NEUROSCIENCE of Consciousness

Neuroscience of Consciousness, 2025, **2025(1)**, niae038

DOI: https://doi.org/10.1093/nc/niae038

Research Article

On the varieties of conscious experiences: Altered Beliefs Under Psychedelics (ALBUS)

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Abstract

How is it that psychedelics so profoundly impact brain and mind? According to the model of "Relaxed Beliefs Under Psychedelics" (REBUS), 5-HT2a agonism is thought to help relax prior expectations, thus making room for new perspectives and patterns. Here, we introduce an alternative (but largely compatible) perspective, proposing that REBUS effects may primarily correspond to a particular (but potentially pivotal) regime of very high levels of 5-HT2a receptor agonism. Depending on both a variety of contextual factors and the specific neural systems being considered, we suggest opposite effects may also occur in which synchronous neural activity becomes more powerful, with accompanying "Strengthened Beliefs Under Psychedelics" (SEBUS) effects. Such SEBUS effects are consistent with the enhanced meaning-making observed in psychedelic therapy (e.g. psychological insight and the noetic quality of mystical experiences), with the imposition of prior expectations on perception (e.g. hallucinations and pareidolia), and with the delusional thinking that sometimes occurs during psychedelic experiences (e.g. apophenia, paranoia, engendering of inaccurate interpretations of events, and potentially false memories). With "Altered Beliefs Under Psychedelics" (ALBUS), we propose that the manifestation of SEBUS vs. REBUS effects may vary across the dose–response curve of 5-HT2a signaling. While we explore a diverse range of sometimes complex models, our basic idea is fundamentally simple: psychedelic experiences can be understood as kinds of waking dream states of varying degrees of lucidity, with similar underlying mechanisms. We further demonstrate the utility of ALBUS by providing neurophenomenological models of psychedelics focusing on mechanisms of conscious perceptual synthesis, dreaming, and episodic memory and mental simulation.

Keywords: Consciousness; Psychedelics; Free-Energy Principle; REBUS; Alpha-band synchrony; Default Mode Network (DMN)

Introduction

The evolving "psychedelic renaissance" has the potential to radically alter society, possibly in ways we are only beginning to understand (Pollan 2018, 2021). Psychedelics, especially under supportive conditions, have been associated with profound (potentially life-changing) personal transformations at rates seldom observed in clinical settings (Johnson et al. 2019). The potency of psychedelics necessitates precise and comprehensive models of their action to optimize therapeutic potential and mitigate adverse outcomes. Such models should capture the full spectrum of neurological and phenomenological effects of these substances, spanning recreational and clinical contexts. Given the diversity of experiences that can arise from psychedelic use, this task is inherently challenging. Alongside these efforts for furthering scientific understanding, access to and acceptance of psychedelics continues to grow as legal barriers are relaxed in different parts of the world. In light of these potentially radical changes for science and society, it is essential that we have detailed and accurate models of these powerful compounds for this potential psychedelic revolution to live up to its promise and avoid undesirable outcomes.

Perhaps unsurprisingly, attempts at trying to understand mechanisms of psychedelic action have led to the development of a variety of (seemingly incompatible) models. The recently proposed model of Relaxed Beliefs Under Psychedelics (REBUS) attempts to understand psychedelic activity as involving a relaxation of high-level priors, which in addition to altering self-representations, also alters constraints on the space of possible

Received 19 May 2023; Revised 9 September 2024

representations in the brain at large (Carhart-Harris et al. 2019). In contrast, earlier models described psychedelics as "non-specific amplifiers" of experience or as "consciousness expanding" (Grof 1980). Inspired by both REBUS and the ways in which psychedelics can engender more intense—and potentially more compelling and/or meaningful (Dupuis and Veissière 2022, Geurts et al. 2022)—conscious states, we here introduce a complementary model involving Strengthened Beliefs Under Psychedelics (SEBUS). The enhanced meaning-making in psychedelic therapy may be the most striking realization of SEBUS effects, but other examples may be found in the perceptual illusions and cognitive delusions that occur under these altered states of consciousness. The more intense realization of one's life priorities, potentially more insightful perspectives on personal challenges—be it existential orientation toward a cancer diagnosis, self-persecutory thoughts in depression, or the battle of competing motivations underlying addictions—seem to suggest some kind of belief strengthening is involved. A solely REBUS-focused account pharmacologically might better describe a dissociative or anesthetic effect, rather than the clinically significant induction of meaningful experiences and insights observed with psychedelic therapy. Our alternative model would suggest an opposite underlying mechanism whereby beliefs (e.g. access and responsiveness to personal meanings) may be transiently strengthened by psychedelic activity. Along these lines, pareidolia (Mavrogiorgou et al. 2021), the propensity to discern meaningful visual patterns in random noise, is a phenomenon consistently observed with psychedelic use—with overlapping neural correlates and associations with creativity (Pepin et al. 2022)—and could be explained by transient belief strengthening (Leptourgos et al. 2020). Psychedelic-related apophenia (Blain et al. 2020), or the potentially misleading perception of meaningfulness (Sack et al. 2005, McGovern et al. 2023), could also be elegantly accounted for with models involving strengthened beliefs. Perhaps most compellingly, we believe strengthened beliefs provide the most parsimonious account of core aspects of psychedelic phenomenology in being able to account for both hallucinations and delusions in terms of experience being more heavily impacted by prior expectations, rather than present observations (Maher 2006, Corlett et al. 2019).

One of our main goals for this manuscript is attempting to bring together different aspects of major theories to create a "minimum unifying model" (Wiese 2020) of the effects of psychedelics on brain and mind, wherein insights from diverse perspectives may be integrated, and the differences between them adjudicated. We refer to this unifying framework as Altered Beliefs Under Psychedelics (ALBUS), with the operative term "altered" being meant to capture the capacity for psychedelics to either strengthen or relax beliefs at different levels of representational hierarchies. Key to the activity of psychedelic drugs is their action in the brain as 5-HT2a agonists (Willins et al. 1997, Johnson et al. 2019). It is through consideration of the potential effects of this agonism across different doses and neural systems that we believe both strengthened and relaxed beliefs may (and must) be accounted for in a single framework. In addition to describing the core features of ALBUS and its implications, we will also explore how such understandings may illuminate fundamental mechanisms of mind, human nature, and potentially even selfhood and consciousness in all their various manifestations.

In proposing ALBUS, we suggest a fruitful consensus and generative conversation can be realized by focusing on ways in which particular beliefs—whether in terms of perceptual synthesis (Evans et al. 2020, Juliani et al. 2022b) or personal meanings (Kaufman 2021, Amada and Shane 2022)—are either strengthened or weakened in different combinations based on multiple factors, including various (i) substances, (ii) doses, and (iii) "[personal] sets and [environmental] settings" (Leary 1969). That is, it is not only the case that we ought to expect both directly and indirectly strengthened and relaxed beliefs at different hierarchical levels (so allowing for both REBUS and SEBUS effects to occur), but we ought to expect further complexities in the ways these admixtures of belief strengthening and relaxation vary as a function of numerous factors that may vary not just across individuals, but even within individuals across contexts, including across the time-course of individual psychedelic sessions (with lower pharmacological levels being present at the ascending and descending limbs of high-dose sessions). As such, regardless of whether or not an ALBUS framework is accepted as a unifying model, we hope to show why it is necessary for us to take caution in ever making blanket statements about psychedelics. That is, rather than saying "psychedelics do X," we would do better to say, "this psychedelic at this range of doses tends to do X, Y, and Z in A, B, and C contexts." This is not just a matter of pedantry, but reflects the kind of precision we need if we are to proceed with the care required for discussing and studying these powerful (and so both promising and perilous) transformative agents.

We begin by providing a brief overview of how 5-HT2a receptor agonism may lead to either strengthened or relaxed beliefs (Fig. 1). Next, we discuss how connecting models of predictive processing to psychedelic phenomenology requires a more thorough account of the nature of conscious perception (Fig. 2). We further consider how various kinds of sense-driven and imaginative experiences are suggested by different models of psychedelic action (Fig. 3). We then go on to extend these neurophenomenological models to "thought," operationally defined as sequences of mental actions, experienced as a "stream of consciousness" (Fig. 4). Finally, we discuss some of the complexities and future directions of our proposal for both basic and clinical research.

SEBUS + REBUS = ALBUS

The "*Relaxed Beliefs Under Psychedelics*" (*REBUS*) (Carhart-Harris et al. 2019) model is contextualized within the Free Energy Principle and Active Inference (FEP-AI) framework (Friston et al. 2006, 2017, Friston 2010). In brief, REBUS suggests that psychedelics alter hierarchical predictive processing (HPP) mechanisms in ways that flatten free energy landscapes, or the differential attracting forces associated with various (Bayesian) beliefs (Sengupta et al. 2016, Hesp et al. 2020, Safron 2021b), so promoting flexibility in inference and learning. Algorithmically speaking, this would correspond to reduced "precision-weighting" over top-down prior expectations—functionally understood as reduced filtering of perception and cognition via attentional selection (Parr and Friston 2017)—so allowing bottom-up prediction errors to have a greater influence on inference and learning. Or perhaps with fewer assumptions, one may consider REBUS effects to arise whenever minds are altered in ways that disrupt typical belief dynamics, with a potentially useful analogy being found in visualizing a physical mechanism having different functioning when deployed under atypical conditions. Such relaxations of beliefs and enhanced capacity for updating may help explain why psychedelics appear to have transdiagnostic relevance across a broad range of conditions, which may be expected because flexibility is almost synonymous with an essential capacity for

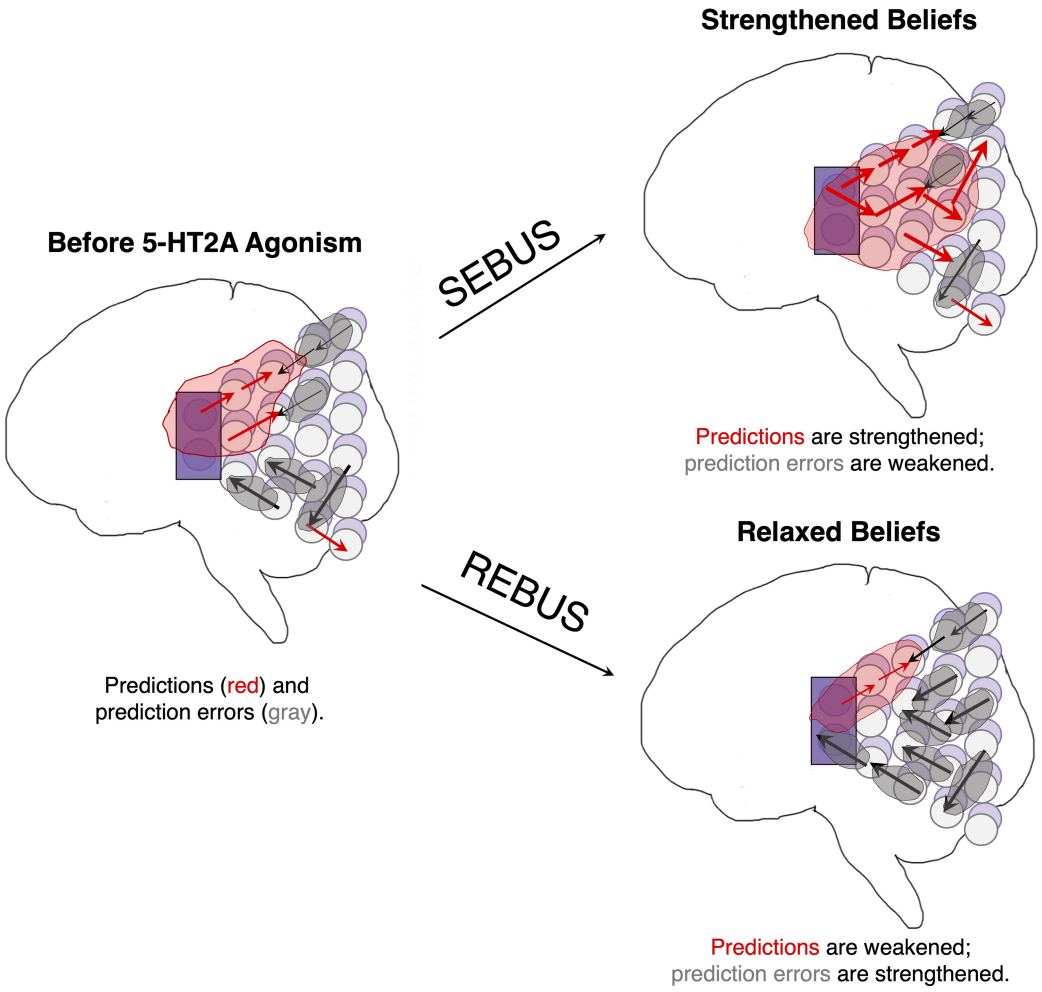

Figure 1 SEBUS and REBUS effects in Hierarchical Predictive Processing (HPP). The left image depicts mechanisms of inference and updating in cortical hierarchies (Safron 2020a, 2022), considered before the administration of 5-HT2a agonists. Dark purple rectangles indicate higher levels of cortical hierarchies (e.g. transmodal cortices and associated networks), encoding more abstract high-level beliefs regarding sources of prior expectations over the causal structure of the world (including oneself and others). Light purple circles indicate deep pyramidal neurons (layer 5), thought to encode predictions (or priors) via their ability to form large-scale synchronous complexes, partially due to the ability of these units to form re-entrant loops with the thalamus. Red shading indicates rhythmic complexes of synchronized neuronal activity forming at beta frequencies (~13–30 Hz), where these probabilistic beliefs are propagated down cortical hierarchies toward primary sensory modalities, indicated by red arrows, where degree of thickness corresponds to relative strengths for these prior expectations. White circles indicate superficial pyramidal neurons (L2/3), corresponding to expectancy violations, providing a bottom-up flow of prediction errors (generated at faster gamma frequencies; gray shading) as the only information passed up cortical hierarchies in predictive coding. The confidence associated with these prediction errors is known as "precision weighting," indicated by thickness of black arrows. Ascending prediction errors are depicted as thinner grey arrows when they are attenuated by descending predictions. A REBUS effect (bottom right) would involve a weakening of priors (indicated by smaller beta complexes with thinner red arrows), so allowing more sensory observations to reach deeper portions of the brain as prediction errors fail to be suppressed (indicated by more numerous gray-shaded regions and somewhat thicker grey arrows). A SEBUS effect (top right), in contrast, would involve a strengthening of priors (indicated by larger beta complexes with thicker red arrows), which are depicted as being more effective at suppressing ascending prediction errors (indicated by thinner grey arrows). An additional SEBUS effect is depicted in terms of thinner arrows for all prediction errors, which could be functionally understood as a kind of default reduction in precision weighting and shielding (or reduced updating) from sense data. This attenuation of the gain on sensory observations may be functionally understood as providing prior expectations with greater (or stronger) influence on inferences and updating. In this way, psychedelics may not only involve strengthened prior expectations, but such beliefs may be given further strength/precision by being less likely to be contradicted by inconsistent sense data.

all complex adaptive systems: open-ended evolution (Stanley and Lehman 2015, Hinton and Kirmayer 2017, Atasoy et al. 2019, Hayes 2019, Brouwer and Carhart-Harris 2020, Safron et al. 2021b).

The foundational premise of REBUS is that 5-HT2a agonism promotes excessive excitability in "deep" pyramidal cells—i.e. layer 5 cortical neurons, as opposed to "superficial" layers (L2/3) associated with bottom-up prediction errors (Fig. 1)—which are thought to encode top-down "beliefs" based on our prior expectations (Bastos et al. 2012), with this effect being especially pronounced with respect to higher levels of cortical hierarchies. According to REBUS, 5-HT2a agonism of deep pyramidal neurons causes overly excited ensembles to fail to synchronize, so resulting in the implicit relaxation of high-level priors, making it more likely that nervous systems will be updated by unsuppressed ascending prediction errors from the external world. This removal of top-down priors then affords a greater latitude for bottom-up sensory evidence to drive belief updating throughout the hierarchy.

Here, we propose an alternative account of the effects of psychedelics that is in many ways compatible with REBUS, albeit

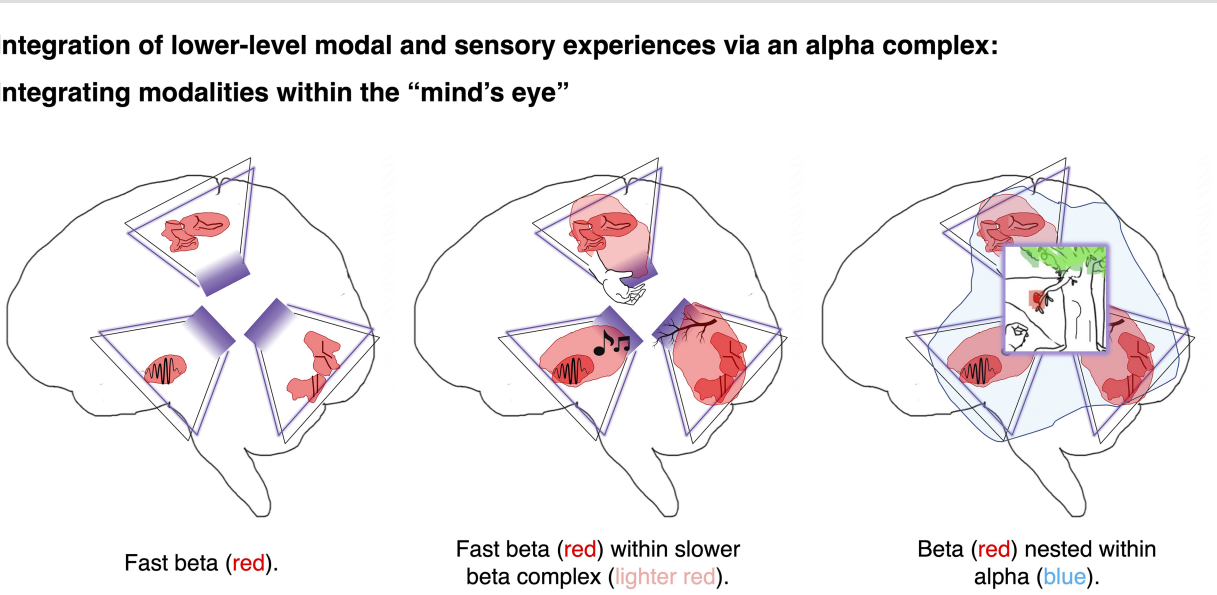

Figure 2 Integration of sense data into a coherent field of experience. Cortical predictive processing hierarchies from Fig. 1 are depicted as trapezoidal shapes with purple-shaded rectangles at their apex. The top, bottom left, and bottom right trapezoids indicate respective hierarchies over somatic, auditory, and visual modalities. Dark red shading indicates smaller and faster forming beliefs from synchronized neural activity communicated at higher beta frequencies (~20–30 Hz), and light red shading indicates larger and slower forming beliefs communicated at lower frequencies (~13–20 Hz). Smaller and faster beta oscillatory complexes are depicted as sometimes nested within larger and more slowly synchronizing beta rhythms, so enabling hierarchical modeling of more complex events evolving across multiple spatiotemporal scales. Blue shading indicates even larger and more slowly unfolding alpha rhythms (~8–12 Hz), providing yet another level of hierarchical depth for deep temporal world modeling (including with respect to self-processes). The left-most panel depicts modeling via fast and small beta complexes, with entailed representations constituting lower-level features such as vibratory patterns for hearing, somatosensation, and fine-grained visual information. The middle panel depicts this information being brought together into more complex compositions, including object information as modeled by each modality. However, these entailed objects are not intended to indicate conscious experiences, which are reserved for the rightmost panel in which modalities can be coherently integrated via egocentric reference frames (i.e. seeing one's hand reaching out to grab an apple from the branch of a tree). See Safron (2020a, 2021b, 2022) for more details on the neural and computational bases of phenomenal (and access) consciousness

with some important differences. In what follows, we introduce a unified model of *ALBUS* in which 5-HT2a agonism also involves *SEBUS* effects (Figs 1–3), particularly at intermediate levels of abstraction associated with conscious experience (O'Reilly et al. 2017, Prinz 2017, Aru et al. 2019, 2020, Safron 2020a, 2021b, 2022). By intermediate-level beliefs, we mean to indicate that SEBUS effects may primarily be observed at levels that are both hierarchically higher to and also more abstract than those that would be found closer to primary modalities where sense data is first processed. However, these beliefs are "intermediate" in that they may be thought of as lower in the predictive processing hierarchy, relative to more abstract "representations" (Safron et al. 2023) as might be associated with/by the hippocampal/entorhinal system (H/E-S) (Çatal et al. 2021). In other words, perhaps intuitively for some, we suggest 5-HT2a agonism will tend to increase the overall intensity of phenomenal consciousness (e.g. with respect to the vividness and/or detail of experience). This increase in the overall intensity of perception (and imagination) may potentially occur along most of the full dose–response curve for psychedelics under both typical and altered conditions. We propose that this intensification of experience may be crucial for understanding (i) what "manifests" in which ways under psychedelics and (ii) what is likely to be acted upon and learned while under potentially intensely altered states.

SEBUS effects may provide the most straightforward account of folk psychological descriptions of psychedelics as "mind manifesting" and "consciousness elevating." That is, we propose that 5-HT2a agonism may allow information to become more consciously accessible by strengthening the activity of particular neuronal ensembles. Perhaps more compellingly, strengthened beliefs—and as we will suggest later, potentially a shielding of these novel imaginings from conflicting sense data—evoke widely held impressions that psychedelic experiences can be similar to "waking dreams" and "transient psychosis" (Sacks 2013, Safron and Sheikhbahaee 2021a, Stoliker et al. 2022, 2023, Smith and Terhune 2023). The complexity of cortical information flows clearly cannot be reduced to either 5-HT2a-mediated SEBUS or REBUS effects. Indeed, psychedelic alterations of working memory capacity may be accounted for by mechanisms that are independent of 5-HT2a receptors (Ekins et al. 2023). Nonetheless, ALBUS (critically) supports a REBUS-like approach in suggesting that attempting to model the impacts of 5-HT2a signaling on predictive processing may be useful for attempting to model the complex effects of psychedelics on brain and mind.

We propose that SEBUS effects are strongly suggested by the nonveridical nature of hallucinations, as well as pareidolia (Mavrogiorgou et al. 2021, Pepin et al. 2022), both of which may be straightforwardly understood as strong prior expectations overwhelming sensory evidence. A strictly REBUS-involving account, in contrast, would suggest more veridical perception from increased driving of dynamics by raw sensory input from the world, with less influence from prior expectations. Further support for SEBUS effects may be found in similarities between psychedelic phenomenology and the varieties of images created with "Deep Dream"-style techniques (Szegedy et al. 2014, Suzuki et al. 2017). With these technologies, specific units in neural networks are made to exert particularly strong top-down influences in the process of generating likely patterns of inputs, resulting in generated stimuli becoming predominated by representations of corresponding features (e.g. superimposing fractal or insect-like forms onto visual fields in unusual combinations). This would be

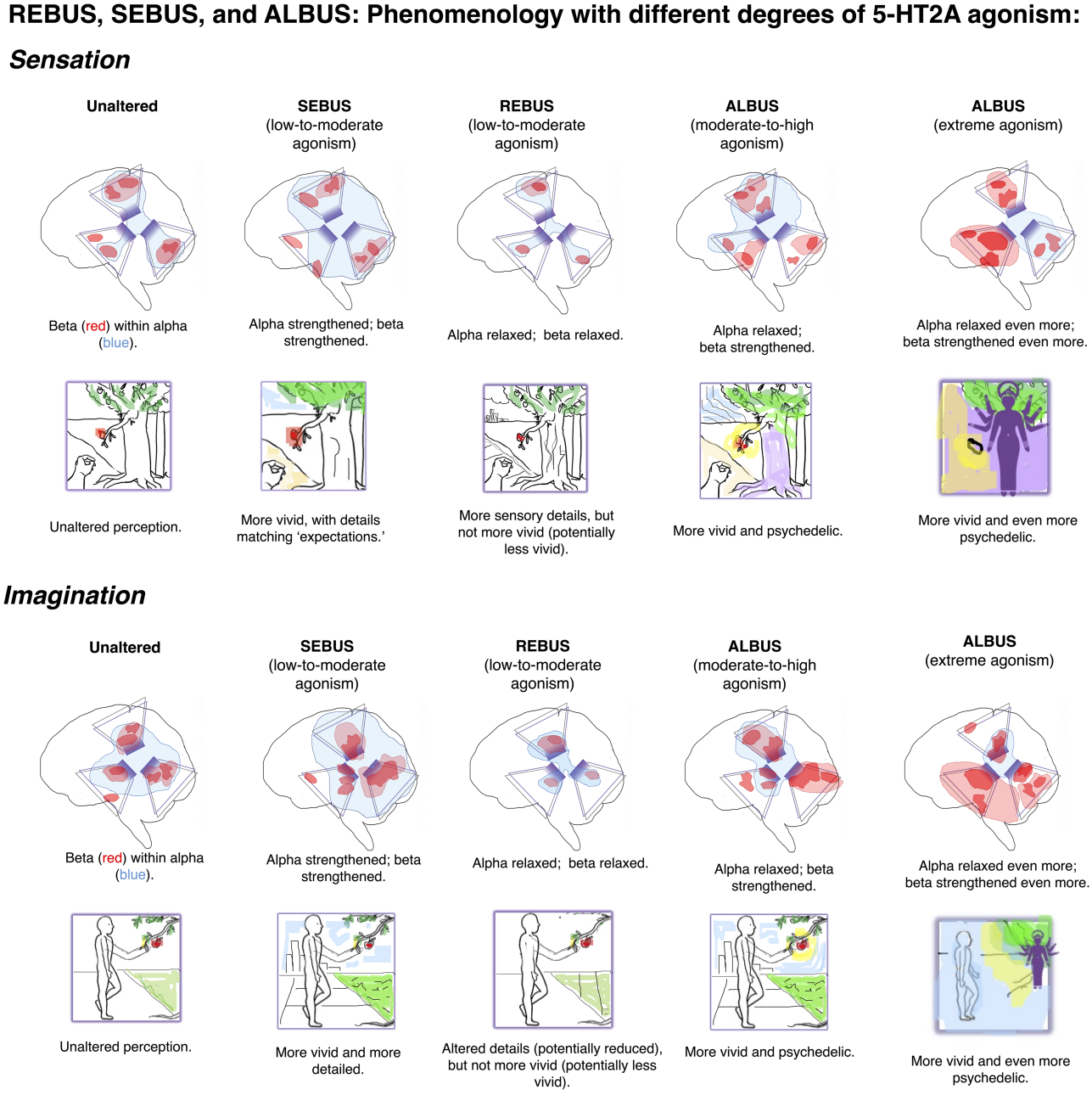

Figure 3 REBUS, SEBUS, and ALBUS effects on brain and mind. These images depict how neurological and phenomenological processes might be altered with different levels of 5-HT2a agonism under different theoretical assumptions. Panels on the top indicate perception-grounded sensation, which is always necessarily experienced from a first-person point of view due to locations of sensors on the body. Panels on the bottom indicate imaginative perception (or dreaming) generated from memory decoupled from sensation, organized according to a third-person perspective. The extent of shaded complexes of rhythmic neural activity is meant to indicate degrees of coherent integration associated with various frequency bands. Sensation is characterized by alpha and beta complexes that extend further down toward primary modalities to indicate information flows being constrained by sense data to a greater degree. For imagination, alpha and beta complexes are hypothesized to be centered in deeper portions of the brain, so realizing imaginative processing as the unfolding of consciousness with reduced tethering by information from the external world

an instance of strengthening, rather than weakening the beliefs entailed by particular units in artificial neural networks; we suggest not dissimilar principles may be at play in biological neural networks when high levels of 5-HT2a agonism drive increased activity from L5 pyramidal neurons.

The increased subjective vividness and detail of experience with psychedelics would seem to suggest increased precision for sensory observations (i.e. more influence from prediction errors). However, models of consciousness centered on HPP suggest that perception and imagination are entailed by predictions, rather than sensory prediction errors (Safron 2020a, 2022). Individuals may feel like they are seeing more details of the world as it is—which could be the case, depending on many factors—when in reality they may actually be experiencing their expectations more vividly, but less accurately. Observations of similar effects in the domain of cognition—cf. the "noetic" quality of mystical

experiences (Barrett et al. 2015)—suggest that SEBUS effects may parsimoniously apply to belief dynamics at multiple levels of abstraction.

We believe that SEBUS effects are further suggested by findings in which gamma power—thought to encode prediction errors—from the primary visual cortex is inhibited with 5-HT2a agonism (Michaiel et al. 2019), as well as by associations between hallucinations and sensory deprivation (cf. Charles Bonnet syndrome or anomalous perceptual experiences sometimes reported with isolation tanks) (Sacks 2013). To the extent that stimulating L2/3 interneurons contributes to imaginings that are more vivid and potentially less constrained, more detailed characterization of the mechanisms and phenomenology of sensory attenuation experiences may be a valuable line of inquiry (cf. "dark meditation retreats," the opening of critical plasticity windows with sensory deprivation (Ismail et al. 2017), etc.). Connections between psychedelics and mental imagery have been compellingly explored in recent work by Stoliker et al. (2023),

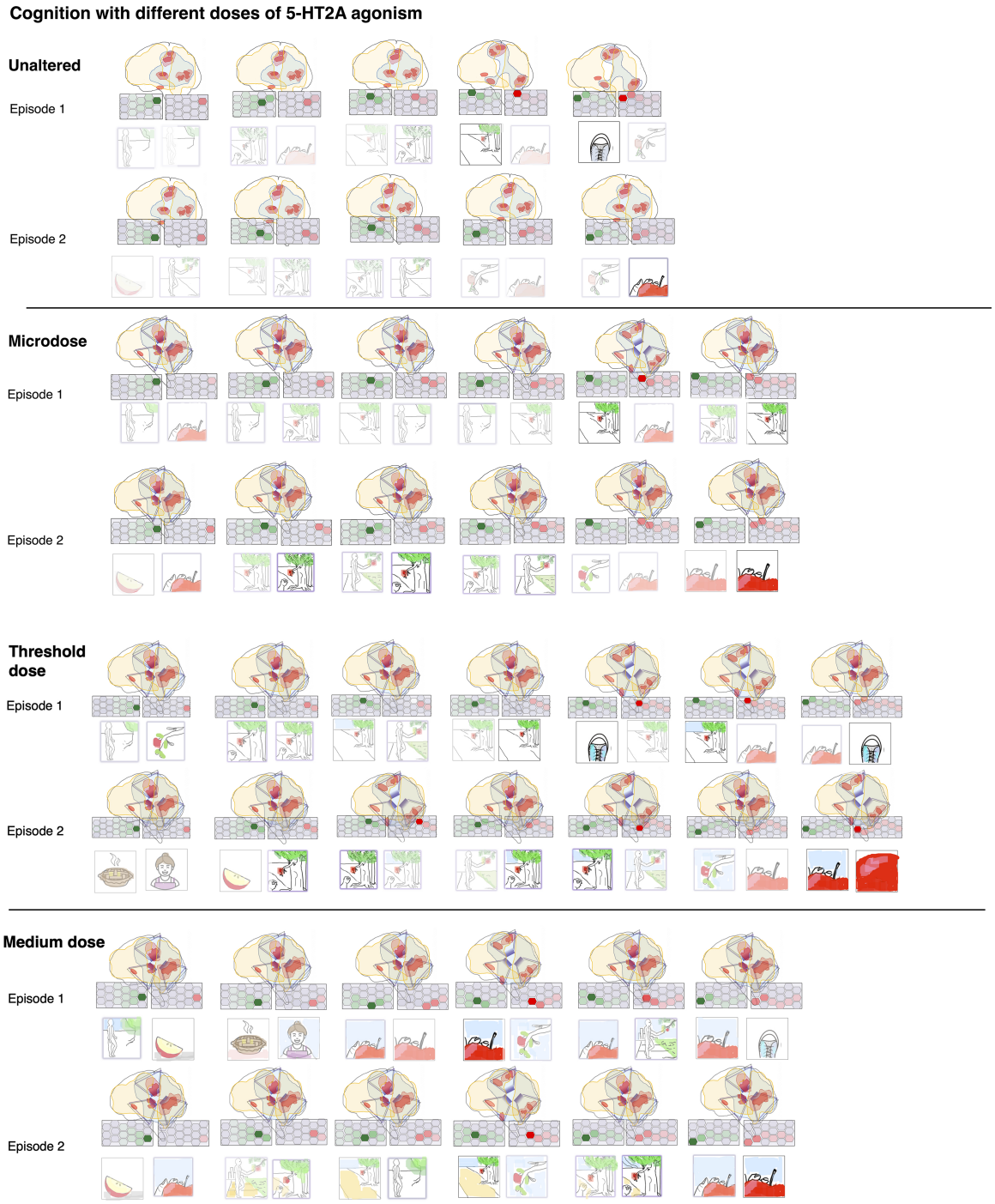

Figure 4 (continued)

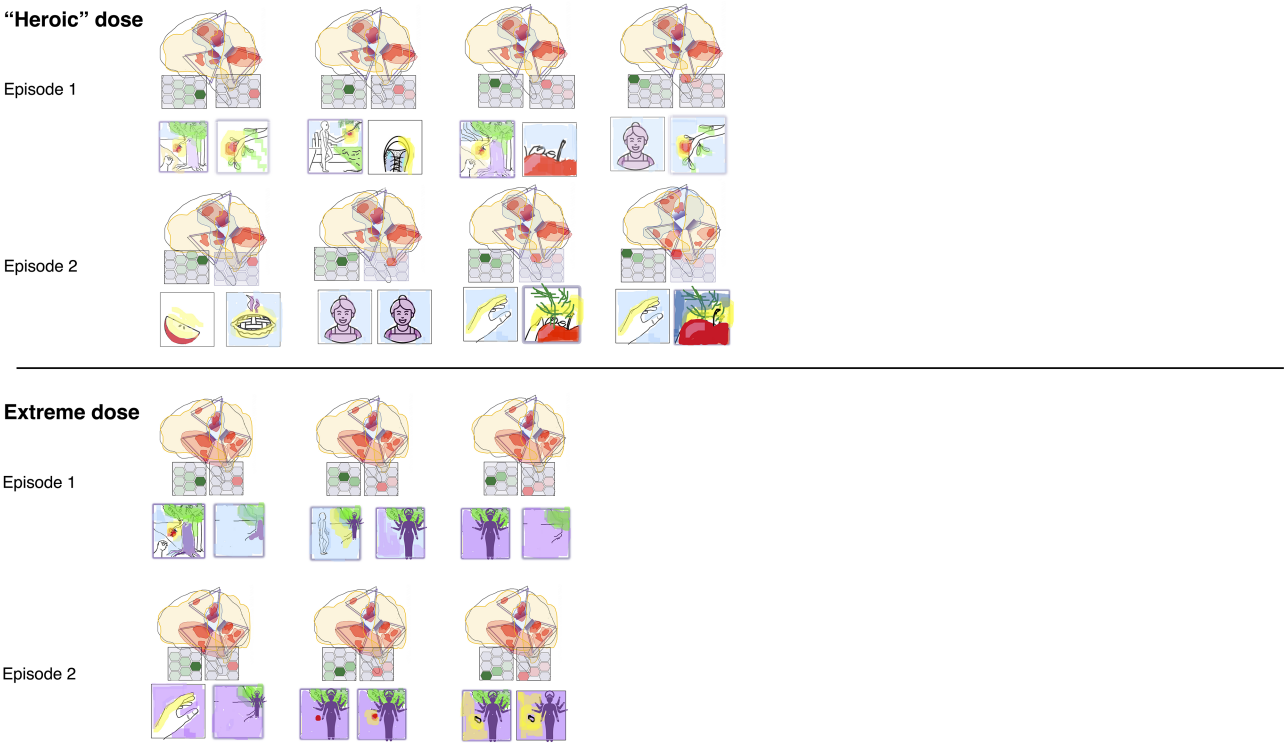

Figure 4 Cognition might be theoretically altered under different levels of 5-HT2a agonism. Please see the main text for a more detailed description. (a) The top set of rows (Unaltered) shows cognition unfolding with low levels of 5-HT2a agonism. (b) The second set of rows (Microdose) shows a slightly more extended sequence with somewhat increased perceptual clarity and continuity across percepts. (c) The third set of rows (Threshold dose) shows even more extended sequences with even greater vividness, detail, and absorption, with the beginnings of more creative associations (e.g. imagining (and possibly remembering) an apple pie). (d) The fourth set of rows (Medium dose) shows the beginnings of psychedelic phenomenology as normally understood, with the number of theta cycles (and cognitive operations) in each sequence beginning to lessen due to reduced coherence. Imaginings become increasingly creative and closer to perception in vividness, which here shows an additional mnemonic association (i.e. one's mother in relation to apple pie) that might not otherwise be accessible under less altered conditions. (e) The fifth set of rows (Heroic dose) shows further truncated sequences with even more intense psychedelic phenomenology, near-complete blurring of imagination and reality, and altered selfhood. (f) The sixth set of rows (Extreme dose) shows radically altered cognition involving the visualization of archetypal images (i.e. core priors) and a near-complete breakdown of the processes by which coherent metacognition and objectified selfhood are made possible

which are highly compatible with the current proposal in emphasizing the nature of such experiences as ranging from dream-like to hyper-real, oftentimes in seemingly paradoxical combinations (Hoel 2021, Safron and Sheikhbahaee 2021a, Stoliker et al. 2022, 2023, Smith and Terhune 2023).

ALBUS should not be taken to suggest a simple account of either strengthened or relaxed beliefs associated with different levels of 5-HT2a agonism. Rather, we should expect different combinations of SEBUS and REBUS effects based on a variety of factors including the consideration of particular neural systems, substances, doses, sets, and settings. There may also be broad trends with respect to things like the availability of high-level schemas, the intensity with which goals are imagined (or consciously represented) (Safron 2021a, 2021b), and perhaps also with respect to the degree to which these intermediate and higher-order attracting states are updated by sense data. In terms of canonical microcircuits for HPP (Bastos et al. 2012, 2020), we suggest the following hypotheses for the effects of altered 5-HT2a signaling:

(i) Low-to-moderate levels of stimulation of L5 excitatory pyramidal neurons may be more likely to strengthen (SEBUS)—rather than weaken (REBUS)—complexes of synchronous activity to which these neuronal populations contribute via oscillations from thalamocortical loops (Aru et al. 2019). Such amplification would have the effect of strengthening entailed beliefs, functionally understood as implicit and sometimes explicit Bayesian prior expectations, or "predictions" with respect to HPP.

(ii) Moderate-to-high levels of stimulation of L5 neurons may produce direct belief strengthening at intermediate levels of cortical hierarchies corresponding to conscious perceptual synthesis, or indirectly via higher-level belief-relaxation (e.g. from reduced suppression or unusual patterns of attention secondary to REBUS effects), or by inducing novel biophysical regimes that diverge from past shaping by experiential histories (e.g. thinking/attending differently because things feel different).

(iii) Low-to-moderate levels of stimulation of L2/3 inhibitory interneurons (Willins et al. 1997)—which are presently not included in REBUS models—may also suppress ascending sensory prediction errors, so decreasing their influence on updating prior expectations. This could have the effect of further shielding (possibly strengthened) beliefs from disruption by inconsistent evidence (cf. hallucinations from sensory deprivation).

In sum, we propose that low-to-moderate doses of psychedelics may often have impacts that are the opposite of what REBUS

models might suggest and may predominantly result in direct SEBUS effects, with perhaps indirect forms of belief-relaxation being generated as a function of expectations. We further suggest that moderate-to-high doses of psychedelics may produce complex admixtures of both direct and indirectly realized SEBUS and REBUS effects. The observation of the dosage-related effects described earlier (and further) would be invaluable for helping to determine the soundness of the ALBUS framework. Unfortunately, as will be discussed in greater detail later, most animal studies capable of addressing these questions tend to use a "head twitch" paradigm (de la Fuente Revenga et al. 2019, Halberstadt et al. 2020), in which animals are provided with increasing doses until they exhibit behavior patterns considered to be indicative of psychedelic-like states. While the absence of such evidence is a limitation of the present discussion, we also believe that one of the primary sources of added value from ALBUS is motivating the collection of new datasets, and in this case experiments capable of reliably characterizing the functional characteristics of the full dose–response curve of 5-HT2a receptors.

Overall, we propose that explaining the effects of compounds such as 5-HT2a agonists and other psychedelics may require a combination of SEBUS and REBUS models for understanding ALBUS. SEBUS-involving models may be necessary to sufficiently account for both the therapeutic and "psychotomimetic" effects of psychedelics. We suggest that strengthened-belief models may provide the most parsimonious explanation for how delusions and hallucinations are generated—and why these phenomena tend to show strong correlations—under both the temporarily altered states of psychedelics as well as in more enduring psychotic states (Wengler et al. 2020). As we hope to demonstrate with the detailed neurophenomenological models presented here (Figs 2–4), we believe a more sophisticated analysis of cognition is required to adequately characterize ways in which beliefs may be altered under psychedelics (Friston et al. 2020, Hesp et al. 2020, Safron and Sheikhbahaee 2021a).

We believe ALBUS can provide a "minimum unifying model" for understanding psychedelics (Wiese 2020), with various combinations of SEBUS and REBUS effects at varying hierarchical levels providing a potentially sufficient conceptual lexicon for describing how belief dynamics may be altered under different circumstances. That is, we do not intend on supplanting theories that exist or will be developed in the future, but instead are proposing candidate mechanisms and principles by which other models can more readily be compared and synergistically integrated with one another. While the ALBUS model may be questioned, one of our main goals is to demonstrate how we may meaningfully specify computational descriptions for nervous systems using the language of probability theory and machine learning, with minds understood as evolving ecosystems of beliefs/predictions (that may be either strengthened or relaxed in myriad ways) for value-driven agents. In this manuscript, we specifically focus ALBUS on classic psychedelics, whose effects are substantially (but not completely) mediated by 5-HT2a receptors. However, in what follows, we hope to show that the study of psychedelics within the ALBUS framework has broader implications for understanding varieties of conscious (and unconscious) experiences, including phenomena such as psychopathological conditions, various meditative states, and even the nature of dreaming.

Any adequate attempt at unification requires considering the precise conditions under which people tend to utilize psychedelics, including with respect to repeated uses. This is especially important in light of the fact that complex behaviors usually require learning as part of their contextualization, especially with respect to interventions whose primary purpose often involves attempting to induce altered states in the service of forming altered traits (Goleman and Davidson 2017, Pollan 2018). Other frameworks have been provided along these lines, such as recently proposed models of psychopathology based on the "canalization" of belief landscapes (Carhart-Harris et al. 2023, Juliani et al. 2023). However, we would also suggest that such models will neither be complete nor accurate if they fail to adequately account for ways in which both (direct and indirect) belief strengthening and relaxation play out in (and through) our minds.

Toward a model of altered states of perception

Explaining alterations of perception under psychedelics may require models that go beyond the simplicity and elegance of HPP as usually understood in terms of a singular algorithm for Bayesian inference. Toward this end, we are required to consider models of the processes that generate different kinds of subjective experiences and their qualities: i.e. phenomenal consciousness. Without this kind of detailed understanding, we will likely fail to achieve sufficiently constrained hypothesis spaces for reliability for both scientific theorizing and clinical interventions.

Safron (2020a, 2022) proposes that a multiscale nested hierarchy over posterior cortices affords phenomenal consciousness, partially by virtue of the scope of alpha-band rhythms. More specifically, these 8–12 Hz oscillations are suggested to afford neuronal synchronization at the spatiotemporal scales required to integrate multiple sensory modalities, and further organize this information according to egocentric reference frames for the sake of both informing and being informed by action–perception cycles on the timescales over which they evolve. Please note: we are not suggesting that we are in possession of a complete account of the neural bases of phenomenal consciousness. For example, it remains unclear whether these distributed rhythmic attractors themselves constitute the physical and computational substrates that generate experience (itself), or something more like an essential—but potentially without consciousness on its own—passive sampling from the environment (cf. carrier waves and multiresolution wavelet analysis). Fortunately, these unsolved technical questions do not impact the core claims made in the present manuscript, and we instead hope that psychedelics may provide valuable data for disambiguating between models of consciousness (cf. neural correlates of 5-MeoDMT experiences and "cessation" events with advanced Jhana meditators (Ermakova et al. 2021, Laukkonen et al. 2023)).

In Fig. 2, a visuospatial sketchpad—and "mind's eye," or "Cartesian theater" (Safron 2021b)—is depicted as centered on posterior medial cortices, which have been demonstrated to constitute major sources of alpha synchronization, implicated in generating both visual imagery and awareness (Freton et al. 2014, Sreekumar et al. 2018, Xie et al. 2020), and as potentially essential for coherently translating between egocentric and allocentric perspectival reference frames (Alexander et al. 2023). While not depicted, an additional source of conscious experience may be found in lateral parietal cortices in terms of somatospatial processing, which may couple with visuospatial modalities in complex ways that would influence things like awareness of embodied selfhood, coherent tracking of causal sequences, and senses of ownership for actions (Darby et al. 2018). If such couplings are disrupted, this could potentially contribute to the generation of a variety of anomalous inferences ranging from hallucinated external voices to the

perception of nonexistent entities (Safron 2021a). Such perceptions of other agents are sometimes reported with psychedelic experiences (Davis et al. 2020), and we believe an ALBUS perspective may be able to provide a mechanistic (and naturalistic) account of some of the processes that might contribute to their generation.

Our emphasis on the importance of the preconditions for establishing coherent perspectival reference frames may be crucially important for understanding psychedelics, especially considering the centrality of constructs such as "ego dissolution" or the ways in which mystic/awe experiences may both further and be furthered by various forms of self-decentering and disinhibiting self/cognitive-control processes (Doss et al. 2021, Sayalı and Barrett 2023). While further work is needed to support our suggested progression from predictive processing to coherent perceptual synthesis, we believe there are good reasons to understand nervous systems in terms of workspace-like architectures for multimodal inference (Safron 2020b, 2022, Juliani et al. 2022b). However, our primary goal here is to provide serviceable (and hopefully useful and accurate) "placeholder" models that provide the basis for the models of sophisticated cognition described later.

Figure 2 describes a progression of information being integrated into increasingly large and encompassing (but more slowly evolving) complexes of synchronous neural activity. An apple, for example, is consciously experienced if multiple sensory hierarchies combine their complementary sources of information to synergistically facilitate inference via cross-modal priors. These inferential capacities may be further enhanced if organized by egocentric perspectival reference frames, which may be required for sufficiently coherent experiences such that we can be made aware of and report on them, or perhaps may be necessary for any consciousness to be generated whatsoever (Safron 2020a, 2022). Across scales, neuronal synchronization is assumed to enable "communication through coherence" (Fries 2015, Deco and Kringelbach 2016), computationally understood as the establishment of joint beliefs from whatever information is capable of being exchanged on the timescales of formation for these metastable attracting states (Safron 2020a, 2022). An inverse relationship between the size and speed of rhythms is depicted, which may be a necessary consequence of the differential challenges of creating coherent oscillatory modes for networks of varying sizes (Buzsáki and Watson 2012).

Differential effects of 5-HT2a agonism on sensation and imagination

Among the many aspects of phenomenology to be accounted for by an adequate account of psychedelics, we believe two key components of ways in which experience may be altered include the qualities of imagination and perception, as well as ways in which self-consciousness is shaped by tendencies and capacities for adopting egocentric and/or allocentric perspectives on oneself. With potential relevance to both spirituality and clinical practice, nondual awareness and dissociative (and potentially pathological) states associated with psychedelics and meditative experiences may involve a breakdown of such processes of self-objectification (Deane et al. 2020, Safron 2021b, Ciaunica and Safron 2022).

The contributions of posterior medial cortices to alpha power are notable in that this region has been shown to contribute to the establishment of coherent egocentric perspectival reference frames (Safron 2020a). Reducing coherence in signaling from these regions could have the effect of destabilizing egocentricity for selfhood on multiple levels, potentially contributing to the attenuation of more extended self-processes while preserving sufficiently coherent models of bodily states for maintaining some degree of conscious perception (Safron 2021b). Speculatively, such a partially dissociated state could allow for elevated absorption with respect to both imagination and perception (Tellegen 1982, Csíkszentmihályi 1991, Ott et al. 2005), potentially achieved by forcing individuals to focus their perceptions and imaginings on "the now" (Tolle 2010, Young 2016).

The strength of rhythmic complexes of neural activity is suggested to reflect the strength of beliefs, some subset of which correspond to conscious subjective experiences. We further propose a model focusing on rhythmic complexes over posterior lobes as potential realizers of phenomenal consciousness, understood as the iterative estimation of likely sensory states, conditioned on a causal world model.

Figure 3 describes REBUS and SEBUS effects in the contexts of imagination (or dreaming) and perception. While imagination can involve either first- or third-person reference frames, only third-person perspectives are depicted to indicate their necessity for constructing objectified selfhood and reflexive meta-aware self-consciousness (i.e. moving from an experiencing "I" to a Jamesian "me") (James 1890, Metzinger 2010).

The second column in Fig. 3 depicts what might be observed under smaller psychedelic doses with strictly REBUS effects (i.e. relaxed beliefs) with all beliefs being relaxed, depicted as less extensive alpha and beta complexes. The expected subjective effects from such modifications are depicted as including greater sensory details from perception, but with less perceptual vividness. Discrepancies between these predictions with actual subjective reports indicate that the REBUS model on its own may not be adequate for accounting for psychedelic experience. If all priors were relaxed for cortical generative models, then we would expect this to also apply to intermediate hierarchical levels at which perceptual synthesis and sensorimotor-grounded cognition may be realized (Varela et al. 1992, Barsalou 2010, Prinz 2017, Safron 2021c).

The third column in Fig. 3 indicates what might be observed under smaller doses with strictly SEBUS effects (i.e. strengthened beliefs)—which could be the case for low-to-moderate levels of 5-HT2a agonism. This is subjectively depicted as including greater perceptual vividness, and details being more likely to match the expectations of potentially richer and more unusual imaginings, with the beginnings of psychedelic phenomenology in the form of fractal patterns and quasi-synesthetic percepts. Synesthetic phenomenology, however, does not appear to be well suited to disambiguate between models of psychedelic action, since such perceptual alterations could be explained either by SEBUS effects as strengthened cross-modal priors or in terms of REBUS effects where (nonstrengthened) priors are afforded greater cross-modal communicative capacity (when normal high-level beliefs are relaxed).

The fourth column of Fig. 3 indicates an admixture of REBUS and SEBUS effects (i.e. ALBUS), involving both strengthened beta and relaxed alpha synchrony, subjectively depicted as entailing both greater perceptual vividness and more intense psychedelic phenomenology, including the beginning of altered self-models.

The fifth column indicates REBUS/SEBUS effects under extreme levels of 5-HT2a agonism, including the breakdown of organization of experience according to coherent self-models. Such highly altered states could be understood as a kind of "ego death" as

sometimes described by "psychonauts" (Martial et al. 2021), and which is normally only reported by meditative adepts, with naturally occurring mystical experiences (James 1902, Safron 2016), or in individuals suffering from severe forms of psychosis (cf. disconnection hypothesis of schizophrenia). Our core claim is that mechanisms of predictive processing suggest that primarily SEBUS effects should be expected with lower levels of 5-HT2a agonism, and also that REBUS effects are unlikely to be observed in isolation without the concomitant strengthening of perceptual beliefs.

We have considered situations in which one might observe both directly and indirectly strengthened and relaxed beliefs in different combinations as a potential explanation for different varieties of psychedelic alterations. We have further suggested that psychedelic states could be understood as being similar to waking dreams with varying degrees of lucidity. Table 1 provides an overview of how the potential alterations of neural dynamics depicted in Fig. 3 could explain different modes of waking and dreaming cognition, potentially (but not necessarily) involving endogenous psychedelic mechanisms. That is, we are suggesting that SEBUS- and REBUS-like effects could be useful for describing different states of consciousness, even without the administration of psychedelic compounds.

The H/E-S and orchestration of streams of consciousness and cognition

ALBUS highlights potential (both direct and indirect) alterations of hippocampal/entorhinal system (H/E-S) functioning as one of the primary explanatory mechanisms for understanding the effects of psychedelics. This emphasis is not arbitrary but is rather motivated by a growing consensus that H/E-S functions may be the key to understanding sophisticated cognitive processes such as episodic memory and imagination/planning, and even capacities for "mental time-travel" and autobiographical selfhood (Safron et al. 2021). It has been suggested that most (and perhaps all) high-level cognition may be productively understood in terms of the problem of an autonomous system/agent/robot simultaneously attempting to locate itself and construct maps of environments within which it attempts to achieve (or forage for) valued goals. If this is indeed a profitable direction of travel for cognitive science and brain-inspired artificial intelligence (Juliani et al. 2022a), then it should no less apply to understanding psychedelic experiences. However, the complexity of the H/E-S is also daunting, with many details remaining unclear. To what extent do different psychedelic states involve alterations in the granularity with which space is organized according to hexagonal grids/tilings? To what extent do psychedelics alter the extent to which obstacles and goals distort these spaces, with what functional significances (e.g. Lilliputian phenomena from atypical modes of body mapping?)? While such unanswered questions suggest it may be premature to try to add further unknowns in investigating such complex phenomena, we propose that the opposite may be the case: by altering minds so profoundly, to what extent can psychedelics provide a "telescope for the mind" in providing edge cases and "exceptions that prove the rule" with respect to the normative functioning of core cognitive/affective systems?

While this interpretation of hippocampal remapping is admittedly speculative, we believe it is also well supported by numerous computational models (Çatal et al. 2021, Safron 2021b; Safron et al. 2021). With respect to psychedelics, we believe there may be an important interpretation of sharp-wave ripple events as indicating an attempt at (re)positioning organisms within the spatial reference frames used to situate themselves in environments within which they pursue valued goals (De Freitas et al. 2023, Paul et al. 2023). Some support for the centrality of the H/E-S for psychedelic cognition may be found in recent work in which reduced sharp-wave ripples correlated with reduced performance with respect to the ability of schizophrenic patients to coherently navigate through "semantic spaces" (Nour et al. 2023).

The models depicted in this section, if found to be accurate, would provide a powerful basis for understanding the effects of psychedelics on cognition. Some theoretical support for these models may be found by considering the H/E-S as a kind of energy-based contrastive learner (Mazzaglia et al. 2022), with potential functional mappings onto machine learning architectures such as spectral graph nets (Greff et al. 2020). Theoretically, we may even find ourselves understanding these operations in terms of well-defined cognitive cycles with clear interpretations of different phenomena (e.g. interactions between hippocampal theta precession and more globally distributed synchronous dynamics across the brain). The details of the models presented here are necessarily preliminary, given our current state of understanding, but we believe they point to the potential and importance of trying to depict the unfolding of streams of experience with respect to their various aspects/qualities, as well as the ways these phenomena might vary both between and within individuals.

Figure 4 describes six different hypothetical regimes of cognition—organized with respect to levels of 5-HT2a-receptor stimulation—expected with various psychedelic interventions or similar endogenously generated states: "Unaltered," "Microdose," "Threshold dose," "Medium dose," "Heroic dose," and "Extreme dose." For each regime of cognition (with potential correspondences with different levels of 5-HT2a agonism and other psychedelic mechanisms), two episodes of ~1–3 s in duration are shown as sequences of imaginative and perceptual states, with the second episode meant to indicate a stream of experience generated subsequent to termination of the first one. Depictions of the brain and associated experiences involve the model of phenomenal consciousness (and its alterations) from Fig. 3 but are expanded to include orchestration by theta rhythms (yellow shading) from the H/E-S.

Figure 4 depicts an inverted-U-shaped function (Yerkes and Dodson 1908) with respect to the extent of the impact of increasing doses on the stability of cognition across time. This prediction is tentative in that there is at present little available evidence supporting nonlinear dose–response curves with respect to behavior or cognition. However, the potential for qualitatively different regimes may be suggested by enhanced attention with low (but not high) doses of lysergic acid diethylamide (LSD) (Hutten et al. 2020) and impaired attention being observed with high-dose psilocybin (Carter et al. 2005, Vollenweider et al. 2007). Some indirect speculative support for nonlinear dose–response effects could potentially also be found with respect to subjective time dilation—a hallmark of flow states characterized by absorbed attention (Csíkszentmihályi 1991)—being most strongly observed for 10 μg (relative to 5 and 20 μg) doses of LSD (Yanakieva et al. 2019). Further (admittedly both indirect and speculative) convergent support for qualitatively different effects may also be found in creativity enhancements being more reliably associated with lower doses of LSD (Wießner et al. 2022).

"Cognitive maps" in the hippocampus are depicted underneath each brain in Figure 4 as embedded in hexagonal tiling of space (Moser et al. 2008, 2017), through which potential future trajectories through possible locations are indicated as green-shaded hexagons, with present-estimated trajectories indicated by red

Table 1. Tentative mechanistic accounts of states of consciousness and their potential relations to SEBUS- and REBUS-like effects (without necessarily involving 5-HT2a receptors).

Modes of experience	Processes contributing to various experiential modes	Direct SEBUS-like effects	Direct REBUS-like effects	ALBUS (indirect and/or admixtures of SEBUS- and REBUS-like effects)
"Normal" sensation-grounded perceiving	Multiscale rhythmic attractors whose extent allows for coupling/enslavement with/by sense data	Unaltered	Unaltered	Unaltered
Vivid and/or rich (relative to normal) sensation-grounded perceiving	Higher power and/or more complex rhythmic attractors coupled to sense data	Potentially accounted for if increased firing increases neural synchrony and/or the complexity of activation dynamics	Difficult to explain via REBUS effects	Potentially accounted for if relaxation of beliefs at higher levels causes strengthening at intermediate and lower levels of perceptual synthesis
"Normal" imagining (relative to sense-coupled perception)	Multiscale rhythmic attractors decoupled from primary modalities	SEBUS at hierarchically intermediate and higher levels	REBUS at hierarchically lower levels	Normal imagination may involve a combination of SEBUS and REBUS effects, relative to sense-coupled perception
Vivid and/or rich (relative to normal) imagining	Higher power and/or complex sense-decoupled rhythmic attractors	Potentially accounted for if increased firing increases neural synchrony and/or the complexity of activation dynamics	Difficult to account for via REBUS effects	Potentially accounted for by SEBUS effects; could involve REBUS effects if relaxation of beliefs at higher levels causes strengthening at intermediate and lower levels of perceptual synthesis
Fused (relative to normal) imagining	Rhythmic attractors that are so strong as to be indistinguishable from sensations, and/or not sufficiently contextualized by other enslaving processes, such as the coherent orchestration of patterns of mental simulation	Potentially involving SEBUS effects if perceptual vividness/richness contributes to both implicit and explicit beliefs about the veridicality of perceptions	Potentially involving REBUS effects if beliefs are relaxed with respect to mental actions involved in contextualizing (causal) sequences (e.g. "reality monitoring")	May involve both SEBUS and REBUS effects
Self-aware (relative to fused) imagining	Imagination coherently contextualized with respect to causal sequences and self-generated actions	Potentially involving SEBUS effects if beliefs involved in self-modeling become stronger and more coherent	Difficult to account for via REBUS effects	Potentially accounted for by SEBUS effects; could involve REBUS effects if relaxation of beliefs results in prediction errors that enhance self-monitoring functions, and potentially via relaxation of "defense mechanisms"
"Normal" dreaming (relative to waking)	Imagination with sensory isolation and reduced enslavement by executive processes	SEBUS at hierarchically intermediate levels	REBUS at hierarchically lower and higher levels	Normal dreaming may involve a combination of SEBUS and REBUS effects, relative to sense-coupled perception
Vivid and/or rich (relative to normal) dreaming	Higher precision and/or complex sensory-isolated mental simulations	Potentially accounted for if increased firing increases neural synchrony and/or the complexity of activation dynamics	Difficult to account for via REBUS effects	Potentially accounted for by SEBUS effects; could involve REBUS effects if relaxation of beliefs at higher levels causes strengthening at intermediate and lower levels of perceptual synthesis
Lucid (relative to normal) dreaming	Imagination with maintained involvement of executive processes that allow for coherent self-reflection and consistent goal-oriented intentional control	SEBUS at hierarchically higher levels, such as those contributing to the intelligent orchestration of streams of experience	Difficult to account for via REBUS effects	Potentially accounted for by SEBUS effects; could involve REBUS effects if relaxation of beliefs results in prediction errors that enhance self-monitoring functions, and potentially via relaxation of "defense mechanisms"

hexagons. Two maps are shown to indicate potential functional divisions between anterior and posterior portions of the hippocampus, which, respectively, more strongly couple to frontal and posterior cortices (Faul et al. 2020). Anterior hippocampal maps show multiple routes through space, which are selected at each moment (darkest green) based on the expected value of choosing that route (Stachenfeld et al. 2017, Kay et al. 2020, McNamee et al. 2021). Posterior maps, in contrast, show a single route through space, corresponding to the perceived path taken and encoded in memory, with the most intense red shading indicating estimates for the present moment of experience, and with this activity gradually fading across subsequent time steps. Notably, while these trajectories are most commonly understood with respect to navigation through physical space, it is increasingly suspected that this core system for localization and mapping was repurposed for the sake of high-level cognition as navigation through generalized space, including for conceptual spaces (Gothoskar et al. 2019, Hawkins 2021, Kaplan and Friston 2018; Safron et al. 2021, Whittington et al. 2019).

Below these maps, within each theta cycle, two frames of experience are depicted as unfolding at alpha frequencies. While the generation of particular experiential frames may be influenced by counterfactual imagination and memory as orchestrated by the hippocampus (Hassabis et al. 2014, Faul et al. 2020), particular moments of experience could be a function of either imagination or perception depending on numerous factors (e.g. degree of driving inputs from the senses). The number of theta cycles in each row indicates tilings of (generalized) space along which trajectories may be planned and recorded in memory, which are shown as variable length sequences due to different levels of 5-HT2a agonism. These chunked sequences could be understood as Edelman's "remembered present" or James' "specious present," wherein "the now" has inherent temporal thickness as past moments both contextualize and are recontextualized by future moments of experience (Varela 1999, Edelman 2001).

Two sequences (Episodes 1 and 2) are depicted for each level of dosing, where different cognitive regimes involve varying degrees of coherence (and potentially conscious access/remembering) maintained across time when separated by hippocampal resetting/remapping events (Colgin et al. 2008). The precise extent of these trajectories through mental spaces may be influenced by "circuit-level" functional properties such as degrees of neuromodulation (Ul Haq et al. 2016, O'Callaghan et al. 2021), with both 5-HT1a and 5-HT2a receptor agonism being capable of inhibiting the sharp-wave ripple events indicative of hippocampally mediated memory consolidation and activation of distributed cortical ensembles. Tentatively, inspired by models from machine learning (De Freitas et al. 2023, Paul et al. 2023), we suggest these suppressed ripples might also be accompanied by suppressed remapping of physical and conceptual spaces, which when refreshed, may afford different modes of sense-making with alternative sets of potential actions. Additionally, hippocampal remapping could potentially occur via surpassing thresholds for cumulative prediction error, such as might be expected as uncertainty builds with respect to the ability of a given set of behavioral policies to be effectively realized through enaction (and where this uncertainty would be likely to increase under highly altered conditions). 5-HT2a agonism may impact the extent of these predictive and remembered "task" sets both by inhibiting hippocampal resetting mechanisms directly, as well as by altering the coherence of streams of experience, so influencing degrees of overall accompanying prediction error, so influencing the likelihood of error-driven remapping.

If the models described in Fig. 4 were found to be usefully accurate depictions of the unfolding of the stream of consciousness and associated cognitive processes, then ALBUS may represent the first unified paradigm for understanding psychedelic phenomena and varieties of conscious experiences more generally. That is, while this may seem like an excessively bold claim, we believe the progression of regimes described in Fig. 4 could potentially not only apply to different levels of 5-HT2a agonism, but could also be used to model various clinical conditions (cf. the "psychotomimetic paradigm"), the progression from sleeping to waking and back again, degrees of lucidity within dreams, or other progressions such as cognitive development and decline (e.g. Lewy body dementia and "terminal lucidity").

Discussion

The ALBUS framework is intended to provide a common basis for integrating models and associated findings from other paradigms, whether emphasizing relaxed beliefs (Carhart-Harris et al. 2019), opening attentional and perceptual thalamic filters (Preller et al. 2019), or altering cortical processing by disrupted coupling with integrative structures such as the claustrum (Doss et al. 2021). Apart from REBUS, other accounts of psychedelic action have tended to remain uncommitted in describing effects on the levels of computational functions and their potential algorithmic realizations. ALBUS suggests that Bayesian cognitive science and machine learning could provide a kind of "lingua franca" for shared (and potentially synergistic) sense-making across different theories. Our goal is not a definitive exhaustive account of psychedelic and related experiences, but to facilitate productive conversations across perspectives that have nonoverlapping strengths and weaknesses (and thereby potential for inferential synergy). Below we will consider some additional complexities and hypotheses before concluding with open questions and directions for future work.

ALBUS and complex causation: SEBUS via REBUS; REBUS via SEBUS

REBUS emphasizes L5 pyramidal neurons (Carhart-Harris et al. 2019), suggesting that increased excitability from 5-HT2a agonism results in asynchronous activation modes, and thereby relaxed beliefs through attenuated coherence. This suggestion provides a potentially sufficient account for reduced alpha power and ego dissolution associated with psychedelic states (Smigielski et al. 2019). In a similar spirit to this paradoxical reduction in coherent signaling via excessive excitation, the inhibitory-interneuron mechanism described earlier as a source of SEBUS effects may be challenged. That is, increasing the excitability of superficial interneurons may not necessarily inhibit ascending prediction errors in those layers, but could potentially have the opposite result via indirect disinhibitory dynamics (Friston 2019; A. Safron, personal communication). Detailed neurophysiological investigations with lower levels of 5-HT2a agonism will be helpful for gaining clarity on these issues.

Perceptual illusions could be illustrative in terms of distinguishing between REBUS and SEBUS effects. Susceptibility to these misleading percepts is well explained by HPP in terms of perception understood as probabilistic inference. If our perception corresponds to our best guess for causes of sensory observations, given past experience, then these guesses can sometimes be mistaken. That is, minds are capable of being tricked in such ways because perception is structured according to prior expectations from (interpretations of) past sensory experiences. According

to a purely REBUS-involving model, relaxation of these priors should raise illusion-susceptibility thresholds, so making us more resistant to going down these perceptual garden paths.

According to a SEBUS model, however, the thresholds for illusory perception may be lowered, so making us even more likely to misperceive. Based on the mechanistic considerations described earlier, we suggest SEBUS effects are likely to predominate with low-to-moderate levels of 5-HT2a agonism (Figs 2 and 3), and with some combination of SEBUS and REBUS effects at higher levels of stimulation for those pathways. Thus, we might expect either increased or decreased illusion susceptibility with, respectively, lower or higher doses of psychedelics.

REBUS emphasizes the high concentrations of 5-HT2a receptors for deeper portions of generative models, suggesting that intermediate hierarchical levels associated with conscious perception could become strengthened as they are released from predictive suppression from hierarchically higher areas. This would be an example in which SEBUS phenomena are generated as an indirect consequence of REBUS effects. The inclusion of such looping causal cascades may make it difficult to establish whether SEBUS effects can occur independently of being driven by 5-HT2a stimulation that results in REBUS effects. Observing increased susceptibility for illusions involving low-level perceptual features with lower psychedelic doses could potentially provide evidence for the independent functional significances of SEBUS mechanisms. Such beliefs may be less likely to be influenced by high-level expectations, and it is also unclear that we should expect excitation-induced desynchronization described by REBUS with low-to-moderate levels of 5-HT2a agonism.

Yet another example of a complex relationship between strengthened and weakened beliefs was proposed by Pink-Hashkes et al. (2017), where predictions form so readily that they are less likely to adequately explain incoming sense data, thereby generating increased prediction errors, and so result in more uncertain—or entropic (Carhart-Harris et al. 2014, Carhart-Harris 2018)—belief landscapes. Under such a state of elevated uncertainty, hallucinations and other psychedelic phenomena are suggested to result as anomalous predictions attempt to explain incoming sense data, potentially involving a compensatory up-regulation of high-level priors. In this view, SEBUS effects produce a greater diversity of less well-fitted beliefs—as opposed to larger joint beliefs—which indirectly produce REBUS effects via conflicting predictions at hierarchically higher levels. SEBUS effects (e.g. hallucinations) may also arise indirectly if relaxed beliefs at upper levels of cortical hierarchies reduce suppression of prediction errors at lower and intermediate levels of organization, so resulting in net disinhibition (Figs 2 and 3). In this view, SEBUS effects would be the indirect result of REBUS effects.

Causal complexity could become even greater if we consider various forms of conscious and self-referential processing. For example, low-to-moderate doses of 5-HT2a agonism could generate strictly SEBUS effects at the level of cortical microcircuitry (Fig. 1), yet produce multiple kinds of REBUS effects in overall belief dynamics such as the following:

(i) Qualitative differences in processing resulting in individuals approaching experience atypically, so "relaxing" typical assumptions.
(ii) Expectations of particular modes of cognition that deviate from typical priors causing such experiences to become more likely (cf. placebo and nocebo effects).
(iii) Explicit expectation of REBUS-like effects producing patterns of cognition characterized by enhanced open-mindedness and creativity.

In these ways, while we believe the account of predictive processing described by REBUS may require additional details to account for the full range of psychedelic phenomena, we want to emphasize that we are not suggesting this theory should be abandoned in favor of SEBUS models. Rather, we suggest the way forward will involve combining both SEBUS and REBUS phenomena (including their potential inter-relations), as well as additional neural process theories (Preller et al. 2019, Doss et al. 2021), into a broader framework that considers the diversity of ALBUS.

Psychedelics, psychopathology, and cognitive spectrums

SEBUS effects may help account for observations of "psychotomimetic" properties for psychedelic phenomenology, for which overly strong priors represent a face-valid model of multiple aspects of schizophrenia (e.g. hallucinations and delusions) (Frith 2005, Maher 2006, Corlett et al. 2019). Yet, REBUS effects may provide a more useful account of psychosis involving disruption of deep beliefs (Adams et al. 2013), including with respect to the integrative properties of self-related processing (Friston et al. 2016, Noel et al. 2017). Carhart-Harris et al. (2019) note the similarities between their suggested mechanisms for psychedelic states and the excessive prediction errors that may represent a partial diathesis for autism (Lawson et al. 2014). However, they go on to argue against this connection based on differences between dynamics unfolding on state and trait levels. While considerations of time scales over which relevant psychological phenomena evolve are surely important, it is nonetheless notable that there are clear dissimilarities between psychedelic and autistic phenomenology, as well as similarities between psychedelic and psychotic states.

SEBUS-like processes may be required to reconcile differences between the altered states suggested by strictly REBUS-based models and particular traits of autism. It has been suggested that autism spectrum disorders may reflect one pole of a cognitive spectrum with schizophrenia on the opposing end (Byars et al. 2014, Crespi and Dinsdale 2019). In this domain and others (Table 2), SEBUS/REBUS mechanisms may be important in suggesting which interventions might be most helpful in which circumstances. For example, by attenuating sensory prediction errors and increasing the ability to form high-level inferences—potentially including the kinds underlying different aspects of social cognition (Call and Tomasello 2008, Penn et al. 2008, Rabinowitz et al. 2018)—low-to-moderate doses of 5-HT2a agonists could potentially provide a valuable treatment for autism (Markram and Markram 2010, De Jaegher 2013).

Furthermore, a purely REBUS-based model might (perhaps questionably) suggest 5-HT2a agonists as beneficial in some cases of psychosis by attenuating overly strong beliefs (Schmidt et al. 1995, Stoliker et al. 2023). Yet a SEBUS-involving model, in contrast, would suggest that classic psychedelics may be strongly contraindicated for anyone at risk for psychosis—with potential exceptions from specific targeted interventions—and would further point to potential benefits from 5-HT2a antagonism for treating psychotic states (Schmidt et al. 1995). Please note: our hypotheses concerning the clinical implications of ALBUS are not meant to constitute a definitive statement of recommendations, with research being needed to inform interventions.

As described earlier, the study of visual illusions with varying susceptibility thresholds could potentially provide valuable data on these matters. While resistance to visual illusions has been discussed with both psychedelics (Pollan 2018) and schizophrenia (Gupta et al. 2016), this association might be more reliable

Table 2. Speculative use cases for psychedelics as therapies under different mechanistic models, with SEBUS effects hypothesized to predominate with microdosing, and a combination of SEBUS and REBUS effects with macrodosing.

	SEBUS effects	REBUS effects	ALBUS (powerfully altering internal working models)
Depression	Behavioral activation; increased ability to imagine and experience positive outcomes	Interrupting depressogenic patterns of cognition and behavior (e.g. rumination)	Microdosing for behavioral activation Macrodosing for cognitive restructuring
Anxiety	Potential improvements through increased confidence, but possibly maladaptive effects due to greater vividness of negative imaginings	Reducing the grip of anxiety-provoking beliefs	Microdosing for increasing confidence, and possibly as an adjunct to exposure interventions Macrodosing for flooding and reconsolidation
Creativity	Both divergent and convergent creativity potentially elevated through enhanced associations and cognitive control	More divergent creativity through freer associations	Microdosing for either convergent or divergent creativity Macrodosing for divergent creativity
Autism spectrum	Potentially beneficial through reducing the gain on excessive prediction errors and increasing the gain on central integrative processes, but possibly contraindicated if accompanied by tendencies toward anxiety	Potentially beneficial for reducing overly rigid patterns and increasing cognitive flexibility, potentially insight	Microdosing for enhanced empathy and attenuated sensory sensitivity Macrodosing for breaking free of rigid patterns and promoting self/other awareness and insight
Schizophrenia spectrum	Likely contraindicated, unless condition is driven by functional disconnection, in which case some strengthening of beliefs could be beneficial	Potentially desirable for reducing some forms of delusions based on self-reinforcing beliefs; contraindicated if condition is driven by functional disconnection	Microdosing for enhancing executive functions Macrodosing as last-line intervention; possible protective effects for prodrome through enhancing integration, and possibly inoculation with respect to epistemic hygiene
Traumatic brain injury	Potentially protective by encouraging sustained cognitive engagement, preventing learned nonuse, and promoting neuroplasticity	Potentially useful for processing distress and maladaptive cognition and behavior patterns (e.g. cognitive avoidance and activity avoidance)	Microdosing for aiding recovery Macrodosing for breaking through maladaptive patterns to make room for new ones; may also be most beneficial for opening plasticity windows
Cognitive decline	Potentially beneficial for similar reasons to those described for traumatic brain injury	Potentially beneficial for similar reasons to those described for traumatic brain injury	Microdosing for prevention Macrodosing for condition management (and possibly prevention if avoidance contributes to cognitive reserve depletion)
Wakefulness disorders	Potentially highly beneficial by increasing consciousness level	Potentially beneficial if relaxed beliefs indirectly produce arousal through increased prediction errors	Microdosing for conditions such as narcolepsy Macrodosing as potentially beneficial for coma and persistent vegetative states
Addiction	Potentially contraindicated, unless microdosing provides an effective substitution for more addictive substances; increased abilities to visualize consequences/goals and greater connections to values could aid in resisting overly steep discounting of future utility	Potentially beneficial by weakening overly strong self-reinforcing memories	Microdosing as potential substitute for stimulants Macrodosing as potentially beneficial for all addictions

(continued)

Table 2. (Continued)

	SEBUS effects	REBUS effects	ALBUS (powerfully altering internal working models)
Personality disorders	Likely contraindicated as a standalone treatment, but potentially beneficial in conjunction with psychotherapy	Potentially beneficial via insight, unless psychedelic experiences promote spiritual bypassing or destabilize already weakened self-processes	Microdosing as adjunct to psychotherapy Macrodosing for updating maladaptive internal working models; potentially more effective with guided sessions
Post-traumatic stress disorder	Potentially contraindicated outside of exposure therapies due to risk of enhancing traumatic imaginings Possibly beneficial if other beliefs are allowed to more effectively compete with dominance from self-traumatizing internal models	Potentially beneficial by weakening overly strong self-reinforcing memories	Microdosing as adjunct for gradual exposure therapies Macrodosing for flooding and compassion-based protocols
Chronic pain	Likely highly variable across individuals, with some experiencing undesirable strengthening of pain-enhancing patterns of cognition, and others experiencing potentially beneficial reward-related analgesia (above and beyond anti-inflammatory properties associated with 5-HT2a receptors); possibly effective as adjunct to hypnosis-based interventions	Potentially beneficial for disrupting self-reinforcing patterns of pain-enhancing cognition; possibly temporarily harmful if reduced gating of prediction errors exacerbates pain sensations	Microdosing for reward-related analgesia and anti-inflammatory effects Macrodosing for enhancing self-compassion and acceptance
Terminal illness	Potentially helpful by strengthening access to sources of meaning from core values and transpersonal connection	Potentially beneficial by weakening schemas involving death anxiety	Microdosing for increased engagement with life Macrodosing for greater acceptance, connecting to higher meanings, and hopefully beneficial (and possibly transcendent) changes in worldview
Existential anxiety	Potentially helpful for similar reasons to those involved in overcoming distress from terminal illness	Potentially beneficial if connections to meaning are actively blocked by preexisting schemas	Microdosing for greater sense of agency, engagement with life, and connection to meanings Macrodosing as potentially beneficial for similar reasons to those involved with terminal illness

This table is neither meant to be exhaustive nor definitive.

Table 3. Speculative accounts of psychedelic phenomena under different mechanistic models.

	SEBUS	REBUS	ALBUS
Hallucinations	Anomalous perceptual inference from overly strong priors	Anomalous perceptual inference from breakdown of integration by deep beliefs, possibly involving indirect strengthening of lower hierarchical levels	Different combinations of SEBUS and REBUS effects would be more-or-less explanatory based on the specific type of hallucinations being considered
Fractal imagery	Revealing useful priors derived from experience, and possibly evolution	Driving of perception by bottom-up prediction errors reflecting the fractal structure of the world	Increased shaping of perception by low-level priors (SEBUS), potentially with less competition from high-level expectations (REBUS)
Synesthesia	Increased cross-modal priors	Anarchic cross-modal signaling due to disorganized integrative processing	Possibly clearest account of synesthetic phenomenology, since cross-modal priors would not necessarily be synesthetic with only strengthened beliefs (SEBUS), and novel modes of perceptual synthesis could be obstructed with only relaxed beliefs (REBUS)
Entity encounters	Strengthened evolutionary and developmental agency priors	Anomalous agency attributions due to breakdown of self-processes	Combination of relaxed self-models (REBUS) and strengthened agent-perception priors (SEBUS), potentially also involving anomalous inference from incoherently integrated efference copies
Feelings of timelessness	Crowding out of temporally extended self-processes by experiential absorption	Relaxing of beliefs related to internal working models of self and world resulting in less engagement with temporally deep and counterfactually rich processing	Conjunction of less elaborative self-modeling (REBUS) and enhanced capacities for absorption (SEBUS and REBUS)
Feelings of unity and deep order	Strengthening of core socioemotional priors from early developmental stages	Reduced modeling of self as separate from world	Conjunction of reduced objectified selfhood (REBUS and SEBUS-via-absorption) and enhanced core priors for connection (SEBUS)
Recovered memories	Increased conscious access	Reduced suppression from defense mechanisms (e.g. experiential avoidance patterns)	Potential for recovering memories that are either weak (SEBUS) or blocked by defense mechanisms (REBUS)
False memories	Misleading vividness	Reduced reality monitoring	High probability of false memories through combination of reduced meta-cognition (REBUS) and enhanced perception (SEBUS)
Personal transformation	Increased perceptual and imaginative abilities enhancing capacity for visualizing desired goals and undesired consequences of behavior patterns	Letting go of rigid beliefs via relaxation of internal working models	Greatest opportunities for change by allowing new patterns (REBUS) to be explored with high experiential intensity (SEBUS)
Dissociation	Indirect consequence of fusion with experience	Relaxation of core beliefs related to selfhood	Different combinations of SEBUS and REBUS effects could contribute to different kinds of dissociative experiences in highly variable ways

(continued)

Table 3. (Continued)

	SEBUS	REBUS	ALBUS
Ego death	Potential consequence of extreme absorption causing a collapse of temporally deep and counterfactually rich modeling by which extended selfhood is actively inferred/constructed	Extreme relaxation of core beliefs related to both extended and embodied selfhood	Ego-death-related self-restructuring from intensely experienced (SEBUS) selfless/nondual experiences (REBUS and possibly SEBUS via extreme absorption)
Ontological shock	Strong experiences causing extreme updating of core (and potentially stabilizing) beliefs (REBUS effects via SEBUS effects)	Difficulty integrating experiences not structured according to internal working models of self and world	Similar explanation as for ego death in terms of combining intense experiences (SEBUS) outside of normal modes of sense-making (REBUS)
Delusional (but potentially generative with respect to creativity) cognition	Misleading vividness resulting in poorly evidenced models becoming resistant to updating/falsification	Relaxation of beliefs relating to active reality monitoring and epistemic hygiene	Kindling delusions (and some forms of creativity) by combining relaxed prior models (REBUS) with strengthened novel information (SEBUS)
Conversion experiences (e.g. adopting new religions, altered political affiliations)	Intense experience of an alternative reality provided by set/setting	Making core beliefs subject to updating/falsification via relaxation	Radical transformation of overarching narratives with respect to self/world by combining relaxed core beliefs (REBUS) with strengthened suggested beliefs (SEBUS)
Personality change	Increased ability to perceive and pursue new goals	Relaxation of internal working models creating a space within which new characteristic adaptations may form	Exploring and being updated by intensely experienced (SEBUS) alternative ways of being (REBUS)

SEBUS and REBUS columns indicate, respectively, strengthened and relaxed beliefs, potentially primarily observed with, respectively, low-to-moderate and moderate-to-high levels of 5-HT2a agonism. ALBUS indicates a mixture of both SEBUS and REBUS effects, with potentially highly variable combinations as a function of set, setting, and substance/dosing. This table is neither meant to be exhaustive nor definitive.

with respect to autism (Turi et al. 2018). Hypothetically, we might expect schizophrenia to be particularly strongly associated with resistance to illusions at early- or mid-stages if it is of a variety that has overlapping diatheses with autism (Barneveld et al. 2011), or at late stages where breakdown of global integration may be observed (e.g. via NMDA-receptor auto-immunity) (Braun et al. 2016). However, we might also potentially expect prodromal individuals and relatives of schizophrenic patients to show the opposite pattern of heightened illusion susceptibility, potentially consistent with findings regarding predisposing factors for pareidolia and apophenia (Blain et al. 2020, Mavrogiorgou et al. 2021). To the extent that such inter- and intra-individual differences in predictive processing and cognitive spectrums apply, the kinds of models described in Figs 3 and 4 could provide valuable means of characterizing these sources of human variation. Thus, we might be able to adjudicate between mechanistic models based on SEBUS or REBUS effects, as well as their combinations (ALBUS) by assessing the extent to which visual illusion thresholds are raised or lowered with 5-HT2a agonists, with potentially notable differences across various kinds of minds.

Breaking free of (and via) default modes; creativity and consciousness

Altered beliefs under classic psychedelics could result in overcoming barriers to breaking typical frames and engaging in non-traditional divergent thinking (Carson 2010, Kenett et al. 2018a, Girn et al. 2020), so allowing novel streams of imagination to be considered (DeYoung et al. 2008). This kind of "out of the box" (or frame) creative thinking can be thought of as driving minds into otherwise uncharted territories of hypothesis spaces. In looking for systems potentially required for enabling robust patterns of counterfactual processing, the default mode network (DMN) may provide this kind of dynamo for creativity and imagination (Beaty et al. 2014, 2015, 2018, Hassabis et al. 2014). By constituting a source of strong internally coherent predictions, the DMN may be capable of temporarily absorbing and then releasing free energy via the shaping of perception and driving of action, perhaps especially when coupled to salience networks (Carhart-Harris and Friston 2010, Rueter et al. 2018, Zhou et al. 2018, Safron 2021b). However, while the DMN is likely essential for constructing things (or processes) like autobiographical selfhood, its effective connectivity with the salience network and neuromodulatory nuclei of the brainstem is likely essential for understanding how dynamics may be orchestrated according to estimates of value based on past experiences (Dohmatob et al. 2020, Hamilos et al. 2021). The connectomic properties of the DMN suggest this core network is ideally suited to serve these functions (in collaboration with other intrinsic functional networks) by virtue of having high centrality, and so high potential for integrating information and exerting control (Kenett et al. 2018a). The DMN is further located distally from primary modalities and is thereby capable of supporting dynamics more decoupled from immediate sensorimotor engagements (Buckner and Krienen 2013, Sormaz et al. 2018). Furthermore, the DMN is likely to support some of the most stable inferences available to embodied embedded persons, with major nodes contributing to egocentric perspective, integrated memory, and even the foundations of selfhood and intersubjective modeling (Hazlett et al. 2005, Hassabis and Maguire 2009, Brewer et al. 2013, Leech and Sharp 2014).

While the precise roles of the DMN may be debated, this kind of trading-off of prediction error across neural systems may be involved in not only the unusual imaginings associated with creativity, but also agentic control, which necessarily involves prediction error generation due to the counterfactual status of yet-to-be-achieved goals. In this way, every intentional action is inherently creative in bringing desired states into being through holding onto prior expectations as a kind of sustained imagination. This is a clear case in which SEBUS effects are relevant and would recast the functional significance of (low-to-moderate) levels of 5-HT2a signaling as crucially involving strengthened beliefs for imaginative planning and goal-oriented cognition more generally (Hesp et al. 2020, Safron 2021a, Safron and Sheikhbahaee 2021b). Perhaps this relates to the reported efficacy of the older model of "psycholytic therapy" in which talk therapy during experiences prompted by moderate psychedelic doses (in contrast to higher doses in "psychedelic therapy" in which there is minimal therapeutic interaction during the experience itself) is leveraged toward therapeutic change (Passie et al. 2022).

The strengthening of DMN-mediated counterfactual imaginings with psychedelics is consistent with recent work involving LSD, in which dynamic causal modeling established increased effective connectivity from posterior portions of the DMN to associated thalamic nuclei (Preller et al. 2019). While recent work has identified additional complexities using similar methods (Stoliker et al. 2023, 2023a, 2023b), these sorts of findings provide intriguing support for a SEBUS-involving account of enhanced creative capacity (and potentially agency) via more vivid imaginings.

In these ways, both SEBUS and REBUS effects may be observed in various ways at different levels of organization, including intermediate levels of hierarchical abstraction for which conscious experience may be realized as a stream of sensorimotor predictions (Prinz 2017, Safron 2020a, 2021b, 2022). However, even if SEBUS effects may be required for explaining some aspects of psychedelic phenomenology, REBUS-informed models may be essential for capturing other aspects of personal experience and clinically relevant outcomes (Tables 2, 3), such as the increased open-mindedness associated with psychedelic-use (MacLean et al. 2011, Erritzoe et al. 2019). In this way, an adequate account of the ways in which psychedelics alter brain and mind likely needs to be expanded into an ALBUS framework capable of integrating across both SEBUS and REBUS phenomena.

Conclusions and future directions

While SEBUS and REBUS effects may converge with moderate-to-high levels of 5-HT2a agonism, we might expect qualitatively different effects with low-to-moderate doses. Under regimes characteristic of microdosing or threshold experiences (Figs 3 and 4), consciousness may be elevated without substantially altering typical belief dynamics. In these ways, microdosing may provide a promising and overlooked therapeutic intervention for depression (e.g. anhedonia), autism, Alzheimer's disease, and disorders of consciousness. In contrast to a purely REBUS-focused model, a SEBUS-involving ALBUS perspective makes different predictions for the potential utility of various psychedelic interventions for these debilitating conditions, for which advances in treatment could have impacts on public health that may be difficult to overstate. We suggest the following lines of inquiry are likely to be informative for testing ALBUS:

(i) Do lower and higher levels of 5-HT2a agonism have different effects on the extent to which particular priors—and at which levels of organization under which circumstances?—are either strengthened or relaxed in HPP?
(ii) To what extent (and under which circumstances) could agonizing L2/3 inhibitory interneurons result in reduced gain on observations (cf. sensory deprivation), so contributing to more intense and/or less constrained imaginings?
(iii) Can high-field strength fMRI (or multiple imaging modalities with complementary resolution in spatial and temporal domains) of psychedelic experiences allow for testing hypotheses regarding the relative strength of predictions and prediction errors from respective superficial or deep cortical layers (Fracasso et al. 2017, Bastos et al. 2020)?
(iv) With respect to such models, could sufficiently reliable estimates of individual-level data be obtained for alignment with subjective reports, so helping to realize some of the hopes of "neurophenomenology" (Rudrauf et al. 2003, Carhart-Harris 2018, Sandved Smith et al. 2020)?
(v) Perhaps the most straightforward approach to investigating when we might expect SEBUS/REBUS phenomena would be the systematic study of perceptual illusions whose susceptibility thresholds have been titrated such that the relative strength of priors can be ascertained. This work could be conducted with a wide range of illusory percepts at multiple hierarchical levels in different modalities, in multiple combinations. Such work can include not only perception but also cognitive tasks such as thresholds of categorization. While this would be a nontrivial research program, it may also be one of the most effective ways of characterizing underlying mechanisms and would also have the advantage of helping us to be more precise in specifying which particular beliefs are suggested to be either strengthened or weakened in which contexts.

Finally, in Tables 2 and 3 we provide a list of potential ways in which an emphasis on SEBUS and/or REBUS effects may suggest different use cases for psychedelics and explanations for commonly reported psychedelic phenomena. While these speculations are tentatively suggested, we believe they help to illustrate what might be at stake in obtaining more detailed models of psychedelic action, and also point to additional testable hypotheses. Given the immense potential of these powerful compounds for both clinical and basic science, we believe substantial further work and funding is warranted to explore the conditions under which we might expect relaxed, strengthened, and more generally altered beliefs under psychedelics and other varieties of conscious experiences.

Conflict of interest

M.W.J. serves as consultant to AJNA Labs, Beckley Psychedelic, Clarion Clinics, Negev Capital, Otsuka Pharmaceutical Development & Commercialization, and Reunion Neurosciences. No other authors have declared conflicts of interest.

Funding

A.S. was supported by a grant from the Survival and Flourishing Fund. N.R. was supported by grants from Tiny Blue Dot Foundation and YSF Innovation Fund.

Data availability

This manuscript does not have any associated data.

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Neuroscience of Consciousness, 2025, 2025(1), niae038 , DOI: https://doi.org/10.1093/nc/niae038, Research Article
Received 19 May 2023; Revised 9 September 2024