1521-0081/74/4/984–1029$35.00
PHARMACOLOGICAL REVIEWS
dx.doi.org/10.1124/pharmrev.121.000514
Pharmacol Rev 74:984–1029, October 2022
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ASSOCIATE EDITOR: ERIC BARKER

Self-Entropic Broadening Theory: Toward a New Understanding of Self and Behavior Change Informed by Psychedelics and Psychosis

Haley Maria Dourron, Camilla Strauss, and Peter S. Hendricks

Drug Use & Behavior Laboratory, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama (H.M.D., P.S.H.) and Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey (C.S.)

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Address Correspondence to: Dr. Peter S. Hendricks, Drug Use & Behavior Laboratory, 434 Ryals Public Health Building, 1665 University Boulevard, Birmingham, AL, 35294. E-mail: phendricks@uab.edu

This work received no external funding.

P.S.H. serves on the scientific advisory boards of Bright Minds Biosciences Inc., Eleusis Benefit Corporation, and Reset Pharmaceuticals, Inc. The authors have no other conflict of interest to disclose.

dx.doi.org/10.1124/pharmrev.121.000514.

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***Abstract*——The extremes of human experiences, such as those occasioned by classic psychedelics and psychosis, provide a rich contrast for understanding how components of these experiences impact well-being. In recent years, research has suggested that classic psychedelics display the potential to promote positive enduring psychologic and behavioral changes in clinical and nonclinical populations. Paradoxically, classic psychedelics have been described as psychotomimetics. This review offers a putative solution to this paradox by providing a theory of how classic psychedelics often facilitate persistent increases in well-being, whereas psychosis leads down a "darker" path. This will be done by providing an overview of the overlap between the states (i.e., entropic processing) and their core differences (i.e., self-focus). In brief, entropic processing can be defined as an enhanced overall attentional scope and decreased predictability in processing stimuli facilitating a hyperassociative style of thinking. However, the outcomes of entropic states vary depending on level of self-focus, or the degree to which the associations and information being processed are evaluated in a self-referential manner. We also describe potential points of overlap with less extreme experiences, such as creative thinking and positive emotion-induction. Self-entropic broadening theory offers a heuristically valuable perspective on classic psychedelics and their lasting effects and relation to other states by creating a novel synthesis of contemporary theories in psychology.**

***Significance Statement*——Self-entropic broadening theory provides a novel theory examining the psychedelic-psychotomimetic paradox, or how classic psychedelics can be therapeutic, yet mimic symptoms of psychosis. It also posits a framework for understanding the transdiagnostic applicability of classic psychedelics. We hope this model invigorates the field to provide more rigorous comparisons between classic psychedelic-induced states and psychosis and further examinations of how classic psychedelics facilitate long-term change. As a more psychedelic future of psychiatry appears imminent, a model that addresses these long-standing questions is crucial.**

I. Introduction

In recent years, classic psychedelic-assisted therapy has garnered substantial interest, largely due to its apparent transdiagnostic applicability and ability to promote enduring change (Johnson et al., 2019; Kočárová et al., 2021). Recent trials of classic psychedelic-assisted therapy have suggested potential efficacy for the treatment of substance use disorders (Bogenschutz and Johnson, 2016), depression (Davis et al., 2020; Carhart-Harris et al., 2021), end-of-life anxiety (Gasser et al., 2015; Griffiths et al., 2016; Ross et al., 2016), and demoralization in older AIDS survivors (Anderson et al., 2020). Moreover, enduring increases in well-being are reported in nonclinical populations in research settings (Griffiths et al., 2006, 2008, 2011, 2018) and with naturalistic classic psychedelic use (Forstmann et al., 2020; Agin-Liebes et al., 2021; Mans et al., 2021). Population-level analyses also suggest that classic psychedelic use is associated with protective mental health effects (Hendricks et al., 2015a, 2015b, 2018; Johansen and Krebs, 2015; Pisano et al., 2017). On a more biologic level, in vivo and in vitro studies have revealed that classic psychedelics produce significant increases in neuroplasticity and have potent anti-inflammatory effects (Flanagan and Nichols, 2018; Inserra et al., 2021a), which suggests therapeutic potential for a range of conditions.

Simultaneously, however, classic psychedelics have also long been considered candidate drug models of psychosis (i.e., psychotomimetics) (Osmond, 1957; Cohen, 1967; Vollenweider et al., 1998; Geyer and Vollenweider, 2008; Nelson and Sass, 2008; Carhart-Harris et al., 2013; Schmid et al., 2015; Carhart-Harris et al., 2016a; Leptourgos et al., 2020). Notably, Humphrey Osmond, who would later coin the term "psychedelic," first proposed that d-lysergic acid diethylamide's (LSD's) most innovative use was to study psychosis "from the inside," to "learn how to devise better methods of helping the sick" (Tanne, 2004). Osmond also developed the hypothesis that schizophrenia is due to a metabolic syndrome leading endogenously produced, psychedelic-like compounds to build up in the body, causing psychosis in some, but not all, individuals with this metabolic trait (Osmond and Smythies, 1952). Such a hypothesis was ultimately faulty but did inspire more research on the biologic basis of schizophrenia, causing a significant

ABBREVIATIONS: ASI, Aberrant Salience Inventory; CHR, clinical high-risk; D2, dopamine 2; DA, dopamine; 5D-ASC, 5-Dimensional Altered States of Consciousness; DMN, default mode network; DMT, N,N-dimethyltryptamine; EBT, entropic brain theory; FEP, first-episode psychosis; fMRI, functional magnetic resonance imaging; FPN, frontoparietal control network; 5-HT1a, serotonin 1A; 5-HT2a, serotonin 2A; 5-HT2AR, serotonin 2A receptor; L-DOPA, L-3,4-dihydroxyphenylalanine; LSD, d-lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; 5-MeO-DMT, 5-methoxy-N, N-dimethyltryptamine; PET, positron emission tomography; REBUS, relaxed beliefs under psychedelics; SEB, self-entropic broadening; SD, self-disorder; SSD, schizophrenia spectrum disorder; SSRI, selective serotonin reuptake inhibitors; SUD, substance use disorder; TRD, treatment-resistant depression; UHR, ultra-high risks; VTA, ventral tegmental area.

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shift from the predominately psychoanalytic atmosphere of the 1950s (Dyck, 2005; Kaplan, 2016). However, the idea that classic psychedelic substances in some way mimic psychosis has since deeply permeated and influenced the literature, even if the origin of this comparison is not well known.

For example, the first positron emission tomography (PET) brain imaging study using psilocybin, a classic psychedelic, stated that "[psilocybin] produces a psychosis-like syndrome in humans that resembles first episodes of schizophrenia" (Vollenweider et al., 1998). More recently, a study showed that LSD produces acutely increased ratings on the Psychotomimetic States Inventory, but also counterintuitively increased trait openness and optimism two weeks post–drug session (Carhart-Harris et al., 2016a). Another study reported that increases in aberrant salience, a prominent phenomenon in psychosis, occur during the acute effects of LSD (Wießner et al., 2021). However, increases in aberrant salience also correlated with increases in mindfulness and mystical experience measures, which have been related to the therapeutic effects of classic psychedelics (Barrett and Griffiths, 2017). This presents a conundrum as it suggests that classic psychedelics may produce experiences that are beneficial for mental health but that also mimic symptoms of psychosis during their acute effects; this is the psychotomimetic-psychedelic paradox.

To solve this paradox, we offer self-entropic broadening (SEB) theory, a novel working theory influenced largely by entropic brain theory (EBT) (Carhart-Harris et al., 2014; Carhart-Harris, 2018) and broaden-and-build theory (Fredrickson, 2001, 2004, 2013). We propose that the level of self-focus in entropic processing states can either facilitate well-being or exacerbate mental illness. To create this theory, we first speculate on how classic psychedelics can produce persisting positive changes in well-being and behavior by drawing on broaden-and-build theory, integrating ideas from awe as a mechanism of classic psychedelics (Hendricks, 2018) and EBT (Carhart-Harris et al., 2014; Carhart-Harris, 2018). However, this potential mechanism does not alone solve the psychotomimetic-psychedelic paradox. We then acknowledge the overlap between psychotic and classic psychedelic-induced states based on their entropic processing styles (i.e., an increase in attentional scope and a decreased predictability in processing stimuli, facilitating a hyperassociative style of thinking). Then, we delve into a discussion of the differential trajectories of "entropic states," based on the level of self-focus (i.e., the degree to which the associations and information being processed are evaluated in a self-referential fashion). Overall, SEB theory offers a potential solution to the psychotomimetic-psychedelic paradox and creates a cognitive-phenomenological-behavioral framework that acknowledges the importance of the self in relation to lasting psychologic change and potential biomarkers of well-being. While much of this work is, for now, speculative, it is our hope that this review energizes new perspectives and directions for psychedelic science and for understanding human flourishing and languishing.

Before beginning this ambitious synthesis, we first offer some points of clarification. Previous work has primarily drawn comparisons between psychotic and classic psychedelic states based on acute psychosis or the late prodromal phases of schizophrenia (Vollenweider et al., 1998; Geyer and Vollenweider, 2008; Nelson and Sass, 2008; Carhart-Harris and Friston, 2010; Carhart-Harris et al., 2014; Brouwer and Carhart-Harris, 2021). Due to this frequent point of comparison, and the confounding effects of long-term antipsychotic use (Goff et al., 2017), we will focus our discussion primarily on first-episode psychosis (FEP) and prodromal individuals, including those at ultrahigh risk (UHR) for developing schizophrenia. However, for the instances where no study examining these populations can be found, we discuss findings in schizophrenia.

The term "classic psychedelic" in this review refers to substances with a long history of human use and/or a significant research literature that derive most of their characteristic effects on subjective experience and cognition from agonism at the serotonin 2A receptor (5-HT2AR), including dimethyltryptamine (DMT), psilocybin, LSD, and mescaline (Nichols, 2016; Sexton et al., 2020). These substances produce a relatively unique receptor conformation at 5-HT2AR and provoke signaling pathways that promote transcription of proteins supportive of neuroplasticity, such as mammalian target of rapamycin and brain-derived neurotrophic factor (Inserra et al., 2021a; Flanagan and Nichols, 2018). Despite diverse secondary pharmacology (see Inserra et al., 2021a, for a review), classic psychedelics often produce similar subjective experiences, as has long been noted in the literature (Isbell, 1959). Recently, it was reported that psilocybin and LSD produce generally indistinguishable subjective effects (Holze et al., 2022); the authors proposed that "any differences between LSD and psilocybin are dose-dependent rather than substance-dependent." Additionally, preclinical studies have noted that rodents are often unable to distinguish between a variety of serotonin 2A (5-HT2a) agonists (Appel and Callahan, 1989; Winter et al., 2007; Winter, 2009; Nichols, 2016), with a few notable exceptions, including the importance of serotonin 1A (5-HT1a) agonism for 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) (which is arguably not a classic psychedelic; Winter et al., 2000; Nichols, 2016) and the importance of dopaminergic effects for LSD in the later time course of the drug (Marona-Lewicka et al., 2005; Marona-Lewicka and Nichols, 2007), which may not be relevant for subjective effects in humans (Pokorny et al., 2020).

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Furthermore, to our knowledge, there are no substance-specific questionnaires to assess the subjective effects of the different classic psychedelics; questionnaires such as the 5-Dimensional Altered States of Consciousness (5D-ASC) questionnaire (Studerus et al., 2010), Ego Dissolution Inventory (Nour et al., 2016), and Mystical Experience Questionnaire (Barrett et al., 2015) are used to assess the effects of all classic psychedelics. The 5D-ASC, for example, has been used to assess the subjective effects of psilocybin (Griffiths et al., 2016; Smigielski et al., 2019a, 2019b), ayahuasca (Uthaug et al., 2021), and LSD (Liechti et al., 2017; Wießner et al., 2021). Naturalistic studies also regularly probe the effects of classic psychedelic use in general and its potential effects on psychologic health (Hendricks et al., 2015a, 2015b; Carhart-Harris et al., 2018c), problematic substance use (Garcia-Romeu et al., 2019, 2020), and creativity (Sweat et al., 2016).

Additionally, other theories of classic psychedelics' mechanism of action, including thalamic gating theory (Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Vollenweider and Smallridge, 2022), EBT (Carhart-Harris et al., 2014; Carhart-Harris, 2018), awe as a mechanism of classic psychedelics (Hendricks, 2018), relaxed beliefs under psychedelics (REBUS) (Carhart-Harris and Friston, 2019), pivotal mental states (Brouwer and Carhart-Harris, 2021), and the cortico-claustrum-cortical model (Doss et al., 2022) propose mechanisms of classic psychedelics as a class of substances, and do not take into account pharmacological differences between classic psychedelics. For these reasons, SEB focuses on a generalized mechanism of the effects of classic psychedelics, rather than the peripheral pharmacological differences between them, with occasional discussions in exception to this framework (see *Chronic LSD Administration: A True Psychotomimetic?* and *The Role of 5-HT1a and Entropic States*).

A. Classic Psychedelics and Broaden-and-Build Theory: Understanding Enduring Positive Change

Classic psychedelics' seemingly broad applicability and potential for producing enduring effects warrant the consideration of general mechanisms of lasting psychologic and behavioral change supported by their physiologic effects. Broaden-and-build theory (Fredrickson, 2000, 2001, 2004; Fredrickson and Joiner, 2002; Van Cappellen et al., 2018) and the related "upward spirals" (Garland et al., 2010) offer general hypotheses about how temporary increases in well-being can produce enduring positive effects. Broaden-and-build theory proposes that positive emotions broaden attentional scope and facilitate increases in momentary thought-action repertoire. Attentional broadening occurs at a basic processing level, with individuals reporting an increase in global over local visual processing after being exposed to a positive stimulus (Fredrickson and Branigan, 2005; Jäger and Rüsseler, 2016). This broadening of attention is thought to facilitate an unusual, flexible, creative, and "open to information" style of thinking that enhances exploratory and social behavior, fostering the building of lasting resources (Fredrickson, 2001). Broaden-and-build theory has been verified by individuals reporting an increase in items they would like to do after positive-emotion induction, suggesting an increase in attentional scope and flexibility of behavior (Fredrickson and Branigan, 2005). Engaging in more exploratory behavior allows the building of more personal resources, including social, intellectual, psychologic, and physical resources, which in turn promotes continued increases in life satisfaction (Johnson et al., 2009). In contrast, in negative emotion states, thought-action repertoire is narrowed. From an evolutionary perspective, this is thought to evoke specific self-preserving action-tendencies such as flee or attack. Examining classic psychedelics through the lens of broaden-and-build theory offers an explanation for how transient changes in cognition can facilitate lasting changes in behavior and well-being, which has largely been lacking in mechanistic models of classic psychedelics. Although broaden-and-build theory does not fully explain the long-term efficacy of classic psychedelics, it does provide a viable starting point for the current SEB theory.

A variety of work suggests that classic psychedelics may increase attentional scope and thought-action repertoire, although this has yet to be tested directly. Classic psychedelics have been found to increase openness to new experiences, both in controlled research settings (MacLean et al., 2011; Lebedev et al., 2016) and with naturalistic use (Erritzoe et al., 2019). This suggests a broadening of thought-action repertoire, as openness to experience is related to the tendency to seek out novel information and activities (Costa and McCrae, 2010). Classic psychedelics have been shown to increase mindfulness capabilities (Soler et al., 2016; Sampedro et al., 2017; Uthaug et al., 2019; Madsen et al., 2020; Murphy-Beiner and Soar, 2020; Mans et al., 2021) and absorption (Barrett et al., 2020a), where mindfulness is defined as an "attentiveness and non-judgmental acceptance of present-moment experience"(Bishop et al., 2004), resulting in a broadening of awareness (Garland et al., 2015; Garland and Fredrickson, 2019), and absorption is the predisposition to have one's attention fully present to an experience to the extent that awareness of the self is reduced (Tellegen and Atkinson, 1974). Both findings suggest a broadening of attentional scope. These postacute increases in mindfulness have been correlated to alteration in neural functioning on both a system (Smigielski et al., 2019b) and metabolic level (Sampedro et al., 2017).

Additionally, according to Fredrickson, an expanded thought-action repertoire encourages the building of enduring psychosocial resources (Fredrickson, 2001; Fredrickson and Joiner, 2002). Increases in social connectedness have been reported after ceremonial (Kettner et al., 2021) and unstructured (Carhart-Harris et al.,

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2018a) classic psychedelic use. Additionally, long-term increases in prosocial behavior have been reported by independent community members (of participants in a psilocybin study), suggesting actual behavior change rather than expectancy effects (Griffiths et al., 2018). Similarly, reductions in antisocial behavior have been associated with classic psychedelic use (Walsh et al., 2016; Hendricks et al., 2018).

More overtly, long-term follow-up interviews in patients with treatment-resistant depression (TRD) after psilocybin-assisted therapy display many themes consistent with broaden-and-build theory (Watts et al., 2017). Themes of reconnecting to past activities or starting new ones and "discovering new values/perspectives" were noted, suggesting increases in thought-action repertoire. Additionally, participants reported an increased appreciation and attention to their surroundings in the postacute effects, representing enhanced attentional scope. Similar findings have emerged in long-term follow-up interviews for a variety of conditions (Breeksema et al., 2020) and with naturalistic use, including after challenging experiences (Gashi et al., 2021).

On a neurophysiologic level, it may be that classic psychedelics open a critical period where increases in neuroplasticity and reductions in neuroinflammation (Inserra et al., 2021a) facilitate the ability to adopt the positive cognitive-behavioral changes that individuals are inspired to make from the acute psychologic effects (Hendricks, 2018) and thus further reinforce broadening-and-building effects. We speculate that these reductions in neuroinflammation and increases in neuroplasticity are subsequently further supported with the building of enduring resources that may contribute to lasting improvements in physiologic and psychologic health. In support of this view, independent of classic psychedelics, exercise (El-Sayes et al., 2019), social connection (Davidson and McEwen, 2012), and meditation (Gomutbutra et al., 2020) support neuroplasticity. This leads us to speculate that increases in thought-action repertoire and psychosocial resources in the postacute effects assist in maintaining the positive effects of classic psychedelics on physiologic and psychologic health.

However, we must briefly note that other substances, such as selective serotonin reuptake inhibitors (SSRIs), are also capable of decreasing inflammation (Tynan et al., 2012; Marcinowicz et al., 2021) and neuronal atrophy (Duman et al., 1997; Duman, 2004) and normalizing resting state network pathologies associated with depression (Posner et al., 2013). However, SSRIs lack the ability to provoke profound alterations in subjective experience, as classic psychedelics do (Hendricks, 2018). It is likely that acute alterations in experience occasioned by classic psychedelics produce a "psychological catalyst" that promotes rapid postacute psychologic change, which may greatly assist in moving toward flourishing, as opposed to normalization of neurophysiologic pathology alone, which conventional antidepressants do promote over extended periods of use (Duman, 2004; Andrade and Rao, 2010).

B. Attentional Broadening: Awe and the Entropic Brain

The distinct ability of classic psychedelics to elicit rapid change, rather than slow improvements seen in other experiences where broaden-and-build theory is applied, may be due to classic psychedelics inducing profound levels of the self-transcendent emotion of awe, perhaps in part due to significant changes in network connectivity (Hendricks, 2018). Awe occurs in response to an appraisal of vastness and novelty (high information density), leading to a rapid accommodation of information, or a broadening of attentional scope, through alteration of mental schemas (Keltner and Haidt, 2003; Chen and Mongrain, 2020; Perlin and Li, 2020). This alteration in mental structures and high information density precipitate an experience of the "small self" (Keltner and Haidt, 2003; Hendricks, 2018), decreasing self-focus. The reorganization of mental structures in response to information-richness is unique to the emotion of awe (Darbor et al., 2016).

Although broaden-and-build theory and awe as a mechanism of classic psychedelics provide emotion-focused perspectives, both overlap with aspects of two complementary conceptual frameworks in the field of psychedelic science: EBT (Carhart-Harris et al., 2014; Carhart-Harris, 2018) and REBUS (Carhart-Harris and Friston, 2019). EBT posits that the higher the neural entropy, the richer the qualia of experience, or the higher the information density (Carhart-Harris et al., 2014; Carhart-Harris, 2018). According to this model, classic psychedelic-induced states, creative thinking, and early psychosis are marked by high entropy. In contrast, states such as depression, addiction, and vegetative states are lower-entropy states. Importantly, according to EBT in its original form, "ego" disruptions are needed to access an entropic state (Carhart-Harris et al., 2014). Despite the differences in terminology, the overlap between the "small self" and "ego disruptions" with a high information density described by both awe and EBT suggests converging constructs. Awe also overlaps substantially with many concepts expressed in REBUS (Carhart-Harris and Friston, 2019). REBUS posits that high-level priors (e.g., beliefs) become less weighted under classic psychedelics and in other entropic states (e.g., early psychosis). This reduction in weighting of high-level priors fosters a more "anarchic" style of information processing. This parallels the rapid accommodation of mental structures induced by the appraisal of vastness and novelty in awe.

Additionally, EBT parallels aspects of broaden-and-build theory. It has been suggested that entropy is related to increases in postacute cognitive-behavioral

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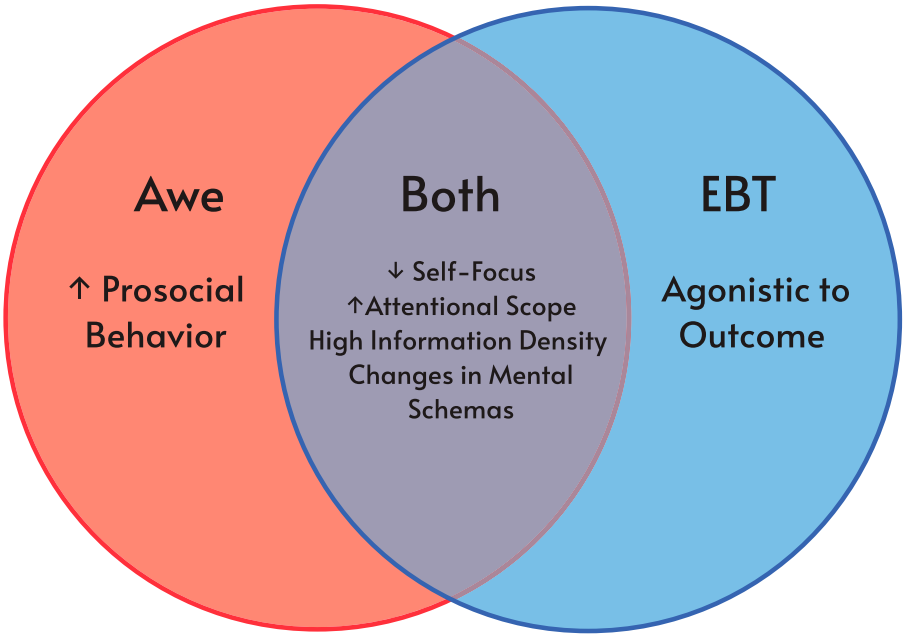

Fig. 1. Awe and the entropic brain. This Venn diagram illustrates the substantial overlap between EBT and awe as mechanisms of classic psychedelics' effects. Both mechanisms suggest that classic psychedelics elicit alterations in information processing, increases in information richness, as well as decreases in self-focus. However, awe specifically accounts for the prosocial effects of classic psychedelics, whereas EBT does not address social effects and is agnostic to the outcomes of entropic states.

flexibility (Carhart-Harris et al., 2014). According to EBT, "…it is the ability of [classic] psychedelics to disrupt stereotyped patterns of thought and behavior by disintegrating the patterns of activity upon which they rest that accounts for their therapeutic potential" (Carhart-Harris et al., 2014). This occurs through classic psychedelics promoting "a wider range of functional connectivity motifs, and correspondingly a broad repertoire of subjective states with high information richness" (Carhart-Harris et al., 2014). High information density and a wider range of subjective states could be described as a broader attentional scope. Moreover, these alterations are thought to facilitate changes in behavior. It is therefore plausible that entropy promotes increases in thought-action repertoire.

Recent research suggests that this may be the case. Increases in neural entropy during the acute effects of LSD are predictive of increases in openness to new experiences two weeks later (Lebedev et al., 2016). Additionally, neural entropy has been shown to be predictive of divergent thinking ability in sober individuals (Shi et al., 2019). Likewise, under the acute influence of LSD, language becomes significantly more entropic, which may reflect more entropic thought processes (Sanz et al., 2021). These studies suggest that the association between neural entropy and expanded thought-action repertoire should be explored further.

Similarly, awe itself promotes broaden-and-building by increasing prosocial behavior (Piff et al., 2015; Darbor et al., 2016; Chen and Mongrain, 2020; Fogarty, 2020; Perlin and Li, 2020), nature-relatedness and ecological behavior (Shapshay et al., 2018; Yang et al., 2018; Zhao et al., 2018), and creativity (Chirico et al., 2018). Moreover, classic psychedelic-induced increases in openness to new experiences may pave the way to more frequent ordinary experiences of awe (Hendricks, 2018). Awe has also been shown to increase flexibility and create more accommodating mental frameworks (Chirico et al., 2018).

In summary, EBT/REBUS and awe suggest that classic psychedelics work in part by decreasing rigidity of mental processing frameworks and increasing information richness, leading to a less constrained style of cognition with alterations in self-focus. We postulate that alterations in mental schemas facilitate a broader attentional scope, expanding an individual's thought-action repertoire, which enables the building of enduring resources. The acute effects are likely produced by significant changes in functional network connectivity (Carhart-Harris et al., 2016b; Lebedev et al., 2016; Barrett and Griffiths, 2017; Viol et al., 2017; Müller et al., 2018; Barrett et al., 2020b), whereas the postacute building of enduring resources is likely facilitated in part by increases in neuroplasticity (Ly et al., 2018; Aleksandrova and Phillips, 2021; Inserra et al., 2021a; Vollenweider and Smallridge, 2022).

However, a dilemma posed by EBT is that early psychosis is also an entropic state that clearly does not facilitate well-being. Crucially, much of the earliest work characterizing the effects of classic psychedelics was based on their ability to produce a psychotomimetic state (Savage, 1955; Osmond, 1957; Hofmann, 1959; Klee, 1963; Cole and Katz, 1964; Dubanský and Vyhnánková, 1965; Cohen, 1967; Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 1998; Vollenweider and Geyer, 2001; Tanne, 2004; Carhart-Harris, 2007; Geyer and Vollenweider, 2008). This suggests that EBT's comparison is drawn on viable overlap between psychosis and classic psychedelic states. An initial attempt to show how the states differ might offer that classic psychedelic-induced experiences have positive emotional

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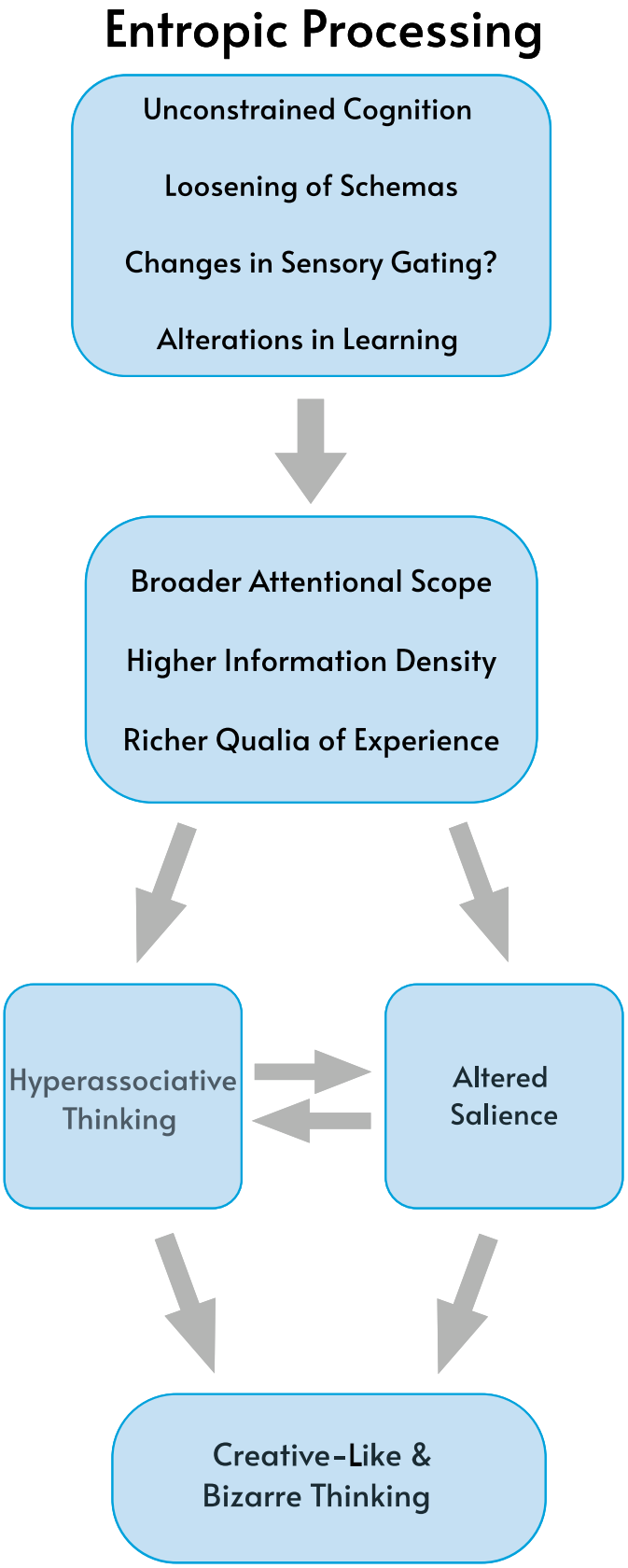

Fig. 2. Entropic processing. Entropic processing is a style of thinking with a loosening of schemas, often resulting in decreases in cognitive efficiency. The decreased reliance on mental schemas leads to a broader attentional scope with higher information density. These alterations foster hyperassociative thinking, promoting altered salience as stimuli are interpreted in novel ways. The increased attention to irrelevant cues and novel connections may facilitate creativity; however, in more extreme forms of entropic processing, deficits in executive functioning prevent these increases in creativity. SEB theory proposes that it is the sense of both altered meaning and reduced predictability of the world in which classic psychedelic states and psychosis significantly overlap.

valence, whereas psychosis is a similar state with negative emotional valence.

However, although classic psychedelics' acute effects are not universally positive in emotional valence (Barrett et al., 2016; Carbonaro et al., 2016; Brouwer and Carhart-Harris, 2021; Davis et al., 2021; Gashi et al., 2021), classic psychedelics do appear to broaden attentional scope, increase thought-action repertoire, and facilitate persisting increases in wellness, as reported by clinical studies (Tullis, 2021). Additionally, they show population-level protective mental health effects (Krebs and Johansen, 2013; Hendricks et al., 2015b). Moreover, the earliest stages of psychosis can occasionally be marked by positive valence (Bowers and Freedman, 1966; Yung and McGorry, 1996; Yeiser, 2017). Emotional valence is therefore an unlikely candidate for differentiating psychosis and classic psychedelic-induced states, and thus perhaps the difference between languishing and flourishing. Therefore, it is first necessary to create an integrative overview of the states' similarities to then be able to define their core differences more accurately.

II. Entropic Processing

In recent years, the overlap between psychosis and classic psychedelic-induced states has primarily been discussed in terms of primary process cognition (Carhart-Harris and Friston, 2010; Carhart-Harris et al., 2014; Kraehenmann et al., 2017; Girn et al., 2020) and alterations in thalamic gating (Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Avram et al., 2021; Vollenweider and Smallridge, 2022). Primary process cognition is a Freudian construct that has been described as a "primitive, animistic style of thinking," marked by magical thinking, bizarre thought content, and "muddled thinking" (Carhart-Harris and Friston, 2010). While the basis of primary process cognition as a "protoconsciousness" (Carhart-Harris and Friston, 2010) is not endorsed by this paper, the construct does suggest potential phenomenological overlaps between psychotic and classic psychedelic states. These alterations can largely be generalized as hyperassociative or unconstrained forms of thinking (Girn et al., 2020). In parallel, REBUS supposes that both states display a "reduced precision weighting on high-level priors" (Carhart-Harris and Friston, 2019). Similarly, psychosis researchers have long independently described psychosis as an overinclusive (Cameron, 1938; Epstein, 1953) or hyperassociative (Miller, 1989) style of thinking with alterations of

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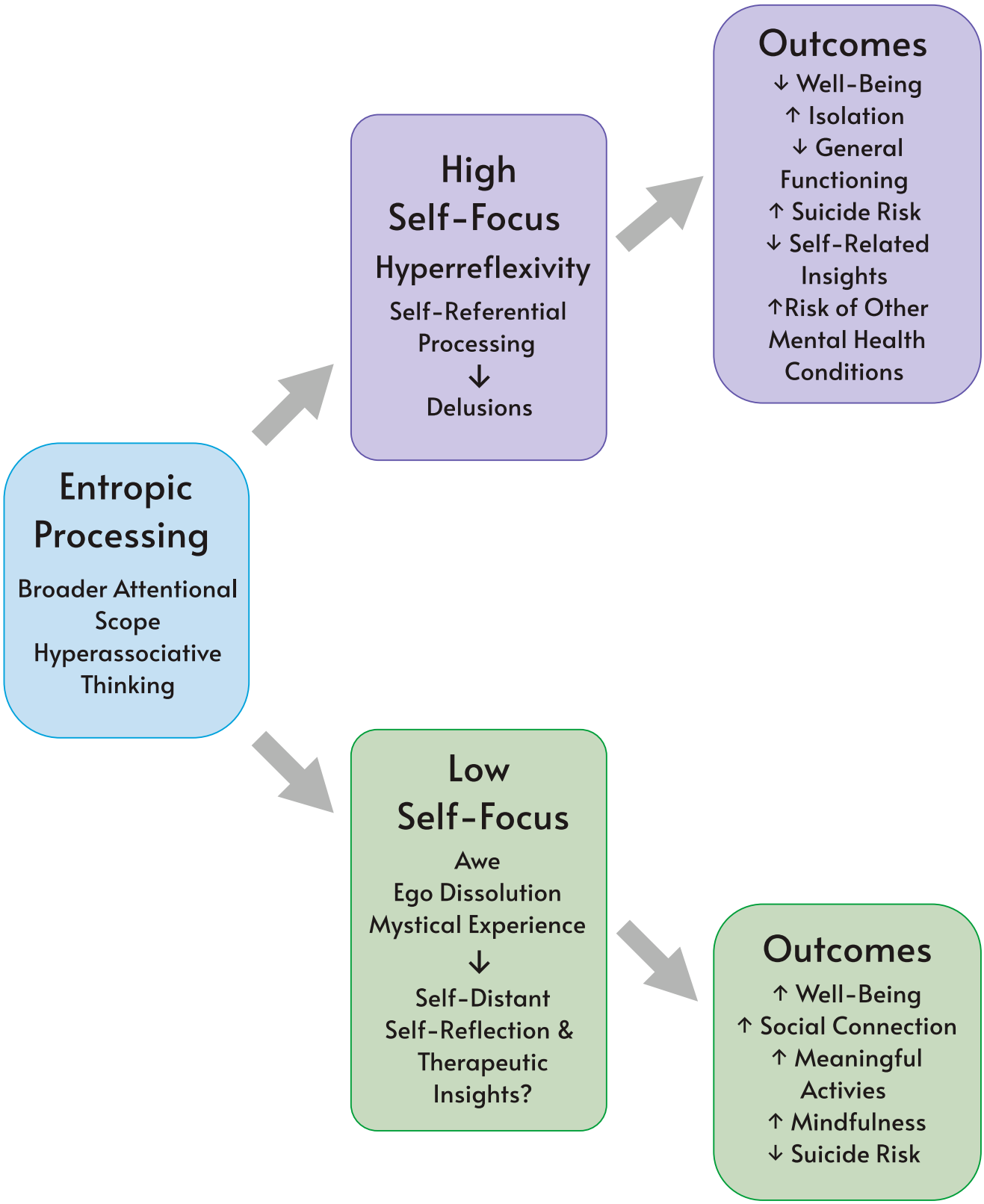

Fig. 3. The trajectory of entropic processing. This figure illustrates how both classic psychedelic states and psychosis develop different trajectories based on levels of self-focus, despite sharing an entropic processing style. The entropic processing style occurs due to a loosening of mental schemas, leading to a broader scope of attention. This leads to a need to reinterpret the world rapidly, which creates a hyperassociative style of thinking and altered salience. However, in psychotic states, there is a high level of self-focus. This is characterized by hyper-reflexivity and a tendency to interpret external stimuli as self-relevant. The increased awareness of the environment with increases in self-focus facilitates the formation of delusions, which are often explicitly self-focused in theme. In classic psychedelic states, alterations to the sense of self often produce feelings of merger into the environment and a hyporeflexive processing style (decreased self-consciousness in the processing of internal experiences). Experiences are often reflected on from a self-distanced perspective. These alterations in self-focus are predictive of long-term benefits, which often include a broad range of changes that promote enduring well-being after exposure to classic psychedelics.

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attentional scope (Dykes and McGhie, 1976; Stavridou and Furnham, 1996; Bredgaard and Glenthøj, 2000) and a blurring of "conceptual boundaries" (Chapman, 1966) with a failure of predictive cues (Gray, 1998).

In many ways, the thalamic gating theory further supports the similarities between psychosis and classic psychedelic–induced states (Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Vollenweider and Smallridge, 2022). According to Geyerand Vollenweider (2008), altered thalamocortical transmission in both psychosis and classic psychedelic–induced states produces "cortical inundation with sensory and cognitive information," inducing "an inability of these patients to screen out, inhibit, filter, or gate extraneous stimuli and to attend selectively to salient features of the environment." This parallels the increases in information richness that EBT proposes is characteristic of both states and shows conceptual similarity with a broadening of attentional scope.

We will add nuance and unity to these frameworks by characterizing entropic processing by several criteria, including alterations seen in learning, salience/meaning attribution, and creativity. In general, entropic processing, a psychologic construct, can be defined as an enhanced overall attentional scope with a decreased predictability in processing stimuli, facilitating a hyperassociative style of thinking that promotes altered salience/meaning attribution. The following sections describe the significant overlap between early psychosis and classic psychedelic–induced states, an overlap that has long been assumed in psychedelic science. However, these comparisons must be carefully specified into testable measures, and defining entropic processing as a construct facilitates this important step in the research process.

Additionally, it is relevant to acknowledge that although classic psychedelics may mimic aspects of psychosis, these alterations in some magnitude also occur with nonproblematic phenomena, such as in individuals with enhanced creativity (Andreasen and Powers, 1975; Carson, 2011; Crabtree and Green, 2016; Wang et al., 2018) or after positive-emotion induction (Phillips et al., 2002; Biss and Hasher, 2011). These discussions clarify that entropic processing itself is of neutral valence and is not predictive of long-term outcomes. Additionally, we will describe how an entropic processing style can be arrived at through a variety of neurobiological states by discussing overlap with other psychosis-like experiences that are largely neurobiologically distinct from the effects of classic psychedelics, including those produced by excessive dopamine (DA) signaling (Poletti, 2018). The role of alterations in thalamic connectivity in potentially provoking a sense of increased information richness will also be explored due to this being a frequent point of comparison.

A. Learning and Attention Filtering

Both psychosis and classic psychedelic–induced states have long been described as involving reduced filtering, leading to a more information-rich state with a broader attentional scope. The writer Aldous Huxley first supposed that classic psychedelics work by limiting the "reducing valve" of the brain to allow the "mind at large" to be experienced (Huxley, 1954). Subsequently, some have proposed that dysregulation of the default mode network (DMN) (Carhart-Harris et al., 2012, 2014; Carhart-Harris and Friston, 2019) or decreased thalamic gating (Vollenweider and Geyer, 2001; Vollenweider and Smallridge, 2022) may be in part responsible for classic psychedelics decreasing the "reducing valve" of subjective experience, further substantiating the importance of a broadening of attentional scope, despite the differences in proposed mechanisms. Additionally, schizophrenia has also long independently been described as an attentional deficit in filtering, leading to an "information overflow" (Braff et al., 1978; Nuechterlein and Dawson, 1984; Geyer and Braff, 1987). The supposed impairments in filtering may lead to a richer information state, but one that does not foster optimal cognitive efficiency, promoting overlapping impairments in some forms of learning and attention in psychosis and classic psychedelic–induced states; however, these similar cognitive deficits do not necessarily imply comparable neurologic etiologies on a molecular level.

In learning tasks, both psychosis and acute classic psychedelic–induced states are marked by a failure to filter out irrelevant stimuli due to a deficit in selective attention or a broadening of attentional scope. In schizophrenia, increased attention to irrelevant cues during a causal learning task has been correlated with positive symptom severity (Morris et al., 2013). Additionally, otherwise healthy people high in schizotypy displayed increased attention to irrelevant cues and alterations in attentional scope (Le Pelley et al., 2010), though not all studies have noted this (Green and Williams, 1999). In classic psychedelic–induced states, decreased filtering of irrelevant information may lead to impairments in associative learning (seen via lack of test-retest effects) during acute effects (Mason et al., 2021). Likewise, impairments in executive functioning and cognitive flexibility during the acute period of LSD action may be due to increased attention to task-irrelevant stimuli (Pokorny et al., 2020). Others have suggested that impairments in attention during the acute effects of psilocybin are due to a reduced ability to suppress distracting information (Carter et al., 2007). It should also be noted that, despite cognitive impairments during acute effects, classic psychedelics have been shown to facilitate learning in the postacute period, at least in animal studies (Cameron et al., 2018; Morales-Garcia et al., 2020).

Additionally, studies have explored the alterations that occur in psychosis and classic psychedelic–induced states using the Color-Word Stroop test, revealing

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impairments in both selective attention and cognitive control in psychosis and in those with a family history of psychosis (Mulet et al., 2007; Hou et al., 2016) and during the acute effects of classic psychedelics (Wapner and Krus, 1960; Quednow et al., 2012). Increases in Stroop reaction times have also been associated with delusional proneness in nonpsychotic samples (Orem and Bedwell, 2010) and in people with schizophrenia (Peters and Garety, 2006). Psilocybin promoted similar reductions in performance, which correlated with experiences of thought disorder and a loss of control over thinking and body, likely due to reductions in inhibitory control (Quednow et al., 2012). Intriguingly, an early study found that both controls and people with schizophrenia exhibited impairments on the Color-Word Stroop test during the acute period of LSD action (Wapner and Krus, 1960), which was attributed to a primary process style of thinking in both states. Overall, similar reductions of performance on the Stroop test suggest similar deficits present in both psychosis and classic psychedelic-induced states; these alterations may be related to the subjective effects characteristic of entropic processing, such as thought disorder, a sign of hyperassociative or chaotic thinking.

Intriguingly, pretreatment with ketanserin, a 5-HT2a antagonist, blocked psilocybin-induced deficits on the Stroop test, leading authors to posit that 5-HT2a signaling may also be implicated in the deficits in filtering in schizophrenia (Quednow et al., 2012). However, there is significant evidence that altered dopaminergic functioning may also be involved in these deficits in schizophrenia, perhaps in part due to aberrant phasic firing of DA neurons in the ventral tegmental area (VTA), producing increases in attention to irrelevant stimuli (Kapur, 2003; Heinz and Schlagenhauf, 2010; Maia and Frank, 2017). This may foster an overlearning of irrelevant information, facilitating associations between unrelated events (Millard et al., 2022) while impairing the ability to learn adaptive predictive cues (Maia and Frank, 2017).

In contrast, there is significant evidence that alterations in cognition from LSD are largely due to agonism of the 5-HT2AR, despite also acting at the dopamine 2 (D2) receptor (Nichols, 2016). Pretreatment with ketanserin has been shown to block LSD-induced increases in primary process cognition (Kraehenmann et al., 2017) and deficits in executive functioning, working memory, and cognitive flexibility (Pokorny et al., 2020). However, it may still be possible that alterations in classic psychedelics produce changes in dopaminergic signaling due to action at nondopaminergic receptors. For instance, an in vivo electrophysiology study in rats reported that high doses of LSD can reduce VTA firing through a complex mechanism involving 5-HT1A, D2, and TAAR1 receptors (De Gregorio et al., 2016). It also should be noted that ketanserin does not block the slowing in binocular rivalry produced by psilocybin (Carter et al., 2007), showing that while 5-HT2a may be primarily responsible for alterations in cognition and subjective experience, other receptor types may cause other, less significant changes elicited by classic psychedelics.

Furthermore, dopaminergic drugs can produce effects paralleling those seen in psychosis, suggesting that psychosis may be largely due to alterations in DA signaling. At high doses, amphetamines produce increases in spontaneous phasic firing of VTA neurons while also diminishing adaptive phasic increases in DA for relevant stimuli (Maia and Frank, 2017). Additionally, L-3,4-dihydroxyphenylalanine (L-DOPA), a DA precursor used as a medication in Parkinson's disease, produces alterations in latent inhibition (Polner et al., 2016; Györfi et al., 2017), even with only a single dose (Györfi et al., 2017), which signifies more attention allocated to irrelevant cues. This is unlikely to be a phenomenon specific to those with Parkinson's disease, as L-DOPA in healthy normals causes increases in attentional capture by distractors (Riedel et al., 2022). In contrast, DA depletion has been found to increase attentional control on the Stroop-Color Word task (Scholes et al., 2007), and, intriguingly, the same study also found these results with serotonin depletion. Still, it should be noted that at more moderate doses, amphetamines can increase adaptive striatal firing to a predictive cue (Maia and Frank, 2017).

It is relevant to note that attention to irrelevant cues in learning paradigms is not necessarily indicative of psychopathology. Increased attention to irrelevant cues has also been noted in people high in creative achievement (Carson et al., 2003) and after positive-emotion induction (Biss and Hasher, 2011; Putkinen et al., 2017), which has also been noted to impair selective attention and inhibitory control (Rowe et al., 2007) and decrease performance on the Color-Word Stroop task (Phillips et al., 2002). Although the magnitudes of these alterations differ, the trend toward similar patterns of deficits again suggests that entropic processing itself is not necessarily pathologic. Furthermore, it is possible that these alterations in attention might be due in part to endogenous releases of serotonin and/or DA: positive emotion induction has long been posited to implicate DA release (Ashby et al., 1999; Mitchell and Phillips, 2007; Yin, 2019; Alexander et al., 2021).

In summary, many cognitive profiles of schizophrenia and classic psychedelics appear remarkably similar, however, their neurobiological etiologies may be partially distinct given the necessity of 5-HT2a agonism for classic psychedelic effects and the ability of dopaminergic drugs to produce effects similar to psychosis. Despite these potential differences, it appears that both psychosis and classic psychedelic–induced states are marked by a reduced ability to suppress distracting information,

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perhaps resulting in a subjective sense of "information overload."

B. Altered Salience

Both psychosis and classic psychedelic–induced states profoundly alter perceptions of reality, largely due to altered salience of ordinary stimuli, provoking an experience that is often described as "ineffable" (Barrett and Griffiths, 2017; Hendricks, 2018; Johnson et al., 2019) or "incomprehensible" (Bürgy, 2008; Sass and Byrom, 2015b; Parnas and Henriksen, 2016; Madeira et al., 2019). Entropic processing is subjectively marked by a sense of unpredictability and increased information richness due to the weakening of mental schemas, facilitating new ways to conceptualize stimuli. This promotes altered salience, where meaning may be attributed to stimuli that are not ordinarily meaningful. This parallels what Sass describes as a "disturbed grip or hold" due to a "loosening of expectations," causing disruptions to the tacit-focal structure in psychotic disorders (Nelson and Sass, 2008; Sass and Parnas, 2017; Sass et al., 2018). Classic psychedelics also precipitate alterations in the appraisal of stimuli, perhaps due to alterations in predictive processing (Carhart-Harris and Friston, 2019), leading one's everyday experience to become awe-evoking (Hendricks, 2018). Overall, both psychosis and classic psychedelic–induced states share significant overlap marked by a sense of heightened awareness and changes in meaning attribution/salience (Nelson and Sass, 2008). However, despite these subjective similarities, there is research suggesting that these alterations may display at least partially distinct neural origins.

In psychosis, alterations in meaning are often discussed in terms of aberrant salience (Kapur, 2003), which likely stems from deficits in focused attention and memory, leading to a "weakening of contextual restraints," or prediction (Nelson et al., 2014b). This may occur in part due to chaotic dopaminergic signaling, causing the attribution of meaning to otherwise tacit stimuli (Heinz and Schlagenhauf, 2010; Pankow et al., 2012; Howes and Nour, 2016; Howes et al., 2020). In the late prodrome of psychosis, aberrant salience is thought to be particularly important (Heinz and Schlagenhauf, 2010), and may play a role in producing a sense of apophanous or a delusional mood (Kapur, 2003; Heinz and Schlagenhauf, 2010). This is a sense of heightened awareness and a feeling of meaningfulness that lies just out of grasp (Sass, 2017, p. 32) that can be described as an increase in subjective information richness. For example, one patient with psychosis remarked, "My senses seemed alive, they hit me harder. Things appeared clear-cut; I noticed things I had never noticed before" (Bowers, 1968). Simultaneously, the increased awareness is followed by enhanced meaning attribution. For example, one case report stated, "he noted a cross on a familiar church for the first time and felt that it had profound, exciting meaning for him" (Bowers and Freedman, 1966). The Aberrant Salience Inventory (ASI) quantifies this experience with five dimensions: Increased Significance, Senses Sharpening, [a feeling of] Impending Understanding, Heightened Emotionality, and Heightened Cognition (Cicero et al., 2010). Importantly, as the ASI illustrates, despite impairments in cognitive performance, people experiencing aberrant salience often feel they are "rapidly approaching the height of [their] intellectual power" and have somehow gained a deeper understanding of the world.

In addition to neurophysiological and phenomenological evidence, basic cognitive-behavioral tasks also support altered meaning attribution in psychosis. The tendency to ascribe meaning when there is none in a white noise task is present in FEP patients (Catalan et al., 2014, 2018) and predicts the subsequent development of a psychotic disorder in UHR patients (Hoffman et al., 2007). Increases in salience attribution to irrelevant stimuli in the Salience Attribution Test have been found in UHR patients (Roiser et al., 2013). Neural hyperactivation and increased emotional arousal to neutral stimuli have been noted in UHR and FEP patients (Modinos et al., 2015; see Potvin et al., 2016 for a review). Furthermore, positive subclinical schizotypy is linked to increases in aberrant salience (Chun et al., 2019). Overall, aberrant salience can be thought of meaning attribution made in an "entropic" or unpredictable manner.

Additionally, studies in individuals without psychosis suggest that altered salience can stem from increases in DA signaling. L-DOPA use in Parkinson's disease patients can increase the experience of aberrant salience (Cicero et al., 2010) compared with drug-naıve Parkinson's patients (Poletti et al., 2014; Poletti, 2018). This has been posited to be due to excessive DA signaling within the ventral striatum, leading to altered reward prediction encoding (Glimcher, 2011; Boehme et al., 2015), similar to that of psychosis patients (Poletti, 2018). Further, in healthy individuals, Salience Attribution Test scores positively correlate with presynaptic DA synthesis levels in the ventral striatum in regions activated during reward prediction errors (Boehme et al., 2015).

It has been suggested that aberrant salience does not occur under classic psychedelics (Carhart-Harris and Friston, 2019). However, it does appear that the meaning of everyday stimuli is altered by classic psychedelics (see Hartogsohn, 2018, for a review discussing "enhanced meaning under psychedelics") and, more recently, increases in aberrant salience were reported during the acute effects of LSD using the ASI (Wießner et al., 2021). Moreover, participants in functional magnetic resonance imaging (fMRI) studies of classic psychedelics regularly endorse statements like "I saw my surroundings change in unusual ways" (Turton et al., 2014) and "things looked strange"

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(Carhart-Harris et al., 2016b), suggesting altered meaning attribution.

Others have suggested that altered meaning attribution may lead to feelings of enhanced creativity in the absence of increased performance on creativity tasks during acute effects of classic psychedelics (Mason et al., 2021). This may be similar to the sense of heightened cognition, a component of aberrant salience, that regularly occurs in psychosis (Cicero et al., 2010). Moreover, "pathological laughter" under the influence of psilocybin might suggest altered interpretation of stimuli (Dubanský and Vyhnánková, 1965). Another study reported that LSD increased the meaning attributed to "meaningless" and "neutral" music, suggesting new interpretations of stimuli that otherwise may not be appreciated as meaningful (Preller et al., 2017).

Qualitative reports are also rich with accounts of increased appreciation of everyday surroundings after exposure to classic psychedelics. For example, Aldous Huxley remarked, "Eternity in a flower, Infinity in four chair legs and the Absolute in the folds of a pair of flannel trousers!" in *The Doors of Perception*, where he recounts his mescaline experience (Huxley, 1954, p. 10). More recently, Michael Pollan stated that "…[psilocybin] cast a pleasantly theatrical light over everything, italicizing the ordinary in such a way as to make me feel uncommonly … appreciative" (Pollan, 2018, p. 254). Even a fixation cross (typically provided for resting-state fMRI scans) can take on religious significance during the acute effects of psilocybin, suggesting that even intentionally neutral stimuli can become interesting, due to an enhancement of potential connotations (Turton et al., 2014). Additionally, the importance of the external environment (often called "setting") is a testament to the heightening of salience in classic psychedelic states (Leary et al., 1963; Johnson et al., 2008; Carhart-Harris et al., 2018b). To be clear, although altered meaning attribution under classic psychedelics can often be interpreted as enjoyable, this is not always the case. For example, Albert Hoffman, the inventor of LSD, remarked upon his first intentional self-experimentation with the substance that "…familiar objects and pieces of furniture assumed grotesque, threatening forms," and his next-door neighbor looked like "a malevolent, insidious witch" (Hofmann, 1980, p. 13).

Classic psychedelics largely seem to produce alterations in salience or meaning attribution primarily through 5-HT2a agonism. Preller and colleagues (2017) reported that alterations in meaning attribution were blocked by pretreatment with a 5-HT2AR antagonist, suggesting a potentially different pathway from what appear to be the largely dopaminergic mechanisms in psychosis (Giacomelli et al., 1998; Nichols, 2016). LSD-induced increases in primary process thinking, including "unlikely combinations or events" and "symbolism" that may suggest an alteration in salience, are also blocked by 5-HT2a antagonism (Kraehenmann et al., 2017). Furthermore, psilocybin's subjective effects are greatly reduced with ketanserin and risperidone, an atypical antipsychotic with 5-HT2a antagonism and D2 antagonism (Vollenweider et al., 1998). This includes reducing Visionary Restructuralization scores on the Altered State of Consciousness rating scale, which includes a subscale assessing Changed Meaning of Percepts. In contrast, the same study reported that haloperidol, an antipsychotic with significant D2 inverse agonism (Aringhieri et al., 2018), did not reduce these effects (Vollenweider et al., 1998). However, the dose used was estimated to occupy approximately 55%–65% of D2 receptors (Vollenweider et al., 1998), which is a lower occupancy than is often recommended for treatment of psychosis (Mauri et al., 2014). Even so, one study also suggested that psilocybin may increase striatal DA release via action at 5-HT2a and 5-HT1A (Vollenweider et al., 1999), leaving open the possibility that changes in salience attribution may be due to downstream alterations in DA signaling, with some similarities to psychosis.

In summary, in both psychosis and classic psychedelic–induced states, salience attribution is altered. There is a reduction in filtering, as previously established mental schemas become less influential on interpretations of the world. This produces a broadening of attentional scope, where senses appear sharpened, providing increased information richness. This unpredictable entropic processing style makes the perception of the ordinary seem highly significant. Furthermore, individuals in both states often report feeling as if they are experiencing a meaningful hidden reality (Brouwer and Carhart-Harris, 2021). However, it may be that in early psychosis the enhanced meaning has a higher quality of uncertainty, leading to a feeling that "the world is full of signs that point to a yet unrevealed secret" (Heinz and Schlagenhauf, 2010). This may stem in part from the involvement of DA in creating feelings of uncertainty (Broyd et al., 2017; Zack et al., 2020). In contrast, classic psychedelics may be more prone to producing a sense of novelty and surprise (Wießner et al., 2022), suggesting a loosening of mental schemas, without inducing an urgent sense of a need to create an "ungraspable" explanatory mental framework, at least in most occasions (Carhart-Harris and Friston, 2019).

Still, we maintain that altered salience and information richness need not be pathologic. For instance, altered salience may play a significant role in the experience of awe (Keltner and Haidt, 2003; Bonner and Friedman, 2011; Hendricks, 2018), which has been a described as a "heightening of sensation and perception" with "unusual vividness and salience of perceptual stimuli" (Bonner and Friedman, 2011). Similar alterations in sensory vividness, broadening of attention, and breaking of mental schemas have been noted with the overview effect, which occurs when astronauts view the earth from afar (Yaden et al.,

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2016). Awe has also been reported to increase "intentional-pattern perception" (Valdesolo and Graham, 2014), including agency detection which is "the tendency to interpret events as the consequence of intentional and purpose-driven agents." This is similar to aberrant salience in that the random events that are otherwise nonsignificant become highly meaningful.

We also must acknowledge that basic cognitive-behavioral and systematic qualitative research examining how classic psychedelics alter salience/meaning attribution is lacking, suggesting a relevant area for future research. We recommend that researchers interested in classic psychedelics use established tasks developed from psychosis research such as the Salience Attribution Test (Roiser et al., 2009; Katthagen et al., 2016) and existing subjective questionnaires, such as the ASI (Cicero et al., 2010). Nevertheless, despite the overlapping experience of altered salience in psychosis and classic psychedelic–induced experiences, it is likely that the neurobiological correlates of such experiences are at least partially distinct. Changes in salience processing in psychosis are typically related to altered dopaminergic signaling (Howes and Nour, 2016; Howes et al., 2020; Kätzel et al., 2020). Conversely, though it is possible that alterations in 5-HT2a signaling play a role in developing psychosis, including the experience of altered salience (Brouwer and Carhart-Harris, 2021), 5-HT2a signaling does not appear as necessary for producing these changes in psychosis as it does with classic psychedelics (Vollenweider et al., 1998; Kraehenmann et al., 2017; Preller et al., 2017). (Also see *Schizophrenia: Antagonist and Agonism at 5-HT2ARs* section).

C. Creativity

Creativity requires the ability to make remote associations and use those associations in a meaningful manner (Mednick, 1962). A "leaky filter," or reduction in cognitive inhibition, facilitating the attending to a broader range of stimuli that otherwise would be deemed irrelevant, is important for creative thinking (Mendelsohn and Griswold, 1964; Andreasen and Powers, 1975; Eysenck, 1993; Carson et al., 2003; Carson, 2011; Zmigrod et al., 2015; Zabelina et al., 2016). As we have seen in previous sections, classic psychedelic states and psychosis are associated with similar increases in attention to irrelevant information and alterations in salience and meaning attribution. These alterations in attention and information processing may facilitate creative thinking (Crabtree and Green, 2016), although adequate executive functioning is required to use novel associations meaningfully (Beaty et al., 2015; Mason et al., 2021; Zamani et al., 2022). Moreover, both classic psychedelics (Sessa, 2008; Gandy et al., 2022) and severe mental illness (Becker, 2001) have long been speculated to be associated with creativity, though the research presents a more complex relationship.

There are relatively few modern studies evaluating creativity and classic psychedelic use (see Kuypers, 2018, for a review). Some studies suggest increases in creativity, during both the acute (Kuypers et al., 2016) and postacute (Frecska et al., 2012; Mason et al., 2021) effects. However, several older studies report no statistically significant effects of classic psychedelics on creativity (see Baggott, 2015 for a review) and two recent placebo-controlled studies report impairment on creativity tasks during the acute effects of classic psychedelics, including psilocybin (Mason et al., 2021) and a moderate dose of LSD (50 μg) (Wießner et al., 2022). The acute decreases in creativity task performance may have been due to decreases in executive functioning, which is known to be impaired during acute classic psychedelic effects (Pokorny et al., 2020), prompting difficulty in assessing the usefulness of spontaneous associations. Still, enhanced feelings of insight were reported during the acute effects of psilocybin (Mason et al., 2021). Similarly, participants on a moderate dose of LSD reported increases in feelings of deep thoughts and abstract flow (Wießner et al., 2021), and their creativity task performance also indicated an increase in novelty and level of "surprise" in creative ideas (Wießner et al., 2022). But the same study also reported that LSD decreased the usefulness of these associations. Subjectively, feelings of insight (Mason et al., 2021), deep thoughts (Wießner et al., 2021), and increases in chaotic thinking (Wießner et al., 2022) may plausibly be mistaken for an increase in creativity. It might be that the alterations in thinking that occur during the acute effects of classic psychedelics are more similar to the sense of heightened cognition that can occur in psychosis than functional creativity (Bowers, 1966; Chapman, 1966; Cicero et al., 2010; Sass, 2017).

On a neurobiological level, increases in feelings of insight, despite impairments in creativity task performance during the acute effects of classic psychedelics, may be due to significant alterations occurring in crucial large-scale brain networks (Mason et al., 2021). Mason and colleagues reported that decreases in resting state DMN, within-network connectivity, and widespread increases in between-network functional connectivity were the greatest predictors of feelings of insight during the acute effects of psilocybin (Mason et al., 2021) (see *The DMN and Self-Focus* section for further discussion of the DMN). The same study also found that increases in connectivity between regions in the DMN and the frontoparietal control network (FPN), which is involved in executive functioning, occurred during the acute effects of psilocybin. According to the dynamic framework of thought theory, the creative process involves shifting between unconstrained and constrained cognition, requiring coordinated functioning of both the DMN and FPN (Beaty et al., 2015; Christoff et al., 2016; Girn et al., 2020), implicating various regions with diverse function within

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the prefrontal cortex (Zamani et al., 2022). Significant alterations in DMN connectivity (Mason et al., 2021) likely play a role in the hyperassociative frame of thought classic psychedelics can provoke (Girn et al., 2020), inducing a state that may not be constrained enough to optimize creative thought (Mason et al., 2021).

In contrast, some evidence suggests that long-term increases in creativity may occur from classic psychedelic use (Frecska et al., 2012; Sweat et al., 2016). Individuals who reported classic psychedelic use concurrent with a mystical experience at some point in their lives showed significantly quicker creative problem solving compared with people with nonpsychedelic mystical experiences (Sweat et al., 2016). Another study reported no increases in fluidity, flexibility, or "relative originality" after an ayahuasca retreat in experienced users but noted that the retreat goers had significantly elevated baseline creative performance compared with the psychedelic-naıve control group (Frecska et al., 2012). Perhaps further study might test the dynamic framework of thought theory and examine the possibility that postacute increases in creativity could be due to better ability to intentionally "control" coordination between the DMN and FPN, producing a broader repertoire of brain states and flexibility in styles of thinking.

Overall, studies on classic psychedelics and creativity suggest potential enhancement of creative thinking, but the evidence is far from conclusive. It is possible that studies of creativity in classic psychedelic users may not find enhancements due to a saturation of potential increases (i.e., ceiling effects). It may be most parsimonious to suggest that classic psychedelics impair creativity acutely but increase the processing traits that facilitate creativity in the postacute period, contingent on executive functioning. Novel insights experienced on classic psychedelics may be experienced as increases in creativity but may in fact be more related to the loosening of mental schemas fostering novel, but not necessarily useful, associations.

Similarly, despite the popular perception of an association between severe mental illnesses and creativity, research suggests a more nuanced picture. In general, the relationship between creativity and mental illness is thought to be more relevant for bipolar disorder than for schizophrenia spectrum disorders (Crabtree and Green, 2016). Schizophrenia, throughout the course of the illness, is associated with reduced creativity across a variety of measures (see Acar et al., 2018, for a meta-analysis of 41 studies). However, a family history of psychotic disorders (Kyaga et al., 2011) and high levels of positive schizotypy (Mohr and Claridge, 2015) may be associated with enhanced creativity (Carson, 2011; Crabtree and Green, 2016). This suggests that limited increases in entropic processing tendencies may facilitate creativity, given a level of executive function. Moreover, the relationship between schizotypy and creativity is mediated by overinclusive thinking and decreased cognitive inhibition, which are part of the entropic processing construct (Wang et al., 2018).

The shared vulnerability model of psychosis and creativity (Carson, 2011, 2014) supposes that creativity and psychosis are marked by a cognitive disinhibition, resulting in "a broadening of stimuli available to consciousness" (Carson, 2014), and enhanced novelty salience, emotional lability, and neural hyperconnectivity. However, in psychosis, these alterations are more likely to result in bizarre ideas than useful novel contributions because deficits in executive functioning decrease the ability to assess the value of associations (Kaufman and Paul, 2014). Overall, the discussed overlap between creativity and psychosis is largely in concordance with SEB theory's entropic processing concept.

DA's proposed twofold role in creativity (Boot et al., 2017) may help us further understand how people with psychosis display decreases in creativity achievement while those with subclinical schizotypal traits and/or a family history in psychosis may display increases. Broadly speaking, it has been suggested that there are two cognitive processes needed to produce useful creativity contributions: a flexibility processing pathway and a persistence processing pathway (Nijstad et al., 2010; Boot et al., 2017). The flexibility pathway displays "a broad attentional scope," which is related to a diversity of ideas, and may involve DA functioning within the striatal system. However, excessive increases in the flexibility pathway may promote bizarre, rather than creative, ideas (Boot et al., 2017). By contrast, persistence processing heavily involves executive functioning and working memory and may implicate increases in prefrontal DA signaling (Boot et al., 2017). In general, both systems are thought to display inverted-U curves for creativity. People with schizophrenia often display hyperdopaminergic functioning in striatal regions (Murray et al., 2008; Heinz and Schlagenhauf, 2010; Maia and Frank, 2017; Sekiguchi et al., 2019; Conn et al., 2020; Katthagen et al., 2020), which may support the development of novel associations (Heinz and Schlagenhauf, 2010; Boot et al., 2017). However, in cortical regions (Rao and Remington, 2014; Weinstein et al., 2017), particularly the prefrontal cortex (Slifstein et al., 2015; Rao et al., 2019), people with schizophrenia display a reduction in dopaminergic functioning, which may relate to impaired cognitive functioning (Rao et al., 2019; Torrisi et al., 2020). These data suggest that hyperdopaminergic processes could facilitate increases in associative thought, but may result in bizarre, rather than useful, ideas without adequate executive functioning. People with subclinical schizotypal traits do display slight alterations in DA functioning, though they are

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much less severe than those that occur in psychosis (Mohr and Ettinger, 2014; Boot et al., 2017).

Additionally, research on DA's role in creativity exists outside of psychosis studies (Chermahini and Hommel, 2010; Boot et al., 2017; Chong et al., 2021; Agnoli et al., 2022; Khalil and Moustafa, 2022). For instance, increases in creativity have been occasionally reported in Parkinson's disease after treatment with DA replacement therapy (Faust-Socher et al., 2014), along with alterations in cognition that often parallel some of those seen in psychosis, as previously discussed (Györfi et al., 2017; Poletti, 2018). Some case studies of Parkinson's disease also associate dopaminergic treatment with an increase in creativity (Schrag and Trimble, 2001; Inzelberg, 2013; Chacko et al., 2019). However, a small study ($n = 13$) recently suggested that L-DOPA may impair creativity task performance in Parkinson's disease patients (Salvi et al., 2021). Furthermore, although classic psychedelics receive much popular press about inspiring creativity (Sessa, 2008; Pollan, 2018), psychostimulants have also long been associated with creativity achievements (Smith, 2015). For instance, the beat generation of writers, including Jack Kerouac, developed a loose, associative writing style which was perhaps partially inspired by a hyperassociative style of thinking provoked during long amphetamine binges (Smith, 2015). Furthermore, studies in nonpsychotic individuals garner more evidence for the potential inverted U-curve between dopaminergic functioning and creativity (Chermahini and Hommel, 2010; Agnoli et al., 2022). It is also likely that dopaminergic substances enhance creativity for some people as mediated by premedication personality characteristics (Gvirts et al., 2017; Käckenmester et al., 2019). For instance, increases in DA signaling facilitating increases in divergent thinking are thought to be moderated by the personality trait of openness to new experiences in the general population (Käckenmester et al., 2019) and methylphenidate has a positive effect on creativity in individuals low in novelty-seeking, but impairs creativity in people in high novelty-seeking (Gvirts et al., 2017).

Unfortunately, to our knowledge, no study has examined yet the role of classic psychedelics' 5-HT2a agonism in producing potential alterations in creativity. However, in general, unlike DA, serotonin is not widely implicated in creativity, outside of studies on classic psychedelics. However, serotonin depletion has been related to reductions of cognitive flexibility (Clarke et al., 2004, 2006; Kehagia et al., 2010; Bălăeţ, 2022), which may plausibly suggest a potential role of creativity (Palmiero et al., 2022; Zhang et al., 2020). It may be, much like excessive DA transmission fostering a decrease in creativity, that there is an inverted U-curve with serotonergic functioning and creativity such that as flexibility of thought increases, it ultimately becomes so chaotic that it promotes impairments in creativity task performance. This would likely be compatible with dynamic framework of thought theory's understanding of classic psychedelics as a style of "unconstrained" hyperassociative cognition (Girn et al., 2020; Zamani et al., 2022).

It is also possible that increases in novel associations and insights catalyzed by classic psychedelics may foster the development of odd, idiosyncratic cognitions. As Carhart-Harris and Friston (2019) state in REBUS, "… the psychedelic initiate may reach for bizarre beliefs or poorly understood platitudes, in an effort to explain away his/her felt uncertainty—in a similar way as may occur in the incipient phase of a psychotic disorder." Take for instance Kary Mullis, who won a Nobel prize for the invention of polymerase chain reaction, which he claimed was inspired by LSD use, but who also held a number of eccentric pseudoscientific beliefs, including a penchant for astrology and, more problematically, HIV skepticism (Mullis, 1998). Might it be that the same classic psychedelic-induced alterations in cognition that can lead to feelings of insight (Mason et al., 2021) or deep thoughts (Wießner et al., 2021) could facilitate bizarre thought processes? Even if this is the case, it is far from unique to classic psychedelics, as other instances of information overload, such as nonsubstance-facilitated awe, can also sometimes increase creativity (Chirico et al., 2018) as well as supernatural beliefs in some individuals (Valdesolo and Graham, 2014).

In short, some aspects of psychosis and classic psychedelic-induced states may include processing styles that can facilitate creativity, however, this does not mean an enhancement in creativity always occurs. In both states, there is a tendency toward reduced filtering and increased attention to irrelevant cues that cause increased associations, facilitating altered salience, which may provoke novel insights. However, both psychosis and the acute classic psychedelic state are often too chaotic and lack the executive functioning needed to increase productive creativity (i.e., associations that are both novel and useful). However, subpathologic levels of psychotic traits (i.e., in those high in positive schizotypy) and the postacute effects of classic psychedelics may benefit creativity as they may promote a more hyperassociative style of thinking with adequate executive functioning to assess the value of associations. There is also significant research suggesting that DA may play a role in creative cognition, as seen in psychosis and in the effects of dopaminergic substances on creative functioning. This suggests that there may be multiple pharmacological "roads" to similar cognitive alterations.

D. Thalamic Alterations: A More Vivid Experience?

Another theory that proposed that multiple etiologies may lead to similar phenomenological states and systems-level neurologic functioning is thalamic gating theory

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(Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Vollenweider and Smallridge, 2022), which in recent years has gained support from studies focused on functional connectivity of the thalamus to various regions (Preller et al., 2018; Avram et al., 2022). Functional thalamic hyperconnectivity to sensorimotor regions has been proposed to be related to reductions in both sensory gating and top-down control (Avram et al., 2021, 2022), suggesting a mechanism that is in concordance with aspects of REBUS (Carhart-Harris and Friston, 2019). Furthermore, substantial evidence suggests that both psychosis (see Giraldo-Chica and Woodward, 2017, for a review) and classic psychedelic–induced states (Avram et al., 2021, 2022) are marked by increases in thalamic-sensory connectivity during resting state. This may appear to support the conjecture that more information-rich sensory experiences are in part driven by alterations in thalamic connectivity, as has long been suggested (Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Vollenweider and Smallridge, 2022), but recent research suggests that some nuances are likely needed.

Classic psychedelics do appear to produce thalamic hyperconnectivity to sensorimotor regions in studies of both psilocybin (Carhart-Harris et al., 2013) and LSD (Tagliazucchi et al., 2016; Preller et al., 2018; Avram et al., 2022). Moreover, the hyperconnectivity of the thalamus to sensory regions under LSD corresponds to subjective alterations in visual and auditory modalities, suggesting that reductions in thalamic gating may play a role in eliciting heightened sensory experiences, such as vividness of color (Müller et al., 2017). Additionally, increases in thalamus and auditory-sensorimotor regions under LSD correlate strongly to "changed meaning of percepts" ($r = 0.58$). Thus, it may be possible that alterations in resting-state thalamic connectivity could help facilitate a more information-rich subjective experience, both in turns of vividness of sensory experiences and meaning ascribed to sensory percepts. Intriguingly, alterations in thalamic connectivity appear to be reliant on 5-HT2a signaling, as they are blocked by pretreatment with ketanserin (Preller et al., 2018). However, at very high doses, LSD may produce alterations in firing in the medial dorsal thalamus that are attributable to D2 agonism as seen by their remittance after administration of haloperidol in mice (Inserra et al., 2021b).

In parallel, increases in thalamic connectivity to sensorimotor regions appear to be well documented in resting-state connectivity in schizophrenia, across the stages of the illness (see Steullet, 2020, for a review). Indeed, increased thalamus-primary somatosensory cortex connectivity was the most consistent finding in a multisite resting state study of 415 schizophrenia patients (Cheng et al., 2015). It is also seen in individuals who are clinically high risk for psychosis and later develop schizophrenia, and is correlated with prodromal symptoms (Anticevic et al., 2015). However, it appears that atypical antipsychotics do not normalize alterations in thalamic hyperconnectivity in patients with schizophrenia (Avram et al., 2020). And yet, LSD-induced changes in thalamic connectivity are normalized with 5-HT2a antagonism (Preller et al., 2018). In total, these findings might suggest that alterations in 5-HT2a and D2 signaling may play less of a role in thalamic alterations with schizophrenia than 5-HT2a signaling plays in thalamic alterations with classic psychedelics. Additionally, although some studies have correlated changes in sensorimotor-thalamic connectivity to psychosis symptoms, findings are very mixed (Giraldo-Chica and Woodward, 2017). This suggests that, at least with schizophrenia, it is unlikely that alterations in thalamic connectivity are associated with a richer sensory experience. It also appears that, although there seem to be neurobiological similarities in thalamocortical hyperconnectivity between psychosis and classic psychedelic–induced states, the molecular mechanisms by which these alterations are elicited may differ, as others have recently suggested (Avram et al., 2021).

Additional findings warrant consideration. A recent study (Avram et al., 2022) reported that hyperconnectivity between the thalamus and auditory-sensorimotor regions is also induced by d-amphetamine, which acts on the DA transporter to release DA (Seiden et al., 1993), and 3,4-methylenedioxymethamphetamine (MDMA), a serotonin-releasing substance (Bradbury et al., 2014). However, alterations in thalamic connectivity with d-amphetamines and MDMA did not correlate with subjective drug effects. This may be in part because neither drug's effects significantly differ from placebo on the 5D-ASC questionnaire scores/subscales, with the exception of increases in blissfulness with MDMA (Avram et al., 2022). Moreover, ketamine, an NMDA receptor antagonist, at subanesthetic doses, has also been shown to increase resting-state thalamic connectivity to the somatosensory and temporal cortices (Höflich et al., 2015). Overall, these findings suggest that reductions in thalamic gating on a neural level are not specific to classic psychedelics, but the association of these alterations in connectivity to subjective increases in information richness (as seen with increases in sensory vividness) are. Importantly, all of the substances shown to produce these effects are known to also alter glutamatergic signaling either directly or indirectly, suggesting a potential shared common pathway (Inserra et al., 2021a). Furthermore, 5-HT2A and D2-like receptors overlap in regions of the thalamus (Avram et al., 2022). It is therefore unclear why thalamic connectivity seems related to subjective experience for classic psychedelics, but not other substances.

Overall, it seems that increases in thalamic-sensorimotor connectivity may play a role in producing subjective increases in information richness in classic psychedelic–induced states. This association appears to be less plausible with psychosis, where increases in

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connectivity between the thalamus and sensorimotor regions is well-documented, but its relation to subjective experience less so (Steullet, 2020). It is relevant to note that there is emerging work examining entropy of thalamic activity in schizophrenia, both on a cellular (Spiros et al., 2017) and systems level (Wei et al., 2022), that appears to be related to subjective experience and clinical outcomes. It is also relevant to note that fMRI studies with classic psychedelics often do not examine the subnuclei of the thalamus, preventing a more thorough understanding (Doss et al., 2022). In short, the idea that thalamic-sensorimotor hyperconnectivity might facilitate subjective entropic processing seems intuitively plausible, but it does not currently appear to be supported in schizophrenia. We suggest that future research examine both entropy of the thalamus and its hyperconnectivity with sensorimotor regions for both psychosis and classic psychedelic–induced states.

E. Summary of Entropic Processing

Entropic processing is a less constrained style of thinking with a reduction in filtering, facilitating a broadening of attentional scope, leading to increased information richness, which further promotes the disintegration of previous processing frameworks. This precipitates rapid attempts to process information in novel ways and facilitates a hyperassociative style of thinking, promoting altered salience and meaning attribution. Increases in novel associations precipitate feelings of insight, which may be perceived as feelings of enhanced creativity in the absence of improved performance. For creativity to occur, adequate executive functioning is needed to meaningfully ascribe value to associations. The defining of the entropic processing construct presents a guidepost for future studies examining the overlap between early psychosis and classic psychedelic–induced states. It is worth noting that molecular mechanisms triggering this processing style display different etiologies, though significant phenomenological and cognitive overlap still seems to occur, at least during acute effects of classic psychedelics. Nevertheless, the "trajectory" of entropic processing depends on the level of self-focus, as the next section describes.

II. The Trajectory of Entropic Processing

"There is an area of the mind that could be called unsane, beyond sanity, and yet not insane."

—Sidney Cohen (The Beyond Within, 1987)

A. Diverging Paths in Entropic Processing: Self-Focus

Both classic psychedelics (Liddell and Weil-Malherbe, 1953; Savage, 1955; Hofmann, 1959; Klee, 1963; Kleinman et al., 1977) and psychosis (Chapman, 1966; Laing, 1970; Exner, 1973; Sass, 1987; Sass and Parnas, 2003; Bürgy, 2008; Raballo et al., 2021) have long been suggested to display significant alterations in sense of self. Previous comparisons of early psychosis and classic psychedelic–induced states have, in part, been based on a "fragmented sense of self" (Geyer and Vollenweider, 2008; Carhart-Harris and Friston, 2010; Carhart-Harris et al., 2013, 2014; Schmid et al., 2015; Kraehenmann et al., 2017; Brouwer and Carhart-Harris, 2021). However, a more nuanced examination of alterations of self-experiences reveals pronounced differences. In general, classic psychedelic states display a decrease in self-focus, or a decrease in the weighting of the self in understanding external and internally generated stimuli. In contrast, the psychotic state is one of hyper-self-focus, where there is an increase in weighting of the self in processing external and internally generated stimuli. In the following sections, we describe the subjective experiences of alterations of sense of self in psychosis and classic psychedelic states and then we delve into the differential outcomes of these "entropic states." The effects of self-focus either facilitate flourishing or languishing and are discussed within the context of neurologic and physiologic alterations that occur in both psychosis and classic psychedelic-induced states. Parallels are also drawn between cases of psychosis and stimulant-induced psychosis, to further showcase that the alterations that occur in schizophrenia may have origins in part due to alterations in dopaminergic signaling, which seems to not be as crucial of a component in the effects of classic psychedelics.

B. Self-Disorder in Psychosis

Disruptions to the sense of self have long been central to our understandings of schizophrenia and psychosis (see Bürgy, 2008, for a history). In fact, the etymology of the word "schizophrenia" means "split mind" (Heckers, 2011; Ashok et al., 2012), and the condition is often described as a "splitting of the I" (Parnas et al., 2005). For quite some time, however, biomedical behaviorist models of the illness have minimized the importance of these abnormalities (Sass, 1987, 2017). But in recent years, there has been a renaissance of research on self-disruptions in an attempt to define a common core feature of schizophrenia spectrum disorders (SSDs), across all stages of the illness, despite the heterogeneity of symptoms. The self-disturbance model proposes that in SSDs, the self is disrupted through hyper-reflexivity, diminished self-presence, and disturbed grip or hold (Sass and Parnas, 2003; Sass, 2017; Sass et al., 2018). We will examine the components of alterations in self-experience presented in this model, before discussing more concrete alterations and externally oriented increases in self-focus as seen in delusions (Bovet and Parnas, 1993; Sass and Byrom, 2015b; Sestito et al., 2017).

Hyper-reflexivity is a sense of exaggerated self-consciousness, where internal experiences are inspected as if they are objects, not lived experiences (Parnas and Handest, 2003; Nelson, Sass, Thompson,

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et al., 2009; Sass, 2017; Sass and Parnas, 2017). In other words, "a subject takes itself as its own object" (Parnas and Handset, 2003). In SEB theory, it is an internally oriented form of self-focus. Although hyper-reflexivity may seem rather abstract, case studies provide helpful illustrations into how it is experienced. For example, consider these remarks describing how early psychosis changed an individual's experience of music:

"… he tried to regulate the sound parameters on his stereo equipment, to no avail and only to finally realize that he was somehow 'internally watching' his own receptivity to music, his own mind receiving or registering musical tunes. He so to speak witnessed his own sensory processes rather than living them. It applied to most of his experiences that, instead of living them, he experienced his own experiences" (Parnas and Harndest, 2003).

In many ways, this experience is the antithesis of mindfulness or flow states (Nelson et al., 2009), which may share similarities with self-experience in classic psychedelic states (Yaden et al., 2017; Millière et al., 2018). Instead of becoming absorbed in a stimulus to the point of a decrease in self-consciousness, the patient describes being pulled out of the experience by attempts to witness himself. This observation of a hyper-self-consciousness in psychosis is not new. In 1960, R.D. Laing described a hyper-self-consciousness in schizophrenia and "schizoid" personalities, where individuals became "compulsively preoccupied with the sustained observation of their own mental and/or bodily processes" (Laing, 1960, p. 120).

The other factor, diminished self-presence, is due to disruptions of the core or minimal self, which is an "unseen point of origin for experience, thought, and action" (Sass et al., 2018) that elicits an experience's inherent "mineness" (Sass, 2017). This may lead the individual to feel as if they are not fully experiencing their life, as illustrated by the following quotation from a patient in early psychosis:

"I have lost all forms of desire. I have no contact with myself. I feel like a zombie; I am unable to feel pleasure; everything appears indifferent. I am not a part of this world; I have a strange ghostly feeling as if I was from another planet. I am almost nonexistent." (Parnas and Handest, 2003)

This sense of not being fully present may precipitate feelings of isolation and separateness from the world from an individual's own experience (Nelson et al., 2009). Early psychosis patients often describe feelings of unreality as a sense of being separated from the world such that "everything seems distant as if it is behind plate glass" (Sass, 2017, p. 29). These feelings of isolation and lack of presence may be relevant for the development of negative symptoms, such as avolition, anhedonia, and social withdrawal (Sass et al., 2018). Others have suggested that hyper-reflexivity leads to an overwhelming amount of information being processed, leading to a sense of alienation from the environment (Wright et al., 2020).

The final component of the self-disturbance model, "disturbed grip or hold," contributes to the general feelings of unreality present in the illness. It is a lack of stability of experiences and "loss of common sense" including changes in "salience-pattern," which would fit within the entropic processing construct (de Vries et al., 2013; Sass et al., 2018). It is plausible that "a disturbed grip" may in part be due to chaotic dopaminergic signaling within midbrain regions (Kapur, 2003; Howes and Nour, 2016; Howes et al., 2020).

Overall, the disruptions to the sense of self in psychosis are paradoxical. Patients describe feelings of not fully being present, which may be described as "a reduced sense of self," yet, simultaneously, psychosis is marked by hyper-reflexive tendencies. In general, psychosis can be thought of as a propensity to lose the self (diminished self-presence) in the act of searching for it (through hyper-reflexivity and other forms of self-focus as seen in delusions).

C. Delusions: Self-Focus Entropically Amplified

Delusions likely derive both from entropic processing and increased self-focus. Delusions are present from the earliest stages of psychosis (Gutiérrez-Lobos et al., 2001; Rajapakse et al., 2011; Paolini et al., 2016; Jones et al., 2020; Kirschenbaum et al., 2020) and are experienced by the vast majority of FEP patients (Paolini et al., 2016; Jones et al., 2020). Additionally, relevant to our discussion, anomalous self-experiences are posited to contribute to the development of delusional beliefs (Nelson et al., 2014a,b; Sass and Byrom, 2015a; Wright et al., 2020). Due to this putative pathway, and the overtly self-focused themes present in delusions, delusions are another way to examine how high self-focus manifests in psychosis.

Cognitive-behavioral tasks and thematic analysis of delusional experiences also support that delusions derive in part from excessive self-focus. The most prevalent delusions in FEP are of persecution and reference (Paolini et al., 2016; Jones et al., 2020) and of being monitored (Rajapakse et al., 2011). More specifically, a retrospective thematic analysis of FEP patients reported that the most common delusions were "being harmed, attacked or killed" (55%), "being monitored or followed" (48%), and "being talked/laughed at" (30%) (Jones et al., 2020). Basic cognitive-behavioral research also suggests that delusions are supported by increases in self-focus. Patients with schizophrenia are more likely to believe that neutral statements are specifically about them (Menon et al., 2011) and that an averted gaze is directed at them, which can support delusions of reference or paranoia (Hooker and Park, 2005; Menon et al., 2010; Chan et al., 2021). Additionally, people with schizophrenia are more likely to classify neutral stimuli as negative (Potvin et al., 2016;

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Sestito et al., 2017), suggesting increased threat detection (Dugré et al., 2019), perhaps an evolutionary mechanism to protect the individual (Neuberg et al., 2011; Raihani and Bell, 2019).

Salience dysregulation, which falls within the entropic processing construct, further supports the idea that entropic processing leads to the development of delusions, and has long been implicated in the formation of delusional beliefs (Kapur, 2003). Source monitoring, or confusion about whether an experience was internally or externally generated, may also be due to reductions/alterations in schematic sorting (Sass and Byrom, 2015a). Others have also suggested that experiences of altered salience with explanations of self-relevance contribute to the formation of delusions (Menon et al., 2011). These experiences may be due to increased self-related prediction errors, which may contribute to otherwise tacit stimuli becoming self-relevant. For a more descriptive understanding of how entropic processing coupled with an increase in self-focus facilitates the development of delusions, consider the experience of a patient during the onset of psychosis:

"I became interested in a wide assortment of people, events, places, and ideas which normally would make no impression on me. Not knowing that I was ill, I made no attempt to understand what was happening, but felt that there was some overwhelming significance in all this, produced either by God or Satan, and I felt that I was duty-bound to ponder on each of these new interests, and the more I pondered, the worse it became. The walk of a stranger on the street could be a 'sign' to me which I must interpret. Every face in the windows of a passing street car would be engraved on my mind, all of them concentrating on me and trying to pass me some sort of message." (Hollandsworth, 2014, p. 77)

In the above quotation, the individual describes becoming increasingly aware of their environment and experiences a broadening of thoughts as they consider the meaning of their environment in greater depth. However, the individual believes the novel associations being made are somehow relevant to them exclusively, showcasing the heightened self-focus present in psychosis. In summary, in psychotic delusions, individuals tend to experience excessive self-consciousness, and take note of otherwise irrelevant stimuli as if self-relevant.

D. Dopaminergic Disruptions and Delusions: Stimulant-Induced Psychosis

Stimulant-induced psychosis may share significant parallels with aspects of endogenous psychosis, both neurobiologically and phenomenologically (Roncero et al., 2014; Wearne and Cornish, 2018), which may highlight the importance of alterations in dopaminergic functioning in instigating self-focused delusions. It must be specified that the alterations discussed in this section are cases of stimulant-induced psychosis, which most often occur after chronic repeated use (Ujike, 2002) and promote sensitization of the DA system, unlike less frequent or moderate use, which may be more conducive to a model of mania than psychosis (Carhart-Harris et al., 2013). In general, increases in suspiciousness, self-consciousness, and self-reference have long been noted in response to amphetamines (Ellinwood, 1969; Griffith, 1972) and cocaine (Siegel, 1978; Baker, 1989). Case reports of amphetamine-induced psychosis frequently feature prominent self-focused delusions, such as believing people on the street were attempting to pass a message to the user (Wallis et al., 1949; Angrist et al., 1974). Similarly, in cocaine-induced psychosis, self-referential and persecutory delusions are among the most common and appear to closely resemble those in patients with non-stimulant-induced psychotic symptoms (Roncero et al., 2014). Furthermore, the delusions that occur in methamphetamine-induced psychosis are often of a self-focused nature, with inpatients hospitalized for methamphetamine-induced psychosis reporting a high prevalence of delusions of persecution (85.5%), reference (38.5%), and grandiosity (32.9%) (Zarrabi et al., 2016). Moreover, such experiences are highly prevalent in people with methamphetamine use disorder, who display a lifetime prevalence of substance-induced psychosis of 42.7% (Lecomte et al., 2018), and in those with lifetime cocaine use, who experience cocaine-induced psychosis at a prevalence of 55.6%, based on a recent meta-analysis of 20 studies (Sabe et al., 2021). To be clear, we do not ignore that classic psychedelics may occasionally be implicated in psychotic episodes, but this appears to be a very rare occurrence (Glass and Bowers, 1970; Johnson et al., 2008; dos Santos et al., 2017). Furthermore, classic psychedelic use is not associated with schizophrenia on a population-level and is associated with a reduced prevalence of some psychotic symptoms (Krebs and Johansen, 2013; also see *Chronic LSD Administration: A True Psychotomimetic?).*

Stimulant-induced psychosis is often posited to be due to sensitization of the dopaminergic system (Ujike, 2002; Featherstone et al., 2007; Shuto and Nishi, 2011). Indeed, repeated exposure to amphetamines causes increasingly greater release of DA even in healthy individuals (Boileau et al., 2006). Thus, stimulant-promoted sensitization may produce hyperdopaminergic mesolimbic systems mirroring some (Weidenauer et al., 2016), but not all (Conn et al., 2020), of the alterations in schizophrenia. Others have suggested that a reduction in GABAergic interneuron functioning, particularly in mPFC pyramidal neurons due to glutamatergic toxicity, may also exacerbate psychotic symptoms with amphetamines (Jiao et al., 2015) and in methamphetamine-induced psychosis (Hsieh et al., 2014), potentially promoting greater dysfunction of the DA and glutamate systems.

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Based on neurobiological alterations and the content of delusions experienced, stimulant-induced psychosis creates a case for aberrant dopaminergic functioning in psychotic-like increases in self-focus and entropic processing. However, it remains to be seen whether individuals with stimulant-induced psychosis experience other alterations in self-experience, such as reductions in self-presence. We suspect that although stimulant-induced psychosis may foster both aspects of entropic processing and increases in self-focus, more fundamental alterations to self-experience may not occur. However, this is an empirical question that may be examined by providing the Examination of Anomalous Self-Experience scale (Parnas et al., 2005) or Inventory of Psychotic-Like Anomalous Self-Experiences (Cicero et al., 2017) to people experiencing stimulant-induced psychosis.

E. Self in Classic Psychedelic States

Studies have reported significant alterations to the sense of self using psilocybin (MacLean et al., 2011; Smigielski, Scheidegger, et al., 2019; Mason et al., 2020), LSD (Carhart-Harris et al., 2016b; Kraehenmann et al., 2017; Liebert et al., 1958; Müller & Borgwardt, 2019; Savage, 1955; Tagliazucchi et al., 2016), and the DMT-containing admixture ayahuasca (Uthaug et al., 2018). In recent years, these alterations have been described in terms of psychoanalytic theory (Carhart-Harris & Friston, 2010; Nour et al., 2016; Tagliazucchi et al., 2016), mystical-type experience (Barrett and Griffiths, 2017), or as feelings of awe (Hendricks, 2018). We will explore these frameworks before discussing how these alterations impact long-term outcomes.

Psychoanalytic theory stresses ego dissolution as core to the classic psychedelic state. Ego dissolution is characterized by a feeling of oceanic boundlessness and a reduction in self-referential awareness (Nour et al., 2016; Nour and Carhart-Harris, 2017; Millière et al., 2018). In ego dissolution, there is a "blurring of the distinction between self-representation and object-representation," which prevents "the synthesis of self-representations into a coherent whole" (Nour et al., 2016). However, it is important to note that "oceanic feelings of oneness" were initially described by Freud as a "neurotic regression," as previously discussed by Yaden and colleagues (2017). This is one reason why psychoanalytic theory may not be an ideal framework for understanding the potential therapeutic effects of classic psychedelics.

Classic psychedelics are also frequently discussed as inducing mystical-type experiences (Barrett and Griffiths, 2017). Mystical experiences consist of a sense of internal and external unity, noetic quality, sacredness, positive mood, transcendence of time and space, and ineffability (James, 1902; Stace, 1960; Barrett et al., 2015). Importantly, profound alterations to the sense of self are central to the phenomenology of mystical experiences. The extroverted mystical experience is characterized by "recognition of the oneness of all, in which one finds unity at the core of the inner subjectivity or inner reality of all things despite the diversity or apparent individual identity and separation of all things" (Barrett and Griffiths, 2017). The introverted mystical experience is described as "loss of all boundaries, such that there is no separation or individual identity." However, as mentioned previously, nonclassic psychedelic–induced mystical experiences do not appear to have the same associations with creative problem solving as classic psychedelic–induced mystical experiences, suggesting mystical experiences themselves may not describe all the factors that produce the enduring effects of classic psychedelics (Sweat et al., 2016).

In both psychoanalytic and mystical interpretations, despite discrepancies, we see a decrease in self-focus as being a core component of the effects of classic psychedelics. This bears similarities to awe's "small self," which has been described as "attention being directed away from the self, feelings of connectedness or oneness with others and/or the environment" (Hendricks, 2018). The decrease in divide between subject and object, often experienced as a sense of merging into the environment and a decreased sense of "I" or individual identity may be due to what SEB theory here deems a hyporeflexive processing style, in which there is a decrease in self-consciousness when processing internal stimuli. To illustrate this, a quotation describing the acute effects of psilocybin from Michael Pollan's (2018) *How to Change Your Mind* is included:

"I lost whatever ability I still had to distinguish the subject from the object, to tell apart what remained of me and what was Bach's music. … I became a transparent ear, indistinguishable from the stream of sound that flooded my consciousness until there was nothing else in it, not even a dry tiny corner in which to plant an I and observe." (p. 268)

In this quotation, we see Pollan describing a state of complete absorption into the experience, to the extent that the experience is so information-rich that a sense of an "I" is unnoticeable. There is a profound sense of a loss of self-consciousness in the processing of stimuli—a dramatic decrease in internal self-focus. This contrasts strikingly with the previously mentioned psychosis patient, who was "internally watching" his perception of the music.

Additionally, these reductions in self-focus may allow people to reflect on personal problems from an adaptive self-distant perspective instead of a self-immersed one. Self-distance is often thought of as thinking of oneself from a "fly on the wall" perspective and has been described as an adaptive perspective for overcoming adversity (Ayduk and Kross, 2010; Travers-Hill et al., 2017; Dorfman et al., 2021). This reduction in self-focus, along with a hyperassociative, entropic processing style, may be key for producing therapeutic

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insights, as discussed in greater detail in subsequent sections.

Additionally, unlike psychosis, classic psychedelics do not appear to diminish self-presence. For example, Richard Alpert (later known as Ram Dass), a psychedelic researcher in the 1960s, remarked that during his first psilocybin experience, after witnessing an externalization of various aspects of his identity, he experienced profound feelings of presence:

"I had just found the 'I'—that perceptual point of view, that essence of identity, that scanning device. I'd found that place of awareness beyond form, where 'I' exists independent of social and psychological roles. I was just presence, unfettered by the usual slipstream of random thoughts, images, and sensations. I nestled into this sense of pure being, feeling my way into this timeless, inner self that was independent of outer identity." (Dass and Das, 2021, p. 67)

In this quotation, despite Alpert's sense of loss of identity, he does not express feeling nonexistent as people in psychotic states often report (Parnas and Handest, 2003; Parnas et al., 2005; Sass, 2017). However, the potential role of self-presence in classic psychedelic states has largely been neglected by research, but has been hinted at in qualitative studies (Belser et al., 2017; Watts et al., 2017). We suggest that this phenomenon be explored further, and to do so will likely require lenses other than psychoanalytic theory (i.e., ego dissolution). In short, despite decades of comparisons of similarities between psychosis and classic psychedelic–induced states based on alterations to the sense of self, a more nuanced comparison displays substantial differences that we propose are highly relevant to outcome.

F. The DMN and Self-Focus

The DMN is a highly researched, large-scale brain network with high resting metabolism (Raichle, 2015) that is implicated in a variety of psychiatric conditions (Menon, 2011; Whitfield-Gabrieli and Ford, 2012), including depression (Zhu et al., 2017; Boeker and Kraehenmann, 2018; Fossati, 2019; Scalabrini et al., 2020), chronic pain (Kucyi et al., 2014), and addiction (Liang et al., 2015; Zhang and Volkow, 2019). It is also related to a variety of cognitive processes including metacognition and self-referential processing (Andrews-Hanna et al., 2014; Raichle, 2015; Davey et al., 2016), mind wandering (Davey et al., 2016), and rumination (Zhou et al., 2020). It is a frequent biomarker for examining responses to interventions, including meditation (Simon and Engström, 2015) and antidepressants (Posner et al., 2013).

The DMN is generally described as including the medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobules, and often the medial temporal lobes (Whitfield-Gabrieli and Ford, 2012). Occasionally, these regions are further parcellated into subsystems including a core, dMPFC, and MTL subsystems (Wen et al., 2020). It is generally described as a task-negative network and shows anticorrelations with task-positive networks, such as the executive control network during many tasks in healthy individuals (Whitfield-Gabrieli and Ford, 2012). However, it may also show increased activity in some tasks, including some evoking social cognition (Wen et al., 2020; Yeshurun et al., 2021), such as theory of mind (Molenberghs et al., 2016). The DMN also expresses a high number of 5-HT2ARs (Yeshurun et al., 2021), and has also been shown to be strongly influenced by 5-HT and DA signaling in general (Cruz et al., 2021).

Some initial work suggested that decreases in DMN connectivity during the acute effects of classic psychedelics are a key contributor to the experience of ego dissolution (Carhart-Harris et al., 2012, 2016; Kometer et al., 2015); decreases in DMN integrity during the acute effects of classic psychedelics are a frequently reported finding (Viol et al., 2017; Müller and Borgwardt, 2019; Madsen et al., 2020, 2021; Mason et al., 2021). However, similar alterations in DMN integrity have also been noted in substances with a range of subjective effects, including MDMA (Müller et al., 2021) and salvinorin A (a κ-opiate receptor agonist) (Doss et al., 2020). These substances have all been shown to alter self-referential processing (Walls et al., 2016) and self-experience (Maqueda et al., 2015), suggesting that similar DMN alterations may correlate with overlapping alterations in subjective experience. Additionally, awe was found to decrease DMN activity when participants were asked to passively watch an "awe-inducing" video, indicating that the DMN may very well be relevant to self-focus (van Elk et al., 2019). Alterations in postacute effects are less consistent, with both increases in (Carhart-Harris et al., 2017; Smigliski et al., 2019b; Barrett et al., 2020) and no effect on (McCulloch et al., 2020; Sampedro et al., 2017) DMN integrity being reported; occasionally these alterations correspond to long-term psychologic and behavioral effects (Smigliski et al., 2019b), but not always (Carhart-Harris et al., 2017). Therefore, seeing DMN integrity as a direct indicator of self-focus or a predictor of resource building currently seems unwarranted. Speculatively, we propose that a "broader repertoire" of DMN activity may be seen in the postacute effects, as was reported by the increases in integrity in resting state and decreases during mediation, after a psilocybin-assisted meditation retreat (Smigliski et al., 2019b).

Aberrant DMN connectivity is a consistent finding in schizophrenia research (Whitfield-Gabrieli and Ford, 2012; Dong et al., 2018; Collin et al., 2020) with stage of the condition playing a significant role in the directions of these alterations. In early-stage schizophrenia, within-network resting state connectivity appears generally elevated (Whitfield-Gabrieli and Ford, 2012; Clark et al., 2018; Collin et al., 2020), including in drug-

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naıve patients (Anticevic et al., 2015; Guo et al., 2017) and in clinical high-risk (CHR) patients who later develop a psychotic disorder (Collin et al., 2020). However, a metanalysis examining schizophrenia in mostly chronic patients with long-term medication use reported decreases in DMN within-network connectivity (Dong et al., 2018). It is likely that these patients would still show alterations in self-disturbances (Sass, 2017), again suggesting that the DMN cannot be considered entirely responsible for self-focus.

In summary, alterations in DMN connectivity seem to be a feature of both psychosis and classic psychedelic–induced states, but the exact relevance is less clear. Larger samples and more diverse methods may help us understand more about the utility of the DMN and other networks in predicting outcomes and the neural correlates of phenomenological alterations in the acute and post-acute effects of classic psychedelics. Real-time fMRI has recently been employed in schizophrenia (Bauer et al., 2020) and mindfulness research (Brewer et al., 2013; Garrison et al., 2013; Kim et al., 2019) and shows significant potential for disentangling the role of a network or region of interest in producing a particular subjective experience, and as such may present a potential method to more directly examine the role the DMN and other networks play in the subjective effects of classic psychedelics, including those related to alterations in self-focus.

G. The Thalamus and Prefrontal Overload: Producing Self-Alterations?

The thalamic gating theory of classic psychedelics (Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Vollenweider and Smallridge, 2022) suggests that due to a reduction of thalamic gating, "cortical inundation with sensory and cognitive information" will occur, producing "cognitive fragmentation and ego-dissolution" in both psychedelic-induced states and psychosis (Geyer and Vollenweider, 2008). Accordingly, cortical regions are expected to show an increase in activity in both classic psychedelics and psychosis, and more specifically the model suggests that "reduced thalamic gating leads to overactivity of prefrontal brain regions" (Vollenweider, 2001). While this theory is somewhat consistent with findings in thalamic connectivity with sensorimotor regions (see *Thalamic Gating: A More Vivid Experience?*) examination of prefrontal cortical activity presents a more complex topic.

It is first important to understand how the thalamic gating theory of classic psychedelics likely developed in light of early pioneering PET and SPECT-based work suggesting increases in frontal lobe metabolism during the effects of psilocybin (Vollenweider, 1997; Gouzoulis-Mayfrank, 1999), mescaline (Hermle et al., 1992), and ayahuasca (Riba et al., 2006). Additionally, PET-based studies have also reported hyperfrontality with ketamine (Vollenweider et al., 1997). Intriguingly, these findings contrast with many studies of schizophrenia suggesting hypofrontality (Hazlett et al., 2019); however, it was suggested that psychosis may be marked by initial hyperfrontality followed by a subsequent decrease (Vollenweider, 1997). Even with this consideration, hyperfrontality in early psychosis is not a consistent finding (Molina et al., 2005).

More problematically, the early PET and SPECT-based findings are in stark contrast to fMRI studies on the acute effects of psilocybin (Carhart-Harris et al., 2012; Lewis et al., 2017) and LSD (Carhart-Harris et al., 2016) which have shown decreases in BOLD signal in prefrontal regions. However, Lewis and colleagues did report increases in CBF in the PFC when using global signal regression, a highly controversial neuroimaging analysis technique (Murphy and Fox, 2017). More recently, a magnetic resonance spectroscopy study suggests that psilocybin increases glutamate in the mPFC, suggesting increases in metabolic activity (Mason et al., 2020). However, increases in glutamate were correlated with anxious ego dissolution. Some have suggested that this may reflect increases in "self-referential schema," despite "an otherwise dwindling autobiographical self-narrative" (Zamani et al., 2022). Even with this potential explanation, in general glutamate levels are reduced in schizophrenia in the mPFC (Smucny et al., 2021).

Overall, it appears that findings relating to frontal regions often display contradictory results. A recent simultaneous PET-fMRI study may partially explain this paradox (Stiernman et al., 2021). Stiernman and colleagues reported that although increases in metabolic signal (measured with glucose metabolism) and BOLD are correlated within task-positive networks, there is a lack of coupling of metabolism and BOLD signal for the DMN; more specifically, DMN glucose metabolism remains high even during task-based deactivations. This suggests that there may be increases in metabolism in prefrontal regions (including the mPFC, a key node in the DMN) while simultaneous decreases occur in BOLD signal. This suggests that hyperfrontality of metabolism and decreased PFC BOLD signal findings may be compatible. However, it makes interpretation of the psychologic findings much more tenuous. Clearly, more work is needed to disentangle why PET, fMRI, and magnetic resonance spectroscopy findings may show seemingly paradoxical results, pointing to a need for more multimodal neuroimaging studies.

Although thalamic gating was not initially developed based on fMRI functional connectivity findings, some may be curious as to how fMRI functional connectivity may relate. In general, psychosis is marked by decreases in functional connectivity between the PFC and thalamus during rest (Anticevic et al., 2015; Giraldo-

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Chica and Woodward, 2017; Avram et al., 2021), including in CHR patients (Anticevic et al., 2015; Woodward and Heckers, 2016). However, very recent research is emerging suggesting that DMN-thalamic connectivity increases sharply during the first years of nonaffective psychosis, followed by a sharp decline in FEP patients who went on to convert to schizophrenia (Chan et al., 2022). This may seem to agree with the hypothesis that thalamic gating may produce "cortical flooding," though we stress that the directionality of these changes is not apparent from studies of functional connectivity. It is also relevant that decreases in connectivity between the thalamus and the cerebellum are well-documented in early schizophrenia (Fryer et al., 2021). This suggests more widespread alterations than thalamic theory initially suggests. During the acute effects of LSD, decreases in connectivity have been reported between the left thalamus with vermis 10, a region within the cerebellum (Müller et al., 2017), but this is in stark contrast to the widespread, replicated decreases in connectivity between the cerebellum and the thalamus in schizophrenia (Fryer et al., 2021). Additionally, no changes in connectivity between the thalamus and DMN occur during the acute effects of psilocybin (Carhart-Harris et al., 2013). Again, these current findings mostly suggest further study is needed.

Overall, thalamic gating theory's proposal that the thalamus instigates increases in activity in cortical regions, particularly the PFC, and subsequently induces alterations in ego dissolution, is not well supported. This may be due in part to the difficulties of drawling similarities between different neuroimaging modalities. It should be noted that SEB theory makes no claims about whether increases in entropic processing or alterations in self-experience occur first with classic psychedelics and psychosis. In short, thalamic gating theory's relation to the PFC mostly serves to illustrate how different neuroimaging modalities have shaped the comparison of psychosis and psychedelic-induced states over time.

H. What About Self-Related Insights?

Self-focus must be distinguished from other types of self-related topics, such as self-related insight or the "clarity of understanding of one's thoughts, feelings and behavior" (Grant et al., 2002). This contrasts with the type of insight discussed previously in the aberrant salience section, which is based on seeing novel connections that are not necessarily driven by presence of one's internal experience. We speculate that classic psychedelics may facilitate self-related insights by decreasing self-focus and potentially increasing self-presence. Conversely, in psychosis, there is a decreased capacity for self-related insight due to hyper-reflexivity and decreased self-presence, as others have previously discussed (Nelson et al., 2009).

Recent research suggests that increases in insights during classic psychedelic drug effects are associated with better clinical outcomes (Carhart-Harris et al., 2018b; Davis et al., 2020) and increases in well-being in nonclinical populations (Carhart-Harris et al., 2018c; Davis et al., 2021). We suggest that classic psychedelics might facilitate such psychologically meaningful insights in part from a decrease in self-focus, fostering spontaneous self-distant self-reflection. Others have suggested similar ideas noting that classic psychedelics "alter the usual frame of reference," creating the experience of "a wide-angle lens giving a much broader picture" (Gasser et al., 2015). For an example of how this might benefit the therapeutic process, consider the experience of a patient with treatment-resistant depression during their psilocybin-assisted therapy session:

"I was thinking about relationships I had with other people and thinking I could see them clearly almost as if for the first time. I had fresh insight into things. It was almost as if suddenly the scales dropped from my eyes, I could see things as they really are" (Watts et al., 2017).

Although the patient experienced thoughts about themselves, these insights required a change in perspective. Moreover, we speculate that insights into maladaptive behaviors and thought patterns may allow an individual to become more present in their lives, by decreasing self-focused tendencies. For example, a patient with cancer-related anxiety treated with psilocybin-assisted therapy remarked, "I feel more in touch with who I really am—my real self, myself that's connected to everyone and everything" (Belser et al., 2017). Another patient in the same study reported, "The percentage of my life that I am able to be present in just a moment has increased dramatically, and it's really just been restored from almost nonexistent to often existent …." These experiences suggest that classic psychedelics may facilitate self-presence and self-related insight. These themes are repeated in other qualitative studies of psychedelic-assisted therapy (Watts et al., 2017; Noorani et al., 2018). Intriguingly, in one study, decreases in resting-state DMN integrity during the acute effects of psilocybin were the best predictor of experiencing insights during the acute drug action out of several neurologic alterations; however, this study examined "insights" more generally (i.e., "I had insights into connections that had previously puzzled me") in nonclinical individuals (Mason et al., 2021).

In contrast, people with psychosis display a decreased capacity for intrapersonal insight and meaningful self-reflection (Lysaker et al., 2019). In its most extreme cases, this manifests as a lack of insight into their condition, which has been correlated to increases in within-network connectivity in the DMN in CHR individuals in resting state (Clark et al., 2018). This lack of self-awareness has

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been suggested to be due to extreme self-focus (Clark et al., 2018), which includes aberrant self-reference (Wong et al., 2012) and hyper-reflexive tendencies (Sass, 2014). These processes contribute to difficulty in internal nonjudgmental awareness of one's thoughts and actions (Ćurčić-Blake et al., 2015). This lack of insight may contribute to some psychosis patients feeling one's "personality is in danger" or that one is "beginning to disappear" (Chapman, 1966; Carhart-Harris and Friston, 2010). It is suggested here that such extreme lack of self-related insight and self-presence may derive from excessive self-focus and are most likely distinct from the classic psychedelic–induced "ego dissolution." Clearly, further work elucidating the role of self-related insights, self-presence, and self-focus in classic psychedelics and psychosis is needed. However, it is maintained that psychologic insights garnered through classic psychedelic use are distinct from self-focus.

I. Psychosis Self-Disturbance: Etiology & Outcomes

Crucially for SEB theory, research suggests that anomalous self-experiences, as described by the self-disturbance model (Sass et al., 2018), are key to the iatrogenesis and long-term outcomes of SSDs (Parnas et al., 2005). This suggests that rather than a tangential phenomenon, understanding these alterations is key to understanding the trajectory of psychosis and the psychotomimetic-psychedelic paradox. Research suggests that self-disorder (SD) is present from the earliest stages of psychosis (Raballo, 2010; Raballo and Parnas, 2012; Raballo et al., 2021); some have even proposed that such alterations are part of the endophenotype predisposing individuals to psychosis (Parnas, 1999; Raballo and Parnas, 2012; Parnas and Henriksen, 2016; Sass, 2017; Raballo et al., 2021; Spark et al., 2021). In support of this, in nonaffected family members with a high genetic risk for psychosis, SD is positively correlated with schizotypal traits (Raballo and Parnas, 2011). Moreover, excessive posterior DMN activation during a self-referential processing task is present in children with a high familial risk for psychosis and correlated with increases in internalization scores, which the authors described as related to "maladaptive (excessive) self-focus" (Collin et al., 2021). This suggests that subpathologic alterations of SDs are present from the earliest stages of schizophrenia, perhaps even before the onset of prodromal symptoms, presenting an important way to predict the outcome of schizophrenia-like symptoms.

Currently, screening based on classic prodromal symptoms is notorious for false positives (Nelson et al., 2012; Herrera and Fietzer, 2021). Moreover, prepsychotic help-seeking patients and other patients are not distinguishable based on prodromal symptoms at intake prior to the development of acute psychosis (Koren et al., 2020). This is because without further probing, the clinical presentation of depression and psychosis often appear similar (Corcoran et al., 2011; Rietdijk et al., 2013; DeVylder et al., 2014; Brouwer and Carhart-Harris, 2021). However, the presence of SD was able to predict long-term outcomes significantly (Koren et al., 2020; Spark et al., 2021).

In addition to predicting the development of SSDs, the level of SD also predicts a range of other outcomes. Patients with more SD at first substantial treatment were less likely to experience recovery or symptomatic remission at 7 years postinitial treatment (Svendsen et al., 2018). Additionally, patients who experienced a full recovery reported lower baseline SD and a decrease in SD over time. The severity of SD has also been associated with poor social functioning (Haug et al., 2014; Raballo et al., 2016) and self-esteem (Haug et al., 2017). Subjectively, these findings may be due in part to individuals feeling alienated from the external world (Sass, 2017). This phenomenon may be due in part to excessive self-focus, to the point that it is difficult to interact with others in a meaningful way. As one individual said, "I have the feeling that everything turns around me" (Sass and Byrom, 2015a).

Most critically for clinical care, SD is also predictive of the likelihood of suicide and self-injurious behavior (Skodlar et al., 2008; Skodlar and Parnas, 2010; Haug et al., 2012; Koren et al., 2019). SD is also a stronger predictor of depression and suicide than positive symptoms in non-help-seeking community-dwelling adolescents (Koren et al., 2019). Several studies have sought to clarify the potential relationship between psychosis, depression, SD, and suicide, finding that feelings of inferiority and depression have been shown to mediate the relationship between SD and suicide (Skodlar and Parnas, 2010; Haug et al., 2012; Koren et al., 2019).

Overall, these studies suggest that considering the severity of self-disturbances in psychosis is essential for predicting real-world functioning and preventing the most severe outcomes. These alterations in self-experience are also generally quite different from those that occur in classic psychedelic states. This suggests that by comparing classic psychedelics and psychosis exclusively based on entropic processing style tendencies or psychoanalytic theory, researchers are missing a vital distinction that appears key to understanding the trajectory of psychosis.

J. Perpetuating Downward Spirals: Stress and Substance Use

Stress can also alter dopaminergic signaling (Howes and Kapur, 2009), particularly in response to social defeat (Selten et al., 2013), suggesting a possible link to the psychosocial elements that are risk factors for developing psychosis and their corresponding alterations within the dopaminergic system. Social defeat, stemming from a range of psychosocial factors including urban upbringing, migration, and childhood trauma, has been hypothesized to potentially promote sensitization of the

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mesolimbic system precipitating schizophrenia in people with genetic liability (Selten et al., 2013). In support of this view, increases in DA synthesis capacity in the associative striatum have been reported in UHR individuals and associated strongly associated with unstable family arrangements (Cohen's d = 0.86) and sexual and physical abuse (d = 0.75) (Egerton et al., 2016). Animal studies have also furthered this hypothesis (for reviews see Hammels et al., 2015; Selten et al., 2013). While the social defeat hypothesis has garnered some criticism (see Schalbroeck, 2020), it provides a potential pathway between the psychosocial risk factors and well-established neurobiological alterations in schizophrenia (Selten, 2021).

Similar to the social defeat hypothesis (Selten et al., 2013, 2017) and the idea of DA as a "final pathway" (Howes and Kapur, 2009), others have suggested that upregulation of 5-HT2a in response to stressors may play a pivotal role in precipitating psychosis (Brouwer and Carhart-Harris, 2021). Indeed, Brouwer and Carhart-Harris (2021) provide ample evidence that chronic stress, anxiety, depression, neuroticism, and social stress all upregulate 5-HT2a; however, their review also acknowledges a number of null or contradictory findings. Brouwer and Carhart-Harris (2021) suggest that endogenous increases in 5-HT in response to stress in individuals with elevated 5-HT2AR density can produce a pivotal mental state, a state marked by heightened plasticity and learning, promoting "psychological transformation," and facilitating either psychosis or psychedelic-like spiritual experiences, depending on context. Might part of the context be the pre-existence or co-occurrence of alterations in dopaminergic functioning due in part to stress or uncertainty? Further compounding the complexities of stress and dysregulation of neurofunction in facilitating a psychotic episode, others have posited that increased inflammation and alterations in microglial activation, caused by a mixture of genetic and environmental stressors, may further perpetuate dysfunction of the DA, glutamate, and serotonin systems in people who develop schizophrenia (Radhakrishnan et al., 2017). Regardless of the primary cause, it seems likely that dysregulation of one system perpetuates aberrant functioning of another, promoting a "downward spiral" that facilitates the development of schizophrenia.

If sensitization to stressors fosters neurobiological dysfunction, it may worsen in response to problematic substance use, which is more likely among stressed individuals (Sinha, 2008; Moustafa et al., 2021). Indeed, substance use disorders (SUDs) are highly prevalent in people who have experienced a psychotic episode and/or who develop schizophrenia. In a sample of FEP patients, lifetime prevalence of an SUD was 74% (Lambert et al., 2005) and studies have found a prevalence of 41.7% SUDs in people with a schizophrenia spectrum condition (Hunt et al., 2018). Substance use may further perpetuate altered neurologic functioning, with complex effects across systems of multiple neurotransmitters. For instance, in mice, one methamphetamine "binge" may lead to lasting downregulation of mGLU2 receptors and upregulation of 5-HT2ARs (Chiu et al., 2014). Various cannabinoid agonists have also been shown in preclinical studies to upregulate 5-HT2a expression (Hill et al., 2006; Franklin et al., 2013) and to alter the signal pathway induced by 5-HT2AR agonists (Ibarra-Lecue et al., 2018). Problematic substance use may facilitate an increase in social stressors, too, as an individual's life becomes more centered around using and obtaining a drug (Garland et al., 2013). It is apparent that both substance use and social stress can increase dysfunction, potentially propelling an individual toward a psychotic episode. To be clear, we are not making a statement about substance use or stress occurring first as risk factors for developing a psychotic disorder, simply that they can often create reciprocal worsening of functioning.

K. Classic Psychedelic-Induced Alterations to Self and Outcomes

Both therapeutic research and studies in nonclinical participants have reported that alterations in self-experience during the acute effects of classic psychedelics reliably predict durable and holistic positive change. Higher mystical experience scores have been correlated with better treatment outcomes of psilocybin-assisted therapy for substance use (Bogenschutz et al., 2015; Johnson et al., 2014) and anxiety and depression in cancer patients (Griffiths et al., 2016). Greater experience of oceanic boundlessness also predicted long-term benefits in patients with TRD (Roseman et al., 2018). Similar results have also been noted in nonclinical populations. In a psilocybin-assisted meditation retreat setting, oceanic boundlessness correlated to positive effects at four months and externally rated increases in prosocial behavior (Smigielski et al., 2019b). Other positive behavior changes, including increased journaling and more consistent meditation practice, have also been associated with higher levels of the mystical experience during a psilocybin session (Griffiths et al., 2018). Increases in mindfulness, positive affect, and life satisfaction were correlated with ego dissolution experienced during an ayahuasca ceremony (Uthaug et al., 2018).

We posit that these findings occur because increases in attentional scope (as occurs in entropic processing) with a reduction in self-focus facilitate the building of new resources and enhance the appreciation of everyday experiences. Postacute increases in mindfulness (Smigielski et al., 2019b) and openness to new experiences (Carhart-Harris et al., 2016a; Lebedev et al., 2016; MacLean et al., 2011) after administration of a classic psychedelic suggest increased awareness of the external environment and opportunities available. These holistic changes are supported by long-term follow up interviews with participants who received psilocybin-assisted psychotherapy for TRD (Watts et al., 2017). Participants

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reported increased appreciation of everyday events, the starting or restarting of new activities, and increases in connection to the self, others, and the world. Moreover, multiple psilocybin sessions in healthy volunteers facilitated "better social relationships with family and others, increased physical and psychological self-care, and increased spiritual practice" at 14-month follow-up (Griffiths, 2011; see also Griffiths et al., 2006, 2008, 2018). These findings suggests that classic psychedelics facilitate the building of resources in a manner that precipitates lasting improvements in psychologic health.

To more fully understand how a broader attentional scope coupled with reductions in self-focus can foster lasting improvements in well-being, we provide the experiences of several participants in psilocybin studies. SEB theory's mechanisms are posited to be transdiagnostic, so quotations are included from both clinical and nonclinical studies. Below, a participant in a study of smoking cessation describes a broader, hyperassociative style of thinking with less self-focus as being pivotal for their commitment to quit smoking:

"I had always had the sense of everything being connected. And [the psilocybin session] reinforced that, very strongly. [If I were to smoke] I would be a polluter … ashtrays and butts all over the place, and you're causing harm to other people's health as well. And so you were re-looking at your place in the universe and what you were doing to help or hinder it. The universe as such. And by smoking, you wouldn't be helping" (Noorani et al., 2018).

The next few quotations describe an increased appreciation of external surroundings (broader attentional scope) in the postacute period. The first quotation comes from a patient with cancer-related distress and the following is from a patient with TRD.

"There's life and so many things going on, just watching that tree over there blowing in the breeze, seeing people in the street, and all the different people in vehicles rushing by! I just feel good about being alive. … It's always there; we just don't notice, and I'm trying to notice and not forget that I can see it at any time, I can hear it any time. It's like waking up in the most profound way, that this is really what life is" (Swift et al., 2017).

"I got a wider perspective, I stepped back. It helped me appreciate that the world is a big place that there's a lot more going on than just the minor things that were going on in my head" (P17) (Watts et al., 2017).

In these quotations, participants report noticing and appreciating their environment more than they previously had. This creates a more information-rich subjective experience. Noticeably, the increase in noticing small details is similar in many ways to the onset of psychosis (Cicero et al., 2010). However, as noted in the last quotation, people experience this broader attentional scope with a decrease in self-focus. In psychosis, similar changes to the world may be experienced, but they would be interpreted with self-focus (Hollandsworth, 2014, p. 77). After a classic psychedelic experience, we suppose these changes may allow individuals to consider previously ignored opportunities and ideas. This can be seen quite directly in the experiences of two participants at 14 months after a series of psilocybin sessions (Griffiths et al., 2011):

"I am more aware and accepting [of everyone]. I have a thousand ideas to write about and am making time and space in my life to accommodate them" (Volunteer, 230).

"I take more time in nature, with art. I feel closer to children and parents. I am more comfortable with friends and acquaintances. I am more committed to my career. I eat better and have taken up dance … " (Volunteer, 211).

In both cases, participants report a wide range of changes, including increases in social connections, starting meaningful activities, and coming up with new ideas. We believe such changes are promoted by the psychologic effects of classic psychedelics and then supported by the potential complementary increases in neuroplasticity (Sampedro et al., 2017; Cameron et al., 2018; Inserra et al., 2021a; Raval et al., 2021) and reductions in inflammation (Flanagan and Nichols, 2018; Inserra et al., 2021a), which may prime the brain to be able to adopt and maintain the new behaviors and mental schemas (Bourgognon and Cavanagh, 2020). Such building of resources may then promote lasting improvements in psychologic and, in some instances, physical health.

In support of this, naturalistic classic psychedelic use has been associated with greater overall health, lower rates of obesity (Simonsson,et al., 2021a) and decreased risk of hypertension (Simonsson et al., 2021b). This was suggested to be due in part to "acute transcendent experiences" precipitating long-term changes in health behavior. One example of how this may occur is through increases in nature-relatedness (Forstmann and Sagioglou, 2017), which may suggest increases in the pursuit of outdoor activities that can contribute to better well-being and physical health (Eigenschenk et al., 2019). These multifaceted changes in behavior suggest that classic psychedelics elicit change in a significantly more holistic manner than only reducing symptoms of depression or other conditions do.

It is also worth clarifying that increases in psychologic health induced by classic psychedelics are not simply increases in positive emotions. Patients with TRD described becoming more accepting of all emotions and experiencing a broadening of an emotional repertoire after their experience (Watts et al., 2017). Such findings again suggest it is not the increase in positive emotions

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driving lasting lifestyle and psychologic change, but rather a broader and less self-focused perspective.

Overall, it appears, the pathway of broaden-and-build theory (increases in thought-action repertoire, building of enduring resources) is accurate for classic psychedelics, but the causal agent differs: positive emotions for broaden-and-build theory versus decreases in self-focus with an entropic processing style in SEB theory. To more fully understand this potential pathway of classic psychedelic–elicited change we suggest future studies use experience sampling (Larson and Csikszentmihalyi, 1983; Csikszentmihalyi and Larson, 1987) to examine how changes in the subjective experience (i.e., self-focus) predict enduring changes in behavior and mental health in daily life. Experience sampling also displays fewer issues with demand effects and recall than do other forms of self-report and allows behaviors to be observed in real-world settings. Predictive models could also be developed to see what aspects of the acute experience best predict lasting positive psychologic and behavioral change. If a confirmation of SEB theory's pathway of change is established, interventions to optimize factors to promote lasting change and prevent adverse outcomes should be explored.

However, SEB theory's mechanism may not be exclusive to classic psychedelics. Decreases in self-focus, often deemed "self-transcendent" experiences, have been described for states of mindfulness, flow, and other non-psychedelic-elicited experiences (Yaden et al., 2016, 2017). These alterations are similar to what has been noted in cases of awe, where the "small self" mediates prosocial behaviors and increases in well-being (Piff et al., 2015; Hendricks, 2018; Stellar et al., 2018). However, the consistency and magnitude of alterations in self-focus and entropic processing make classic psychedelics distinct. This being said, more research is needed comparing increases in well-being and positive behavior outcomes of such non-substance-induced experiences to classic psychedelic–induced experiences.

III. Pharmacological Considerations

A. Dopamine's Role in Schizophrenia

The DA hypothesis of schizophrenia, suggesting that alterations in DA signaling are crucial to the etiology of the disorder, was developed in the 1970s in part due to the efficacy of first-generation antipsychotics and the ability of amphetamines to produce psychotic symptoms (see Seeman, 2021, for a historical overview). Today, there is substantial evidence that efficacy of antipsychotic drugs correlates with D2 receptor occupancy (Chestnykh et al., 2021); all currently approved antipsychotics display action at D2 receptors (Ebdrup et al., 2011), including first-generation antipsychotics, atypical antipsychotics (Jones and Pilowsky, 2000; Mauri et al., 2014; Aringhieri et al., 2018; Torrisi et al., 2020; Chestnykh et al., 2021), and D2 partial agonists as seen in third-generation antipsychotics (Mailman and Murthy, 2010; Ito et al., 2012).

People with schizophrenia show a hyperresponsiveness to psychostimulants, including amphetamines and methylphenidate, including a worsening of symptoms and a production of "a psychotogenic response" at dosages that are "subpsychotogenic" for healthy normals (see Lieberman et al., 1987, for a review). Additionally, excessive DA release in response to amphetamine has been reported using PET in unmedicated FEP patients (Weidenauer et al., 2016). Furthermore, increases in presynaptic striatal DA availability in schizophrenia have been widely replicated (Howes and Kapur, 2009) and are also found in CHR individuals, particularly in the dorsal striatum (Egerton et al., 2013). It is also thought that elevated DA transmission may facilitate alterations in the cortico-striato-thalamic circuit (Conn et al., 2020), which, as previously discussed, shows significant functional abnormalities in schizophrenia (Giraldo-Chica and Woodward, 2017). On a genetic level, large genome-wide association studies have also implicated the importance of genes related to D2 in schizophrenia, among additional genes associated with synaptic plasticity, the glutamatergic system, and voltage-gated calcium channel subunits (Ripke et al., 2014); we stress that schizophrenia is a widely heterogeneous condition genetically (Bansal et al., 2018). Alterations in dopaminergic signaling also seem to be associated with schizotypy, a personality trait associated with subclinical "schizophrenia-like" behaviors (see Mohr and Ettinger, 2014, for a review). As previously discussed, dopaminergic PD medication can produce psychotic-like symptoms (Poletti et al., 2014; Polner et al., 2015, 2016; Poletti, 2018). Furthermore, repeated dosing of amphetamines in healthy volunteers produced a sensitization of DA release such that alterations were no longer significantly different from FEP patients exposed to amphetamines (Weidenauer et al., 2016). Collectively, these findings seem to be in concordance with DA alterations being a "final pathway" to schizophrenia (Howes and Kapur, 2009) and likely to altered states with related symptomatology, such as stimulant-induced psychosis (Angrist et al., 1974; Shelly et al., 2016; Wearne and Cornish, 2018; Sabe et al., 2021).

It is important to keep some nuances in mind. Although DA hyperactivity in the mesostriatal pathway contributes to positive symptoms, some cognitive and negative symptoms are associated with hypodopaminergic activity in the cortical regions, particularly the PFC (Slifstein et al., 2015; Rao et al., 2019; Chestnykh et al., 2021). Moreover, there is some evidence that antipsychotics can worsen some cognitive symptoms (Sakurai et al., 2013; Husa et al., 2017; Conn et al., 2020) and up to 66.9% of patients do not reach symptom remission with antipsychotic treatment in randomized control trials (n = 6,221) (Samara et al., 2019).

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It is also unclear how helpful antipsychotics are for reducing self-disturbances (Nelson et al., 2021), which, as we have stressed, appear to be crucial to predicting the long-term trajectory of a psychotic episode (see Burgin et al., 2022, for a review). It was recently shown that reductions of self-presence were associated with a lower sense of coherence in people with schizophrenia and other psychotic disorders (Svendsen et al., 2020). Sense of coherence indicates a "subjective experience of good health," despite having a severe illness and is related to a sense of ability to manage the disorder and to feel that life has meaning (Svendsen et al., 2020). As self-presence may not be affected by antipsychotic treatment, patients using antipsychotics might still feel that life is difficult to manage, even if positive symptoms are reduced. Speculatively, we suggest that although antipsychotics show the ability to reduce delusions, which may stem from entropic processing coupled with excessive self-focus, they may be less effective at treating reductions in self-presence (Parnas and Handest, 2003; Brent et al., 2014; Burgin et al., 2022).

A lack of antipsychotic efficacy in treating anomalous self-experiences in psychosis could indicate that a non-DA-dependent abnormality or hypodopaminergic function in cortical regions (Sekiguchi et al., 2019) fosters reductions in self-presence. This may explain the lack of efficacy of antipsychotics for more negative aspects of the disorder (Correll and Schooler, 2020), if they are indeed based partially on reductions in self-presence (Sass and Parnas, 2003; Sass, 2017). However, the role of DA transmission in the etiology of self-disturbances has not been directly researched to our knowledge. We suggest further study using the Examination of Anomalous Self-Experience scale (Parnas et al., 2005) and Inventory of Psychotic-Like Anomalous Self-Experiences (Cicero et al., 2017) in conjunction with other scales of psychotic symptoms to examine the role of altered DA transmission, such as availability of presynaptic DA, throughout the stages of schizophrenia. Further studies might also probe how antipsychotic medications may or may not affect SD. These lines of work will help the SD theoretical framework move beyond its focus on predicting the outcomes of people during early psychosis and distinguishing schizophrenia from related conditions (Nordgaard et al., 2021) to understanding how schizophrenia symptoms may be improved. Still, even with these unknowns, we stress that DA alterations are very strongly implicated in schizophrenia, even though their role in alterations in self-experience is less clear.

B. Schizophrenia: Antagonist and Agonism at 5-HT2ARs

One of the most obvious arguments for the psychotomimetic view of classic psychedelics is the antagonism of atypical antipsychotics at the 5-HT2AR (Baumeister and Hawkins, 2004; Geyer and Vollenweider, 2008). Indeed, atypical antipsychotics, such as clozapine and risperidone, do show higher receptor affinity for 5-HT2a than for D2 receptors (Mauri et al., 2014). Might the use of atypical antipsychotics imply that similar 5-HT2a binding effects produce similar psychologic, cognitive, and systems-level neurobiological effects between psychosis and classic psychedelic–induced states? Such a hypothesis has been implied by earlier work (Geyer and Vollenweider, 2008).

First, it must be understood how atypical antipsychotics differ clinically from typical antipsychotics. A recent metanalysis of randomized placebo-controlled trials of both typical and atypical antipsychotics of 402 studies with data from 53,463 patients reported minor and most often nonsignificant differences between 32 antipsychotics in reducing overall symptoms, but reported that differences in side effects between drugs were more significant (Huhn et al., 2019). However, it should be noted that this metanalysis focused on the treatment of acute schizophrenia, not FEP patients. In terms of FEP patients, a large ($n = 376$) study reported better efficacy of atypical antipsychotics compared with typical antipsychotics, however, effectiveness in antipsychotic medications is largely based on tolerability as many patients discontinue medication due to side effects (Gómez-Revuelta et al., 2020). There is some evidence that atypical antipsychotics may display better efficacy at treating the cognitive deficits in schizophrenia (Hou et al., 2020; Meltzer and Gadaleta, 2021). However, this remains controversial as others have reported a lack of improvements (Anda et al., 2021) or have suggested that 5-HT2a agonism may worsen cognitive deficits (Takeuchi, 2015; Singh et al., 2022) or impair learning (Brouwer and Carhart-Harris, 2021).

It is also crucial to keep in mind that atypical antipsychotics display promiscuous binding affinities, often significantly impacting glutamatergic, muscarinic, histamine, and α-adrenergic receptors (Nasrallah, 2008), earning them the name "magic shot-guns" (Roth et al., 2004). Many atypical antipsychotics also impact 5-HT1a and 5-HT2c receptors, with some also affecting 5-HT6 and 5-HT7 receptors (Aringhieri et al., 2018). Furthermore, there is great diversity in the secondary pharmacological profiles of atypical antipsychotics. This plays a greater role in the development of side effects than it does on the amelioration of symptoms (Huhn et al., 2019; Meltzer and Gadaleta, 2021).

With these complex pharmacological profiles, some may wonder, what is 5-HT2a antagonism or inverse agonism contributing to the efficacy of these substances? Early work suggests that 5-HT2a antagonism's primary effect may be reductions in extrapyramidal side effects (Janssen et al., 1988; Meltzer et al., 1989; Roth et al., 2004), in part due to increases in DA release in the PFC (Ichikawa et al., 2001). However, more recent work suggests that association kinetics at the D2 receptor may play a more substantial role in

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the development of extrapyramidal side effects than 5-HT2a antagonism (Sykes et al., 2017). Further complicating the role of 5-HT2a in atypical antipsychotic mechanisms, clozapine, the "gold standard" atypical antipsychotic (Meltzer and Gadaleta, 2021), with high 5-HT2a inverse agonism, displays some action that makes it a functional agonist, including 5-HT2a downregulation after chronic administration (Yadav et al., 2011) and Akt phosphorylation, as endogenous 5-HT2a does (Schmid et al., 2014). Therefore, seeing the atypical antipsychotics as an "inverse" of the effects of classic psychedelics is likely an oversimplification, given that some antipsychotics display downstream effects closer to an agonist (López-Giménez and González-Maeso, 2018) and the likely larger impact on side effect profiles than symptom reduction (Huhn et al., 2019).

Further suggesting the lack of necessity for 5-HT2a alterations in developing psychosis, numerous potential antipsychotics with 5-HT2AR antagonism, or inverse agonism, but without D2 action, have shown low efficacy (Ebdrup et al., 2011). M-1000907 (de Paulis, 2001) and pimavanserin (Meltzer et al., 2010) are selective 5-HT2a and 5-HT2c receptor inverse agonists without D2 antagonism and showed initial promise at reducing symptoms in animal modes of schizophrenia, including those produced by 5-HT2a agonism (Padich et al., 1996; Vanover et al., 2006). But M-1000907 was halted in human trials due to poor results (de Paulis, 2001). Similarly, pimavanserin as adjunctive therapy failed to show clinically significant improvements in individuals with inadequate responses to other antipsychotic treatments, although trends toward improvements in negative symptoms were observed (Bugarski-Kirola et al., 2022). Furthermore, in the treatment of PD-related psychosis, pimavanserin shows low efficacy (15%) as a monotherapy in clinical practice (Akbar and Friedman, 2022). In contrast, there are some successful cases (n = 4) of pimavanserin as monotherapy in schizophrenia patients who had failed to respond to other antipsychotics (Nasrallah et al., 2019), however, these patients may have a differential etiology of schizophrenia. More familiar to those in the psychedelic field, ketanserin, which readily blocks the effects of classic psychedelics (Preller et al., 2018), is not approved for the treatment of schizophrenia. However, in a case study of a patient with rare, childhood-onset, treatment-resistant schizophrenia, ketanserin did show a reduction in visual hallucinations, but did not improve auditory hallucinations or delusions while the patient remained on olanzapine, an atypical antipsychotic (Sommer et al., 2018).

People with schizophrenia have been reported to have a reduced sensitivity to LSD (Cholden et al., 1955; Cline and Freeman, 1956; Krus, 1963) and DMT (Böszörményi and Szára, 1958), in contrast to drugs with dopaminergic action (Lieberman et al., 1987; Breier et al., 1997; Seeman, 2011, 2021; Weidenauer et al., 2016). The findings of a "resistance" (Cline and Freeman, 1956) or "tolerance" (Chessick, 1964) to classic psychedelics in people with schizophrenia initially furthered the comparison of classic psychedelics to schizophrenia. It was proposed that "LSD might be considered a trace element in the development of endogenous psychoses," and thus, those endogenously exposed to it through a metabolic deficit would show a reduced response to exogenous exposure (Cholden et al., 1955). A more likely explanation for the reduction in response are alterations within the 5-HT2a or glutamatergic systems. In support of this view, it was recently found that lower 5-HT2AR binding prior to psilocybin administration is associated with higher MEQ scores (Stenbæk et al., 2021) and greater occupancy of 5-HT2ARs is associated with greater subjective effects of psilocybin (Madsen et al., 2019). It may then be that increases in 5-HT2AR densities in people with schizophrenia require a higher dose to achieve the same receptor occupancy binding compared to nonpsychotic individuals. However, findings regarding alterations in 5-HT2AR densities in psychosis are mixed (see Ebdrup et al., 2011, for a review), in part due to pharmacological variation of the radiotracers used (Diez-Alarcia et al., 2021). Nevertheless, increases in 5-HT2AR density have recently been shown with [^{3}H]LSD as a radiotracer in postmortem medication-naıve patients with schizophrenia (Diez-Alarcia et al., 2021). Thus, early work suggesting that people with schizophrenia display a reduced response to classic psychedelics might suggest higher 5-HT2AR density. With regard to glutamatergic transmission, a knockout study in mice found that the mGLU2 receptor is necessary to produce classic psychedelic effects (Moreno et al., 2011), likely due to the necessity of 5-HT2a-mGLU2 heterocomplexes (López-Giménez and González-Maeso, 2018), which may display alterations in schizophrenia (Muguruza et al., 2013; Aringhieri et al., 2018). Although the cause of reduced response remains a mystery, it is relevant to discuss this instead of a hypersensitivity, as is seen with DA agonists (Lieberman et al., 1987; Breier et al., 1997; Seeman, 2011, 2021; Weidenauer et al., 2016), there is evidence of a reduced response to classic psychedelics in very early literature (prior to the widespread use of antipsychotics).

If the dopamine hypothesis of schizophrenia originates primarily out of the efficacy of D2 antagonism (Seeman, 2021) and the hypersensitivity of people with schizophrenia to dopaminergic drugs (Lieberman et al., 1987; Breier et al., 1997; Seeman, 2011, 2021; Weidenauer et al., 2016), we cannot use the same logic to purport that 5-HT2a signaling is crucial in psychosis. There is evidence of a lack of necessity of 5-HT2a antagonism to treat psychosis and evidence of hyposensitivity to 5-HT2a agonism. Atypical antipsychotics are also used in nonpsychotic conditions, such as depression and OCD (Meltzer and Gadaleta, 2021), which may respond well to classic psychedelic-assisted therapy (Carhart-Harris et al., 2016, 2021; Davis et al., 2020; Lugo-Radillo and Cortes-Lopez, 2020). An agonism-

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verses-antagonism model of one receptor's action is an overly simplistic method of comparing the neurobiological similarities of classic psychedelic–induced states versus psychosis. However, at this juncture, it seems that evidence supports that the 5-HT2AR alterations are more crucial for classic psychedelic–induced states than for psychosis.

C. Chronic LSD Administration: A True Psychotomimetic?

There is evidence from animal models that chronic administration of LSD may represent a true psychotomimetic (Marona-Lewicka et al., 2011; Nichols, 2016). Indeed, LSD administered to rats every other day for 3 months produced lasting neurobiological and behavioral changes consistent with animal models of psychosis (Marona-Lewicka et al., 2011). Specifically, chronic LSD-exposed rats became hypersensitive to stimuli, such as noise outside of the experimental room, even 3 months after the last administration of LSD. This may suggest difficulty in filtering relevant from irrelevant sensory cues, consistent with increases in entropic processing. Increases in aggressive, exploratory behavior, and significant decreases in prosocial behavior also occurred. The increases in exploratory behavior may mirror the occasional increases in aberrant behavior in the early phases of psychosis, as previously discussed. The aggressive behavior may be a form of paranoia, which might be a rodent proxy for self-focus.

Furthermore, alterations in mRNA expression in the prefrontal cortex at 1 month after chronic LSD administration showed increases in D2D2 and NOR1 and decreases in HTR2C (Marona-Lewicka et al., 2011). Marona-Lewicka and colleagues suggested that alterations in D2D2 (Tallerico et al., 2001) and 5-HTRC gene expression (Castensson et al., 2003) may parallel those noted in schizophrenia. However, it is worth recognizing that the later, larger study did not report changes in gene expression of D2D2 (Castensson et al., 2003). Furthermore, a similar study by the same group reported decreases in DRD1 and D2D2, suggesting downregulation of these receptors (e.g., D2 and D1) (Martin et al., 2014). These ambiguities suggest that chronic LSD exposure does affect gene expression related to the dopaminergic system, although the direction of effects is unclear. It also must be acknowledged that recent research suggests a lack of altered D2/D3 receptor densities in schizophrenia across the stages of the illness (see Howes et al., 2020, for a review). Nonetheless, D2 antagonism or inverse agonism is implicated in the action of all approved antipsychotics (Aringhieri et al., 2018). Overall, these findings suggest that although DA signaling is implicated across all stages of schizophrenia, the alterations produced in a mouse model, are just that, a model, and do not precisely correspond to those in schizophrenia itself. However, it must be noted that neither study (Marona-Lewicka et al., 2011; Martin et al., 2014) documented significant changes in gene expression related to 5-HT2ARs; overall, changes in gene expression primarily included genes related to GABA, glutamate, and DA (Martin et al., 2014).

Intriguingly, chronic administration of DOI and psilocybin were also investigated and not observed to produce psychotic-like changes in behavior (Nichols, personal communication). This suggests that rather than indirect alterations in DA signaling due to 5-HT2a agonism, the particularly psychotomimtic effects of chronic LSD administration likely stem from LSD's unique agonism at the DA, D1, D2, and D4 receptors (Inserra et al., 2021a). Chronic alterations in glutamatergic signaling due to stimulation of the postsynaptic 5-HT2ARs on the pyramidal cells in the PFC also likely play a role (Muschamp et al., 2004), but most likely are not sufficient to produce a psychotic model, as DOI (Aghajanian and Marek, 1999; Scruggs et al., 2003) and DOM (Muschamp et al., 2004) also alter glutamatergic signaling. Furthermore, both atypical and typical antipsychotics reduced the LSD-produced syndrome, suggesting a lack of specificity for the 5-HT2a antagonism/inverse agonism produced by atypical antipsychotics and the criticality of the dopamine system (Marona-Lewicka et al., 2011).

In humans, the chronic LSD model of psychosis may parallel changes in cases of "long-term psychotomimetic drug abuse," where extremely heavy LSD use was associated with a psychotic-like syndrome in people (Glass and Bowers, 1970). The case of Syd Barrett, the frontman of Pink Floyd who purportedly left the band due to the development of schizophrenia precipitated by excessive LSD use, may further illustrate this potential relationship between *chronic* LSD exposure and psychosis (Fusar-Poli, 2007). However, it is worth mentioning these cases were likely confounded by use of cannabis, which is a well-known risk factor for development of schizophrenia (Masroor et al., 2021), and has also been shown to alter dopaminergic signaling in the striatum (Sami et al., 2015), including the associative striatum (see Sami et al., 2015, for a review) which is widely implicated in psychosis (Conn et al., 2020). Further complicating the picture, first generation antipsychotics, with significant antidopaminergic action, were tried in three of the four cases of LSD-induced psychosis and found to be ineffective (Glass and Bowers, 1970). This may provide some preliminary evidence suggesting changes outside of the dopaminergic system, perhaps alterations in glutamatergic signaling or 5-HT2C. Further study would be needed to validate this speculation. Additionally, we acknowledge that these patterns of use, (e.g., often purportedly biweekly or more), are likely extreme outliers among naturalistic classic psychedelic users (Glass and Bowers, 1970). This raises the possibility that such patterns of use may be a form of self-

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medication, which has long been speculated to occur in people with psychotic disorders (Šagud et al., 2018).

Still, we stress the chronic LSD model of psychosis cannot be generalized to other classic psychedelics, or to infrequent LSD exposure, which, at least in humans, has been shown to increase emotional empathy and prosocial behavior in a research setting (Dolder et al., 2016). Intriguingly, increases in explicit emotional empathy produced by LSD have also been noted to not be blocked by ketanserin, suggesting this effect may be mediated by a 5-HT2a–independent pathway (Holze et al., 2021). Additionally, in contrast to 3 months of exposure in rats, 1 week of repeated exposure to a low dose of LSD has been shown to increase prosocial behavior in mice, implicating both 5-HT2a and AMPA signaling (Markopoulos et al., 2021). Nonetheless, it appears LSD may have dopaminergic signaling properties rendering it more akin to a true psychotomimetic, primarily after chronic repeated exposure, in comparison with other classic psychedelics.

D. The Role of 5-HT1a and Entropic States

5-Meo-DMT, a compound of recent interest, is often construed as a classic psychedelic, however, it displays far greater binding affinity at the 5-HT1a receptor than at the 5-HT2AR (Nichols, 2016; Inserra et al., 2021a; Ermakova et al., 2022). Cortical pyramidal cells often co-express 5-HT1a and 5-HT2a receptors, suggesting that 5-MeO-DMT impacts some overlapping regions with classic psychedelics. However, these receptors often show opposing action, with 5-HT1a inhibiting pyramidal cell activity, whereas 5-HT2a leads to the excitation of pyramidal neurons (Araneda and Andrade, 1991; Celada et al., 2013).

It appears that 5-HT1a agonism is often inhibitory of the effects of 5-HT2a agonists. Administration of buspirone, a 5-HT1a agonist, with psilocybin has been shown to diminish (but not completely block) subjective psilocybin outcomes, particularly visuoperceptual effects (Pokorny et al., 2016). Furthermore, pretreatment with pindolol, a 5-HT1a antagonist, increased the subjective effects of DMT (Strassman, 1995). This suggests that despite many classic psychedelics displaying some agonism at the 5-HT1a receptor, this agonism may dampen 5-HT2a–induced activity.

In concordance with the differences in receptor binding profiles, 5-MeO-DMT induces subjective effects that are often described as qualitatively different from classic psychedelics, including a lack of visual pseudohallucinations (Ermakova et al., 2022). Alexander Shulgin, a renowned chemist who developed over 50 tryptamines, described his experience with 5-MeO-DMT below:

"It's as if the mind is capable of experiencing a very large number of objects, situations and feelings, but normally perceives them only one at a time. I felt that my mind was perceiving them all at once. There was no distance, no possibility of examining the experience. This was simply the most intense experience possible; a singularity, a white-out (as opposed to a black out), I have little memory of the state itself." (Shulgin and Shulgin, 1997, p. 164).

This may be described as an increase in entropic processing to the degree that information richness is so great it cannot be comprehended. Similarly, it was suggested that this experience may indicate an increase in neural entropy enough to lose ability to comprehend and subsequently recollect the experience, although feelings of "presence" may be maintained (Carhart-Harris, 2022). Some studies have shown that 5-MeO-DMT is capable of producing a mystical-type experience to a greater extent than psilocybin (Barsuglia et al., 2018), but it has also been argued that questionnaires used to measure classic psychedelic effects may not be best at capturing the unique effects of 5-MeO-DMT (Pollan, 2018).

While 5-MeO-DMT does produce increases in psychologic health consistent with classic psychedelics in studies of naturalistic use (Davis et al., 2019; Uthaug et al., 2019; Ermakova et al., 2022), there are aspects of the experience that should be carefully considered. Reactivations, or sudden brief feelings of re-experiencing drug effects, are prevalent after 5-MeO-DMT use, occurring in up to 69% of users. These experiences are often positive or neutral in valence and occur 1–2 weeks after drug use (Uthaug et al., 2020). As 5-MeO-DMT reactivation is so prevalent, it is likely distinct from hallucinogen persisting perception disorder, which is a much rarer phenomenon (Johnson et al., 2008; Nichols, 2016; Carhart-Harris and Friston, 2019).

Basic research may provide a hint as to the origin of 5-MeO-DMT reactivation. Animal research suggests that 5-MeO-DMT can produce seizures (Gharedaghi et al., 2014; Ermakova et al., 2022). Further, complex partial seizures can often be described as mystical, blissful, and ecstatic for some, to the point that some patients intentionally induce them (Lindsay, 2014). It may be that the brief re-experience of drug effects is a partial complex seizure that shares overlapping symptoms with psychosis and classic psychedelic effects (Trimble, 1982; Brewerton, 1997; Carhart-Harris, 2007). This is in concordance with the entropic brain theory proposal that some forms of epilepsy are entropic states (Carhart-Harris, 2018). We encourage further studies utilizing 5-MeO-DMT to be cautious to ensure participant safety and to carefully consider how to best capture subjective effects. 5-MeO-DMT also showcases how, despite the focus on the 5-HT2AR in producing subjective classic psychedelic effects, other serotonin receptors likely play a complex role in producing these experiences.

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IV. Caveats and Concerns

A. Spiritual Experiences in Psychosis

Psychosis can have a significant spiritual quality and can occasionally elicit ecstasy in early stages (Bowers and Freedman, 1966; Nelson and Sass, 2008). Despite apparent similarities to classic psychedelic experiences and the potential overlap of religious undertones and positive valence, psychosis is marked by high self-focus. Religious delusions frequently feature a sense of being "chosen," of being God or a religious figure (e.g., the Messiah), or of being persecuted or possessed by entities such as evil spirits (Anderson-Schmidt et al., 2019). For example, one patient reported, "God actually touched my heart. The next day was horror and ecstasy. I began to feel that I might be the agent of some spiritual reawakening" (Bowers and Freedman, 1966). These experiences can begin in the earliest stages of an episode, with one case report noting, "The patient's illness began with daydreams of success which progressed to the grandiose delusion of having discovered the secrets of the universe and of being able to prove rationally the existence of God" (Kleinman et al., 1977). Although such delusions can at first be exciting for the patient, grandiose delusions most often cause distress (Isham et al., 2021). In general, this suggests that the experience of positive emotion or spiritual significance is not sufficient for beneficial long-term outcomes. This supports SEB theory's proposal that self-focus is key to predicting the outcomes of entropic processing.

B. Challenging Experiences with Classic Psychedelics

Despite the frequently reported increases in well-being, challenging experiences are common among naturalistic classic psychedelic users (Carbonaro et al., 2016; Gashi et al., 2021) and feelings of intense anxiety are often found in therapeutic settings during a portion of the session (Barrett et al., 2016; Griffiths et al., 2006). However, challenging experiences still often facilitate improvements in well-being. In the "bad trips survey," 84% of individuals reported benefiting from their most challenging experience, and 76% attributed increases in life satisfaction from their "bad trip" (Carbonaro et al., 2016). This occurs despite 39% of participants rating their most challenging classic psychedelic experience as among the top five most difficult experiences of their lives. However, it should also be noted that "dread of ego dissolution" predicts less positive outcomes in patients with TRD (Roseman et al., 2018).

Overall, the effects of challenging classic psychedelic–induced experiences are incongruent with broaden-and-build theory, but in support of SEB theory. According to Barrett and colleagues (2016), challenging experiences likely develop from a decrease in self-referential processing, the same process underlying positive experiences. The decreases in self-referential processing, while acutely anxiety-inducing, may encourage a broader, less self-focused perspective afterward. This may be marked by increases in gratitude or insights from the experience, as shown below:

"In the following three weeks, I woke up each morning so happy just to be alive. I felt that I had been given a gift, that I was allowed to live, that I can take trips in the nature, that I have so many good people around me. I just felt so extremely lucky. I don't think that I would experience this feeling if it weren't for the extreme distress that I experienced" (Gashi et al., 2021).

This experience and others mentioned in the study suggest that classic psychedelics' acute effects do not need to be acutely positive to have a beneficial impact on well-being. Challenging experiences with classic psychedelics and initially euphoric experiences in early psychosis suggest that the alteration in trajectories is not dependent on emotional valence.

It also must be acknowledged that paranoia, a form of self-focus, can be provoked acutely from classic psychedelics. When paranoia is measured in research studies of classic psychedelics, it is regularly the least endorsed factor out of all factors tested (Carhart-Harris et al., 2012, 2016; Schmid et al., 2015). However, its prevalence in recreational settings is unclear. Speculatively, we suppose paranoia may be more likely to occur in environments where people feel uncertain or unsafe. For example, two teenage girls who had become disoriented after ingesting LSD for the first time at a festival experienced delusional thoughts and paranoia about the all-male paramedic team threatening to harm them (Oak, 2017, p. 237). Additionally, concerns of legal consequences may make naturalistic classic psychedelic users more prone to paranoia, in contrast to those administered classic psychedelics in legally sanctioned, controlled research environments. In therapeutic settings, we suggest that psychologic preparation, focus on building therapeutic rapport, and education on how classic psychedelics work could help reduce risks of paranoia.

C. What About the "Low Side" of the Entropic Continuum?

While this review is focused on understanding two states from EBT's "high entropy" side of the entropic continuum, similar patterns may also emerge for "low entropy" states. Depression and addiction can be described as conditions of heightened self-focus (Ingram, 1990; Franken, 2003; Pennebaker, 2013; Fineberg et al., 2016; Travers-Hill et al., 2017; Garland and Fredrickson, 2019; Tackman et al., 2019) with a narrowing of attentional scope/entropy (Garland et al., 2010; Krentzman, 2013; Whitmer and Gotlib, 2013; Carhart-Harris et al., 2014;

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Garland and Fredrickson, 2019; Hoeppner et al., 2019). In substance use disorders, people become preoccupied with obtaining and using a drug (Koob and Volkow, 2010). This isolates them from nonusing individuals and narrows their repertoire of coping mechanisms. Additionally, substance users develop attentional biases toward drug-related cues, suggesting a narrowing of attentional scope (see Franken, 2003 for a review; Hicks et al., 2015).

Sedated states, which EBT claims are low entropy, are low in self-focus and attentional scope/information richness. In support of this, propofol has been previously suggested to fit the "ego dissolution" construct, suggesting that it induces a decrease in self-focus (Barrett and Griffiths, 2017). Moreover, it has also been shown to be a promising potential treatment of TRD (Mickey et al., 2018). This may suggest that extreme decreases in self-focus are also advantageous for promoting mental health improvements, although much more work in this area is needed. Examination of the low side of the entropic continuum is an area for further theoretical mapping and research, but is outside the scope of this review.

D. The Claustrum: Worth Further Exploration

The claustrum is a forebrain nucleus that displays extensive cortical and subcortical projections (Bota et al., 2015), including to the PFC (Milardi et al., 2015), but its function has long remained mysterious due to difficulties in studying it in both humans and animals (Nichols, 2016; Nikolenko et al., 2021). The structure is extremely thin (submillimeter in some regions in humans) making functional imaging a challenge and, until recently, signal was often mixed extensively with adjacent structures, including the insula and putamen (Krimmel et al., 2019). However, as technology improves, more studies are examining the region (Krimmel et al., 2019; Liu et al., 2019; Barrett et al., 2020). The structure has recently been implicated in epilepsy, schizophrenia, autism, a variety of neurodegenerative diseases, and depressive disorders based largely on anatomic alterations (Nikolenko et al., 2021). Primarily on a theoretical basis the claustrum has been suggested to function in "multimodal information processing" including integration of sensory information and emotional and behavioral response (Nikolenko et al., 2021). This elusive region has recently been of interest in psychedelic science (Nichols, 2016; Barrett et al., 2020; Doss et al., 2022), likely in part due to its high expression of 5-HT2AR (Pazos et al., 1985, 1987; McKenna and Saavedra, 1987).

The recently proposed cortico-claustro-cortical model suggests classic psychedelics produce alterations in the FPN and DMN in part by the prefrontal cortex decoupling with the claustrum as mediated by 5-HT2a signaling, producing a state of "aberrant cognitive control" (Doss et al., 2022). At this time, only one small study (n = 15), in advanced long-term mediators who had previously been administered a high dose of psilocybin in another study, has examined the acute effects of a classic psychedelic (psilocybin) on the claustrum (Barrett et al., 2020). This study reported that psilocybin decreased the functional connectivity between the right claustrum and the DMN and that this correlated with decreases in within-network connectivity (integrity) of the DMN. In contrast, the right claustrum showed an increase in connectivity with the FPN. Increases in variance and the amplitude of low-frequency fluctuations also occurred in the claustrum. It is unknown how long-term meditation practice might impact claustrum functioning in relation to the DMN/FPN compared with the general population. However, it has previously been shown that intensive mediation training can significantly alter DMN functional connectivity (Shen et al., 2020) and produces increases in between DMN and salience network functional connectivity (Vishnubhotla et al., 2021). Regions within the salience network in fMRI studies often include parts of the claustrum (Krimmel et al., 2019), as it is adjacent to the insula, which is a node of the salience network (Menon, 2011). Since intensive mediation may alter functioning of key networks implicated in the cortico-claustro-cortical model, it is difficult to draw inferences about this study to a generalized mechanism of classic psychedelics.

In schizophrenia and psychosis, a limited number of studies suggest that claustrum functioning is likely abnormal, but the diverse scope of studies makes it difficult to draw any inferences about the alterations. Bilateral reductions in volume of the claustrum have been found in patients with both schizophrenia and depression, but are largely confounded by chronic medication use (Bernstein et al., 2016). Decreases in gray matter volume of the left claustrum have been correlated with delusions in both Alzheimer's Disease and schizophrenia (Rootes-Murdy et al., 2022). Lesions to the claustrum have been implicated in a number of case studies where patients develop delusions and/or seizures (Milardi et al., 2015; Patru and Reser, 2015), but these case studies often include adjacent structures making it difficult to infer the claustrum-specific function. In FEP patients with auditory hallucinations, alteration with claustrum seed-based functional connectivity were found with the cerebellum and the postcentral gyrus, but not the posterior DMN regions (precuneus/posterior cingulate cortex) (Mallikarjun et al., 2018). The claustrum displays a relatively low number of D2 receptors based on postmortem human brain studies (Hall et al., 1996), however, it does receive projections from both the VTA and nucleus accumbens (Patru and Reser, 2015). Others have suggested that κ-opiate receptors, which are highly expressed in the claustrum (Doss et al., 2022), may show alterations in psychosis (Patru and Reser, 2015). This has led some to suggest that

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alterations in κ-receptor functioning may play a role in alterations in claustrum functioning in psychosis (Patru and Reser, 2015).

As it stands, the cortico-claustro-cortical model (Doss et al., 2022) and psychosis studies of the claustrum leave room for further work examining how changes in functional connectivity might relate to subjective experience and long-term outcomes. Others have suggested that the claustrum may play a role in saliency mapping (Remedios et al., 2014) and attentional filtering (Naghavi et al., 2007; Liu et al., 2019), suggesting altered claustrum function may facilitate entropic processing. Indeed, on a neural level, salvinorin A, a κ-opiate receptor agonist, produces significant increases in neural entropy (Doss et al., 2020). Although salvinorin A is not a classic psychedelic, the overlap between κ-opiate receptor expression and 5-HT2a expression in the claustrum suggests that salvinorin A may have some overlapping neural effects with classic psychedelics (Doss et al., 2022). These findings are not at odds with EBT (Carhart-Harris et al., 2014; Carhart-Harris, 2018) or REBUS (Carhart-Harris and Friston, 2019), as both theories suggest that overlapping alterations with classic psychedelics and other experiences occur. Overall, it may be too soon to propose a role of the claustrum within SEB theory based on the limited number of functional studies with both psychosis and classic psychedelics. However, the existing evidence suggests the region is worth further exploration.

E. Limitations

"All models are wrong, but some are useful."
—George Box (Box, 1976)

SEB theory is not an attempt to explain what makes classic psychedelics unique. Similar alterations in entropic processing and self-focus most likely do occur in other states, as previously mentioned; however, the magnitude and consistency with which these alterations occur are distinct. Additionally, this model does not capture all relevant comparisons between psychosis and classic psychedelics. For example, we did not discuss comparisons based on hallucinations, as this has been done elsewhere recently (Leptourgos et al., 2020). It is also worth acknowledging a variety of substances with vastly different mechanisms and subjective effects have been described as psychotomimetics (Hofmann, 1959; Efron, 1970; Carhart-Harris et al., 2013; Steeds et al., 2015), including various cannabinoids (Theunissen et al., 2022), ketamine (Beck et al., 2020), phencyclidine (Garey, 1979), anticholinergic drugs (Volgin et al., 2019), the plant *Piper methysticum* or kava (Hofmann, 1959), and the non-*Psilocybe* mushroom *Amanita muscaria* (Hofmann, 1959). A comparison between these substances and classic psychedelics is an interesting area for further discussion but is outside the scope of this review. Moreover, we do not suggest that our model fully explains the mechanisms of the therapeutic efficacy of classic psychedelics.

It also must be acknowledged that classic psychedelics are not universally beneficial and can produce decreases in self-reported mental health, although these instances are rare and are often associated with multiple successive doses and/or combinations with other substances (Bienemann et al., 2020; Carhart-Harris and Nutt, 2010). Psychosis itself also has a variety of trajectories. For example, post-traumatic growth can occur after a psychotic episode and may partly be due to factors that contribute to decreasing self-focus, such as high levels of social support (Jordan et al., 2016, 2017, 2020a, 2020b). SEB theory intends to describe the general trajectories, rather than the exceptions, of both experiences.

Additionally, decreases in self-focus may not be universally positive. As with many potentially beneficial activities, such as mediation (Lindahl et al., 2017; Britton, 2019), and positive traits, such as conscientiousness (Carter et al., 2018), there is a possibility of too much of a good thing. Early case reports of excessive classic psychedelic use feature descriptions of individuals developing what Rossi (1971) deemed "a psychedelic syndrome" marked by a preoccupation with the mystical and rejecting "societal values" (Glass and Bowers, 1970; Rossi, 1971; Hays and Tilley, 1973). It may be that a lack of self-focus produces a decreased aversion to violating social norms and an increased fascination with other experiences related to reduced self-focus (i.e., mediation, etc.). Conversely, there is some evidence that increasing self-referential processing in public health campaigns can be used to promote health behavior, such as smoking cessation (Falk et al., 2011). However, in general, we maintain that self-focus is more likely to elicit maladaptive patterns of thought and behavior than beneficial ones.

Another point of clarification is that the entropic processing construct in SEB theory intends to describe the overlap in subjective experience and cognition in psychosis and classic psychedelic states. It does not endorse all of EBT's claims. EBT suggests that the classic psychedelic state is a "primitive state," like those that "preceded the development of modern, adult, human, normal waking consciousness" (Carhart-Harris et al., 2014). Such a claim is not easily falsifiable. EBT also argues that access to primitive states with classic psychedelics would "herald the beginning of a new scientifically informed-psychoanalysis." These aims are not relevant for SEB theory. With these limitations in mind, we will now turn toward how SEB theory can inspire future research.

F. Future Directions

All theories' primary purpose is to predict the behavior of the natural world. Future research examining

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SEB theory should use self-report measures and tasks intended to study psychosis to measure the effects of classic psychedelics, as well as the converse. These should include measures related to both entropic processing and self-focus constructs. Below, we outline several of the most novel future directions:

- SEB theory provides a potential transdiagnostic pathway suggesting that classic psychedelic induces entropic processing concurrent with decreases in self-focus, which predicts positive enduring change in both clinical and nonclinical populations. This can be measured using the experience sampling method, as previously discussed. This should be conducted in a variety of different populations and drug exposure conditions (i.e., clinical research, ceremonies, festivals, etc.).
- Quantitative linguistic analysis is a potential method for examining indicators of entropic processing and self-focus (Pennebaker, 2013). Recent work suggests that both classic psychedelic–induced states and patients with schizophrenia display elevated entropy in free speech (Sanz et al., 2021). Self-focus can be assessed by first-person singular pronoun usage, which has been associated with a variety of types of psychologic distress, including psychosis and depression (Pennebaker, 2013; Fineberg et al., 2016; Tackman et al., 2019; Corcoran and Cecchi, 2020; Haas et al., 2020; Tang et al., 2021). We posit that classic psychedelics will decrease self-focus in language, both during and after administration. In support of this, early work in patients with schizophrenia reported decreased self-focused language and increased positive socioemotional behaviors during the acute effects of LSD (Abramson et al., 1958).
- SEB proposes that the postacute effects of classic psychedelics produce a state prone to positive change. It follows that interventions capitalizing on seemingly intrinsic tendencies toward broadening and building may be especially efficacious during this time, as previously suggested (Hendricks, 2018). It is predicted that such interventions shall have a more persistent effect on well-being during the postacute effects of classic psychedelics in both clinical and nonclinical populations than control conditions. The magnitude of effect is predicted to be moderated by the quality of the acute experience.
- We also encourage rigorous qualitative studies of both the acute and enduring effects of classic psychedelics. Although qualitative studies are not deductive by nature, they do provide insight into the subjective experience and therefore help understand the construct validity of SEB theory. Additionally, exploring the experiences of individuals who have had both psychotic episodes and classic psychedelic experiences may assist in developing a more holistic understanding of how the experiences compare.
- To further understand the role that regions and networks implicated in classic psychedelics' effects play in subjective and psychologic effects during acute and postacute effects, we suggest employing real-time fMRI neurofeedback (Watanabe et al., 2017; MacInnes et al., 2020), a technique that allows direct causal relation to be drawn about a region of interest's role in subjective experiences (Brewer et al., 2013; Garrison et al., 2013; Bauer et al., 2020). We predict that real-time fMRI will support that decreases in DMN integrity do cause alterations in self-focus in the acute period of classic psychedelics, such as experiences of "ego dissolution," but acknowledge that there are different aspects of classic psychedelic–induced alterations to self-experience and complexities of accounting for subnetworks of the DMN (Kernbach et al., 2018). Real-time fMRI neurofeedback may allow such complexities to be explored. We also predict that the DMN will become "more malleable" in the postacute period of classic psychedelics, such that fewer mindfulness training sessions (Haugg et al., 2020), which often modulate the DMN or key regions within, will be needed to produce a significant response (Garrison et al., 2013; Kim et al., 2019; Bauer et al., 2020). Additionally, other regions that have been repeatedly implicated in the effects of classic psychedelics (McCulloch et al., 2021) and are responsive to real-time fMRI neurofeedback (Garrison et al., 2013, 2021; Kim et al., 2019) should be examined.

V. Conclusions

SEB theory is a novel theory examining the psychedelic-psychotomimetic paradox, or how classic psychedelics can be therapeutic yet mimic symptoms of psychosis. It also provides a cognitive-phenomenological-behavioral framework for understanding the transdiagnostic applicability of classic psychedelics and co-occurring alterations in self-experience. Psychosis and classic psychedelic–induced states share an entropic processing style, a style of cognition in which previously developed cognitive schemas are given less emphasis and more information is attended to, provoking rapid attempts to process information in novel ways. This facilitates a hyperassociative style of thinking, promoting altered salience/meaning attribution of stimuli.

SEB theory further posits that psychosis is marked by an increase in self-focus, including hyper-reflexivity, or an extreme form of self-consciousness of internal experiences, as well as a tendency to interpret tacit stimuli as self-relevant, which may facilitate delusions. Individuals often report feeling cut off from the world and distant from their

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experiences. In contrast, classic psychedelics tend to decrease self-focus, creating a hyporeflexive processing style, where internal experiences are observed with less self-consciousness, and feelings of merger with the environment and a sense of connection to others are prevalent. These alterations may facilitate self-distant self-reflection, potentially promoting psychologically meaningful insights. We speculate that increases in self-presence may also occur.

Finally, SEB theory suggests that classic psychedelics foster lasting positive change by broadening attentional scope through entropic processing and decreasing self-focus. This promotes a variety of changes in thoughts and behavior that encourage the building of enduring resources, facilitating lasting improvements in mental health. Overall, we hope this theory invigorates the field to provide rigorous comparisons between psychosis and classic psychedelic states and to study how the acute effects of classic psychedelics may facilitate long-term change in clinical and nonclinical populations.

Acknowledgments

Haley Dourron thanks Jessica Turner, her honors thesis adviser who helped her develop some of these initial ideas. The authors also thank Charles D. Nichols, Agasthya Vedre-Kyanam, Noah Wiles Sweat, and Gaige Allen-Clark for discussions about earlier versions of the manuscript.

Authorship Contributions

Wrote or contributed to the writing of the manuscripts: Dourron, Strauss, Hendricks.

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