states (Chong et al., 2017). According to Paulus and Stein (2010), a neural circuitry involving the medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), and the ACC evaluates afferent interoceptive signals through the use of a self-referential processing system. If this process is impaired, individuals can no longer correctly identify the relevant interoceptive signals that predict pleasant or aversive consequences (Riva, 2012). Therefore, disorders of the bodily self can be related to a degree to which these inaccurate interoceptive prediction schemas evolve; for example, lower interoceptive sensitivity can heighten inaccuracy between arousal and interoceptive cues and thus enhance anhedonia symptoms (Dunn et al., 2010; Riva, 2018b), whereas increased interoceptive sensitivity may instead augment perception of aversive body states in patients with anxiety (Khalsa et al., 2018; Paulus and Stein, 2010; Riva, 2018b). Indeed, several clinical populations evince deficits in interoceptive accuracy: patients with depression (Pollatos et al., 2009) and anorexia (Pollatos et al., 2016) score lower on interoceptive accuracy when processing self-related bodily information, but not necessarily when the judgment pertains to the accurate recognition of others (Pollatos et al., 2016), suggesting that this deficit is specific to processing of information pertaining to oneself.

4. Disorders of the bodily self

Predictions are, however, vulnerable to the generative model, and disadvantages may materialize in the presence of inaccurate or inflexible beliefs that could negatively affect experience (Fletcher and Frith, 2008; Ma, 2012). Impaired feedback affecting any level of the multisensory hierarchy could disturb the coherent integration of lower-level signals with the bodily self and disrupt the individual's optimal interaction with the external and social world. Inputs that stand in accordance with existing beliefs or autobiographical memories continuously strengthen those beliefs and reduce the energy required to process them; on the other hand, the presence and continual reinforcement of incorrect beliefs can produce abnormal perceptions (Fletcher and Frith, 2008; Friston, 2010). These aberrations might strengthen the neural network underlying these processes and further disrupt what is experienced as the (bodily) self (Apps and Tsakiris, 2014; Chekroud and Mathys, 2015). Compromised integration and computation of predictive perception could hinder the ability to suppress attention to negative stimuli (Keefe et al., 2011) while simultaneously exacerbating their salience. Such disturbances in self-referential mechanisms may therefore disrupt the continuity and consistency of the pre-reflective self and result in the alienated experiences in disorders of the bodily self (Millière, 2017).

Phenomenological approaches suggest that mental disorders are often accompanied by atypical body representations, which can include experiences of disembodimemt, hyperembodiment, or aberrant perceptions of body image (Fuchs and Schlimme, 2009; Zatti and Zarbo, 2015). Bayesian mismatches in the estimated cause of a sensory event such as these could be driven by abnormal encoding of neural prediction error signals and thus drive several symptoms in disorders that affect the bodily self (Fig. 1).

In the following section, we will use depression as an example of a disordered pre-reflective self, and anorexia as an example of a disordered narrative self. However, it is important to note that the dichotomous approach we employ here does not exclude a reciprocal interaction, as the clinical picture remains complex and the disorders we discuss here can rarely be simplistically deduced to disorders of solely the pre-reflective or narrative self; rather, it is the reciprocal interaction that shape the phenomenology and clinical picture.

4.1. An example of a disordered pre-reflective self: hyperembodiment in depression

Although disorders that affect the pre-reflective self are numerous and variable, we will use the sense of hyperembodiment, often experienced in depression, as a representative disorder. Several scholars have proposed that the core properties of the pre-reflective self are produced by generative models used for forward modeling of re-afferent signals (e.g., Frith, 2005; De Vignemont and Fourneret, 2004). The pre-reflective self may be more generally based on generative models of predictive coding (e.g., Friston, 2002), since a basic feeling of oneself requires a cognitive frame of reference in which to place experiences that stand distinct from the narrative self (Hohwy, 2007). The pre-reflective self maintains an implicit role in conscious experience so long as the multisensory integration at the subpersonal level functions without error; i.e., the actions of a functioning agent should yield consequences that confirm the expectations of the sensory system and thus keep prediction errors low (Apps and Tsakiris, 2014). In the presence of discrepancies, however, a disruption in the encoding of prediction error signals can contribute to the symptomatology that affect disorders of the bodily self (Gradin et al., 2011). The loss of fluidity and the sensation of a heavy, resistant body (e.g., feeling pressure or tightness around the chest) often reported in depression can be understood as a form of 'hyperembodiment', which is often additionally linked psychomotor retardation (Michalak et al., 2014). Individuals suffering from depression often exhibit reduced walking speed and slumped posture (Michalak et al., 2009), which, however, can be counteracted by adopting an upright posture that decreases self-focus and fatigue while increasing positive affect (Wilkes et al., 2017). Bidirectionally, the motor system also modulates emotional processes: patients with depression who sit in a slumped posture during a memory task recalled a higher proportion of negative over positive self-referential material than those who sit in an upright position (Michalak et al., 2014), while reduced walking speed resulted in a higher rate of negative self-relevant information during memory recall (Dijkstra et al., 2007; Michalak et al., 2015). In turn, negative memory recall and rumination have repeatedly been linked to the etiology and maintenance of depression (e.g., Mclaughlin and Nolen-hoeksema, 2011), suggesting that the relationship between the bodily self and memory processes could a play key role in depression. Maladaptive cognitive appraisals of physiological states could hinder individuals with depression from optimizing priors and minimizing free energy (Chekroud and Mathys, 2015). In a disordered state of predictive coding, representations of the (bodily) self and its surroundings are no longer properly integrated, with manifestations of rigid thinking patterns and a concomitant sense of hyperembodiment.

4.2. An example of a disordered narrative self: anorexia nervosa

The body and its surrounding space, in which contents are shaped by predictive multisensory integration (Apps and Tsakiris, 2014), serves as the foundation for the construction of the more advanced, narrative self and its autobiographical components. Anorexia nervosa has been posited to constitute a disorder of bodily self-awareness due to patients' spatiotemporal disturbances in self-referential processing (Amianto et al., 2016), as well as particularly low scores on reflective functioning (Fonagy et al., 1996). One essential characteristic of the narrative self is episodic memory; based on this, Riva (2012) recently developed a neurobiological framework (Allocentric Lock Hypothesis) positing that anorexia results from multisensory processing disturbances, where there exists a mismatch between the way expected (using predictive

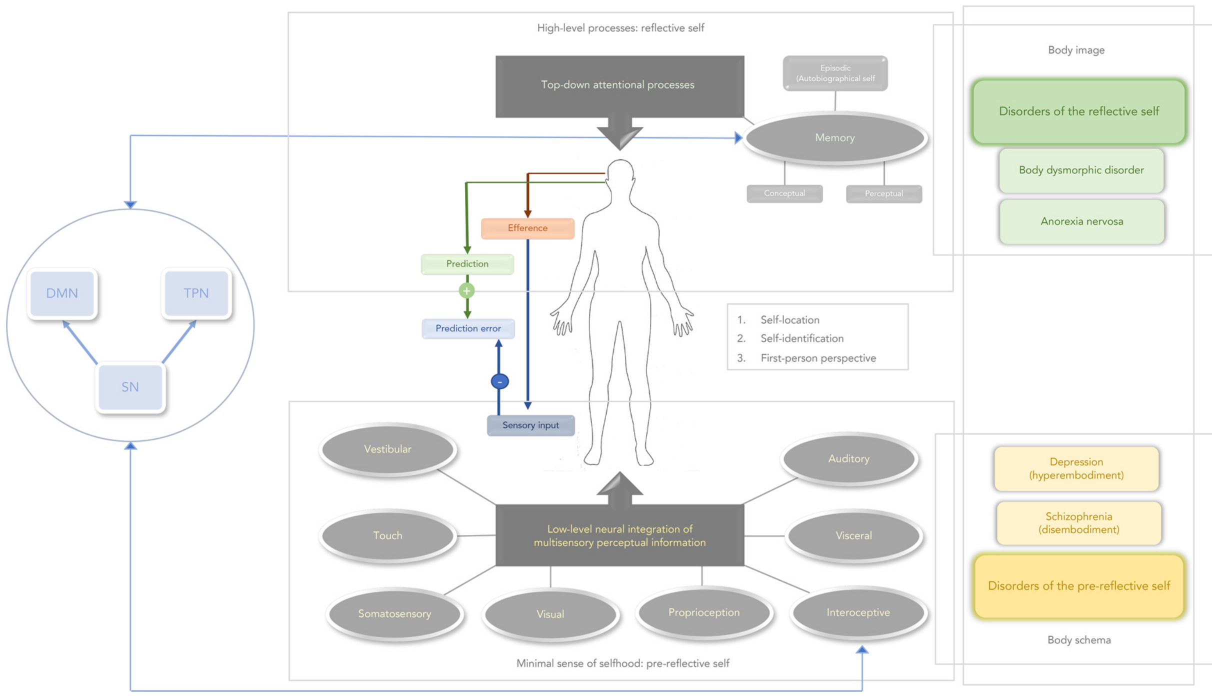

Fig. 1. Model of the bodily self. Overview of a model of the bodily self, including its purported disorders. Bottom-up multisensory information is integrated and contrasted against top down attentional processes that include prior information, such as self-referential memory, leading to the most probabilistic sense of "me". Disorders of the bodily self can roughly be dichotomously distinguished by pre-reflective and reflective aspects. Information from bottom-up multisensory information and central priors are processed by associative neural networks.

coding) versus experienced (from perception) bodily representations are integrated. Deficits in multisensory processing to effectively integrate real time perceptual data might impair the egocentric system's capacities to update the beliefs and attitudes stored in long-term allocentric memory (Riva, 2012, 2018b). The Allocentric Lock Hypothesis suggests two possible impairments in the multisensory processing of anorexia: (1) Allocentric (offline) body representations stored as body memory are either no longer updated by real-time egocentric perceptual (online) inputs from sensory systems, or (2) there exists an impairment in linking interoceptive bodily signals to potential pleasant or aversive consequences. Autobiographical memories represent attempts to construct and maintain a coherent self over time, during which content is continually evaluated and updated according to current self-goals (Conway, 2005). This process requires the translation of schematic (allocentric) contents of the retrieved memory into perceptual (egocentric) data, which entails an evaluation of the self-relevance of a memory, and whether the memory is congruent with bodily self-awareness (Sutin and Robins, 2008).

5. Altered states of the (bodily) self

Apart from the disturbances of the bodily self present in the aforementioned (and other) mental disorders, there are also ways to transiently alter the bodily self through experimental manipulations in healthy individuals. A number of these experimental studies have substantiated the plasticity of the bodily self by demonstrating how conflicting multisensory information can alter bodily self-awareness. Illusions such as these include swapping bodies with another person (Petkova and Ehrsson, 2008), embodying a virtual avatar (Pavone et al., 2016), experiencing ownership over a foreign limb (Botvinick and Cohen, 1998), or alterations in self-location and first-person perspective (Ehrsson, 2007; Lenggenhager et al., 2007). The application of such bodily illusions has further revealed that clinical populations seem to exhibit a more plastic and malleable sense of the body, evinced by differences in the experienced strength of such illusions when compared to healthy populations (Rubber Hand Illusion in body dysmorphic disorder: Kaplan et al., 2014; anorexia: Keizer et al., 2014; Rubber Foot Illusion in body integrity dysphoria: Lenggenhager et al., 2015). Higher malleability of the bodily self in clinical conditions could point at potential underlying abnormalities in multisensory integration in the development of a coherent (bodily) self.

Such induced altered states of the body have also been used to normalize a disturbed bodily self in patients, which might offer a promising therapeutic direction. Inducing a sense of bodily lightness through use of augmented walking sounds promoted the perception of a thinner body and thus increased motivation for physical activity (Tajadura-Jiménez et al., 2015), while the persistent distorted experience of body size in patients with anorexia was successfully improved using a virtual reality full body illusion (Keizer et al., 2016). These studies both highlight the flexibility of disturbed body experiences and further demonstrate how interventions modulating bodily self-awareness could be used to alter aberrant perceptions linked to the bodily self.

Experimental manipulations have not only substantiated the degree of its plasticity, but also further elucidated the neurological signature of the body and its relation to the bodily self. Failure to effectively integrate multisensory information pertaining to the bodily self in the insular cortex (Blanke et al., 2015; Yu et al., 2018) or at the temporoparietal junction (TPJ) has been proposed to constitute the underlying neural signature of clinical out-of-body experiences (Blanke and Arzy, 2005). Whereas the insula plays a modulatory role in interoceptive coding, the TPJ, as a key neural locus for self-processing, self-location, and the integration of multisensory cues, could represent a central hub in the maintenance of the bodily self (Blanke and Arzy, 2005; Eddy, 2016; Ionta et al., 2011). A structural overlap between the bodily self and a more overarching self-consciousness is further supported by psychotropic studies evincing functional activation of temporoparietal networks (i.e., the precuneus and TPJ) in ketamine-altered states of consciousness (Vlisides et al., 2018), corroborating that disintegration of the ego seems to correlate with altered activity of neural networks that underlie the multisensory integration of the bodily self.

Altered experiences of the bodily self have also transpired through the use of classical psychedelics. In psilocybin-assisted therapy of treatment-resistant depression (Watts et al., 2017), patient accounts contain body-specific components in the alleviation of depressive symptoms, including spatial modification of depressed feelings ("I felt spatial, not depressed", p. 9), changes from feeling no sensations in the body to strong bodily connections of ("pure, sensory, tactile, sexual bliss", p. 11), embodiment of emotions ("I didn't understand the emotions, it opened a box in my chest I didn't know was there", "I felt an ulcer where I was holding onto grief", p. 21), and relaxations of the body. Reports such as these suggest that psychedelics might work via paradigmatically novel means, where an alteration in self-consciousness subjectively simulates a sense of disconnection from the body, and avoidance of difficult emotions are restructured towards more positive autobiographical memory recall, as well as a reconnection to the bodily self.

6. Neurophenomenology of psychedelic substances and effects on the (bodily) self

Psychedelic substances produce profound changes in (bodily self-) consciousness that often generate meaningful spiritual experiences (Hood, 2002); but certain aspects, such as depersonalization experiences, have been suggested to transiently mimic properties of acute psychosis (Sass et al., 2013). Alterations in mood and perception, reflective insight, ego dissolution and feelings of unity, as well as alterations of the bodily self (i.e., disembodiment, detachment between the body and mental processes, or blurring of boundaries between the body and environment) constitute an integral phenomenal part of the psychedelic experience (Preller and Vollenweider, 2018; Vollenweider and Kometer, 2010). Interestingly, the feeling of disembodiment and loss of self can also be connected to an altered sense of time, or 'timelessness', pointing to a potential link between the bodily self and the sense of time (Wittmann, 2015). The changes in the bodily self through psychedelic substances have provided an informative window into better understanding the neurobiological mechanisms that underlie both the standard and non-uniform self (Preller et al., 2017; Preller et al., 2018a, 2018b). Psychedelically-induced effects, such as changed meaning of percepts and disembodiment, are experienced particularly strongly by individuals with increased connectivity in the somatomotor network (Preller et al., 2018a, 2018b). A putative role of the supplementary motor area has been implicated in the meaning and personal relevance of LSD-induced subjective effects (Preller et al., 2017), substantiating the previously both theoretically and empirically suggested key role of presence and agency in the self (Seth et al., 2011).

Desynchronized default mode network (DMN) activity, increased hippocampal BOLD signal variance (i.e., amplitude fluctuations), and DMN-hippocampal decoupling under psilocybin may reduce constrained cognition and thus allow for more possible states (Carhart-Harris et al., 2014). Increased excitatory connections from the thalamus to the posterior cingulate cortex (PCC) following LSD could reduce the amount of filtering and change the precision of ascending prediction errors (Preller et al., 2019). Psychedelic experiences may result from a break-down of top-down predictions from high-level association cortices into many overly detailed predictions via 5-HT_{2A} receptor-mediated excitation of layer V neocortical pyramidal cells (Muthukumaraswamy et al., 2013; Pink-Hashkes et al., 2017). Synchronous neural activity is believed to reflect the brain's top-down Bayesian inferencing mechanisms (Bastos et al., 2012), suggesting that a disruption of these prediction processes could lower the firing threshold of individual neurons and effect a desynchronization of neuronal populations. The relaxed beliefs under psychedelics (REBUS) model proposes that psychedelics may relax the precision weighting of prior beliefs while increasing the bottom-up flow of information (Carhart-Harris and Friston, 2019). In patients with mental illness, easing the precision weighting of pathologically overweighted priors could increase the sensitization of high-level priors to bottom-up signals and enable a potential revision and de-weighting of such maladaptive priors. This relaxation process most profoundly affects the highest levels of the brain's functional architecture that instantiate high-level models, such as those related to the self. As a result, ascending prediction errors from lower levels of the system that would ordinarily be suppressed by heavily weighted priors can actually reach and impress on higher levels of the hierarchy in the psychedelic state. Whereas lower doses may primarily alter the sensory (particularly visual) domain via 5-HT_{2A} receptor modulation, higher doses may induce more profound subjective effects through the disruptive influence on higher levels of the global hierarchy, thereby revising high-level priors, perspectives, or beliefs. The authors note that relaxed precision weighting of prior beliefs would ideally result in a recalibration of relevant beliefs that would subsequently better align with bottom-up information via interoceptive and exteroceptive inputs.

Cognitive fragmentation of maladaptive priors could disrupt the rigid and negative rumination patterns in disorders, such as depression, and open patients' minds to new and alternative – particularly positive – forms of cognitive restructuring. Disordered self-referential processing in depression has been linked to a failure in effectively downregulating activity in the DMN (Sheline et al., 2009), suggesting that negative thinking patterns are represented by a neural pathophysiology in brain regions implicated in cognition related to the self. The negative loop experienced by patients suffering from disorders of the bodily self could potentially be disrupted by psilocybin. Psychedelically induced alterations of self-referential processing are believed to occur through disruption of activity and connectivity in associative networks, particularly the DMN and SN (Preller et al., 2018a, 2018b). While the DMN is involved in self-referential and internally oriented cognitive processes (Fox and Raichle, 2007), activation of the SN is tied to the detection and processing of emotionally salient events (Seeley et al., 2007). Furthermore, the SN also holds a putative role in switching between the DMN and the task-positive network (TPN), which is engaged in cognitively demanding tasks requiring attention (Fox et al., 2006). Psychedelics function as modulators that produce novel forms of information integration and thus promote enhanced capacity for specific forms of cognitive restructuring. The consistent effects on phenomenal alterations of the bodily self, coupled with the significant alleviation of clinical symptoms following ingestion of psychedelic substances, allude to a potential role of embodied cognition in these altered experiences (Fig. 2).

To summarize, disorders of the bodily self ostensibly link to those primarily affecting the pre-reflective and those primarily affecting the narrative self. We have employed neurofunctional and predictive coding approaches to both explicate how (aberrant) predictive coding promotes construction and updating of the bodily self, and how psychedelics may reduce the overweighting of maladaptive priors via 5-HT_{2A} receptor modulation and disruption of the higher levels of the global hierarchy. Based on our review of these frameworks, the next part of our paper will adopt a novel embodied cognition approach to hypothesize the potential mechanisms of psychedelic substances in modulating representations of the bodily self and cognition, and how they could remediate symptoms in disorders affected by an aberrant bodily self. We will argue that remediation involving psychedelics might follow a predictive coding framework that unfolds in a two-part process comprised of: 1. The disintegration of associative (DMN, SN, TPN) and somatomotor networks that usually maintain the pre-reflective self through desynchronized predictive coding mechanisms, and 2. A re-adaptation process in self-referential processing that restructures autobiographical memories and the narrative self in higher levels of the global hierarchy through decreased functional coupling of the DMN.

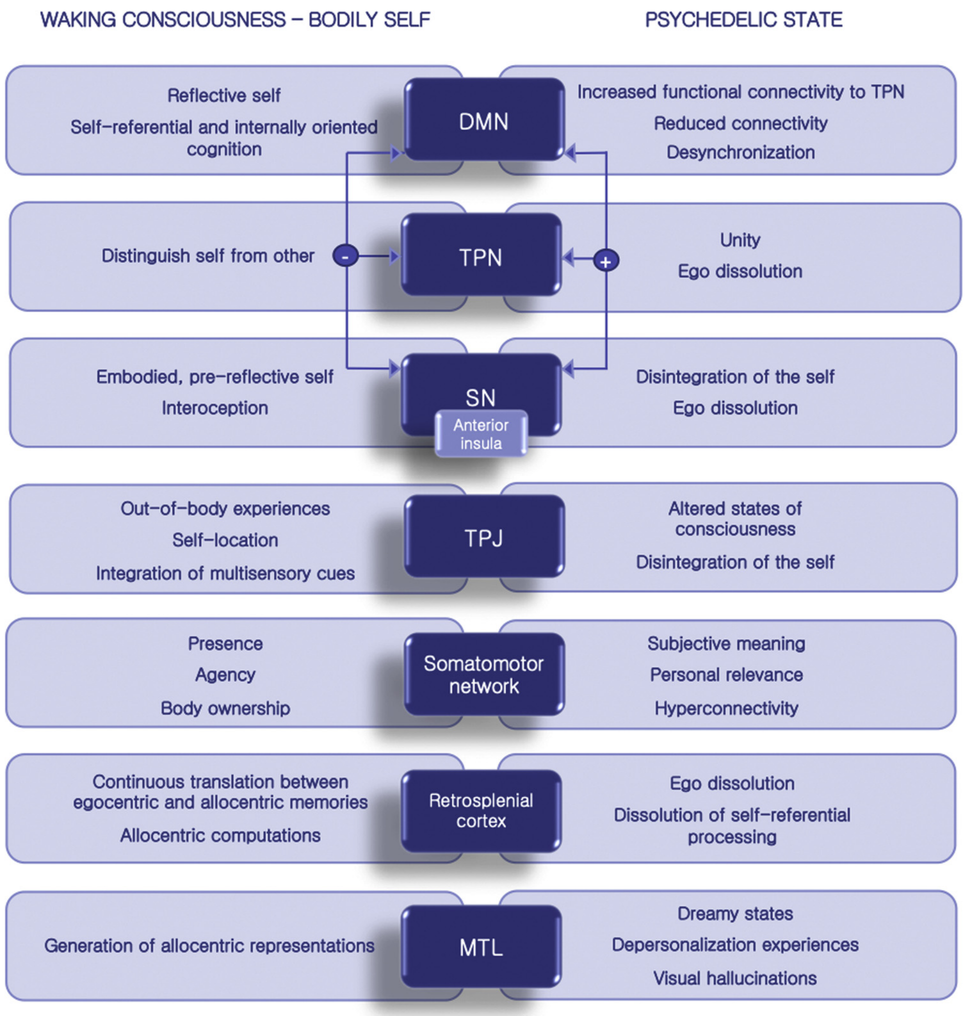

Fig. 2. Comparison of neural regions underlying the bodily self and psychedelics. Suggested neural regions with functional overlap between body-related states of waking consciousness and psychedelic states.

6.1. Disintegration of the embodied pre-reflective self

Disintegration of the feeling of one's (bodily) self during psychedelic experiences dissolves the perceived boundaries between the self and the external world. Although knowledge on the precise neural correlates of the self and its disturbances remain to be further elucidated, neuroscientific findings from consciousness research suggest a central role of the medial temporal lobe (MTL) circuitry (Lebedev et al., 2015), in addition to the neural regions mentioned above. Electrical stimulation of the MTL produces dreamy states (Lee et al., 2013), depersonalization experiences, or visual hallucinations comparable to those present in psychedelic states (Rangarajan et al., 2014). Normal waking consciousness is characterized by a functional decoupling between the DMN and TPN; in the psilocybin-induced psychedelic state, however, an increase in DMN-TPN functional connectivity has been observed following psilocybin ingestion (Carhart-Harris et al., 2013), which is also observed during meditation (Josipovic et al., 2012; for a detailed review on psychedelics and meditation, see: Millière et al., 2018). Additionally, LSD induces hyper-connectivity across sensory and somatomotor networks (i.e., occipital cortex, superior temporal gyrus, postcentral gyrus, precuneus), but decreases global brain connectivity and desynchronizes associative networks of the medial and lateral prefrontal cortex, insula, and TPJ (Preller et al., 2018a, 2018b). Moreover, the subjective effects, including disembodiment, induced by LSD seem to be specifically tied to global brain connectivity changes in the somatomotor networks, as increased connectivity in this region predicts the strength of subjective effects (Preller et al., 2018a, 2018b).

Neuroimaging studies evince an increase in regional cerebral blood flow in right frontal and temporal regions and bilaterally in the AI, while the left parietal and occipital regions, as well as the amygdala, globus pallidus, insula, and thalamus display decreases in regional cerebral blood flow (Lewis et al., 2017). Post-psilocybin (Carhart-Harris et al., 2012a, 2012b; Lewis et al., 2017) and DMT (Palhano-Fontes et al., 2015) decreases in both global cerebral blood flow and BOLD signal of high-association hubs along cortical midline structures evidence a reduced connectivity of associative networks, particularly in the DMN (Buckner et al., 2008); a large-scale intrinsic network that is activated during rest, deep meditative states (Brewer et al., 2011) and metacognitive operations such as introspection and memory retrieval (Qin and Northoff, 2011). It has been suggested that the anticorrelated temporal dynamics of the DMN-TPN during normal wakefulness could reflect the self-reflection and processing necessary to distinguish between self and others, whereas a disintegration of this negative network coupling during the psychedelic state may underlie the perceived feelings of unity and ego dissolution (Carhart-Harris et al., 2014; Millière, 2017). More specifically, dissolution of the self or general self-referential processing following LSD administration seem to be reflected by altered resting-state connectivity of the PCC, including the retrosplenial cortex (Preller et al., 2018a, 2018b), and disintegration of the SN (Lebedev et al., 2015).

The SN, which entails the AI, usually enables switching between the DMN and task-related states of brain connectivity and has independently been considered a potential core neural correlate of the pre-reflective self and interoceptive awareness (Craig, 2009; Seth, 2013). As a key region in bodily sensations and emotion related processes, the insula holds a putative role in our ability to sense our self (Craig, 2009; Damasio, 2008; Damasio et al., 2000). However, more recent information suggests that the insular cortex constitutes one of a number of interoceptive hubs (Barrett and Simmons, 2015), and while it may not be essential for interoceptive experience, it is important for higher-order functions such as episodic memory, imagination, decision making, and language (Damasio et al., 2013). Hypoactivation of the AI has been linked to diminished emotional responsiveness in patients with depersonalization disorder, whose experiences are qualified by more subtle anomalies of the self: while basic self-awareness is retained, these patients exhibit an attenuation of the self and the surrounding world (Medford et al., 2016). On the other hand, alterations in the functional connectivity of the somatomotor network have been shown to correlate with the subjective effects (e.g., experience of unity, spiritual experience, blissful state, insightfulness, disembodiment) following LSD administration (Preller et al., 2018a, 2018b). The supplementary motor area, which represents a core region of the somatomotor network, is associated with both body ownership and agency as fundamental aspects of the bodily self (Tsakiris, 2017).

Ego dissolution likely constitutes a multidimensional experience that results from a disruption in the integrated functioning of hierarchical, multisensory predictive models that usually govern the stable self (Letheby and Gerrans, 2017; Millière, 2017). Against the brain's default state of free-energy minimization, psychedelic-induced activation of 5-HT_{2A} receptors on deep-layer pyramidal neurons may sensitize and functionally dysregulate the highest levels of the brain's functional hierarchy by temporarily lightening their precision weighting and flattening the hierarchical organization, thereby reducing the top heaviness of human cognition (Carhart-Harris and Friston, 2019). As the drug effects begin to subside, the brain will revert back to its default free-energy minimization as the sense of familiarity begins to return. Perception of unity and ego loss may transpire from the psychedelically induced disruption of the hierarchical structure of information integration that usually gives rise to the self and of the brain's ability to minimize prediction errors, resulting in the complete inability to distinguish between the environment and the self (Pink-Hashkes et al., 2017). A strong correlation between functional disintegration of the SN and ego dissolution has resulted in a purported role of the SN associated with the pre-reflective self (Craig, 2009; Seth, 2013). Ego dissolution post-LSD is accompanied by a decrease in global functional connectivity in high-level association cortices, including a partial overlap with the DMN, the SN, frontoparietal attention network, and thalamus (Preller et al., 2018a, 2018b; Tagliazucchi et al., 2016). Furthermore, disintegration of the self seems to be tied to increased connectivity with the bilateral TPJ and bilateral insular cortex; two brain regions that putatively constitute fundamental neurological signatures of the self (Lenggenhager et al., 2006; Tagliazucchi et al., 2016). Altered states of consciousness following ketamine injections (Vlisides et al., 2018) and out-of-body experiences from disrupted integration of multisensory information at the TPJ (Blanke and Arzy, 2005) reinforce that these temporoparietal networks constitute a key neural region in the maintenance of the self.

Beyond the recently identified modulatory role in the subjective effects of psychedelic experience (Preller et al., 2018a, 2018b), altered somatomotor activity and connectivity has been linked to a pathophysiological sense of presence or agency present in several disorders characterized by aberrations of the pre-reflective self, such as schizophrenia (Anticevic et al., 2014) and bipolar disorder (Doucet et al., 2017). Aberrations in the self and agency present in schizophrenia may arise from alterations in the sensorimotor gating usually necessary for efficiently distinguishing whether an event was self-produced (Synofzik et al., 2010), further corroborating the key functional role of the somatomotor network in the LSD-induced psychedelic state (Preller et al., 2018a, 2018b). In contrast to the hyperembodiment that typifies melancholic depression, however, schizophrenia has been positioned at the other end of the spectrum: personified by a state of disembodiment, patients suffer from a disruption of implicit bodily functioning and diminishment of basic self-awareness that is characterized by a pervasive lack of presence (Fuchs and Schlimme, 2009). An impaired ability to recognize and distinguish familiar patterns, coupled with a sensory overload of details that are separated from the situational context, characterize the disembodied state that is reminiscent of an altered bodily self reported during psychedelic experiences.

6.2. Readaptation of the narrative self

Impairment in the system to update autobiographical memory with new information from online sensory input has been suggested to "lock" patients into an allocentric body image (Riva, 2018a), particularly evident in those pathopsychological disorders that are based on negative self-referential processing of the body image, such as anorexia nervosa and body dysmorphic disorder. Although egocentric and allocentric systems rely on different primary sources of input, the construction of spatial cognition is posited to occur through an interface between long- and short-term memory processes (Byrne et al., 2007), where a continuous translation between egocentric and allocentric representations occurs via a coordinate transformation in the posterior parietal and retrosplenial cortices (Dhindsa et al., 2014). According to this model, long-term spatial memory involves the generation of allocentric representations in the hippocampus and medial-temporal lobe structures. On the other hand, egocentric representations integrated at the parietal lobe model short-term spatial memory and imagery, which in turn are driven by perceptions or long-term memory.

The increased attention to the self and self-focus in depression (Mor and Winquist, 2002) runs parallel to a weakened first-person perspective (Lemogne et al., 2006), suggesting that visual perspective taking, including the first- and third-person perspective, could represent a hallmark for disordered bodily self-awareness. Disordered perspective-taking could also comprise suggested links to the serotonin system (Riva, 2016): serotonergic neurotransmission is closely related to working memory, including spatial strategies for working memory performance (González-Burgos et al., 2012). Indeed, the presence of at least one S or L_G allele of the serotonin-transporter-linked promotor region (5-HTTLPR) polymorphism can moderate visual perspective during life stress through modulation of amygdala and hippocampus activity (Lemogne et al., 2009). Specifically, there is an observable decrease in first-person perspective for positive memories, suggesting that there exists an interaction between visual perspective and serotonin in the vulnerability for depression.

Serotonergic dysfunctions in disorders that affect the bodily self, such as anorexia nervosa, have been identified in key neural areas relevant for allocentric to egocentric computation (Ekstrom et al., 2014; Gaudio and Riva, 2013; Riva and Gaudio, 2012). The hippocampus, retrosplenial cortex, and parahippocampal cortex involved in allocentric computation are influenced by significant serotonergic innervations (Ekstrom et al., 2014; Riva, 2016). Rodent studies have demonstrated the regulatory role of 5-HT receptors to induce spine growth in the CA1 of the hippocampus (Restivo et al., 2008); an area "involved in spatial autobiographical memory and in the development of allocentric view independent representations" (Riva, 2016, p. 6, 7). Decreased serotonin transmission in disorders of the bodily self could impair the positive regulatory factor of serotonin synthesis on the granule layers of the retrosplenial cortex through decreased cell proliferation and resultantly disrupt the transformation of allocentric to egocentric representations in the hippocampus (Riva, 2016; Vann and Aggleton, 2005; Vann et al., 2009).

In addition to their serotonin-dependent mechanisms, autobiographical memories are, at least partially, also associated with memory- and body-related processing that correlate to activity in the insula, midline cortical structures, as well as lateral frontal, temporal, and parietal cortices, hippocampus, and amygdala (Araujo et al., 2015). Involvement of cortical midline structures, particularly the MPFC and other regions of the DMN, in self-related mental states seems to be greater for self-referential processing of the narrative self. As a network of structural and functional hubs that underlie (bodily) self-awareness and self-representation (Andrews-Hanna, 2012), the DMN could represent a potential anatomical marker for the autobiographical and narrative self (Lebedev et al., 2015; Millière, 2017) that begets the progressive construction of one's identity based on cultural and social factors (Gallagher, 2000).

Theoretical models have suggested a link between embodied experiences of the world and hippocampus-based memory: psychiatric conditions characterized by dissociative symptoms, such as out-of-body experiences or feelings of detachment, often report impairments in long-term episodic memory (Brewin et al., 2010), while empirical studies have demonstrated that an experimentally-induced out-of-body experience can impair hippocampal binding and recall (Bergouignan et al., 2014). These findings provide a neuroscientific framework for the long-term memory problems present in patients suffering from dissociative experiences and could further present an account for the memory restructuring from psychedelic experiences.

In psychedelic, meditation, or hypnosis-induced states of ego dissolution, reduced connectivity between the parahippocampus and retrosplenial cortex has been shown. Some have suggested that decoupling of the parahippocampal cortex from the neocortex effects a disruption of several major DMN hubs (PCC, dorsal MPFC) that are usually implicated in self-referential processing (Carhart-Harris et al., 2012a, 2012b). A number of studies have reported altered DMN activity after ingestion of psilocybin (Carhart-Harris et al., 2012a, 2012b; Kometer et al., 2015), ayahuasca (Palhano-Fontes et al., 2015) and LSD (Carhart-Harris et al., 2016a, 2016b; Preller et al., 2018a, 2018b) and also identified DMN involvement in mental time travel, during which autobiographical memories, as a reflection on one's past, are contrasted against the future self with imagined possible outcomes (Scheibner et al., 2017). The primary connections of the DMN extend to the thalamus, PCC, and MPFC, as well as to the information integration systems of the brain (i.e., parahippocampal cortex and hippocampus) (Raichle, 2015). Interruption of the sensory gating from cortico-striato-thalamo-cortical loops increases the availability of information normally repressed by these systems to reach high-level association areas (Vollenweider and Geyer, 2001; Winkelman, 2017) through a disruption of normal rhythmic oscillations of excitatory cortical neurons at 5-HT_{2A} receptors (Carhart-Harris et al., 2014). Increased serotonergic activation by psychedelics reduces effective connectivity from the ventral striatum to the thalamus, opening the thalamic filter and thereby decreasing information gating, while increasing bottom-up information flow to certain cortical areas (Preller et al., 2019). This could reduce the functional connectivity between the DMN, parahippocampus, and retrosplenial cortex (Carhart-Harris et al., 2016a, 2016b; Lebedev et al., 2015; Tagliazucchi et al., 2016) and consequently bias self-referential processing during memory reconsolidation.

Alterations of DMN and SN activity may constitute a marker of altered bodily self-awareness in anorexia and suggest state-dependent abnormalities that could be related to impaired processing of interoception and body image (McFadden et al., 2014). Recently, ingestion of ceremonial ayahuasca demonstrated a therapeutic effect for patients with eating disorders, possibly mediated by attenuation of the DMN, and concomitant changes in self-perception, including an enhanced ability to decenter and distance themselves from maladaptive and intrusive thoughts (Renelli et al., 2018). A body image that is subjectively distressing to patients constitutes a key characteristic in disorders marked by aberrant bodily self-awareness and is often linked to previous negative autobiographical experiences. Elevated functional connectivity of the AI with the DMN and concomitant decreases in interoceptive awareness have been identified in anorexia patients, where high levels of self- and body-focused ruminations at rest might correlate with such aberrant activations (Boehm et al., 2014). Difficulty in switching out of self-referential thinking has also been linked to functional DMN alterations in body dysmorphic disorder, where lower activity in the parahippocampal gyrus and precuneus reflects imbalances in global vs. local processing that maybe indicative of disorder-typical rumination in these disorders (Feusner et al., 2011). Difficulty to disengage from a self-objectifying allocentric body representation could potentially develop from a hyperconnectivity between the insula and DMN, wherein the function of the insula to switch between the DMN and fronto-parietal network is impaired, and a resultant inability to effectively disengage from an internally-oriented stimulus results in rumination (Boehm et al., 2014). Increased assignment of the insula to the DMN instead of to the SN has also been reported in patients with major depression (Horn et al., 2010), alluding to a potential DMN hyperconnectivity that could explain the excessive rumination present in several psychopathological disorders that affect the bodily self (Berman et al., 2011).

Purported enhanced recollection of autobiographical memories after psilocybin ingestion allude to its potential to facilitate the recall of salient memories, or to reverse negative cognitive bias (Carhart-Harris et al., 2012a, 2012b). Whereas the MPFC usually exerts top-down inhibitory control over the limbic system during normal waking consciousness (Milad and Quirk, 2002), psilocybin-induced deactivation of resting-state MPFC (Carhart-Harris et al., 2012a, 2012b) and coupled disinhibition of the limbic system could facilitate the spontaneous recollection of autobiographical memories. Research on psychedelic-assisted therapy in depression found that psilocybin activated autobiographical memories from a previous state of deactivation, which were accompanied by vivid recollections (Carhart-Harris et al., 2012a, 2012b). The authors suggest that facilitating the recall of positive life events with subsequent restructuring of negative biases could be attained with psilocybin-assisted therapy entailing positive memory cues.

The significant decrease in MPFC activity under psilocybin (Carhart-Harris et al., 2012a, 2012b), coupled with the normalization of MPFC hyperactivity present in patients with depression following successful treatment (Hamani et al., 2011), offer a potentially promising therapeutic outlook for patients with a disordered body image as well. Hyperactivation of the MPFC (Miyake et al., 2010) and a negative correlation between parahippocampal gyrus activation and severity of psychological symptoms in anorexia patients (Gaudio and Quattrocchi, 2012; Shirao et al., 2003) imply a dysfunction in the translation and storage of autobiographical memories related to the body image. Psilocybin has demonstrated an ability to bias emotional processing towards positive emotions by enhancing positive mood states, decreasing recognition of negative facial expression, and increasing behavior toward positive cues (Kometer et al., 2012). An increase in psilocybin-induced positive mood states seems to be tied to attenuation of amygdala reactivity (Kraehenmann et al., 2015), where psilocybin decreases the connectivity of the amygdala to important emotion processing nodes, such as the frontal pole or striatum (Grimm et al., 2018). Sustained amygdala hyperreactivity pattern in anorexia (Joos et al., 2011), depression (Siegle et al., 2007), and body dysmorphic disorder (Feusner et al., 2008) could thus be stabilized with psilocybin administration, and restructure negative bias towards more positive emotion processing mechanisms.

It is worth noting that emotional processing deficits in anorexia have been linked to obsessive-compulsive symptoms (Castro et al., 2010). The presence of an obsessive-compulsive disorder (OCD) comorbidity is common in anorexia (Altman and Shankman, 2009) and body dysmorphic disorder (Frías et al., 2015), while patients with a primary diagnosis of OCD reciprocally display bias towards negative emotions (Aigner et al., 2007). These disorders seem to be characterized by serotonin impairments, since tryptophan depletion (Barr, Barr, Goodman, & Price, 1992 as cited in Hanes, 1996) or 5-HT_{2A} antagonists (Craven and Rodin, 1987) seem to worsen symptoms. However, treatment with SSRIs often provide little remediation, suggesting that 5-HT_{2A} receptor agonism could offer a novel and more effective neuropharmacological modulation. An interesting case report of an individual with body dysmorphic disorder describes this patient's ability to alleviate his perceptions of alleged deformed facial features following psilocybin ingestion (Hanes, 1996). Remediation seemed to specifically be tied to the serotonergic modulation by psilocybin, since a treatment attempt with marijuana only exacerbated distress. Another patient was able to successfully treat his OCD with psilocybin for several years after all other treatment approaches had provided no relief (Wilcox, 2014). In another, double-blind, study using 29 psilocybin doses to treat OCD in nine patients, marked decreases in symptoms, as well as psychologically and spiritually enriching experiences, were reported (Moreno et al., 2006).

An effective mechanism of psychedelics could stem from their potential to restructure maladaptive memories, including those pertaining to aberrant self-referential processing. Within the predictive coding framework, changes in network connectivity from psychotropic 5-HT_{2A} receptor-mediated hyperactivation could lead to long-term learning (Pink-Hashkes et al., 2017). In animal studies, 5-HT_{2A} receptor agonists enhanced associative learning, likely due to increased activity at the 5-HT_{2A} receptor in the frontal cortex and hippocampus (Harvey, 2003), and facilitated mnemonic processes occurring in prefrontal pyramidal cells that participate in spatial working memory (Williams et al., 2002). Although memory-specific long-term effects of psychedelic experiences in humans remain to be further elucidated, long-lasting subjective positive effects, such as increased positive attitudes about the self, were reported up to 12 months post-experience (Schmid and Liechti, 2018).

Within the predictive coding framework, disorders such as depression, anorexia, and OCD have been suggested to stem from overly rigid predictions that are no longer correctly updated by incoming sensory information (Edwards et al., 2012; Riva, 2016). For example, a predictive coding account of OCD suggests that the 'formal narrative' of human cognition, or the "temporal sequence of cognitive states inferred from sense data" (Moore, 2015, p. 1), relies on a hierarchy of inference layers used to predict the global surroundings. Interruptions at any level of the hierarchy can lead to phenomenal experiences of something feeling not quite right, which are responded to by automatic corrections manifested as compulsions (Moore, 2015). Disruption of 5-HT_{2A} agonists in an appropriately positive and rewarding therapeutic setting could restructure long-term updates to the model and alleviate symptoms that are disruptive to the system.

Whether symptom alleviation is tied to a residual sense of well-being from the psychedelic state (the "afterglow phenomenon") (Majić et al., 2015), or alterations in memory processes that restructure the autobiographical self, remains to be elucidated. Although speculative, prolonged pharmacologic effects may ensue from down-regulation of 5-HT_{2A} receptors that cognitively restructure the narrative self. LSD has been shown to induce intracellular signal transduction changes that differ from endogenous 5-HT receptor binding (Backstrom et al., 1999) and decrease subsequent gene expression in the rat brain after a single dose (Nichols and Sanders-Bush, 2002). These changes could eventually effect downregulation of 5-HT_{2A} receptors via classical hallucinogens (Gresch et al., 2005) and improve serotonergic disturbances in aberrant states of the bodily self. The recently suggested link between serotonin and dysfunctional encoding/storage, consolidation, and retrieval/reconsolidation memory processes could account for impaired body memory and body image disturbances (Riva, 2016). Specifically, decreased serotonin levels purportedly facilitate encoding of allocentric episodic memories, consolidate emotional episodic memories precipitated by stress, reduce voluntary inhibition of mnestic contents, and impair allocentric spatial memory.

The ability of psychedelics to activate autobiographical memory in visual and other sensory modalities through an initial loosening the boundaries of the pre-reflective self, followed by cognitive restructuring in autobiographical memories of the narrative self (Fig. 3) could offer a holistic approach to disrupt maladaptive integration of multisensory information, increase interoceptive processing, reduce intrusive thoughts, and bias reconsolidation of memories towards positive emotional processing.

7. Future horizons for empirical approaches

It should be noted that psychedelics are not the only psychotropic substances to induce profound changes in consciousness and bodily self-awareness, and it is therefore debatable whether the hypothesized effects are specific to agonistic activation of the 5-HT_{2A} receptor, or whether psychotropic treatment of bodily self disorders could effectively include different neuropharmacological pathways. For example, while serotonergic hallucinogens such as psilocybin and LSD induce visual hallucinations through serotonergic modulation, they also enhance glutamatergic responses to sensory stimuli in the frontal cortex (Vaidya et al., 1997), and perhaps even enhance N-methyl-D-aspartate (NMDA) glutamate receptor signaling (Lambe and Aghajanian, 2006) in rodents, suggesting that excessive AMPA signaling without concomitant NMDA antagonism could increase sensory noise in the context of normal priors and lead to hallucinations (Corlett et al., 2016). Indeed, dissociative anesthetics (ketamine, phencyclidine, dizocilpine, and dextromethorphan) constitute a class of psychotropic substances that primarily act as antagonists of the NMDA receptor (Anis et al., 1983), inducing strongly dissociative experiences, such as disembodiment and ego transcendence (Vlisides et al., 2018), or altering multisensory processes in foreign limb ownership and physical hand mislocalization (Morgan et al., 2011). Psychotomimetic effects have been reported in clinical trials using ketamine for treatment-resistant depression, where common phenomenological reports include feelings of lightness and floating (Kreitschmann-Andermahr et al., 2001) or a sense of detachment (dissociation) from the body (Feifel et al., 2017). Blocking long-term potentiation (LTP) of the hippocampus through inhibition of glutamate-NMDA receptors could reduce symptoms in disorders such as OCD, since decreased LTP would moderate the intensity of repeated recall and block the formation of new memories. Indeed, partial block of NMDA glutamate receptors through ketamine infusions effectively reduced compulsive behavior in nine out of 15 anorexia patients who had a long history of eating disorder and had been resistant to several other forms of treatment (Mills et al., 1998). Another class of substances associated with altered bodily self-awareness are kappa opioid receptor (KOR) agonists such as salvinorin-A; the psychoactive component of the Mexican plant *Salvia divinorum* (Roth et al., 2002). It exerts its primary mechanism of action through an increase in dopamine levels of the dopaminergic reward circuit (Ebner et al., 2010), although it may also interact with the brain's endocannabinoid system (Braida et al., 2008). In contrast to the serotonergic effects of classical hallucinogens, salvinorin-A typically does not involve visual hallucinations (Addy, 2011); however, it does produce similar ego dissolution experiences that are accompanied by strong somatic sensations, such as loss of body ownership (Addy et al., 2015) or other strong alterations or sensations of the body. Therefore, although our focus was primarily placed on the serotonergic agonism of 5-HT_{2A} receptors induced by classical psychedelics, alterations of bodily experiences seem to constitute an essential component of other psychotropic substances as well, and it would certainly be of relevance to consider their effects not only for phenomenal bodily experiences, but also for disorders of the bodily self.

We believe that our arguments suggest a potentially strong scientific case for exploring the hypothesis that psychedelics could help remediate psychiatric disorders that affect the bodily self. In this section, we will now turn to the applicability of our hypothesis, including a few methods that deserve consideration as complementary approaches in psychedelic therapy. We expect that the protocol for patient inclusion criteria and recruitment would be comparable to previous clinical studies in patients with depression. Exclusion criteria should include a personal or family history of psychosis (drug-induced psychosis,

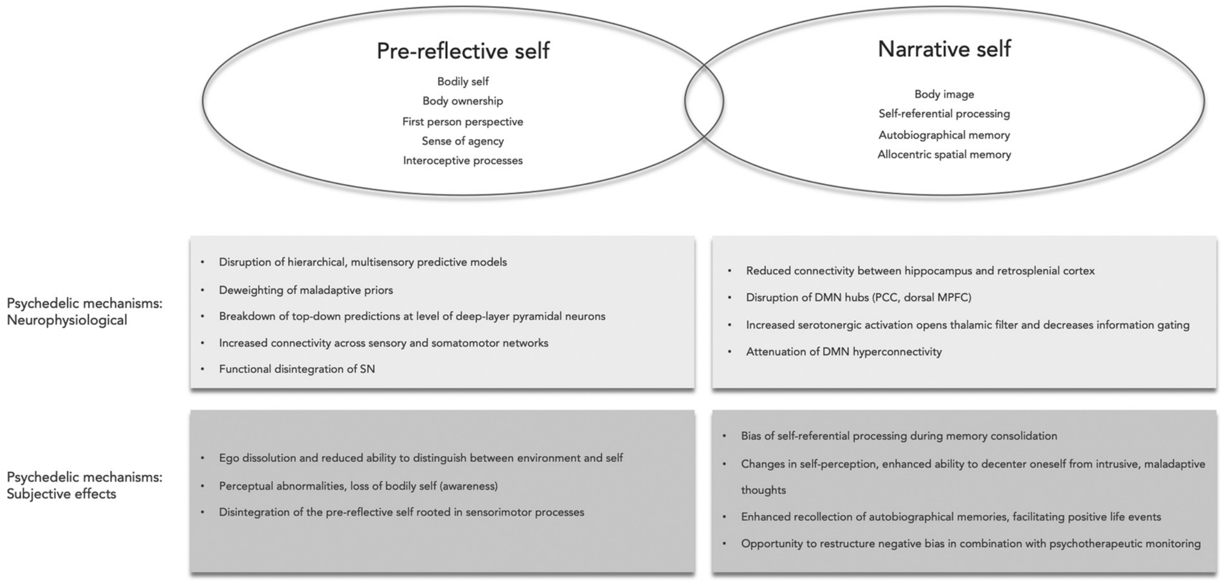

Fig. 3. Central characteristics of the pre-reflective self and narrative self, and the mechanisms through which psychedelics may modulate the bodily self on a neurophysiological and subjective level.

schizophrenia, bipolar disorder), current addiction to alcohol or any illicit drugs, or conditions such as epilepsy or serious heart conditions. Furthermore, downregulation of 5-HT_{2A} receptors from chronic administration of SSRIs in patients could attenuate the subjective effects of psychedelics (Bonson et al., 1996), so patients should not have received SSRI treatment, or there would need to be enough time allotted for a washout period from these medications.

Although psilocybin has demonstrated a very high safety ratio (Tylš et al., 2014) and low risk profile even in unsupervised settings (Nutt et al., 2010; van Amsterdam et al., 2011), precautionary measures for controlled and safeguarded settings to enhance positive memory recall while preventing or professionally managing the potential emergence of negative emotions generally associated with a so-called ‘bad trip’ are imperative for successful psychedelic therapy. Monitored sessions with a licensed practitioner may include a few sessions with psychotropic substances, accompanied by preparatory and integrative drug-free sessions (for a more detailed review, see Schenberg, 2018). Moreover, the number of sessions not only depend on the type and severity of the condition, but may further be modulated by the type of substance administered. While ketamine generally necessitates approximately one to 12 administrations for effectiveness, MDMA has shown positive effects within three sessions, while psilocybin and LSD could be effective within a single administration (Schenberg, 2018). To assure meaningful autobiographical and social-psychological experiences during these therapeutic sessions, patients should be continuously monitored and supported by trained mental health professionals following specific guidelines (Johnson et al., 2008), who encourage patients to stay introspective or open to feelings and attentive to thoughts and memories while receiving psychological support. Using such appropriate guidelines, psilocybin can switch autobiographical memory from a pattern of deactivation to activation (Carhart-Harris et al., 2012a, 2012b). When treating disorders such as depression, psilocybin could be combined with positive memory cues to facilitate the recall of positive life events to restructure autobiographical memory (Carhart-Harris et al., 2012a, 2012b).

While psychotropic modification of the bodily self may instigate possibly the most radical and instantaneous alterations in the bodily self and self-referential reorganization, it is worth noting that other physiotherapeutic modalities have also established successful applications. Transient alterations of the bodily self through experimental manipulation using bodily illusions have demonstrated positive results in treating health disorders. The use of virtual full body illusions have been employed to improve the disturbed experience of body image in patients with anorexia (Keizer et al., 2016), and have further demonstrated that embodying a virtual avatar can modify allocentric memory of the body by updating egocentric memory (Serino et al., 2016). The results from these studies highlight the flexibility of the bodily self and the ability to change it even for highly emotional body parts. There has been considerable research on virtual reality’s capacity to modify stereotypes (e.g., racial bias: Peck et al., 2013), the experience of pain (Hänsel et al., 2011; Martini et al., 2013; Pamment and Aspell, 2017), and even to increase self-compassion in individuals with depression (Falconer et al., 2016), evidencing that modifying bodily self-awareness through use of bodily illusions can change not only aberrant perceptions of the bodily self, but also induce restructuring of maladaptive thought processes. Bodily illusions could thus cognitively restructure forms of negative self-referential processing, such as rumination, in disorders such as depression or anorexia nervosa. The efficacy of virtual reality may stem from embodied simulations that emulate the bodily self in the real, physical world: both the brain and experiences in virtual reality maintain a simulation of the body and the surrounding space, and similarly entail predictions following multisensory input (i.e., morphological characteristics of the virtual avatar, movements) (Riva et al., 2019). Particularly, a combination approach employing bodily illusions as a complementary tool to psychedelic substances could potentiate remediation by reducing the precision weighting of aberrant priors through psilocybin while providing visual feedback tailored to the patient’s symptomatology with use of virtual reality and other bodily illusions. For example, in patients with depression, inducing a feeling of bodily lightness or disembodiment from the perceived heavy body could be achieved with virtual reality, wherein patients start to float away from the embodied virtual avatar and thus experience a decrease in perceived hyperembodiment. Potentially, continued use of bodily illusions following the initial psychedelic session could yield more remediating responses to disorders than use of either methodology alone. Virtual and augmented reality as embodied technologies are a particularly promising method of inducing such illusions, as the precise control of sensory information would allow for cognitive modeling by designing individualized environments that can simulate both the external and internal body and world (Riva et al., 2019).

Since aberrant bodily self-awareness could stem from an impaired ability to correctly to link afferent bodily signals to aversive or pleasant

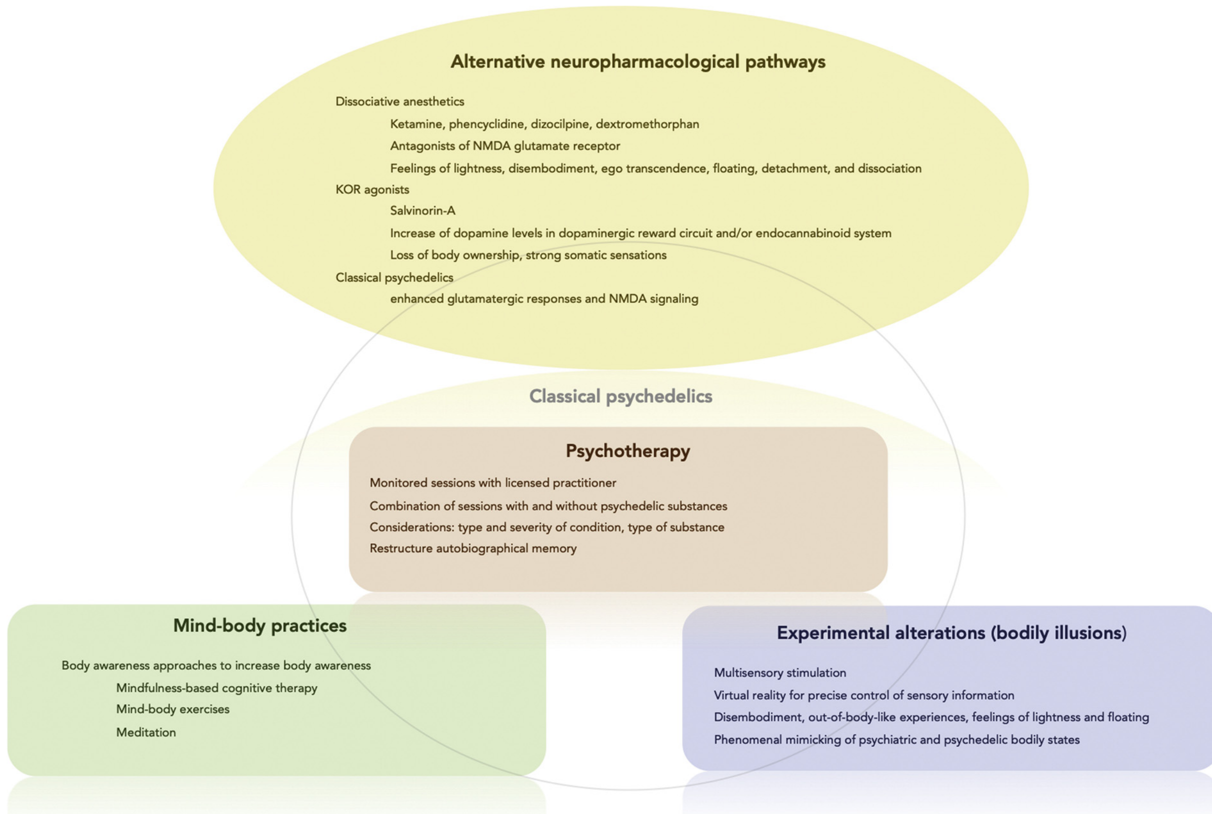

Fig. 4. Future considerations of potential therapeutic applications using psychedelic substances. A combination approach using psychedelic substances in combination with psychotherapy is recommended to assure monitored sessions with a licensed practitioner to restructure autobiographical memory. Additional inclusion of mind-body practices and/or experimental bodily illusions that further modulate perception of the body could complement the use of psychedelics in remediation of bodily self disorders.

outcomes (Riva, 2018a), body awareness approaches, such as yoga, mind-body exercises, or body awareness therapies aimed at improving the sensation and accurate interpretation of bodily signals, while increasing the awareness of oneself as an embodied agent, have demonstrated success in alleviating symptom severity in anorexia (Kolnes, 2012), depression (D'Silva et al., 2012; Schuver and Lewis, 2016), and even neurodegenerative diseases such as Parkinson's disease (Kwok et al., 2016). Moreover, mindfulness-based cognitive therapy modalities and meditation practices have evinced similar neuroplastic changes in the structure and function of brain regions implicated in self-awareness, while improving interoceptive accuracy (Tang et al., 2015). Future studies will benefit from more direct comparison between the efficacy and longevity of mindfulness-based modalities and psychedelics on the bodily self and wellbeing.

A combination approach integrating psychedelics and mind-body practices or bodily illusions with standard cognitive behavior therapy (Fig. 4) could prove complementary in providing significant and enduring remediation, especially in those cases that have failed to respond to more standard therapies. Adjunctive cognitive behavior therapy has already demonstrated success in sustaining or extending antidepressant effects of ketamine (Wilkinson et al., 2017), suggesting that utilizing psychedelic substances as a cognitive catalyst could render psychotherapeutic practices more effective.

8. Conclusion

There is converging evidence that the transient and reversible alteration of consciousness induced by psychedelic drugs can stimulate changes in a broad range of affective, sensorimotor, and cognitive functions. While well documented for acute states, less is known about the long-term changes. However, first evidence suggests that these multidimensional experiences can be broken down into several qualities that include phenomenal distortions of the body and alterations in autobiographical memory processes. We contrasted how the symptomatology of several disorders of the bodily self are characterized by disturbances across pre-reflective and narrative aspects, and related their shared impairments in multisensory processing to a Bayesian predictive coding framework. As neuropharmacological modulators of serotonergic activity via agonistic 5-HT_{2A} receptor activation, classical psychedelics induce phenomenal alterations of the bodily self. We posit this to occur through the entropic disintegration of associative networks that usually maintain the pre-reflective self, combined with a decreased functional coupling of the DMN that restructures self-referential processes pertaining to the narrative self. The psychedelically-induced perturbation of predictive filters that usually constrain the neural systems central to perception, emotion, and cognition opens avenues to novel and alternative ways of perceiving our self, and we have here presented potential functional mechanisms through which these psychedelically-induced changes of the pre-reflective and narrative self putatively occur.

However, it should be noted that these purported mechanisms are presently still largely speculative. While the Allocentric Lock Hypothesis (Riva, 2012) could credibly account for an ostensible shift in body-centered cognitive processing in disorders such as anorexia nervosa, and predictive coding may provide a plausible and widely-accepted theoretical framework for the bodily self, substantiating behavioral tasks will be required to empirically test the veracity of such models. Furthermore, psychedelic states have traditionally been compared with psychosis, but there has been some disagreement whether psychotic hallucinations could result from enhanced or weakened top-down predictive signaling (Sterzer et al., 2018). However, some emphasize that the psychedelic state and early psychosis do not fit the strong priors model, and that while high-level priors seem to be ineffective (i.e., less constraints on bottom-up prediction errors) in both schizophrenia and in the psychedelic experience, weak priors and high prediction error developing psychosis is more sustained than in the psychedelic state (Carhart-Harris and Friston, 2019).

Additionally, despite a prior-based mathematical approximation of psychopathological behavior, the neuronal activation underlying these mechanisms needs to be informed through anatomically and functionally plausible models that locate the aberrant coding mechanisms. Despite these limitations, the potential applications of psychedelic substances are extensive: while their symptom remediating benefits have already been demonstrated for a variety of disorders, we encourage future research to consider and more closely examine the potentially modulating phenomenal quality of body-specific effects during such experiences, as well as their therapeutic potential for disorders of the bodily self. Recently, a hypothesis that psychedelics increase brain complexity lead to a proposal to test classic psychedelics on disorders of consciousness (Scott and Carhart-Harris, 2019), suggesting that these substances may evince benefits for an impressively wide range of disorders.

Research employing psychedelic substances will not only provide prospective clinical alleviation for several disorders, but will further benefit from examining how the pre-reflective self and the narrative self are phenomenologically differentially represented along (bodily) dimensions of the self. Integrating these models with computational predictive coding frameworks and neuroimaging data will provide a more comprehensive interpretation of the underlying neurological signature of psychedelically-induced altered states of consciousness, and further elucidate the functional relevance of these substances in producing the purported enduring cognitive-affective alterations in remediation of aberrant bodily self.

Declaration of Competing Interest

None.

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