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Aqil, Marco; Roseman, Leor

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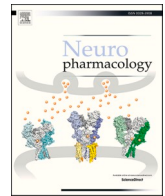
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More than meets the eye: The role of sensory dimensions in psychedelic brain dynamics, experience, and therapeutics

Marco Aqil^{a,b,c,*}, Leor Roseman^d

^a Spinoza Centre for Neuroimaging, Amsterdam, the Netherlands

^b Computational Cognitive Neuroscience and Neuroimaging, Netherlands Institute for Neuroscience, Amsterdam, the Netherlands

^c Experimental and Applied Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands

^d Centre for Psychedelic Research, Imperial College London, London, United Kingdom

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ABSTRACT

Psychedelics are undergoing a major resurgence of scientific and clinical interest. While multiple theories and frameworks have been proposed, there is yet no universal agreement on the mechanisms underlying the complex effects of psychedelics on subjective experience and brain dynamics, nor their therapeutic benefits. Despite being prominent in psychedelic phenomenology and distinct from those elicited by other classes of hallucinogens, the effects of psychedelics on low-level sensory - particularly visual - dimensions of experience, and corresponding brain dynamics, have often been disregarded by contemporary research as 'epiphenomenal byproducts'. Here, we review available evidence from neuroimaging, pharmacology, questionnaires, and clinical studies; we propose extensions to existing models, provide testable hypotheses for the potential therapeutic roles of psychedelic-induced visual hallucinations, and simulations of visual phenomena relying on low-level cortical dynamics. In sum, we show that psychedelic-induced alterations in low-level sensory dimensions 1) are unlikely to be entirely causally reducible to high-level alterations, but rather co-occur with them in a dialogical interplay, and 2) are likely to play a causally relevant role in determining high-level alterations and therapeutic outcomes. We conclude that reevaluating the currently underappreciated role of sensory dimensions in psychedelic states will be highly valuable for neuroscience and clinical practice, and that integrating low-level and domain-specific aspects of psychedelic effects into existing nonspecific models is a necessary step to further understand how these substances effect both acute and long-term change in the human brain.

1. Introduction

"Even if we consider this state as a hallucination of vision and perception, that is to say as a negation of reality, it conveys a real and plastic life of the soul, like the religious visions of Benvenuto Cellini when imprisoned in the dungeons of St. Angelo, and other which have been described in times past on the part of many other individuals, saints and others, the so-called visionaries."

- Lewin, 1924

Classic psychedelics - serotonergic hallucinogens such as psilocybin, DMT, LSD, and mescaline - are undergoing a major resurgence of scientific, clinical, and popular interest. These substances elicit an extremely varied array of effects, spanning the entire brain functional hierarchy, from low-level sensory, to mood, and high-level cognitive

alterations (Halberstadt, 2015; Nichols, 2016; Preller and Vollenweider, 2016; Kyzar et al., 2017; Vollenweider and Preller, 2020; Inserra et al., 2021; Kelmendi et al., 2022; Kwan et al., 2022; van Elk and Yaden, 2022). Multiple theoretical frameworks are available describing how psychedelics achieve their characteristic effects on brain dynamics and subjective experience (Carhart-Harris, 2018; Swanson, 2018; Doss et al., 2021; Vollenweider and Smallridge, 2022). While there is no universal agreement, perhaps one of the few widely accepted characterizations of the psychedelic state is as one of reduced top-down cognitive control, and increased bottom-up influence of sensory information. However, besides the involvement of the 5-HT_{2A} receptor, it is still not fully clear how this state is achieved, and what the relations between low-level and high-level alterations would be, if any. One of the most prominent existing models, the RELaxed Beliefs Under pSYchedelics [REBUS] model, suggests that the relaxation of top-down expectations

* Corresponding author. Spinoza Centre for Neuroimaging, Netherlands Institute for Neuroscience, Amsterdam, the Netherlands.

E-mail address: m.aqil@spinozacentre.nl (M. Aqil).

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(“high-level priors” in the language of predictive coding) encoded by high-level regions and networks, in particular the Default Mode Network [DMN], may be the defining characteristic of psychedelic brain dynamics and subjective experience (Carhart-Harris and Friston, 2019). Complementary or alternative models have focused on subcortical structures such as the thalamus and the claustrum, which are proposed to have roles of gating sensory inputs, or orchestrating brain dynamics, respectively (Vollenweider and Geyer, 2001; Geyer and Vollenweider, 2008; Doss et al., 2021). Despite differences in implementation, all of these models take conceptual inspiration from Huxley’s “reducing valve” hypothesis (Huxley, 1954), and reflect the historical qualifications of psychedelics as generic “mind-manifesting”, or “nonspecific amplifiers”, or “meaning-enhancing”, or “suggestibility-inducing” substances. These nonspecific frameworks are certainly valuable and applicable to the observation that psychedelics can indeed elicit an extremely varied and diverse array of experiences, often spanning diametrically opposite extremes, for example in terms of emotional valence. However, they do not take into account that particularly, but not only, in the visual domain, psychedelic phenomenology presents highly specific characteristics, distinct from other classes of hallucinogens, such as deliriant or dissociatives (Fortier, 2018). In other words, psychedelics do not elicit *any* potential experience with similar probability, as could be expected from truly nonspecific amplifiers; rather, they tend to elicit experiences from a distinct and specific (while still very wide) “slice” of phenomenological space. As such, the psychedelic-induced visionary state cannot easily be captured as a nonspecific amplification.

Notably, there is currently also no universal agreement on the mechanisms underlying the therapeutic potential of psychedelics. Supported by studies in animal models, some authors have proposed neurobiological mechanisms, such as increased neuroplasticity (Ly et al., 2018; Olson, 2020; Lu et al., 2021; Lepow et al., 2021); others, supported by clinical studies in humans, have proposed “mystical-type” experiences as a key driver of the therapeutic benefits of psychedelics (Griffiths et al., 2016; Barrett and Griffiths, 2017; Roseman et al., 2018; Yaden and Griffiths, 2020).¹ Interestingly, alterations in low-level sensory dimensions of experience have been regarded by both camps as not particularly important, or possibly even counterproductive for therapeutic outcomes, and hence largely relegated to a status of ‘epiphenomenal byproducts’ in clinical research. However, this notion may represent a throwing out the baby with the bathwater, partially due to the evolution of narratives around psychedelics. In recent years, psychedelic research narratives have moved away from the historically-charged and negatively-laden ‘hallucinogenic’ characterization, and towards the more positively-laden (and more easily marketable) ‘entheogenic’ or ‘neuroplastogenic’ characterizations. This disregard for low-level dimensions of experience also sits squarely within broader trends in brain sciences. For most of the 20th century, research on low-level sensory-motor dimensions has constituted most of neuroscience and psychology research, since it was essentially all that available techniques allowed access to; only in the last decades of the 20th century, advances in neuroimaging methods have allowed unprecedented investigations into the high-level cognitive functions of the human brain. The conjunction of this broader trend with the shift in narrative around psychedelics is likely to have contributed to further removing the interest of psychedelic researchers away from the low-level bodily and sensory dimensions, and towards high-level cognitive ones. Nonetheless, many researchers (Vollenweider and Geyer, 2001; Kometer and Vollenweider, 2016; Frecska et al., 2016; Winkelman, 2021; Millière et al., 2018; Preller and Vollenweider, 2016) have, to varying degrees, recognized the potential roles of low-level sensory dimensions of experience in causally influencing alterations of

high-level dimensions and therapeutic outcomes; and neuroimaging studies have robustly measured effects of psychedelics in sensory brain areas, such as increased functional connectivity of the primary visual cortex with the rest of the brain (Carhart-Harris et al., 2016), increased bottom-up traveling waves (Alamia et al., 2020), increased retinotopic coordination and increased BOLD signal in visual areas (de Araujo et al., 2012; Roseman et al., 2016), and changes in oscillatory activity in occipital brain regions (Muthukumaraswamy et al., 2013; Timmermann et al., 2019).

The emerging picture suggests that the present characterizations of psychedelics might be underestimating the role played by low-level sensory dimensions in psychedelic brain dynamics, experience, and therapeutics. To fill in this gap, here we review findings from neuroimaging, pharmacology, questionnaires, clinical studies, propose extensions to existing models, provide computational simulations of psychedelic-induced visual phenomena, and propose testable hypotheses for the potential therapeutic roles of visual hallucinations. In sum, we find that psychedelic-induced alterations in low-level sensory dimensions of experience 1) are not entirely causally reducible to alterations in high-level dimensions, but rather co-occur in a dialogical interplay with the latter, and 2) play a causally relevant role in determining high-level alterations and therapeutic outcomes. We conclude that integrating low-level and domain-specific aspects of psychedelic effects into existing models is a necessary step to improve the current understanding of how these substances effect both acute and long-term change in the human brain. The considerations presented here are relevant for the fundamental understanding of psychedelic phenomenology and pharmacology, but also for the design of future clinical protocols and therapeutic practices.

2. Models and neural dynamics

In recent years, the framework of hierarchical predictive coding has arguably become the most common approach to model neuroscientific and psychological phenomena (Friston, 2010; Bastos et al., 2012). An invaluable contribution of predictive coding to contemporary brain sciences has been emphasizing the critical role of Bayesian “priors” in brain function and behavior, i.e. the brain’s ability to construct and leverage expectations, predictions, and internal models of the world to inform subsequent perception and action; little doubt is left about this insight which we owe to predictive coding. Far from lacking explanatory power, one notable challenge of this framework is perhaps its *overability* to explain phenomena. It is not uncommon to find diverging, but internally consistent, predictive-coding accounts for the same observations, particularly for complex phenomena such as psychedelics. Indeed, multiple such accounts have been proposed, suggesting overly detailed priors (Pink-Hashkes et al., 2017), weakened or relaxed priors (McKenna and Riba, 2016; Carhart-Harris and Friston, 2019), or both (Safron, 2020a,b) as an explanation for psychedelic effects. The most prominent and widely accepted account, the REBUS model (Carhart-Harris and Friston, 2019), posits that the crucial component of psychedelic states is the relaxation of high-level priors, i.e. a reduced top-down influence exerted by cognitive processes sitting at the highest level of the brain functional hierarchy; in particular, the DMN is most often identified as the key neural correlate of these high-level processes. In turn, this process is said to imply an increased flow of bottom-up information from low-level sensory regions, ‘unsuppressed’ by the original priors. It is important to remark that, despite the emphasis placed on the causal primacy of (reduced) top-down control, the authors maintain a degree of openness as to the possibility that bottom-up components may be concurrent. For example, by acknowledging that “The exceptionally high expression of 5-HT_{2A}Rs in the brain’s highest hierarchical levels provides a solid anatomic basis for this [the REBUS] assumption, although we recognize expression is also particularly high in the primary visual cortex” (Carhart-Harris and Friston, 2019). In more speculative sections, the authors leave the door open for a possible

¹ Note that the psychological construct of mystical experience is itself currently a subject of debate (Taves, 2020; Sanders and Zijlmans, 2021; Breksema and van Elk, 2021).

causal role of bottom-up information flow, although this role is always implicitly characterised as occurring *after* top-down prior relaxation: “How these acute brain changes and associated mind states trigger the relevant long-term changes in beliefs is, at this stage, not fully understood—but increased bottom-up information flow (i.e., from lower-level intrinsic systems such as the limbic system) impacting on sensitised high-level priors (e.g., high-level networks and their dynamics) are logical places to look.” (Carhart-Harris and Friston, 2019). Going further in the direction of this intuition, we argue that taking stock of the specific effects of psychedelics on low-level sensory brain areas, and of the impact of sensory content on top-down priors and high-level dimensions of psychedelic experience, is a necessary step towards a more comprehensive description of psychedelic brain dynamics and phenomenology.

An existing line of work combines models of neural dynamics with retinotopic considerations (Bressloff et al., 2002; Cowan, 2014), or more recently, connectome graphs (Atasoy et al., 2016; Aqil et al., 2021). This approach has already provided many fruitful insights into psychedelic phenomena (e.g. Atasoy et al., 2017; Deco et al., 2018; Kringelbach et al., 2020; Luppi et al., 2021a). Of particular relevancy in this context, consider ‘simple’ visual hallucinations - geometric, abstract visual patterns of concentric spirals, circles, tunnels, honeycombs, webs - which are among the most widely recognized features of psychedelic states (Kometer and Vollenweider, 2016); they are specific to psychedelics, in the sense that they are very rarely reported in other classes of hallucinogens, such as deliriants, which crucially also differ from psychedelics in terms of the *sense of reality* that people attribute to the experience (Fortier, 2018) (more on this in Sec 3); and they appear cross-culturally, suggesting a potential biological underpinning. The cortical-retinotopic mapping implies that subjective experience of geometric visual hallucinations should correspond to regular patterns of neural activity in the visual cortex. Indeed, existing mathematical models have shown that such regular patterns of neural activity can emerge when the excitatory-inhibitory balance, coupled with the anatomical lateral connectivity of visual cortex, is pushed away from its normal stable equilibrium and into oscillatory dynamics (Bressloff et al., 2002; Cowan, 2014). A natural question at this point concerns the source of this instability. Could the relaxed priors serve this purpose? The REBUS authors do not discuss this possibility directly, perhaps because such an argument presents a risk of circularity, since the relaxed priors would then become both the explanans and the explanandum. Given that the high density of 5-HT_{2A} receptors in primary visual areas, it is possible to hypothesise that a direct, local activation of 5-HT_{2A} receptors in these areas could cause an increase in excitability, leading to oscillatory dynamics, which would take shape and be experienced based on the local retinotopic architecture. Importantly, a direct effect of the 5-HT_{2A} receptor in visual areas would also provide an explanation for why psychedelic phenomenology presents such specific and prominent visual characteristic, whereas the effect of a generic relaxation of high-level priors could be expected to be largely modality-independent.

The REBUS model provides, as an example, an explanation for the classic psychedelic visual phenomenon of ‘breathing walls’, i.e. the psychedelic-induced illusory perception of regular motion in inanimate objects, which can be interpreted as a ‘breathing’ of sorts. The authors state that a psychedelic-induced reduction of confidence in the prior assumption that ‘walls don’t breathe’ could force extrastriate visual areas to negligently transmit farther up the hierarchy an “increased signalling arising from lower-level units”, which would then be interpreted as breathing walls. In this example, it remains unclear what the source of “increased signalling” would be; and more importantly, it is left unsaid why *this specific prior* should be so robustly relaxed by psychedelics, and not one of the many others that might be available regarding walls (for example, why not ‘walls don’t emit peculiar smells’ or ‘walls don’t emit peculiar sounds’). Notably, these objections may be addressed by integrating the REBUS model with considerations on visual-spatial geometry and oscillatory neural dynamics. The structural harmonics of an object are its fundamental spatial patterns of resonance,

much like the modes of vibrations of a guitar string; mathematically, the harmonics are the basis of the Fourier transform, and the eigenfunctions of the Laplacian operator. In one-dimension, such as on a guitar string, they are sinusoidal waves; in higher dimensions or more complex objects, such as connectome graphs, they take more complex shapes (Atasoy et al., 2016, 2018). Consider a retinotopic region of interest such as V1, approximated as a flat surface,² it is possible to show that temporal oscillations of pairs of harmonics would determine neural dynamics indistinguishable from the representation of spatially moving objects (Supplementary Materials); even though there are no actual moving objects, but only simple temporal oscillations of structural harmonics. Is it plausible to propose that psychedelics would alter the harmonic-temporal patterns of brain dynamics? Indeed, existing evidence shows that psychedelics robustly alter temporal oscillations in occipital brain regions (Kometer et al., 2013; Timmermann et al., 2019), shifting the relative balance of temporal power away from the normally dominant alpha, and towards other frequencies; as well as the harmonic spectrum of global brain activity (Atasoy et al., 2017; Luppi et al., 2021a), shifting the balance of spatial power in favour of higher harmonics, i.e. harmonics of higher spatial frequencies. Hence, a parsimonious bottom-up account of the ‘breathing walls’ phenomenon could be provided by a psychedelic-induced excitation of specific harmonic-temporal oscillations in visual areas, which would be experienced as illusory motion, and could be interpreted by high-level systems as a ‘breathing’ of sorts when superimposed to the visual input of inanimate objects such as walls.

Another highly influential model describing the effect of psychedelics on brain dynamics, focusing on the role of the thalamus in the ‘gating’ of sensory stimuli, is the cortical-striatal-thalamic-cortical (CSTC) model (Vollenweider and Geyer, 2001). Briefly, in the CSTC model, a reduced thalamic gating is posited to allow sensory information to inundate the cortex, leading in turn to the cascade of effects that comprise psychedelic phenomenology (Vollenweider and Preller, 2020; Vollenweider and Smallridge, 2022). While this model may appear antithetical to REBUS, since one chiefly focuses on subcortical levels and the other on the highest cortical levels, both share their roots in Huxley’s hypothesis that psychedelics would generically relax constraints on the brain as a ‘reducing valve’ (Huxley, 1954). The main difference is in the placement of the valve: at the highest levels, in the form of top-down priors, in one model, and at the lowest levels, in the form of thalamic gating, in the other. Hence, the issue of unspecificity also appears to be present the CSTC model: the specific phenomenology of psychedelic visionary states implies that they cannot easily be captured as ‘nonspecific amplifications’ of ungated external sensory input. Additionally, the CSTC model was developed in an explicit analogy between psychedelic states and schizophrenic psychosis; in the past decades, this analogy has been largely abandoned. Other classes of substances, such as amphetamines or anticholinergic hallucinogens, are now considered more fitting analogues for the sensory symptoms of schizophrenic psychoses, which tend to be far more often of an auditory nature, in contrast with the specificity and predominance of visual alterations in psychedelic phenomenology. Hence, while we share with the proponents of the CSTC model the proposal for a role of low-level sensory dimensions in causally influencing high-level effects, we suggest that this model, much like REBUS, could benefit by integrating domain-specific aspects of psychedelic phenomenology, and corresponding low-level cortical dynamics.

This is not to say that all psychedelic sensory phenomena arise entirely via bottom-up cortical dynamics, nor that top-down processes do not impact subjective experience: somewhat in contrast with the REBUS proposal, the influence of sociocultural factors, beliefs, and personal expectations on psychedelic experience has long been

² For simplicity; a more complex and realistic structure would not change the principle demonstrated here.

recognized (La Barre, 1938; Wallace, 1959; Dobkin de Rios, 1984; Reichel-Dolmatoff, 1972, 1975; Díaz, 2010; Hartogsohn, 2020; Dupuis, 2021). The key point here is that bottom-up effects of psychedelics are unlikely to be entirely byproducts of top-down processes, but rather might be caused by a direct involvement of psychedelics in low-level sensory areas; and that the two are likely to exist in a dialogical interplay, where low-level processes also play a causally relevant role in influencing high-level effects. In this sense, it is important to note that psychedelic alterations in low-level sensory dimensions of experience occur temporally earlier, and at lower doses, than alterations in high-level dimensions; and even earlier than emotional alterations (Knauer and Maloney, 1913; Reichel-Dolmatoff, 1975; Shanon, 2002; Preller and Vollenweider, 2016; Griffiths et al., 2016; Timmermann et al., 2019). What could one expect to be the impact on of an extremely intense, novel, unpredictable sensory experience on preexisting high-level priors? More specifically, what about an experience of immersive visual content of highly non-naturalistic (abstract) character, not relayed by subcortical structures, but rather instantiated directly at the cortical level,³ such as is experienced during a high-dose psychedelic state? Given that high-level priors are built via a lifetime of naturalistic sensory stimuli, we predict such an experience would lead to a profound alteration of the brain's model of what visual input is 'supposed to look like'; and given the particularly significant impact of visual input for the development, maintenance, and revision of these constructs, of what the world is; as a consequence, such an experience might trigger a revision of beliefs even at more abstract levels, bordering into the metaphysical, as is indeed the case for psychedelics (Timmermann et al., 2021). High-level systems could react to such a shock of novelty by broadening and flattening their expectations on the range of possible experiences; and by attempting (while not necessarily succeeding at) the crucial task of integrating the newly available information into a coherent world-model narrative, as the experience progresses and subsides. In other words, we suggest that psychedelic-induced activity in sensory regions might, to some extent, causally underlie the relaxation of high-level priors described by the REBUS model; and in particular, the specific characteristics (e.g. non-naturalism) of information encoded in psychedelic-induced low-level sensory activity may play a crucial role in this sense (see also Sec. 3). Furthermore, this need not be the only way in which psychedelic-induced sensory alterations impact high-level dimensions in a bottom-up fashion. For example, the increased sensitivity to sensory stimuli (i.e. the 'setting'), already effected at medium and low doses, might significantly increase the correlation between the external and internal state models, and by this virtue underlie the psychedelic sense of connectedness (when positively interpreted) or feelings of anxious ego dissolution (when negatively interpreted), with the direction of interpretation likely depending on existing priors (i.e. the 'set'), in top-down manner.

In other words, we suggest that top-down and bottom-up processes amalgamate to produce the complexity and variety of psychedelic experience. Disentangling the underlying brain dynamics is an open and challenging empirical question; to begin addressing it, the study of the visual system may represent a valuable beachhead (Heeger et al., 2017). For example, an important dimension in the space of psychedelic-induced hallucinations ranges from abstract ('simple') to figurative ('complex') content. While both may feature in psychedelic states, they are likely to rely on different mechanisms, and hence may be differentially represented in brain dynamics. In particular, abstract visual hallucinations are more likely to arise bottom-up, due to the intrinsic anatomical and functional properties of neural dynamics in

low-level visual areas (Bressloff et al., 2002; Cowan, 2014), and indeed are reported cross-culturally. On the other hand, figurative hallucinations often include content and themes that are specific to the individual (e.g. personal life events) and their culture (e.g. deities or spirits of the local religion) (Dupuis, 2021). Memories, beliefs, expectations, intentions, sociocultural factors can powerfully shape the content and interpretation of figurative hallucinations, implying the involvement of top-down mechanisms of attention (preferentially directed to aspects of visual experience that are deemed important for the individual and their culture), and the persistence of (at least some) high-level priors. Hence, the investigation of abstract and figurative visual hallucinations could provide a window into the processes and brain areas involved in the interplay of top-down and bottom-up dynamics of psychedelic experience. A potential route in this sense may be the combination of detailed phenomenology of visual experience, neuroimaging data, and recent computational approaches which have allowed, to an extent, the reconstruction of subjective visual experience from brain activity in different areas (Nishimoto et al., 2011; Van Bergen et al., 2015; Huth et al., 2016).

In sum, we contend that psychedelic-induced alterations of low-level sensory dimensions of experience are unlikely to be entirely a consequence of top-down effects, but rather coexist in a dialogical interplay with, and in some cases may causally underlie, alterations in high-level dimensions of experience. Hence, alongside considering the top-down > bottom-up direction of causality, accounting for the converse bottom-up > top-down direction, including the visual specificity of psychedelic phenomenology, appears as a necessary step for the extension of existing models.

3. Questionnaires and therapeutics

The Altered States of Consciousness [ASC] questionnaire is one of the most widely used instruments for the measurement of alterations of subjective experience (Dittrich, 1998; Studerus et al., 2010; Preller and Vollenweider, 2016). Importantly, the ASC questionnaire spans a variety of dimensions of subjective experience, including both low-level sensory and high-level cognitive components; other questionnaires, such as the Mystical Experience Questionnaire [MEQ] (MacLean et al., 2012; Barrett et al., 2015), do not allow a direct comparison between these different dimensions, since they focus on a singular construct. Clinical studies employing the ASC have shown that high-level dimensions of experience provide good predictions for therapeutic outcomes, better so than low-level dimensions (Roseman et al., 2018). This is supported by studies employing the MEQ, which have found positive correlations of mystical experience dimensions with therapeutic outcomes (Barrett and Griffiths, 2017; Griffiths et al., 2016). Low-level ASC dimensions still show positive correlations with therapeutic outcomes, albeit more weakly than high-level dimensions (Roseman et al., 2018); interestingly, one study investigating the efficacy of ayahuasca in the treatment of depression and employing a different questionnaire, the Hallucinogen Rating Scale (Riba et al., 2001), found intensity of perceptual experience to be a significant predictor of remission in people that responded to treatment (Palhano-Fontes et al., 2019). Hence, the existing evidence speaks in favour of the primacy of high-level dimensions for the prediction of therapeutic outcomes; but also hints at a possible concurrent role of low-level dimensions.

Despite the valuable dimensional inclusivity of the ASC, a notable asymmetry is present between its low-level and high-level dimensions: high-level dimensions have far greater phenomenological specificity, and crucially, they have clearly distinct and built-in emotional valence, as opposed to low-level dimensions, which are broad in scope and emotionally unchanged. The high-level dimensions of the 5D-ASC, pertaining mainly to alterations in the sense of self, are dubbed 'oceanic boundlessness' and 'dread of ego dissolution'. These dimensions attempt to capture specific aspects of experience; and the distinction of opposite emotional valence is stark and directly embedded in the dimensions.

³ Note that this dynamic is distinct, while not incompatible with, the CSTC model, which proposes a reduced gating of incoming sensory inputs going through the thalamus; content instantiated directly in the cortex, for example the visual phenomena described in the previous section and simulated in Supplementary Materials, would be *gateless*.

Conversely, the main sensory dimensions ('visionary restructuring' and 'auditory alterations') do not attempt to distinguish specific kinds or aspects of experience, but rather measure the strength of a generic alteration of a dimension of experience; and crucially, they lack any distinction based on emotional valence. In the 11D-ASC (Studerus et al., 2010), a more recent and improved variant of the original 5D-ASC, the first issue is ameliorated by an increased phenomenological specificity of sensory dimensions, which come to include distinct 'simple' and 'complex' dimensions for visual hallucinations; but even in the 11D-ASC, there is no additional possibility to capture specific content, themes, and crucially, emotional valence is not embedded in sensory dimensions. On the other hand, the high-level dimensions of the 11D-ASC ('spiritual experience', 'insightfulness', 'experience of unity', 'impaired control and cognition') are still more phenomenologically diverse than low-level dimensions, and are still embedded with a clear emotional valence.

This asymmetry has important consequences for the interpretation of results based on the ASC questionnaire. Subjective experience is integrated: a person engrossed in the vivid sensory experience of a complex, realistic, nightmarish hellscape would not, in most cases, be simultaneously reporting a blissful experience of oceanic boundlessness. However, because of the asymmetry in the ASC dimensions, this will not be reflected by the questionnaire results: two people who experienced visual hallucinations of similar intensity, but opposite in terms of content and emotional valence, will not be distinguished by the ASC questionnaire on the low-level dimensions; however, they will be clearly separated on the high-level dimensions, which carry distinct emotional valence. Furthermore, many of the high-level dimensions often have sensory components: for example, spiritual experiences can take the form of visions of angels, entities, the universe as a whole, or simply the white light; emotional, cathartic moments can be sparked by vividly re-experiencing personal memories; insights can involve a strong moment of imagination in which the insight is seen, before being consciously understood (Shanon, 2002). Many of these low-level aspects of experience will be diluted in ASC results, and often implicitly integrated in high-level dimensions. Interestingly, in the construction of the 11D-ASC, Studerus et al. noted that "the 'oceanic boundlessness' and 'visionary restructuring' factors could be combined on a high level of the construct hierarchy" (Studerus et al., 2010), hinting at potential unexplored relationships between low-level and high-level dimensions of experience; and other authors have already pointed out that high-level constructs, such as the sense of self, arise via a multidimensional integration which includes low-level sensory aspects (Millière et al., 2018; Luppi et al., 2021b). Aside from the development of more balanced questionnaires, one route to address these limitations is via qualitative and quantitative analyses of narrative self-reports; indeed, existing studies in this sense have reported a prominent presence of sensory themes (Breeksema et al., 2020; Zamberlan et al., 2018; Ballentine et al., 2021). In sum, a critical examination of existing questionnaire studies provides an additional line of evidence for the underappreciated role of low-level sensory dimensions in psychedelic experience and therapeutic outcomes, which may be addressed by employing methods that are more faithful to the phenomenological richness of psychedelic states.

3.1. Testable hypotheses for the potential therapeutic roles of psychedelic-induced visual hallucinations

A natural question at this point concerns whether there is any potential causal role for low-level sensory dimensions of experience in psychedelic therapeutics. While the ongoing development of novel 'non-hallucinogenic psychedelics' may certainly be an appealing business model and lead to valuable outcomes, we contend that the role of sensory dimensions in psychedelic therapeutics is far from exhaustively understood. In particular, some authors have suggested the sense of awe as a possible key mediator of psychedelic therapeutics (Yaden et al., 2019; Hendricks, 2018); in the absence of pharmacological agents, the

sense of awe is often elicited by sensory - particularly visual - stimuli (Shiota et al., 2007; Chen and Mongrain, 2021). Hence, rather than occurring 'in a vacuum', it seems plausible that the sense of awe may also be elicited by low-level sensory alterations in psychedelic experience. For example, a highly intense and immersive experience of geometric visual hallucinations might trigger a feeling of aesthetic, and even spiritual, awe; it is perhaps not surprising to note in this sense the presence of abstract, concentric motives - reminiscent of psychedelic-induced geometric hallucinations - in many traditions of religious art. The experience of awe is also known to be characterized by a reduction in the sense of self (Keltner and Haidt, 2003), a feature of psychedelic experience which is thought to be of major therapeutic value, but also generally considered unrelated and independent from low-level sensory dimensions; instead, we suggest that psychedelic-induced sensory alterations might, to some extent, causally underlie alterations of high-level constructs, such as the sense of self. Interestingly, the perception of awe-inspiring visual stimuli includes stronger DMN deactivation among its neural correlates (Van Elk et al., 2019). Furthermore, considering their immersive, non-naturalistic and abstract character, geometric hallucinations of sufficient intensity (such as those experienced during a DMT peak) may directly produce a disruption of the sense of reality. Indeed, the feeling of being transported to a realm 'other' than everyday reality, 'seeing through the matrix', or 'lifting of the veil' experiences, are common narratives in high-dose psychedelic trip reports. Notably, such experiences are often reported to feel 'more real' than everyday reality; in a sense, this intuition might be correct. Not in the literal sense that psychedelics would allow us to peer at an external, supernatural reality; rather, in the sense that they could allow us to peer at the structure of our own systems of perception, revealing the nature of our everyday reality as far more contingent and less objective than we normally think; in turn, this process could trigger reflections on high-level concepts pertaining to the relations between self and world, reaching the highest metaphysical levels (Timmermann et al., 2021). It is interesting to note that some reports describe the psychedelic experience as *less* real than everyday reality - like a movie or a cartoon. It seems plausible that, when interpreting psychedelic visual experiences, top-down effects of culture, expectations, and prior beliefs may still play a key role, leading to diverging interpretations. Crucially, note that in both these seemingly opposite interpretations ('more real' or 'less real'), the psychedelic experience is still most often judged as *other* than, and distinct from, everyday reality. Unlike the experience induced by deliriant hallucinogens, rarely (if ever) a psychedelic experience is confused with everyday reality (Fortier, 2018). A parsimonious explanation for this may be that the low-level sensory content of psychedelic experience - in particular abstract, geometric hallucinations - is unlikely to be confused with the percepts of everyday reality, because of its intrinsically non-naturalistic aspect. In other words, the specific content and visual characteristics of simple hallucinations might play a key role in determining alterations in the sense of awe (increased), self (reduced), and reality attributed to the experience ('other than everyday reality'); while the integration and interpretation of these experiences (e.g. 'more real' or 'less real') is likely to be influenced, in a top-down fashion, by prior beliefs and expectations.

Complex hallucinations - non-abstract visions of entities, objects, people, animals - can also be elicited by psychedelics. Note that 1) the binary distinction between simple and complex hallucinations is a simplification, and a scale varying in degree would be more appropriate; 2) 'simple' hallucinations are only simple insofar as they are of an abstract nature: they can be of extremely high intricacy and complexity in their own right; 3) the 'realism' of psychedelic complex hallucinations does not imply that they are taken at face value and confused with the percepts of everyday reality (Preller and Vollenweider, 2016), possibly because they often still contain a degree of the characteristic geometric patterns of simple visual hallucinations. It is possible to hypothesise a role for complex visual hallucinations in the therapeutic effects of psychedelics; to some extent, this has been proposed before, e.g. (Kometer

and Vollenweider, 2016; Frecska et al., 2016), but it is worth revisiting this idea in light of recent findings. Complex hallucinations elicited by psychedelics often contain subjectively meaningful elements (Dittrich, 1998; Studerus et al., 2011): for example, they might involve autobiographical memories of traumatic experiences, loved ones that passed away, childhood memories. The vivid experience of personally relevant sensory content, in the form of complex hallucinations, in combination with altered senses of reality, self, and awe, which we hypothesised may be elicited by simple visual hallucinations, could represent an important therapeutic mode of psychedelics. Of course, the subsequent, fruitful integration of these profound experiences into high-level narratives is also a crucial step for therapeutic outcomes, as well-documented by psychedelic therapy practice; but the role of sensory experience in the acute phase should not be disregarded. In this context, it is important to mention existing evidence suggesting that psychedelics do increase the attribution of meaning to otherwise neutral or meaningless stimuli, an effect which could be attributed to a purely top-down process (Preller et al., 2017). However, Preller et al. also report that, under the influence of psychedelics, stimuli that were personally meaningful before the experience remain far more meaningful than ones that were previously meaningless or neutral. Hence, it seems likely that the experience of personally relevant sensory content would have a higher chance to trigger therapeutically valuable revisitation, reappraisal, and subsequent integration, compared to personally-irrelevant content. In other words, the specific content, and in particular the personal relevance, of complex hallucinations experienced in the acute phase of psychedelic effects might hold the potential to unlock additional avenues for psychedelic therapeutics.

In sum, we contend that the constellation of therapeutic processes set in motion by psychedelics are unlikely to rely exclusively on mechanisms independent of subjective experience, or on nonspecific top-down processes, such as an increased attribution of meaning or relaxed priors. We argue that the sensory phenomena elicited by psychedelics are far from being ‘epiphenomenal byproducts’ and rather may constitute, if not the engine, at least a valuable propellant for psychedelic therapeutics. As an important caveat, we note that this is not to say that any and all sensory phenomena elicited by psychedelics will be relevant for therapeutic outcomes; nor that high-level processes do not play a crucial role, particularly at the stages of interpretation and integration of experience; our argument here is only that the available evidence does not warrant disregarding all sensory phenomena elicited by psychedelics, in particular visual hallucinations, as irrelevant for therapeutic outcomes. Specifically, we have hypothesised that simple hallucinations may contribute to psychedelic therapeutics by eliciting the sense of awe, and by triggering changes in the sense of reality and sense of self, in turn relaxing the normal bounds on these constructs; while complex hallucinations may allow the vivid revisitation of personally relevant sensory content, which may be reappraised during a critical period of shifted perspective (Lepow et al., 2021); both contributing significantly to the revision of high-level beliefs and narratives of self and world, bordering into the metaphysical (Timmermann et al., 2021).

4. Neuroimaging and pharmacology

Is the available neuropharmacological evidence consistent with a direct action of psychedelics in low-level sensory areas? PET and autoradiography studies have found high 5-HT_{2A}R binding and mRNA expression in the primary visual cortex (Beliveau et al., 2017; Burnet et al., 1995; Erritzoe et al., 2009; Ettrup et al., 2014; Hall et al., 2000; Lidow et al., 1989; López-Giménez et al., 2001; Pazos et al., 1987; Saulin et al., 2012; Watakabe et al., 2009; Zilles et al., 2002). 5-HT_{2A}R binding and mRNA expression were found in all cortical layers with high expression in layer V pyramidal neurons (Andrade, 2011; Burnet et al., 1995; De Almeida and Mengod, 2007; Lidow et al., 1989; López-Giménez et al., 1998, 2001; Pazos et al., 1987; Watakabe et al., 2009). Within the primary visual cortex (V1), highest expression of the

5-HT_{2A} receptor was found in layer IV (and not in layer V pyramidal neurons, as in the majority of other regions), the main input layer in the cortex, receiving direct sensory input from the lateral geniculate nucleus of the thalamus, which in turn receives input from the eye (Burnet et al., 1995; Lidow et al., 1989; López-Giménez et al., 1998, 2001; Pazos et al., 1987; Watakabe et al., 2009); furthermore, 3 hours of monocular deprivation (covering the eye) can lead to downregulation of 5-HT_{2A}R mRNA in layer IV of V1, suggesting V1 specific expression patterns of receptor mRNA are sustained by ongoing visual activity (Watakabe et al., 2009). Additionally, electrophysiological studies in animal models have indicated the involvement of the 5-HT_{2A} receptor in modulating responses to visual stimuli in the primary visual cortex (Shimegi et al., 2016; Michael et al., 2019; Azimi et al., 2020). Neuroimaging of the human visual cortex under the influence of psychedelics has revealed increased cerebral blood flow, increased correlations with the rest of the brain (Carhart-Harris et al., 2016), patterns of brain activity analogous to those recorded during the viewing of spatially localised stimuli (Roseman et al., 2016), and increased BOLD signal during an eyes-closed mental-imagery task (but not during eyes-open viewing of natural images) (de Araujo et al., 2012). Together, these findings provide a solid neuropharmacological basis for direct action of psychedelics in low-level sensory (and specifically visual) regions.

Next, we ask whether neuroimaging evidence is consistent with the underappreciated roles of psychedelic action in low-level sensory areas described in the previous sections. In this context, it is important to note that ‘resting-state’ is a term commonly used in neuroscience to denote brain imaging or recordings performed in the absence of a specific external sensory stimulus or cognitive task. The resting-state characterization is often also applied to recordings carried out under the influence of psychedelics, when there is no external stimulus or task (Drummond et al., 2022). However, the psychedelic state is one of rich sensory content: while an external stimulus may not be present, vivid and intense subjectively experienced sensory content most often is; importantly, any psychedelic-induced neural activity at lower levels of the brain’s functional hierarchy would likely be interpreted by higher areas, and thus experienced as, content-encoding activity. The presence of neural activity encoding sensory content is generally not taken into account by resting-state models and analyses, but it is an important caveat to be kept in mind when attempting to disentangle which aspects of high-level function are altered by the direct action of psychedelics, and which may be indirectly altered by activity in low-level sensory areas, alongside other important methodological considerations (Drummond et al., 2022).

The increase in functional connectivity (FC) between primary visual areas and the rest of the brain under the influence of psychedelics is a broadly replicated finding from psychedelic neuroimaging (Carhart-Harris et al., 2016; Mason et al., 2020; Müller et al., 2018; Preller et al., 2018, 2020; Roseman et al., 2014; Tagliazucchi et al., 2016). Carhart-Harris et al., (2016) interpret this finding as “a far greater proportion of the brain contributes to visual processing in the LSD state than under normal conditions”. However, since FC does not have a directionality, one could have also interpreted this finding as “visual processing contributes to a far greater proportion of brain dynamics in the LSD state than under normal conditions”. In other words, it is plausible to ask whether it is activity in early visual regions that becomes increasingly ‘broadcasted’ throughout the brain during a psychedelic experience, increasing its influence over global brain activity, rather than the other way round. This interpretation also seems to square better with the reduced influence of top-down priors prescribed by the REBUS model: assuming relaxed priors, the rest of the brain should presumably contribute *less*, not more, to low-level visual processing, while the converse should be true. Indeed, Alonso et al., (2015) found that, after ayahuasca administrations, oscillations in occipital regions increased their influence over signals measured at frontal locations, while oscillations at frontal sources decreased their influence over activity at occipital sites. An fMRI study by Preller et al. (2018) contrasted LSD, with

placebo, and LSD + ketanserin (a 5-HT_{2A} receptor antagonist). The main pattern observed is one of hypo-connectivity in high-level association networks, and a converse hyper-connectivity in low-level sensory and somatomotor networks; furthermore, notably, the two patterns are correlated: “participants with the highest LSD-induced coupling within sensory and somatomotor networks also showed the strongest LSD-induced de-coupling in associative networks. This suggests that LSD-induced alterations in information flow across these networks”. Roseman et al., (2016) found activity in visual cortices to be more dependent on its intrinsic anatomical (retinotopic) organisation during psychedelic effects, consistent with neural activity encoding anatomically-constrained, excitation-driven visual hallucinations (Cowan, 2014). Interestingly, brain-wide analyses have indicated that on a global level, brain-activity is less dependent on its anatomical constraints during the effects of psychedelics (Luppi et al., 2021a). This may be explained by proposing that activity in sensory (particularly visual) cortices, driven by 5-HT_{2A} activation and intrinsic anatomical constraints, becomes more widely broadcasted throughout the brain, which would then become globally less tethered to their own anatomy. In other words, the psychedelic state could be characterised as one of ‘seeing with the brain’, instead of ‘seeing with the visual cortex’, as we do under normal circumstances (de Araujo et al., 2012). Taken together, the available findings are consistent with the hypothesis that neural dynamics in sensory cortices during the psychedelic experience might exert far-ranging effects throughout the brain.

The decrease in power of alpha oscillations generated by occipital sources in the brain is another robust finding from ‘resting-state’ psychedelic neuroimaging (Muthukumaraswamy et al., 2013; Timmermann et al., 2019). In the absence of pharmacological alterations, alpha oscillations are prominent in occipital regions during eyes-closed resting-state, and are thought to subserve an inhibitory function; hence, the finding of psychedelic-induced reduction in alpha oscillations has often been interpreted as a reduced influence of top-down inhibitory processes in the visual cortex. However, the relationship between alpha oscillations and sensory content in the visual cortex is mutual: alpha oscillations suppress incoming inputs, but incoming inputs also strongly suppress alpha oscillations. In other words, the presence of neural activity encoding sensory content in the visual cortex suppresses the otherwise dominant alpha oscillations. Hence, it is important to at least question whether alpha power reduction observed under the influence of psychedelics is best modelled as a reduction of top-down effects, or whether the presence of neural activity encoding visual hallucinations could be the causal driver of suppression of occipital alpha oscillations. fMRI of the visual cortex under the influence of psychedelics has found it to be processing eyes-closed psychedelic imagery as if a visual stimulus was present (de Araujo et al., 2012) and spatially localized (Roseman et al., 2016); research on ayahuasca also highlighted a specific connection between suppression of alpha oscillations and the visual effects of psychedelics (Valle et al., 2016); and analysis of traveling brain waves during DMT experience found remarkable similarity with the dynamics observed during visual stimulation (Alamia et al., 2020), arguably making the DMT state more similar to one of highly intense and immersive visual stimulation, than to a resting-state with abolished alpha oscillations; if the psychedelic state was only or solely one of reduced top-down influence, causing an abnormal, nonspecific increase of permeability into consciousness of normal or close to normal bottom-up activity, perhaps one could expect a more clearly marked distinction with respect to the dynamics of traveling waves induced by regular visual stimulation. Together, these findings suggest the possibility that the alpha power reduction and changes in traveling waves observed in psychedelic states may be a consequence of the presence of content-encoding neural activity in visual areas.

The deactivation or ‘disintegration’ of the default mode network (DMN), and its correlation to dissolution of ego (or more broadly, reduction in the sense of self), is perhaps the most well-known finding from psychedelic neuroscience (Carhart-Harris et al., 2016).

Carhart-Harris et al. report a significant correlation of DMN disintegration with ego-dissolution (at a 0.05 level, with a p-val = 0.03). Notably, the correlation of ego-dissolution with the visual medial network is also close to significance at the same level (with a p-val = 0.07), closer to significance than all other RSNs aside from the DMN itself; and all three visual networks considered in the analysis show correlations with ego-dissolution in the same direction (Carhart-Harris et al., 2016) (Supplementary Materials), begging the question of whether the partitioning of visual areas into three separate networks might have diluted the correlation significance. Another milestone result of (Carhart-Harris et al., 2016) is a very significant correlation between the LSD-induced increase in V1 functional connectivity, and subjective ratings of both elementary and complex hallucinations. This is a seemingly straightforward finding to interpret, since classically visual areas of the brain are expected to be involved in subjective visual experience. To further understand the relations between imaging measures and subjective experience, in Table S7 the authors evaluate the specificity of the correlations between changes in functional connectivity and different dimensions of subjective experience. No significant difference is found between the correlation of increased V1 FC with elementary imagery and that with several high-level dimensions of the ASC questionnaire. In other words, *the correlation between increased V1 FC and elementary hallucinations is not significantly different from the correlation between increased V1 FC and high-level dimensions of subjective psychedelic experience such as experience of unity, spiritual experience, and insightfulness*. This is echoed by an independent analysis of the VAS scale: the correlation between increased V1 FC and elementary visual hallucinations is found to be significantly different from the correlation between increased V1 FC and complex hallucinations, positive mood, emotional arousal; but it is not found to be significantly different from its correlation with ego-dissolution. Taken together, these findings suggest that the effects of psychedelics on the DMN (and subjectively, on the sense of self) may be related to alterations in low-level sensory areas.

Could the effects of psychedelics at the highest levels of the brain’s functional hierarchy be causally influenced by low-level alterations? In light of the considerations presented in the previous sections, and of the characteristics of the DMN, this is perhaps not a completely implausible proposal. The DMN is a demand-negative network: it deactivates in the presence of tasks or sensory stimuli. Ordinary tasks and ordinary sensory stimuli deactivate the DMN in the ordinary, functional way that we are all subjectively familiar with from everyday life, temporarily diminishing one’s narrative, self-centred, ruminating focus. What would an astoundingly intense, highly unpredictable, highly novel, gateless⁴ sensory experience do to the DMN? Perhaps, not just ordinarily deactivate it, but effectively disrupt it to a much more profound degree, leading not to a brief decrease, but to a unique disintegration, and possibly to a complete loss of the sense of self. In other words, psychedelic-induced low-level sensory activity may causally contribute to the DMN deactivation, and related alterations of the sense of self; it is perhaps then not surprising to note that sensory overload has been employed in ancient and modern routes to loss of self, from shamanic traditions to rave parties. Furthermore, interestingly, recent empirical work on large-scale fMRI datasets has revealed a visual-spatial organisation of the DMN (Szinte and Knäpen, 2020); and recent theoretical work has provided hypotheses of ways in which low-level sensory experience could affect high-level constructs like the sense of self, from an information-theoretic perspective (Luppi et al., 2021b). Together, these findings suggest that future models could benefit from taking into account alterations in low-level sensory areas when attempting to describe psychedelic effects on global brain dynamics and high-level dimensions of experience.

In sum, the available evidence from pharmacology and

⁴ Not reaching the cortex through the thalamic gate, but rather directly instantiated in cortical neural dynamics.

neuroimaging provides a solid basis for a direct and specific effects of psychedelics in sensory (particularly visual) brain areas, and is consistent with the hypothesis of underappreciated causal relations between brain dynamics in low-level sensory regions, and high-level dimensions of psychedelic experience. In particular, activity in low-level areas may causally contribute to key features of psychedelic states, such as DMN deactivation and reduction in sense of self.

5. Conclusion

Classic psychedelics are currently thought to induce a mode of brain activity and subjective experience characterised by reduced top-down, and increased bottom-up dynamics. However, there is no universal agreement on how this state is achieved, nor on the mechanisms underlying their therapeutic benefits. In Sec. 2, we argued that influential contemporary models present largely nonspecific accounts of psychedelic effects, which do not fully account for the specificity of psychedelic phenomenology, and we provided considerations pertaining to the role of neural dynamics in visual cortices (see also [Supplementary Materials](#)); in Sec. 3, we discussed how asymmetries in existing questionnaires may have confounded the causal influence of low-level sensory dimensions on high-level dimensions and therapeutic outcomes, and presented hypotheses for the potential therapeutic roles of psychedelic-induced visual hallucinations; in Sec. 4, we examined evidence from pharmacology and neuroimaging, showing that it is consistent with an underappreciated role of sensory regions and networks in psychedelic brain dynamics.

In sum, we contend that psychedelic-induced alterations of seemingly distinct dimensions of experience do not occur ‘in a vacuum’ with respect to each other, but rather are intertwined in a dialogical interplay. As influential contemporary models have described the influence of high-level alterations on low-levels ([Carhart-Harris and Friston, 2019](#)), so we argue that low-level alterations are also likely to causally influence high-levels, and that extending existing models will require explicitly accounting for both causal directions. In particular, we contend that reevaluating the currently underappreciated role of sensory dimensions in psychedelic states will be highly valuable for neuroscience and clinical practice. We conclude that integrating the domain-specific and nonspecific aspects of psychedelic dynamics, as well as unraveling causal connections between seemingly unrelated dimensions of experience, is a necessary step to further understand how these remarkable compounds effect both acute and long-term therapeutic (or possibly harmful) changes in the human brain.

CRedit authorship contribution statement

Marco Aqil: Conceptualization; Investigation; Software; Visualization; Writing - original draft; Writing - review & editing. Leor Roseman: Conceptualization; Investigation; Supervision; Writing - review & editing.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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