12-2024

Relaxed Beliefs After Psychedelics: From Sensory Processing to Mystical States

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Relaxed Beliefs After Psychedelics: From Sensory Processing to Mystical States

by

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

in the College of Arts and Sciences

Georgia State University

2024

ABSTRACT

This dissertation explores the lasting impact of psychedelic use on brain networks, ranging from basic sensory processing to abstract mystical experiences. Recent research has highlighted the potential of these substances for treating psychiatric disorders, with therapeutic effects persisting weeks after a single dose. We focus on serotonergic psychedelics such as psilocybin and LSD, which are 5-HT_{2A} receptor agonists, and the 5-HT_{1A}-selective psychedelic 5-MeO-DMT. Through human electroencephalography and mouse electrophysiology, we explore how psychedelic use alters sensory processing and behavior. Using visual oddball and saccadic prediction paradigms, our findings demonstrate that recent 5-HT_{2A} psychedelic use weakens top-down modulation and increases bottom-up signaling in visual cortical circuits. In our human participants, we observed reduced express saccade production and a generalization of prediction errors (deviance detection). Mouse studies reveal similar alterations, with disrupted deviance detection during the acute psychedelic experience and enhanced bottom-up drive persisting for days. These findings support the 'Relaxed Beliefs under Psychedelics (ReBUS) Model' by demonstrating that 5-HT_{2A} psychedelics shift the balance from top-down to bottom-up information flow in sensory cortical circuits. Recent 5-MeO-DMT users displayed similar changes in saccade production but showed unaltered deviance detection, suggesting circuit-specific effects. Further distinct effects of 5-HT1A and 5-HT_{2A} psychedelics were revealed in our resting-state global dynamic functional connectivity analysis. Recent 5-HT_{2A} psychedelic users tended to shift between states more frequently and occupy hyper-connectivity states, while recent 5-HT_{1A} users tended to occupy hypo-connectivity states. The distinct effects of 5-HT_{2A} and 5-HT_{1A} psychedelic use on sensory processing and brain network dynamics highlight unique mechanisms of 5-MeO-DMT that warrant further investigation. Additionally, we review mystical experiences across

various induction methods. Based on shared phenomenology, consequences on beliefs, and some shared neural correlates, we propose the ReBUS model as a framework for understanding mystical experiences beyond just psychedelics. Finally, we emphasize the critical role of context in shaping 5-HT_{2A} psychedelic outcomes, discussing the concept of the "matrix"—the post-acute environment—as crucial for consolidating belief changes.

INDEX WORDS: Psychedelics, Predictive Processing, Belief Updating, Deviance Detection, Sensory processing, Saccades

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December 2024

DEDICATION

To my daughter Liliana, whose presence brings endless joy and inspiration. May this research serve as a reminder to never lose your childlike wonder. And to anyone struggling with their mental health, may you find hope and healing in the realization that psychedelics can change the world by transforming your perception of it.

"If the doors of perception were cleansed, everything would appear to man as it is, infinite."

— Aldous Huxley

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to the following individuals and groups who have supported me throughout my research journey:

To my mentors, Jordan Hamm and Neil Van Leeuwen. Your expertise and guidance have been invaluable. Jordan, your support and insights have guided me through the complexities of my research, helping me grow as a scientist and realize my full potential. Neil, you taught me the importance of making bold claims, provided I can back them up with solid reasoning and evidence.

To my committee members, Jessica Turner and Albert Garcia-Romeu, whose expertise and support have been indispensable to my work.

To my lab-mates, past and present, who have been an integral part of my journey: To Annabel Duran, for being an incredible right-hand woman and the embodiment of joy. Your ability to connect deeply with people from all walks of life is truly admirable. To Georgia Bastos, my co-author and friend, for always entertaining my wildest ideas and providing invaluable insights that have shaped our research. To Anna Radar, for your friendship and support. Your attention to detail, proactive attitude, and warm heart have been a constant source of inspiration. To all the other lab members who have contributed to a collaborative and enriching research environment. Your diverse perspectives and shared passion for science have made our lab a truly special place.

To my collaborator, Brad Baker, your time, dedication, and expertise were instrumental in bringing our resting-state connectivity data to life. You've been a wonderful collaborator, and I look forward to future work together.

To the Georgia State University Neuroscience Institute faculty for providing a supportive and intellectually enriching environment. Special thanks to Nancy Forger, Dan Cox, Chuck Darby, Anne Murphy, Emily Hardy, and Elizabeth Weaver for supporting my psychedelic research

journey. To my first mentor, Javier Stern, for your invaluable guidance during my first two years of graduate school. Your expertise and encouragement laid the foundation for my research career. To Alex Castillo-Ruiz, my “unofficial” mentor and friend. Your work ethic and compassion have been a constant source of strength and inspiration throughout my graduate school journey. You embody all the best qualities of a good mentor and scientist.

To my parents, Todd and Tammy West, and my sister, Cassidy Seuradge, for your wholehearted support and belief in me and my research. Your encouragement has been a driving force behind my academic pursuits.

To my village, especially my mom and dad, mother-in-law Lisa Jacobs, sister-in-law Isabella Jacobs, and Aunt Amal Yacoub. Your support has made it possible for me to balance motherhood and my academic pursuits. To Maya Lemberg, thank you for helping me find my path and follow it.

And finally, thank you to my husband Andrew, whom I met during my first-year lab rotation in the Forger Lab. From my very first experiments, through studying for the qualifying exams, to engaging in countless intellectual conversations about my research, you have been an unwavering pillar of support. Your dedication to understanding my work and encouragement to pursue my passion mean the world to me. You believe in my potential to achieve great things. Your kindness, intelligence, and love have not only nurtured our daughter but also provided me with the strength and inspiration to chase my dreams. Thank you for being an amazing partner and an incredible father.

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1 INTRODUCTION

1.1 Overview

Psychedelics, with their profound ability to alter consciousness, have long been a source of fascination. Modern research is now revealing that these substances may offer novel therapeutic approaches by, in part, reshaping the brain's predictive processing framework[1,2]. Lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT), and psilocybin are examples of serotonergic psychedelics that have shown promising results in the treatment of various mental health and substance abuse disorders. While the evidence is particularly robust for their efficacy in treating depression, anxiety, and some forms of substance abuse[3–10], preliminary research also suggests potential benefits for conditions such as post-traumatic stress disorder, obsessive-compulsive disorder, and anorexia nervosa[11–15]. Further studies are needed to establish their effectiveness in these domains. What sets psychedelics apart from traditional pharmaceutical interventions is their therapeutic efficacy with very few doses[4,8,9,16,17]. These benefits are often accompanied by significant, lasting transformations to individuals' beliefs and cognitive perception[18–20]. However, the mechanisms underlying psychedelics' ability to provide lasting relief for such a diverse array of disorders remain imprecisely mapped out. Thus, elucidating the mechanisms that underpin their therapeutic potential is the central focus of this dissertation.

One prominent theory regarding the biological mechanism of psychedelics' therapeutic potential is couched within the predictive processing framework[1,21]. The predictive processing framework offers a unified account for how we make sense of novel, incoming information across multiple levels, spanning basic sensory inputs like vision up through higher-order cognition, such as our perception of self-identity[22]. In this framework, in order to infer the ever-changing structure

of our environment, the mammalian brain is constantly generating and updating internal models of our external world. The brain constructs these models using prior knowledge, beliefs, and experiences. Importantly, the context in which information is received plays a crucial role in determining whether that information is well-predicted or not. When sensory input aligns with the contextual expectations built from prior experiences and current environmental cues, it generates minimal prediction errors. Conversely, when information deviates from its contextual expectations, it results in larger prediction errors, signaling the need for model updating.

To illustrate this point, consider sensory perception. When visual sensory stimuli are detected, this bottom-up information is fed forward to the visual cortex. Simultaneously, higher brain regions send expectant predictions of that stimuli to visual cortex, where the top-down prediction and bottom-up sensory information are compared. Local cortical neuronal circuits compute the difference to generate prediction errors. Empirical evidence from oddball paradigm studies has shown that stimuli that are well-predicted generate small prediction errors, and therefore minimal neuronal activity in visual cortex[23,24]. Inversely, contextually novel, surprising, or deviant stimuli, that are not well-predicted, generate larger prediction errors, comprised of strong evoked neuronal activity[23,24]. These prediction errors are passed forward into hierarchies to signal the need to update the model so that future predictions can be made more accurately.

Predictive processing involves two key stages: deviance detection and belief updating. Deviance detection occurs when the brain identifies new or unexpected stimuli, while belief updating involves revising the internal models based on this new information. This process aligns with the free energy principle, which posits that the brain and all biological systems strive to minimize free energy (prediction errors) or entropy[25]. By continuously updating the predictions,

the brain's predictive information processing mechanisms work to minimize future prediction errors, reducing uncertainty and enhancing stability in its internal model of the world. Ultimately, this process of refining the internal model leads to a state where sensory inputs become redundant because the internal model is so accurate that it can predict sensory experiences with high precision[25].

The predictive processing framework has been proposed as a model for explaining multiple neurological disorders and psychopathologies[25,26]. For example, individuals with chronic depression may have overly rigid and heavily weighted prior beliefs that are negative and pathological, disrupting the balance between top-down predictions and bottom-up sensory information. Psychedelics may help by relaxing these overweighted priors, increasing sensitivity to novelty, and allowing for the revision of these negative beliefs[1]. This has yet to be studied systematically.

While directly investigating high-order cognitive belief updating can be challenging, studying predictive processing and belief updating at the more basic sensory processing level can provide valuable insights into the network activity and cortical dynamics underlying perceptual processes and the changes induced by psychedelic use. Crucially, research suggests that the belief updating mechanisms underlying low-level sensory beliefs may also be responsible for hierarchically updating higher-level cognitive beliefs[1]. The research presented in this dissertation contributes to the growing body of work that aims to elucidate the effects of psychedelics on deviance detection and belief updating, with a particular emphasis on the sensory cortices, as research in this domain may be more tractable experimentally and more translatable across species and paradigms. By investigating these fundamental processes at the sensory level, we lay the

groundwork for future studies that will further explore the far-reaching consequences of psychedelics on perception, cognition, and mental health. Furthermore, our experiments investigate these processes both during and beyond the acute psychedelic experience, allowing us to explore long-term changes rather than just immediate effects. Together, this approach provides more precise insights into the sustained impact of psychedelics. This line of research holds the potential to revolutionize our understanding of the brain's information processing mechanisms within the predictive processing framework and inform the development of novel therapeutic interventions that harness the unique properties of psychedelics.

1.1.1 Chapter Breakdown

The introduction of this dissertation will be divided into two chapters. In Chapter 1, I explore the predictive processing framework, focusing on key concepts such as Bayes' Theorem, the Bayesian brain hypothesis, and the free-energy principle. I examine neurophysiological markers related to deviance detection and belief updating, and introduce the neural mechanisms that underpin predictive processing in the visual system. Additionally, I discuss the oddball paradigm, a crucial experimental model for studying these processes[27].

Furthermore, I provide a brief overview of serotonergic psychedelics, discussing the phenomenology of the psychedelic experience and its effects on neural activity, perception, belief, and mental health[1,2,4,20,28,29]. This overview includes an exploration of the connection between disrupted predictive processing and various psychopathologies. Finally, I introduce the Relaxed Beliefs Under Psychedelics (ReBUS) model and the entropic brain hypothesis, which suggest that psychedelics alter information processing mechanisms within the predictive processing framework, potentially explaining their therapeutic effects[1,30,31].

Chapter 2 presents a narrative review that explores the phenomenology of mystical experiences, comparing those induced by psychedelics to those induced by meditation, near-death experiences, and breathwork. The review examines unity, a core feature of these experiences, in the forms of ego dissolution and encounters with seemingly divine or supernatural entities. It investigates the long-term impact of these experiences on individuals' metaphysical beliefs and worldviews. The chapter proposes that mystical experiences, regardless of induction method, may be underpinned by similar alterations in information processing. While acknowledging the complexity and diversity of mystical experiences, this review suggests that a unified framework for mystical experiences, based on the ReBUS model, could provide a valuable lens through which to empirically study these profound states of consciousness. By dedicating an entire chapter to this comprehensive review, I aim to provide a thorough background on the mystical nature of the psychedelic experience, the beliefs that emerge from it, and the relevance of these beliefs to the central themes of my dissertation, such as predictive processing and the therapeutic potential of psychedelics.

In **Chapter 3,** I present a pre-print of an original research paper I co-authored that investigates the effects of psychedelic use on deviance detection and belief updating in cortical networks using electroencephalography (EEG)[32]. In this study, we recorded data from psychedelic users and matched controls during two oddball tasks. The first task was the saccadic prediction task, a visual oddball task with guided saccades to predictable and unpredictable target locations. This task allowed us to separate out deviance detection and belief updating processes. The second, which was also conducted in mice given psychedelics, was a simpler visual oddball paradigm. By comparing psychedelic users to controls and drawing parallels with our rodent experiments, we

aimed to elucidate the neural mechanisms underlying the impact of psychedelics on specific cortical circuits involved in sensory-level predictive processing.

Chapter 4 is a pre-print of an original research paper exploring the effects of serotonergic 5-HT_{2A} psychedelics (i.e., psilocybin and LSD) and the 5-HT_{1A} psychedelic 5-MeO-DMT on resting-state Lempel-Ziv complexity (LZc), a measure of entropy, and dynamic functional connectivity (dFC)[33]. In this study, we recorded 5 minutes of EEG in three groups of participants: sixteen individuals who had used psilocybin or LSD within the previous fourteen days, fifteen individuals who had used the 5-MeO-DMT within the previous fourteen days, and sixteen age- and gender-matched controls. By comparing these three groups, we aimed to identify unique patterns of neural activity associated with different classes of psychedelics and their potential impact on brain function beyond the acute exposure period. Our study hypothesized that the 5-HT_{2A} psychedelic group would exhibit increased time in global hyper-connectivity states and more frequent transitions between states compared to controls, while the 5-MeO-DMT group, due to its distinct pharmacological profile, would show unique functional connectivity patterns, potentially opposing some effects seen in the 5-HT_{2A} group.

Finally, in **Chapter 5**, I discuss the broader implications of this research, exploring how our findings contribute to understanding the neural mechanisms underlying psychedelic experiences and their enduring effects on perception and cognition. This chapter examines the concept of "relaxed beliefs after psychedelic use" and its potential to explain both acute and lasting changes in information processing. I discuss the "afterglow" period and its neural basis, exploring how a generalization of prediction errors to novel and redundant stimuli may underlie enhanced present-moment awareness. This chapter also addresses the critical roles of context, integration,

and the post-acute "matrix" period in shaping therapeutic outcomes. I explore the ethical considerations for practitioners in handling mystical-type experiences and debate the necessity of subjective effects, both during and beyond the acute exposure period, for therapeutic benefits. Finally, I outline future research directions, emphasizing the need to investigate cascading effects on higher-order cognition, optimize integration processes, and further elucidate the relationship between acute experiences and long-term outcomes in psychedelic-assisted therapies.

1.2 Predictive processing

Predictive processing, proposed by Karl Friston, is a framework that aims to explain a diverse array of neurobiological processes such as action, attention, learning, and, most notably for this dissertation, perception[21,25]. This approach is deeply rooted in the Bayesian brain hypothesis, which posits that the brain operates like a statistician, constantly updating its beliefs about the world based on incoming sensory information[34,35]. Central to this hypothesis is Bayes' Theorem, a fundamental principle in probability theory that provides a mathematical formula for updating probabilities in light of new evidence. Developed by the 18th-century mathematician Thomas Bayes, the theorem calculates the likelihood of a hypothesis based on prior knowledge and new data[36]. In the context of the brain, this means that prior beliefs, or predictions, about sensory input are continuously updated in light of actual sensory information to minimize the difference between our brain's expectations and what is actually experienced.

Friston's predictive processing model extends this Bayesian approach by suggesting that the brain is a hierarchical prediction machine. At every level of neural processing, predictions about incoming sensory inputs are generated based on hierarchical models. These predictions flow downward through the neural hierarchy and are compared against actual sensory input. Any errors

in prediction are sent back up to refine the brain's models. Furthermore, this allows the brain to select relevant information to be processed. The brain conserves energy by filtering out well-predicted information (sensory inputs), which is not passed forward in the hierarchy, and only processing novel information that needs to be sent forward for updating. This dynamic interplay between prediction and sensation underlies our perceptual experience and allows for a fluid and effective interaction with our ever-changing environment.

1.2.1 Neurophysiological markers of predictive processing

Traditionally, in congruence with EEG and Magnetoencephalography (MEG), event-related potentials (ERPs) have been used to study predictive processing in the visual system. Two of these ERPs are visual mismatch negativity (vMMN) and P300. vMMN is a negative deflection in the ERP waveform that occurs in response to deviant (i.e., stimuli that are novel or surprising, or statistically unlikely based on the preceding redundant stimuli) stimuli, typically emerging around 150-250ms post-stimulus[37,38]. This component is thought to reflect the brain's automatic detection of deviant stimuli and is hypothesized to reflect prediction errors. On the other hand, P300 is an attention-dependent ERP, a positive deflection occurring approximately 300-600ms after stimulus onset. The P300 component is associated with the conscious processing of rare, task-relevant stimuli, reflecting the updating of mental models in response to prediction errors[39,40].

For the research presented in this dissertation, we opted to use time-frequency analysis instead of traditional ERP measures. Time-frequency analysis is an innovative approach that decomposes EEG data into both time and frequency domains, allowing for examining event-related changes in power and phase synchronization across specific frequency bands and time ranges[41]. Time-frequency analysis offers several advantages over traditional ERP measures. It is

less sensitive to temporal jitter and other stimulus-specific features, resulting in less noisy data[42], and is more adaptable to variations in electrode positioning within the brain and differences in stimulus presentation timing[43].

Time-frequency analysis also captures persistent oscillatory activity, revealing consistent patterns in frequency space despite variations in experimental conditions. This approach allows for a more nuanced understanding of neural dynamics, capturing transient changes and interactions that are not easily observed with traditional ERP measures[44]. Moreover, time-frequency measures have been shown to have larger effect sizes and be more heritable compared to traditional ERP measures in studies of auditory dysfunction in schizophrenia and psychotic bipolar disorder[45,46]. Importantly, time-frequency analysis still allows for distinguishing between deviance detection and belief updating processes, with early transient changes in low frequency band power reflecting deviance detection and later, sustained changes in high frequency bands being associated with belief updating of new information[47,48]. Furthermore, time-frequency analysis can be combined with connectivity measures such as Granger causality to investigate the directionality of information flow between brain regions, providing insights into which areas drive the observed changes in oscillatory activity[49,50]. Interestingly, distinct frequency bands play specific roles in the hierarchical processing of visual information[51]. This frequency-specific organization of information flow is thought to be crucial for predictive processing in the visual system[21,52,53].

The translational nature of the study presented in Chapter 3, which draws parallels between human EEG and mouse local field potential (LFP) recordings, further motivates our use of time-frequency analysis[54]. By comparing psychedelic users to controls and drawing parallels with our rodent research, time-frequency analysis enables us to elucidate the neural mechanisms underlying

the impact of psychedelics on specific cortical circuits involved in sensory-level predictive processing across species. The ability to examine activity in specific frequency bands at different time points allows for more precise comparisons between human EEG and LFP recordings in rodents. Our previous research using time-frequency analysis has yielded critical insights into the neural mechanisms of deviance detection and contextual processing, highlighting its utility in studying predictive processing in both health and disease[24,55–58].

In summary, while ERPs such as vMMN and P300 have historically been used to study predictive processing, the use of time-frequency analysis offers several advantages. It is sensitive to deviance detection deficits in disorders such as schizophrenia and provides a robust, translational framework for studying predictive processing across species. It captures both magnitude and phase information across frequencies, allowing for a more nuanced understanding of the neural dynamics and the distinction between deviance detection and belief updating processes. Furthermore, time-frequency analysis can be used to measure the directionality of information flow between regions, revealing the specific roles of distinct frequency bands in the hierarchical processing of visual information.

1.2.2 Saccadic prediction and visual oddball paradigms

Rodent research in our lab has demonstrated that predictive processing-based models of sensory processing dysfunction can be effectively applied to sensory oddball paradigms[58]. The oddball paradigm was first introduced by Squires, Squires, and Hillyard in 1975[27]. Since then, these paradigms have been widely used to study deviance detection across species and clinical populations[59–61]. In a typical oddball paradigm, participants are presented with a series of repetitive

"standard" stimuli interspersed with rare "deviant" stimuli. The deviant stimuli elicit distinct neural responses, such as those discussed in the previous section[27].

The research presented in this dissertation utilizes both the oddball paradigm and a more complex variant, the saccadic prediction task. In this task, different colored stars appear at one of eight locations marked by placeholders on the screen. The task includes three trial types: redundant trials, where the stimulus is presented repeatedly in the same location and color; deviant no-update trials, where the stimulus appears once in a new location and color, similar to the simple oddball paradigm; and deviant update trials, where the stimulus appears in a new location and color and continues to repeat, prompting the participant to update their beliefs. Color cues indicate whether the next stimulus will appear at a new location or the same location, allowing us to experimentally separate the neurophysiological processes related to deviance detection and belief updating.

Furthermore, saccade movements in this task serve as a behavioral measure of top-down influence and belief updating. The latency of saccades reflects the strength of prior beliefs about the location of upcoming stimulus. When the stimulus appears at an unexpected location, saccadic latencies increase, indicating a violation of predictions and the need to update one's internal model; inversely, faster saccades mean more top-down influence. This effect has been demonstrated in humans[62,63] and non-human primates[64].

In the research presented in Chapter 3, we employ both the visual oddball paradigm in mice and humans and the saccadic prediction task in humans to investigate the effects of psychedelic use on predictive processing at the sensory level. With this approach, we aim to elucidate the neural mechanisms underlying the impact of psychedelics on specific cortical circuits involved in generating and updating sensory-level predictions.

1.2.3 Neural mechanisms of predictive processing in the visual system

The oddball paradigm and its variants have been instrumental in uncovering the neural mechanisms that support predictive processing in the visual system. Recent research using time-frequency analysis has provided valuable insights into the neural mechanisms underlying predictive processing in the visual system. Studies have shown that visual mismatch negativity (vMMN), a neurophysiological marker of deviance detection, is primarily represented in the theta frequency band (4-7 Hz) and reflects increased theta power and phase locking to deviant stimuli[65,66]. Phase locking, which measures the consistency of neural oscillation phases in response to stimuli, is thought to reflect synchronous neural activity and bottom-up information flow[67]. Furthermore, during deviance detection, distinct oscillatory patterns have been observed in different cortical layers of the visual cortex. Increased high-gamma (70–80 Hz) oscillations in layer 2/3 (L2/3) and decreased beta (26–36 Hz) oscillations in layer 1 (L1) suggest differential engagement of cortical layers in predictive processing[58,68]. High-gamma oscillations are thought to reflect local processing, while beta oscillations may be related to long-range communication and top-down modulation within the visual cortex[51].

Our lab's research has further contributed to the understanding of predictive processing in the mouse visual cortex. Our proposed model suggests that during a visual oddball paradigm, the anterior cingulate area (ACa) sends contextual information to V1 via synchronized activity in the theta and alpha frequency ranges, specifically around 10 Hz[24,69]. This top-down input engages specific local inhibitory circuits in V1, primarily those involving vasoactive intestinal peptide-expressing (VIP) and somatostatin-expressing (SST) interneurons. The interplay between these interneurons leads to the disinhibition of a subset of pyramidal neurons (PYRs), priming them to

respond strongly to unexpected or deviant stimuli, thereby generating deviance detection (DD) responses[55].

The interplay between these interneurons is crucial for generating DD responses. Specifically, when a stimulus is repeatedly presented (i.e., becomes redundant), SSTs show decreased activity, a phenomenon known as stimulus-specific adaptation (SSA). This reduction in SST activity leads to a disinhibition of VIPs, which in turn show increased activity to redundant stimuli. Due to the known mutually inhibitory relationship between VIPs and SSTs, the increased VIP activity further suppresses SST activity[24]. The net result of this circuit interaction is a disinhibition of a subset of pyramidal neurons (PYRs), leaving them in a potentiated state, primed to respond strongly to unexpected or deviant stimuli[24].

Key findings supporting this model include the observation of enhanced ACa-V1 synchrony at 10 Hz during redundant stimuli[24,69], differential responses of VIP and SST interneurons to contextual information[55,58], and the disruption of both ACa-V1 synchrony and DD responses in V1 when VIP interneurons are suppressed[24]. This work provides a novel, testable framework for understanding how top-down predictions and local circuit interactions shape sensory processing and give rise to DD in the visual system. Having established a foundation for understanding the neural mechanisms of predictive processing in the visual system under normal conditions in mice, we can explore how these findings translate to humans using EEG and how psychedelic use perturbs this process. We will now turn our attention to serotonergic psychedelics and their potential to alter these processes, which may contribute to their therapeutic effects.

1.3 Serotonergic psychedelics

Serotonergic psychedelics, such as Lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT), and psilocybin, have demonstrated a unique and sustainable therapeutic potential for the treatment of mental health disorders such as depression and anxiety[4,7–10,70]. These psychedelics are unique in that they elicit long-term results in the treatment of these various psychopathologies with very few doses, typically in the context of psychological support[9,17,71,72]. With current research providing favorable results and the FDA repeatedly granting "Breakthrough Therapy Status," it is very likely that the popularity of these substances will continue to rise in therapeutic settings.

1.3.1 The psychedelic experience

The psychedelic experience is characterized by a profound altered state of consciousness, which is often mystical in nature, that can be both deeply meaningful[18] and challenging to articulate[73]. Despite the inherent difficulty in describing this altered state of consciousness, researchers have identified several consistent features that characterize the psychedelic experience, with the intensity of these features being dose-dependent[74].

One of the most prominent features is a profound sense of transcendence, where individuals feel they have surpassed the boundaries of their ordinary self and everyday reality. This is often accompanied by an intense sense of unity or interconnectedness with the divine, the universe, or all of existence – an experience frequently described as "cosmic consciousness". Encounters with seemingly autonomous entities, such as spirits, deities, or alien intelligences, are also reported, typically in high-potency experiences[75]. These entities often communicate insights or messages

that feel deeply meaningful or transformative to the individual. Psychedelic experiences are also characterized by vivid and intense sensory alterations, including intricate visual patterns, enhanced colors, and synesthesia, a blending of sensory modalities. Distortions in the perception of time and space are also prevalent, with many individuals reporting a sense of timelessness or a feeling that time has slowed down or sped up significantly[73]. On an emotional level, psychedelic experiences often evoke profound feelings of awe, wonder, and reverence, along with intense sensations of love and compassion. challenging emotions such as fear, anxiety, or paranoia can also arise, particularly at higher doses or in unsupportive settings. Moreover, set (mindset) and setting (external environment) are critical predictors of whether an individual will have a challenging experience, likely due to increased sensitization to sensory information during psychedelic experiences[76–78].

1.3.2 Consequences of the psychedelic experience on belief

The impact of psychedelics on belief is both complex and nuanced. Research indicates that these substances may profoundly influence an individual's perceptions of the self, reality, and the concept of God[20,28,75]. They are often associated with significant shifts in worldview, fostering increased open-mindedness, empathy, and a heightened sense of connection to and care for nature[18,79,80]. Additionally, psychedelic experiences may alter religious and spiritual beliefs, with evidence suggesting that both atheists and religious individuals often become more spiritual following such experiences[20,28,75]. This may provide people with a renewed sense of meaning and purpose in their lives and a decreased fear of death[17].

Psychedelics may promote the adoption of beliefs that are non-physicalist, such as the existence of realms beyond the physical world, the presence of a unifying principle beyond

material explanation, and the idea that consciousness or mind is fundamental to all things matter[20,28]. However, recent research presents conflicting findings. While there is a notable increase in mind attribution—where individuals ascribe greater levels of consciousness or agency to entities previously considered non-conscious[81]—significant shifts in metaphysical and spiritual beliefs may not always occur.

Notably, psychedelics can also alter an individual's perspective on future outcomes, fostering a more optimistic outlook that, additionally, aligns more closely with actual future outcomes[19]. This is particularly relevant for people struggling with depression, as psychedelics can help them develop a more evidence-based view of their future, countering the pessimistic and negatively biased predictions often associated with depression.

The observed shifts in belief and perspective highlight the potential of psychedelics to address the root causes of various mental health issues. By facilitating the relaxation of rigid, negative, and often distorted beliefs that permeate an individual's perception of themselves, others, and the world around them, psychedelics may promote a more flexible, adaptive, and realistic worldview. This, in turn, may contribute to the therapeutic benefits observed in psychedelic-assisted treatments for a range of mental health conditions, as individuals are able to break free from the confines of their pathological belief patterns and embrace a more well-balanced perspective. However, it is important to acknowledge that psychedelic experiences can also lead to the formation or reinforcement of delusional or problematic beliefs[82,83]. This underscores the importance of proper screening, preparation, and integration of psychedelic experiences to minimize the risk of adverse outcomes[84,85].

The relationship between psychedelic use and belief changes is complex and multifaceted. While some effects may be directly attributable to the pharmacological action of psychedelics, the influence of set (mindset) and setting (environment) cannot be overlooked. the context in which a psychedelic experience occurs, including pre-existing beliefs, expectations, and the physical and social environment, may play a crucial role in shaping subsequent belief changes. Additionally, the integration process following the experience may significantly impact how insights are interpreted and incorporated into one's belief system. A more in-depth exploration of the nature and implications of psychedelic-induced belief changes will be provided in Chapters 2 and 5 of this dissertation.

1.3.3 The mechanism of action of serotonergic psychedelics

The dramatic sensory and cognitive perceptual changes induced by psychedelics are thought to result from alterations in cortical dynamics[86]. Serotonergic psychedelics primarily exert their effects by binding to and activating serotonin 5-hydroxytryptamine 2A (5-HT_{2A}) receptors, which are excitatory postsynaptic G-protein coupled receptors primarily found on the apical dendrites of excitatory glutamatergic cells[87]. These receptors are highly expressed in cortical regions, particularly in layer five pyramidal neurons, which are involved in top-down signaling—from higher cortical areas to lower cortical and subcortical regions — and the integration of sensory information[88]. The subjective effects of psychedelics can be blocked in both humans and rodents by administering selective 5-HT_{2A} antagonists[89].

When psychedelics activate 5-HT_{2A} receptors, they lead to significant alterations in the structure and function of the cortex[90]. Activation of these receptors increases the excitability and alters the firing patterns of neurons, resulting in a cascade of downstream effects on cortical

activity and network dynamics[1,86]. One key effect of psychedelics is the desynchronization of cortical oscillations, particularly in the alpha and theta frequency bands associated with top-down control and the maintenance of stable perceptual and cognitive states[86].

Recent research suggests that psychedelics alter predictive processing by modulating the integration of top-down predictions and bottom-up sensory input[1,2,31]. Optogenetic stimulation of serotonergic neurons in the dorsal raphe nucleus (DRN), which activates 5-HT_{2A} receptors, has been shown to divisively suppress visually evoked responses in the primary visual cortex (V1) of mice[91]. This suppression is characterized by a reduction in response gain, which is applied evenly across both standard and deviant stimuli in a visual oddball paradigm while preserving the relative difference in response between the two stimuli. Furthermore, the activation of 5-HT_{2A} receptors differentially modulates ongoing spontaneous activity and visually evoked responses, suggesting a state-dependent alteration in the balance between top-down predictions and sensory inputs[91]. These findings provide insight into the potential mechanism by which psychedelic use disrupts normal visual processing within the predictive processing framework.

1.3.4 Psychedelics' effects on global network activity

The effects of psychedelics on global brain connectivity and network dynamics provide compelling evidence for their influence on sensory processing mechanisms. Psychedelics increase global integration, which refers to the enhanced functional connectivity between brain regions that are typically segregated, resulting in a more globally integrated state of brain activity[2,29,86,92–94]. Static functional connectivity analyses have shown that psychedelics increase connectivity between networks such as the default mode network (DMN) and the task-positive network (TPN)[94–96]. The DMN, associated with self-referential thinking, introspection, and ego dissolution,

is typically anti-correlated with the TPN, which is active during goal-directed tasks. Under the influence of psychedelics, these networks become simultaneously active, suggesting a breakdown of their normal antagonistic relationship[94–96]. This increased integration is thought to underlie the profound alterations in consciousness and perception reported during psychedelic experiences, such as the dissolution of self-other boundaries and a sense of unity and interconnectedness often reported during psychedelic experiences[95,97]. Conversely, psychedelics also induce global desynchronization, disrupting the typical synchronized patterns of neural activity[98]. This desynchronization reduces the usual coherence and temporal alignment of brain activities, meaning that while brain regions are more interconnected in terms of their connectivity, the synchrony, or the coordination of activity timing between these regions, is disrupted.

The entropic brain hypothesis, proposed by Carhart-Harris and Friston, offers a compelling framework for understanding the effects of psychedelics on network activity and information processing in the predictive processing framework[30,31]. This hypothesis suggests that psychedelics increase the entropy or disorder of brain activity, allowing for a greater diversity of neural states and more flexible cognition. In the context of the predictive processing framework, increased entropy can be understood as a reduction in the precision or confidence of prior beliefs, leading to a greater influence of bottom-up sensory information on perception and belief updating[30,31]. However, recent work by McCulloch *et al.* calls the entropic brain hypothesis into question, highlighting the need for a more nuanced understanding of the complex effects of psychedelics, and the challenges associated with interpreting neuroimaging data in this context[99]. Despite these critiques, the entropic brain hypothesis remains an influential and widely discussed model in the field of psychedelic research.

According to the entropic brain hypothesis, psychedelics disrupt the brain's normal hierarchical organization and the top-down flow of predictions by increasing the entropy of neural activity. This increased entropy is thought to correspond to a more flexible and open state of consciousness, in which the brain is less constrained by prior beliefs and more receptive to novel information. In this state, the brain may generate a broader range of predictions and be more likely to update its internal models based on prediction errors, potentially explaining the novel insights, enhanced creativity, and altered perceptual experiences associated with psychedelics[30,30,31].

The entropic brain hypothesis is consistent with empirical findings from static functional connectivity analyses. These analyses have demonstrated increased functional connectivity between typically segregated brain regions, suggesting a breakdown of the brain's modular organization[86,95]. Similarly, EEG studies have shown increased signal complexity and decreased alpha power, which may reflect a reduction in top-down control and a shift toward bottom-up processing[29,93,100].

Chapter 4 builds upon this foundation by examining LZc in the post-acute phase of psychedelic use. LZc is a commonly used measure of signal randomness or compressibility, providing an estimate of the diversity of patterns within EEG data[33]. By applying this measure to individuals who have previously used psychedelics, we can assess whether the increased neural entropy typically observed during acute psychedelic states persists beyond the immediate effects. Together with the findings on altered sensory processing presented in Chapter 3, this analysis of LZc contributes to a more comprehensive understanding of how changes in neural entropy may underlie the observed alterations in predictive processing and sensory information processing following psychedelic use.

Additionally, we investigate dynamic functional connectivity (dFC) in the post-acute phase of psychedelic use. dFC captures the time-varying properties of functional brain networks, revealing how they change and reconfigure over time[101]. We hypothesize that the increased entropy and bottom-up sensitization associated with psychedelic use may persist beyond the acute experience, leading to enhanced dynamic switching between brain states in the post-acute period. This enhanced dynamic switching may reflect heightened neural plasticity and belief updating following psychedelic[102]. Investigating dFC in the post-acute phase is particularly interesting, as it may provide insights into the mechanisms underlying the sustained therapeutic effects of psychedelics. By examining how brain networks reconfigure and interact over time after psychedelic use, we can better understand the neural processes that may support the relaxation of rigid beliefs and the exploration of alternative perspectives, which are thought to be key drivers of therapeutic change[1,30].

1.3.5 The ReBUS model and persisting effects of psychedelics

This ReBUS model posits that psychedelics induce a state of relaxed high-level beliefs or priors about the world. In this state, well-predicted sensory inputs that would normally be filtered instead propagate prediction errors up the hierarchy, allowing for the revision of broader predictive models. This allows psychedelics to temporarily loosen the constraints of hierarchical predictive models, potentially enabling the assimilation of new perspectives and experiences into our internal models[1].

The ReBUS model has particular relevance for understanding the therapeutic potential of psychedelics in treating conditions such as depression. In depression, individuals often exhibit rigid, negative beliefs about themselves, the world, and the future, which can be conceptualized as

overly strong, inflexible priors in the predictive processing framework. These beliefs are often accompanied by excessive self-referential thinking, rumination, and potentially a diminished ability to update one's internal models based on new contradictory information[103,104]. A compelling example of how psychedelics may facilitate the revision of these pathological priors comes from a study by Lyons and Carhart-Harris, which found that treatment with psilocybin fostered a more optimistic outlook in depressed individuals - an outlook that more accurately reflected their future circumstances[80]. Specifically, before treatment, depressed individuals exhibited a pessimistic bias, predicting future events to be worse than they actually turned out to be. After treatment with psilocybin, their predictions were more accurate and reflective of actual future outcomes[19]. This suggests that psilocybin enabled these individuals to revise their overly rigid, pessimistic beliefs and develop a more balanced, realistic view of the future - possibly by relaxing the grip of entrenched negative biases and enhancing mental flexibility. These findings align with the ReBUS model's proposition that psychedelics facilitate the relaxation of pathological priors, allowing for the integration of new, more adaptive information into one's worldview. By inducing a state of relaxed beliefs, psychedelics may create an opportunity for individuals to explore alternative ways of relating to themselves and the world, potentially leading to enduring shifts in perspective and alleviation of depressive symptoms[1].

Crucially, emerging evidence suggests that the impact of psychedelics on brain activity and predictive processing may persist beyond the exposure period. A recent study by Daws *et al.* found that psilocybin therapy for depression was associated with decreased brain modularity, reflecting increased global integration for up to 3 weeks post-treatment[2]. Moreover, this effect correlated with the magnitude of symptom improvement. The response to psilocybin was also associated with increased flexibility of higher-order brain networks involved in cognitive control, learning, and

task-switching. Suggesting that psychedelics may induce a prolonged period of heightened neural plasticity and belief updating following the exposure period[2].

This extended window of altered predictive processing and heightened sensitivity to new information is of particular interest to us as we aim to investigate the persistence of these effects beyond the exposure period. Understanding the time course and mechanisms underlying these prolonged changes in brain activity is crucial for optimizing the therapeutic application of psychedelics. As insightfully pointed out by Martin and Sterzer, the therapeutic success of psychedelics cannot be solely attributed to the temporary dissolution of one's sense of self during the acute experience[105]. Rather, the enduring benefits of psychedelic therapy likely depend on the guided formation of new, more adaptive self-representations in the aftermath of the psychedelic journey. Potential sustained alterations in predictive processing following psychedelic experiences highlight the importance of integration therapy and the individual's environment in shaping the long-term mental health benefits of these substances.

By focusing on the post-acute phase, our research aims to elucidate how psychedelics continue to influence perception, belief updating, and cognitive flexibility beyond the immediate effects of the experience. This knowledge will not only deepen our understanding of the unique therapeutic profile of psychedelics but also inform the development of targeted interventions and supportive environments that can maximize the potential for long-lasting, positive changes in mental health and well-being.

1.4 Conclusion

In conclusion, the studies presented in this dissertation aim to test the overarching hypothesis that *serotonergic psychedelics induce a prolonged period of belief updating following the acute exposure period, reflected by a transient relaxation of top-down modulation of bottom-up signaling.* In Chapter 3, we investigate the impact of serotonergic psychedelics, such as psilocybin and LSD, on visual processing and behavior. This chapter explores how these substances influence saccadic responses and deviance detection in both human participants and mice, particularly focusing on the potential shift from top-down to bottom-up processing in sensory cortical circuits during and after the acute exposure period. Chapter 4 builds on these findings by examining the effects of psychedelics on neural entropy and dynamic functional connectivity, aiming to provide a deeper understanding of the neural dynamics associated with 'relaxed' beliefs and cognitive flexibility after psychedelic use. Together, these studies offer comprehensive insights into the therapeutic potential of psychedelics across species and timescales, which are further contextualized in Chapter 5.

2 PREDICTIVE PROCESSING AS A UNIFYING FRAMEWORK TO EXPLAIN HUMAN CAPACITY FOR MYSTICAL EXPERIENCES

2.1 Introduction

Mystical experiences (MEs) have been widely reported across cultural and societal boundaries and belief systems throughout history. These experiences are typically characterized by an altered state of consciousness that transcends ordinary sensory perception and rational understanding[106], in which the experiencer reports a sense of connection, communication, and/or identification with a divinity or ultimate reality[107]. A defining feature of MEs is the temporary dissolution of the perceived boundaries between the self and the surrounding reality, leading to a sense of self-transcendence that can induce profound psychological transformations[108].

To quantify and study MEs empirically, researchers have developed and employed various psychological assessment tools such as Hood's Mysticism Scale, the Mystical Experiences Questionnaire, and variations of these[109,110]. For the purposes of this review, we will focus on MEs that, in the literature, have met the criteria outlined by these assessments and have been investigated using neuro-imaging techniques like functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Despite vastly different cultural frameworks and interpretations across religious and spiritual practices, these cognitively rich experiences frequently exhibit common phenomenological characteristics and potentially shared neural correlates.

MEs can occur spontaneously, in response to intense or emotional physiological states such as grief, childbirth, or near-death experiences[111,112], or through intentional practices and techniques designed to induce altered states of consciousness. Examples of such practices include fasting, isolation, pilgrimage, sensory deprivation, sleep deprivation, yoga, rhythmic

drumming/dancing/singing, meditation, and breathwork[113,114]. MEs may also be intentionally induced through the ingestion of psychedelic substances, termed PMEs, for psychedelic-induced mystical experiences[108,115]. While all MEs share characteristics of profound meaning, spirituality, and changes to self-perception, there are notable differences between PMEs and naturally occurring mystical experiences (NMEs)[108]. PMEs often have a clear onset and duration, beginning within seconds or minutes of ingesting the psychedelic substance and exhibiting dose-dependent and temporary effects[116]. In contrast, NMEs may require prolonged engagement in spiritual practices and can have less defined boundaries between the mystical state and ordinary consciousness. The strength or "completeness" of NMEs is also much more variable within and across different methods of induction[107,117,118]. PMEs, given their dose-dependent nature, seem to more reliably induce stronger MEs than NMEs[108,116].

In this review, we focus on three specific types of naturally occurring mystical experiences: near-death experiences, breathwork, and meditation-induced MEs. Near-death experiences refer to deep psychic, conscious, semi-conscious, or recollected experiences of someone who is approaching or has temporarily begun the process of dying[119]. These usually occur in life-threatening conditions[119]. Breathwork refers to controlled breathing techniques to induce meditative altered states of consciousness and changes in physiology through the combination of attentional guidance and spontaneous, deep, accelerated breathing[120]. Meditation-induced MEs are profound, altered states of consciousness that can occur during or as a result of intensive meditation practice that meet the criteria for mystical experiences as defined by the established measures discussed above[121]. It's important to note that we are not examining meditation practices in general but rather instances where deep meditative states have led to reported mystical experiences. These

MEs can occur across various meditation traditions and techniques, including but not limited to mindfulness, Zen, and Vipassana meditative practices[115].

Recent studies have begun to investigate the neural correlates and potential mechanisms underlying MEs. Due to their amenability to controlled experimental paradigms and translational relevance, psychedelic-induced mystical experiences (PMEs) have emerged as the most extensively investigated subtype of mystical experiences within the neuroscientific literature[3,18,73,84,110,116,122–124]. This research has revealed a complex and multifaceted picture of psychedelic effects, spanning molecular interactions, neural network dynamics, and profound alterations in cognition and perception. The ReBUS (Relaxed Beliefs Under Psychedelics) model is a proposed unifying model that aims to explain psychedelic brain action to integrate these diverse findings and provide a cohesive explanatory framework[1]. ReBUS is based on the predictive processing framework, which posits that the brain is constantly generating and updating internal models of the environment based on prior experiences and beliefs, which are updated in response to new information[21].

In this framework, information processing in the brain is conceptualized as an interplay between bottom-up (feedforward) and top-down (feedback) signaling. Bottom-up processing involves the propagation of sensory information from primary sensory areas to higher-order association areas. Conversely, Top-down processing involves the modulation of lower-level sensory processing by higher-order cognitive areas based on prior experiences, beliefs, and expectations. The integration of bottom-up sensory input and top-down modulation is crucial for how we perceive and interact with our environment. This integration allows the brain to compare incoming sensory information with existing internal models, detect prediction errors or novel information, and update these models accordingly. This process is fundamental to how we learn,

adapt, and respond to new or unexpected stimuli in our environment[25]. By applying this framework across multiple levels of information processing, from low-level perception to abstract reasoning, we can begin to understand how profound perceptual changes during MEs might lead to significant shifts in abstract beliefs, including those related to self-perception and worldview.

The ReBUS model suggests that psychedelics disrupt information processing by shifting the balance from top-down influence to bottom-up[1]. Psychedelics are thought to facilitate the revision of these internal models and beliefs by weakening top-down influence and allowing for a more flexible and open processing of bottom-up sensory information. ReBUS was initially proposed to explain the therapeutic mechanism of psychedelics by allowing for the revision of negative beliefs and biases that become pathologically rigid. However, similar disruptions of the balance between top-down influence and bottom-up sensory information may underlie MEs more broadly, regardless of their induction method. Importantly, therapeutic benefits have been associated not only with PMEs but also with near-death experiences, meditation-induced MEs, and breathwork[72,112,125,126]. This shared therapeutic potential across diverse experiences points to the need for a unifying explanatory framework. Simultaneously, it lends support to the idea that models initially developed for psychedelic experiences, such as ReBUS, may be applicable to MEs more broadly[1]. In this review, we aim to explore the hypothesis that the ReBUS model can be applied to all MEs despite their different induction methods. To test this hypothesis, we will compare and contrast the phenomenological features, effects on beliefs and worldviews, and neural correlates across different types of MEs.

2.2 Phenomenological features of mystical experiences

Empirical studies have identified a set of shared phenomenological features across the different types of MEs investigated in the literature. Yaden *et al*. were the first study to

systematically compare these experiences, demonstrating that both psychedelic-induced and naturally occurring mystical experiences share common features, such as a sense of unity, transcendence of time and space, and deeply felt positive mood. Subsequent research further solidifies the "common core" thesis of MEs, originally proposed by Stace who first posited that MEs share a universal phenomenological structure despite their diverse cultural, religious, or personal contexts[75,118,127,128]. Table 1 compares these phenomenological features across different induction methods using case studies[127].

Various psychological assessment tools, such as the M-scale MEQ, Revised MEQ, and 5D-ASC scale, have been used to measure MEs' characteristics, allowing them to be empirically studied. While these tools may differ slightly in their specific wording or emphasis, they consistently assess the presence and intensity of the core phenomenological features, which include (a) unity, (b) sacredness, (c) noetic quality (i.e., insights into profound truths), (d) deeply felt positive mood, (e) ineffability (i.e., difficulty expressing the experience accurately), (f) paradoxicality, and (g) transcendence of time and space[109,110,129,130].

The most ubiquitous of these features is unity, the experience of becoming one with all that exists[128]. Unity can be further categorized into two distinct components: extraverted unity, or the ‘relational component, and introverted unity, the ‘self-annihilation component’[128].

Table 1: Case studies of the phenomenological characteristics of mystical experiences.
Table originally published in: Woollacott, M., & Shumway-Cook, A. (2020). The mystical experience and its neural correlates. Journal of Near-Death Studies, 38(1), 3–25. https://doi.org/10.17514/JNDS-2020-38-1-p3-25. Reprinted by permission.

Stace mystical experience characteristic	Case 1: NDE	Case 2: Meditation	Case 3: Meditation	Case 4: Psilocybin
Unity	I feel one with the void, one with all	everything became one unified whole	I felt a connection with other living things that I had never felt before	I was in the void
Sacredness	enveloped by the shimmering light	I merged with the light	energy from my heart radiated and filled my whole being and beyond	I bowed to this force
Noetic quality	a state of wonder, enveloped by the shimmering light	I merged with the light	a new sense of wholeness, of integrity inside, which words cannot describe	I bowed to this force
Deep positive mood	awestruck, ecstatic, serene	entered an ecstatic state	I experienced pure love pouring through me	feeling of unconditional and undying love
Ineffability	suspended within this silent and dark void	words or discursive thinking stopped	a new sense of wholeness, of integrity inside, which words cannot describe	this void had a strange and indescribable quality
Paradoxicality	shimmering void is full of pure awareness	I merged with the light	as if a tiny lightning bolt leapt from his fingers... to my heart	it felt more real than any reality I have experienced
Transcendence of time and space	all knowledge... all time... all space	sense of time passing stopped entirely; only the present moment existed	--	time and space did not exist there

Extraverted unity refers to the perception of an underlying oneness or interconnectedness among all things, often including a sense of unity with a divine entity or ultimate reality despite the apparent diversity and separation of individual identities. Conversely, introverted unity involves the experience of ego dissolution, characterized by a loss of self-boundaries and the notion of an individual identity. Logically, these two components seem related. As Yaden *et al.*

illustrate, “When a raindrop falls into the ocean, it simultaneously ceases to be a single drop when it becomes part of the ocean”[115]. However, it is possible that that MEs can occur with more of one component than another, or perhaps with only one component.

In the following sections, we examine the experience of unity across various ME induction methods. We focus on both extraverted unity, in the form of divine encounters, and introverted unity or ‘ego dissolution,’ as these aspects have been studied across different MEs. By comparing these manifestations of unity, we aim to identify potential differences across induction methods and deepen our understanding of this core feature of MEs.

2.2.1 Ego dissolution

Ego dissolution refers to a disruption of one’s subjective experience of one's “self” or “ego”[131]. The experience and degree of ego dissolution can be measured through scores of unity using the tools discussed above, as well as the ego dissolution inventory (EDI)[131]. There can be degrees to the state of ego dissolution; the ego can be diminished completely or a little[115,132]. Many subjective reports of ego dissolution include feelings of connectedness and oneness with “God” and/or the universe[75,131].

Ego dissolution, to varying degrees, can be achieved through a variety of induction methods, including psychedelic experiences[131], meditative practices[125,133,134], near-death experiences[135], sensory deprivation[136,137] and breathwork[117,138]. When comparing ego dissolution experiences in PMEs and NMEs, similarities can be observed in the subjective reports of unity and connectedness. However, the onset and duration of ego dissolution may differ between PMEs and NMEs. PMEs, near-death experiences, and breathwork can induce rapid and intense ego dissolution[131,135,139]. The effects of meditation on ego dissolution may be more gradual and cumulative.

Research has shown that the subjective experience of ego dissolution positively correlates with the therapeutic benefits of psychedelics, meditation[123,131,140] and potentially breathwork as well[139]. This is because an over-active ego or overemphasis on the self may contribute to various mental health pathologies. For example, self-focused attention, which refers to excessive and rigid self-focus, is considered closely related to depression[103]. However, it is important to note that adverse effects following mindfulness meditation, breathwork, and psychedelic use have also been reported[141–144]. These adverse effects can include anxiety, depression, psychotic symptoms, and cognitive disturbances. Potential factors contributing to these effects include the intensity and duration of practices, individual susceptibility, pre-existing conditions, lack of support, and, notably, the context of use[141–144].

2.2.2 God Encounters

God encounters are the phenomenon of perceived contact or connection with a "Higher Power," "Ultimate Reality," or divine entities. God encounters share striking similarities across PMEs and NMEs[75]. A study by Griffiths *et al*. directly explored these encounters across induction methods[75]. Participants in both PME and NME groups report multi-sensory experiences, communication with the divine, emotional responses, and the acquisition of messages or insights. The encountered divine entities were often described as benevolent, intelligent, sacred, conscious, eternal, and all-knowing[75].

However, some differences emerged between PME and NME God encounters. PME participants were more likely to report a sense of unity or oneness with the encountered divine, while NME participants tended to maintain a sense of separation. Additionally, NME participants more frequently use the term "God" to describe the encounter, while PME participants preferred

terms like "ultimate reality"[75]. This difference in terminology is an interesting puzzle that warrants further exploration.

2.2.3 Highly potent mystical experiences

Highly potent MEs induce a complete 'annihilation of the self' and/or unity with God and/or ultimate reality[115]. These MEs often are interpreted as a sensation of death and rebirth[145]. Near-death experiences are a type of NME that induces this sensation of death and rebirth[135]. In the context of psychedelic use, these complete experiences are dose-dependent and dependent on the potency of the psychedelic, most commonly occurring with high doses of the serotonergic psychedelic N,N-Dimethyltryptamine (DMT)[146]. High doses of DMT or ayahuasca, a brew made from DMT, induce subjective experiences described as transportation to 'other dimensions' or 'heavenly realms' in which visual encounters with separate, otherworldly entities are often reported; these are referred to as breakthrough DMT experiences[75]. In these breakthrough experiences, communication with these entities, in which insights are often received, is commonly reported[146]. Research comparing DMT break-through experiences to actual near-death experiences found them to be indistinguishable[118].

In these highly potent MEs, as the individual's sense of self re-emerges from the state of complete unity and dissolution, they may feel as though they have been "reborn" with insights and a new perspective on reality and their place within it[132,133]. These experiences can lead to profound changes in an individual's beliefs, self-perception, and overall worldview, which will be explored further in the following section.

2.3 Mystical experiences alter belief

The profound nature of MEs has been linked with changes in belief. These belief changes fall into four categories: the divine, the metaphysical nature of reality, mind-perception, and the self. A large-scale study by Davis *et al.* involving 2,561 participants reported significant shifts in religious beliefs following DMT-induced ME, with self-identified atheists decreasing from 28% to 10% and belief in an 'ultimate reality' or higher power increasing from 36% to 58%[146]. However, the cross-sectional nature of this study, relying on retrospective self-reports, introduces a potential for recall bias and other confounds. Complimentary research by Griffiths *et al.* revealed similar trends in PMEs and NMEs belief changes regarding the divine[75]. In their 'God encounters' experiments, in both groups, identification as atheist decreased significantly after MEs. Similar shifts in belief have been observed following near-death experiences as well[112]. In contrast, a recent prospective study by Nayak *et al.* which aimed to minimize potential biases by not disclosing the specific research focus to participants, found minimal changes in atheist-believer status following psilocybin use[81]. These findings suggest that the perceived encounter with a divine entity during MEs may influence an individual's belief in the existence of a higher power, but further research is needed to more clearly understand this potential effect of MEs.

Metaphysical beliefs about the nature of reality may be altered after MEs as well. For example, following PMEs, there may be shifts toward believing in telepathy, reincarnation, communication with the dead, and other non-physicalist views. These include beliefs in the existence of another separate realm or dimension beyond the physical world, supernatural phenomena, the existence of a unifying principle beyond material or scientific explanation, and the proposition that the physical world is an illusion generated by consciousness or the mind Additionally, there is often an increased belief in determinism—the idea that all events, including

human actions, are causally inevitable. However, these studies have methodological issues, such as cross-sectional designs and potential biases like recall and response bias, making it difficult to distinguish between pre-existing beliefs and those that persist following the experience. Nayak *et al.*'s study, which attempted to mitigate these biases, found only increased belief in determinism[81]. Thus, in sum, there may be a shift in belief following PMEs that follow particular patterns (i.e., toward non-physicalist beliefs) and even the hardening of such beliefs in those who already possess them[20]; however, biases in research methodology leave this unclear; and future research is needed.

NMEs, such as those triggered by meditation and near-death experiences, also result in comparable shifts in metaphysical beliefs, including the adoption of non-dualistic and panpsychic views[147]. The pace at which these belief changes occur can vary; they may happen swiftly during transcendent meditative experiences, mirroring the rapid shifts observed in PMEs and NDEs, or they may develop gradually through dedicated meditation practice over extended periods[147,148]. Research on belief changes following breathwork is sparse; however, one qualitative study suggests that metaphysical beliefs may be altered after engaging in this practice[149]. This remains an open area of research.

The concept of mind perception, which involves attributing consciousness to various living entities (i.e., mammals and non-mammals) and non-living matter (i.e., organic substances such as rocks), is another belief that may be altered following MEs. This change in mind perception can be linked to the experiences of ego dissolution and unity during MEs, where individuals feel their own consciousness merging with all things, including mammals and rocks[132,133]. Research has shown that psychedelic experiences can lead to increased attribution of consciousness to non-human entities and inanimate objects[28,81]. Similarly, meditation practices that cultivate a sense of interconnectedness and non-dual awareness have been associated with greater mind

perception[150,151]. These changes in mind perception may contribute to the shifts in metaphysical beliefs observed after MEs, particularly those related to panpsychism and the primacy of consciousness[20,28,81].

Regarding beliefs about the self, research has shown that both meditation-induced and psychedelic MEs tend to shift one's beliefs about oneself from fixed self-beliefs towards a more fluid, impermanent view of the self[132,148,152], which may stem from the ego dissolution experience. Belief in the oneness of all things also increases after MEs, which has been associated with psychological well-being.

MEs have also been associated with increased self-acceptance and a more balanced sense of agency. Research has shown that psychedelic experiences and meditation practices can lead to greater self-acceptance and reduced self-criticism[153–156]. These changes in self-perception may be related to the experiences of ego dissolution and the realization of the impermanent nature of the self during MEs[132,133]. Regarding one's sense of agency, some studies suggest that psychedelic experiences can lead to a temporary reduction in the sense of agency[123,157], which may be related to ego dissolution. However, in the long term, MEs may promote a more balanced and flexible sense of agency as individuals integrate the insights gained during these experiences[158,159]. Similarly, meditation practices have been shown to modulate the sense of agency, fostering a more non-reactive and accepting stance toward one's thoughts and actions[160,161].

It seems that the belief changes following MEs, regardless of the induction method, lead to predictable patterns of belief change regarding the divine, the metaphysical, mind-perception, and the self. While psychedelics and certain NMEs, such as near-death experiences, appear to offer a rapid induction of such experiences and their associated belief changes, other NMEs, like meditation, foster a slower transformation of beliefs through repeated practice[147,148]. Despite these

differences in the speed of belief change, the overall trajectory of these changes seems consistent across various types of MEs with a shift away from physicalist beliefs and towards non-physicalist ones, such as panpsychism and dualism[20,28].

The specific direction of belief changes following MEs, such as increased mind perception of the universe and belief in determinism, suggests that the content and interpretation of the experience play a crucial role in shaping the resulting beliefs. This observation aligns with the idea that the context and the individual's attempt to make sense of the mystical experience are key factors in determining the specific types of beliefs adopted. The finding that God encounters lead to increased belief in a higher power, while the experience of unity with all things results in heightened mind perception, indicates that the phenomenological content of MEs directly influences the nature of the belief changes.

2.3.1 Belief and psychological well-being

Research has shown that shifts in beliefs and attitudes following MEs may play a causal role in the lasting improvements in mental health and well-being associated with these experiences[4,8]. Psychedelic-induced belief changes have been found to correlate with improvements in psychological well-being. For example, Timmerman *et al.* found that metaphysical belief changes, such as shifts away from hard materialistic beliefs and towards ideas like transcendentalism, panpsychism, and dualism, were positively correlated with improvements in psychological well-being scores four weeks and six months after a psychedelic experience[20]. Additionally, a study by Lyons and Carhart-Harris demonstrated that psilocybin treatment for treatment-resistant depression led to more realistic forecasting of future life events[19]. These findings suggest that psychedelic-induced belief changes may contribute to more adaptive and

resilient thinking patterns, as well as more accurate and optimistic beliefs about the future, which could play a crucial role in the therapeutic effects of these substances.

The therapeutic benefits associated with MEs and their consequential belief changes extend beyond psychedelic interventions. Diebels and Leary explore the psychological implications of the belief that everything is interconnected, a belief that often arises from various types of MEs[162]. They highlight the potential for such beliefs to enhance well-being, empathy, and prosocial behavior. Additionally, near-death experiences have been associated with increased well-being, decreased fear of death, and enhanced spiritual growth[20,112,163,164]. Meditation-induced MEs have also been linked to improvements in mental health, stress reduction, and overall well-being[165,166]. Breathwork is gaining traction as a potential therapeutic modality, supported by preliminary evidence suggesting its efficacy in promoting psychological well-being[139,143,149] and facilitating changes in self-awareness[167]. However, further rigorous research is needed to establish the effectiveness and underlying mechanisms of breathwork interventions.

MEs and their consequential beliefs may help alleviate existential anxiety and death anxiety, as demonstrated by studies showing sustained decreases in death anxiety and improvements in quality of life, life meaning, and optimism in cancer patients following psilocybin treatment[4]. A small pilot study by Puente indicates that breathwork may also help alleviate death anxiety as well[28]. Research by Davis *et al.* found that following a highly potent ME induced by DMT, 80% of participants reported alterations in their fundamental conception of reality, with 60% of those participants specifying that these alterations were desirable[146]. This finding supports the idea that the changes in beliefs resulting from MEs are often perceived as positive and meaningful by the individuals who undergo them. The desirability of these beliefs may be linked

to their capacity to provide a sense of connection, purpose, and transcendence, which can serve as a buffer against existential anxiety and contribute to overall psychological well-being. As Letheby argues, the 'disenchantment of the world'—the transition from a religious worldview to a naturalistic one—has caused an increase in existential anxiety, which can be resolved through PMEs[168]. These experiences can lead to the development of a sense of wonder, appreciation for life, and the adoption of broader perspectives that extend beyond personal concerns[168].

It is important to note that some researchers argue that the subjective experiences that lead to these belief changes are epiphenomena unnecessary for the long-term therapeutic effects of psychedelics[169]. However, the profound impact people attribute to these experiences[18], and the potential psychological benefits associated with the resulting belief changes[20], suggest they should not be ignored in treatment models. Thus, some argue that we should integrate a mystical framework into psychedelic-assisted therapy with the help trained spiritual health practitioners[170,171]. Of course, there are ethical considerations like the imposing of beliefs on people while under the influence or in the aftermath of a psychedelic experience[81]. Research on this discusses important qualifications for these practitioners to possess to ethically do this work, such as competency to work with spiritual material, awareness of power dynamics, familiarity with non-ordinary states of consciousness, holding space, integrating spiritual dimensions alongside scientific approaches, the use of generalizable therapeutic repertoire when conducting PAT, and contributing to interdisciplinary collaboration[171].

Additionally, these experiences are not always beneficial and can sometimes be harmful[141–144]. For instance, MEs could lead to unhealthy delusional beliefs[140] or pathological ‘magical thinking,’ such as in obsessive-compulsive disorder, where magical thinking refers to the

belief that certain thoughts or behaviors exert a causal influence over outcomes. These negative outcomes may be related to predisposition or personality traits[172,173].

Despite these limitations, the evidence suggests a relationship between the belief changes resulting from MEs and improvements in psychological well-being. This may be due to the restructuring of negative beliefs and the adoption of more adaptive, flexible, and meaningful worldviews, which aligns with the ReBUS model[1]. With these findings in mind, the integration of psychedelic-assisted therapy and non-pharmacological methods like meditation and breathwork into clinical practice is offering new avenues for treating mental health conditions resistant to conventional treatments both individually and in combination[140]. By inducing profound shifts in perception and self-understanding, these approaches may facilitate psychological healing, growth, and emotional regulation skills. The increased sense of unity, purpose, and connection to something greater than oneself may provide a more stable foundation for navigating life's challenges.

It is important to note that while these belief changes may have therapeutic implications, they also raise ethical concerns regarding the use of psychedelics in clinical settings. As Smith and Sisti point out, the potential for psychedelics to induce significant changes in an individual's belief system underscores the need for robust informed consent procedures and careful consideration of the ethical boundaries between therapy and spiritual or philosophical influence[174]. Clinicians must navigate these challenges to ensure that patients are fully aware of the potential for belief changes and that their autonomy is respected throughout the therapeutic process.

2.4 Neurobiology of mystical experiences

The shared phenomenological characteristics and similar potential impacts on beliefs in MEs suggest there may be common neural correlates across different types of MEs. Most research on the neural correlates of MEs has focused on PMEs rather than NMEs. This is partly due to the logistical challenges of studying spontaneous or unpredictable events like near-death experiences or sudden spiritual awakenings during meditation. The transient and highly personal nature of these experiences makes capturing their neural correlates in real-time using conventional neuroimaging techniques like fMRI or EEG difficult.

Despite these challenges, disparate neuroimaging studies on MEs across various induction methods point to potential overlaps in the neurobiological mechanisms underlying these experiences. We propose that the ReBUS model, when applied to MEs, provides a unified framework for understanding and directly comparing their underlying neural mechanisms across induction methods. In the following sections, we draw comparisons between different induction methods, acknowledging differences in experimental design and analytical methodology.

2.4.1 The default mode network

The default mode network (DMN) has been heavily implicated in MEs, specifically regarding ego dissolution. Key regions of the DMN include the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and lateral parietal cortices[175]. These regions are highly correlated in their fMRI or EEG signals when one is engaged in self-referential thinking or introspection and do not form a correlated network when one is engaged in an externally driven task or tasks generally[176].

Researchers have postulated that the DMN is involved in moderating the sense of self[123]. Their studies have found that altered DMN dynamics are associated with ego dissolution[92,94,132,177–179]. These alterations may manifest in a variety of different ways. Some studies show that MEs are correlated with DMN alterations, including reduced intra-network integrity and increased between-network connectivity[93]. Others show altered functional connectivity[180,177], the strength of connections across a network, or decoupling of specific brain regions within the DMN, specifically the PCC and mPFC[97]. Interestingly, during a psychedelic experience[94,96,122] and in experienced meditators[181], there is reduced anticorrelation between the DMN, an intrinsic network, and the task-positive network, an extrinsic network of brain regions active when one is engaging in a task or responding to external stimuli. It is important to note that while there is a whole field of existing literature on meditation, we chose to largely omit this because the neural correlates of meditation and ME during meditation may be vastly different. However, the findings above are consistent with the notion that meditation and psychedelic use both alter the relationship between self and external environment.

While the DMN has received significant attention for its potential role in MEs, particularly in the psychedelic literature, the role of DMN alterations in ego dissolution remains unclear due to several limitations. For instance, in some MEs like mediumistic trance, where mediums actively seek to achieve a 'state of emptiness,' DMN dynamics may not be altered at all[182]. Furthermore, DMN dynamics are impacted by other substances that do not necessarily give rise to ego dissolution[183]. Further research is needed to fully understand the complex neural mechanisms underlying these experiences, including investigations of global and thalamic brain connectivity[184,185], regional alterations in glutamate[186], modulation of cortical-subcortical circuits[187], and the functional connectivity of the claustrum with networks supporting perception,

memory, and attention[188], as well as the potential role of serotonin 2A receptors in mediating these changes[189]. Thus, while altered DMN activity may play a part in ego dissolution and MEs, it is not the whole picture. The relationship between DMN alterations and these experiences is complex and not yet fully understood, and further research is needed.

2.4.2 The fronto-parieto-temporal network

While the majority of DMN research has been done in the context of psychedelics, the fronto-parieto-temporal network (FPTN) has been implicated in MEs across induction methods using fMRI and EEG. The FPTN is an extrinsic, task-positive network that shows anti-correlated activity with the DMN, meaning these networks tend to have inverse patterns of activation[176]. The fronto-parieto-temporal network includes regions such as the dorsolateral prefrontal cortex, posterior parietal cortex, and parts of the temporal lobe[190]. The FPTN has been implicated in various aspects of conscious experience, including attention, self-referential processing, and the integration of sensory and cognitive information[191].

fMRI studies have revealed increased functional connectivity between frontal, parietal, and temporal regions in PMEs[94,177,184,192] and increased synchronization between frontal and parietal regions in meditation-induced NMEs[193,194]. EEG studies investigating FTPN activity in the frequency domain have implicated theta and gamma band power in MEs. Theta oscillations (4-8 Hz) have been associated with memory retrieval, emotional regulation, and meditative states[195–197]; while gamma oscillations (30-100 Hz) are most commonly associated with higher-order cognitive functions such as attention, perception, and consciousness, as well as neural synchrony and information processing across different brain regions[67,198]. Beauregard and Paquette found increased theta power in frontal and parietal regions during meditation-induced MEs, potentially

reflecting focused attention and visual imagery[107]. This study also reported greater gamma power in right temporal and parietal areas, which they argue may be linked to the sense of union with the divine and altered perceptual experiences[107]. Similarly, Berkovich-Ohana *et al.* found increased gamma power in posterior regions during mindfulness meditation, which correlated with the subjective experience of self-transcendence[199]. In PMEs, studies have reported increased theta and gamma power in frontal, temporal, and parietal regions, associated with the intensity of subjective effects, ego dissolution, and altered perceptual experiences[86,200,201].

While there is no current research specifically on the fronto-parieto-temporal network's involvement in near-death experiences alone, Beauregard *et al*. investigated the neural correlates of a meditative state in individuals who had reported near-death experiences compared to those who had not[202]. Using EEG, they found that during the meditative state, participants who have had near-death experiences exhibited significantly greater theta power and coherence, particularly in frontal and parietal regions, compared to non-experiencers. This study doesn't disclose how much time had passed between the near-death experiences and study participation. It is important to note that the study is limited by the lack of control over whether the participants had similar life-threatening experiences that did not result in a near-death experience, which introduces potential confounding factors. Therefore, the differences observed might be due to predisposing factors that make certain individuals more likely to experience near-death experiences rather than the near-death experience itself. More research is needed to know whether these highly potent MEs affect brain function long-term.

The increased theta and gamma power within the fronto-parieto-temporal network during MEs may reflect the profound alterations in consciousness, self-perception, and emotional

processing that characterize these experiences. These findings have significant ramifications, as they suggest that MEs might induce long-term alterations in brain function that support therapeutic effects. For instance, Skosnik *et al*. found that a single dose of psilocybin increased EEG theta power two weeks post-administration, correlating with improvements in depression symptoms[203].

Recent research on breathwork provides an interesting contrast to findings from psychedelic and meditation studies. *Bahi et al.* found that a single session of conscious connected breathing, which refers to a technique involving faster and deeper-than-normal cyclical breathing without pauses between inhales and exhales, led to decreased delta and theta power in frontotemporal and parietal regions as well as reduced beta power in parietotemporal areas[139]. This decrease in theta power differs from the increased theta activity observed in psychedelic experiences and meditation-induced mystical states. However, like psychedelic and meditation studies, experienced breathwork practitioners showed increased gamma power[139]. Despite these differences in EEG patterns, participants' subjective experiences during breathwork, as measured by the 11D-ASC scale, were comparable to those reported after medium to high doses of psilocybin. This suggests that while the underlying neural mechanisms may differ, breathwork can induce subjective mystical-type experiences similar to psychedelics.

In sum, neuroimaging research has revealed potential common neural correlates of MEs induced by psychedelics, meditation, near-death experiences, and breathwork. These include alterations in DMN and FPTN activity, increased functional connectivity between these usually anticorrelated networks, and changes in theta and gamma power. While psychedelics and meditation tend to increase theta power, breathwork appears to decrease it, demonstrating that similar subjective states can arise from different patterns of brain activity. Nonetheless, the

increase in gamma power among experienced practitioners is consistent across methods. Together, these findings highlight the complexity of neural correlates across various methods of inducing mystical experiences and suggest that different induction methods may engage distinct but overlapping neural processes to produce similar subjective states. The subjective and extraordinary nature of these experiences, coupled with logistical challenges in researching them, makes it difficult to draw definitive conclusions about shared neural underpinnings.

2.4.3 Endogenous psychedelics and near-death experiences

DMT, which produces potent MEs, is found endogenously in the mammalian brain[204]. Recent research has shed new light on the potential endogenous role of DMT, particularly in relation to normal waking states[205] and near-death experiences[206]. A very recent, yet to be peer-reviewed study by Glynos *et al.* provided compelling evidence for the presence of pharmacologically-active endogenous DMT during normal wakefulness in both the prefrontal and somatosensory cortices of rats[205]. The levels of DMT reported were comparable to those of serotonin and dopamine, suggesting a potential physiological role for endogenous DMT in everyday brain function. This opens up new avenues for understanding DMT's potential role in consciousness and cognition.

DMT could play a physiological role in near-death experiences as well. Dean *et al.* reported that DMT levels in rat occipital cortex increased to ‘pharmacologically active levels’ within one hour of induced cardiac arrest[206]. These findings expand upon the hypothesis, originally proposed by Strassman that DMT may be released at the time of death, potentially contributing to the phenomenology of near-death experiences[207].

Recent research has expanded our understanding of DMT's potential physiological roles. Studies have shown that DMT may have protective effects against hypoxia, a condition where oxygen levels in tissue are low[208]. This is particularly intriguing given that hypoxia is hypothesized to be a feature of near-death experiences[119] and cardiac arrest[209]. Interestingly, the symptoms of oxygen deprivation are remarkably similar to those reported in near-death experiences[163]. Patients with higher concentrations of carbon dioxide in their blood, indicative of lower oxygen levels, report significantly more near-death experiences than those with lower levels[210]. This connection between hypoxia and near-death experiences, coupled with DMT's protective effects against hypoxia, suggests a potential adaptive role for endogenous DMT release during extreme physiological states. Moreover, DMT has been shown to increase the overall entropy of the brain's functional connectivity[30,31]. Higher neural entropy has been associated with richer states of consciousness and, importantly, with better outcomes in cardiac arrest patients[211].

These findings raise intriguing questions about the potential link between DMT, hypoxia, and certain forms of breathwork. Some breathwork techniques intentionally induce mild hypoxic states, which could potentially trigger endogenous DMT release[212]. While this connection remains speculative, it offers an interesting avenue for future research into the mechanisms underlying the profound effects of both breathwork and endogenous DMT on consciousness and physiological states.

It's important to note that while these findings are provocative, the role of endogenous DMT in humans remains a subject of debate[213,214]. The potential connection between endogenous psychedelics and both normal waking states and near-death experiences adds another layer to our understanding of the neural correlates of consciousness and mystical experiences. It suggests that

the brain may have innate mechanisms for producing altered states of consciousness similar to those induced by exogenous psychedelics, not only in extreme physiological states but potentially in everyday functioning as well. This line of research offers an intriguing avenue for understanding the potential biological underpinnings of mystical experiences and consciousness more broadly.

2.4.4 Temporal lobe epilepsy

There is extensive evidence of case studies where people who suffer from epilepsy reported experiencing hallucinations either right before the seizure onset, during (ictal period), or after (post-ictal period). These are commonly called seizure "auras," and doctors sometimes use these hallucinations to infer the sources of seizures[215]. In such cases, the hallucinations can be sensory driven, such as visual, auditory, or olfactory, which are traced back to sensory regions of the cortex. They can also be complex and involve rich phenomenology that involves different senses and are sourced to integrative areas of the brain, such as the temporal lobe. Particularly, temporal lobe seizures lead to a wide range of out-of-normal experiences that are often characterized as vivid "dreamy states"[216]. Many of the phenomenological features of these states, such as feelings of unity, sacredness, ineffability, and transcendence of time and space, are strikingly similar to those that define MEs.

In such states, people report feeling like they have been taken back to a time in the past, recollect memories, and experience strong emotional feelings toward the experience[216,217]. In addition, there are several cases of out-of-body experiences during a seizure where the person sees themselves from an above perspective as if they left their bodies[218]. Patients also report seeing people or beings that are not there. A lot of these experiences are also reported as feeling an intense connection with the divine, encountering God, receiving prophetic messages, and experiencing a

reality beyond the known experience shared between others. These experiences can be referred to as “experiential seizures” and can also be triggered by electric activation of the temporal lobe[219].

There are clear similarities between temporal lobe seizures, psychedelic experiences, and NMEs, particularly in terms of the vivid, memory-like phenomenology, emotional intensity, and alterations in one’s sense of self and reality[216,217] as well as similar neural underpinnings[107]. This overlap suggests that the temporal lobe may be a key brain region involved in generating the profound subjective effects of both temporal lobe epilepsy and PMEs. The activity in the temporal lobe, whether caused by epilepsy, electrical stimulation, or a psychedelic compound, may create specific patterns of neuronal activity across extensive networks, forming a matrix that represents the basis of a particular experience. These neuronal networks can (1) recreate the entire experience when only a portion of the network is activated and (2) tolerate significant degradation without substantial loss of information[219]. This is how, after strong dissolution of brain functional networks during seizures or psychedelic experiences, people can still report specific experiential states and sensations.

In one case study, a patient with refractory temporal lobe epilepsy was treated with responsive neurostimulation system (RNS), which monitors brain activity and prevents seizures before they occur. This patient took a high dose of psilocybin mushrooms recreationally while wearing the RNS device; during the psychedelic trip, the RNS system detected 32 seizures. The patient reported feeling similar symptoms of seizures during the psychedelic trip, but in a much calmer sense. This case study suggests that psychedelics may involve patterns of electrical activity in the brain similar to those observed in epilepsy and could potentially induce seizures[220].

While a detailed discussion is beyond the scope of this review, it's worth noting that 5-MeO-DMT, despite its structural similarity to DMT, has a distinct pharmacological profile and produces different phenomenological effects[221]. It primarily acts on 5-HT_{1A} receptors rather than 5-HT_{2A} receptors[222] leading to experiences often described as a 'white-out' or void[223] in contrast to the vivid imagery and entity encounters associated with DMT[146]. Interestingly, 5-MeO-DMT experiences share some features with temporal lobe epilepsy, such as alterations in bodily sensations and sense of self, though with notable differences[221]. The case of 5-MeO-DMT further illustrates how different pharmacology can lead to different phenomenology yet still potentially yield therapeutic benefits. This further supports the idea that the ReBUS model may be applicable across a range of altered states, regardless of their specific neurochemical induction.

The inclusion of endogenous DMT and temporal lobe epilepsy in the discussion of mystical experiences adds another layer of complexity to an already intricate puzzle. The similarities between epileptic auras, psychedelic experiences, and other forms of mystical experiences highlight the multifaceted nature of these phenomena and the challenges in fully understanding their neural underpinnings. Fortunately, the ReBUS model provides a valuable lens through which researchers can investigate and better understand the relationship between these diverse experiences and their underlying neural mechanisms, unifying our understanding of mystical states regardless of their origin.

2.5 Predictive processing and the entropic brain

The preceding analysis aimed to elucidate the complex neural mechanisms underlying the multifaceted phenomenology of MEs. However, the predictive processing framework offers a unifying theoretical model through which to interpret these experiences across diverse induction

methods. This framework provides a mechanistic account that may reconcile the heterogeneous neuroimaging findings associated with MEs.

The theory of predictive processing proposed by Karl Friston explains various neurobiological processes such as action, attention, learning, and perception. Rooted in the Bayesian brain hypothesis[34,35], this theory suggests that the brain operates as a prediction machine constantly updating its models of the world to minimize the difference between expectations and actual experiences[21]. The brain generates predictions about sensory input, compares these predictions to actual sensory data, and uses any discrepancies, known as 'prediction errors' to refine its internal models. This mechanism allows the brain to focus on novel or relevant information while conserving energy by filtering out well-predicted inputs, facilitating effective interaction with the environment.

Friston's free-energy principle suggests that the brain's primary goal is to reduce uncertainty about its environment[25]. Within this framework, the brain's prioritization of reducing uncertainty over accuracy can sometimes lead to the formation and entrenchment of pathological beliefs. These aberrant constructs, while potentially maladaptive, serve to minimize perceived uncertainty in accordance with the free-energy principle[1]. In essence, even inaccurate beliefs can be self-protective if they help reduce an individual's sense of uncertainty about their world.

The entropic brain hypothesis suggests that the subjective effects of psychedelics result from increased entropy in brain activity. In information theory, entropy is a measure of uncertainty or disorder in a system[224]. Psychedelics, primarily acting as 5-HT_{2A} receptor agonists, are thought to increase neural entropy by disrupting the normal patterns of neuronal firing, particularly in the cortex where these receptors are densely expressed[1]. This agonism leads to increased excitability

and asynchronous firing of these neurons, resulting in a more disordered and unpredictable pattern of brain activity, which manifests as increased entropy in neuroimaging and electrophysiological measurements[33]. This increased entropy disrupts the brain's normal hierarchical organization and top-down flow of predictions, leading to a more disordered and less constrained state of consciousness. This state is thought to correspond to a more flexible and open consciousness where the brain is less constrained by prior beliefs and more receptive to novel information. Consequently, the brain generates a broader range of predictions and is more likely to update its internal models based on prediction errors, potentially explaining the novel insights, enhanced creativity, and altered perceptual experiences associated with psychedelics[1].

The entropic brain hypothesis is supported by empirical findings from static functional connectivity analyses, which have shown increased functional connectivity between typically segregated brain regions, indicating a breakdown of the brain's modular organization[86,95]. Similarly, EEG studies have demonstrated increased signal complexity and decreased alpha power, reflecting a reduction in top-down control and a shift toward bottom-up processing[29,93,100]. Both meditation[225] and breathwork[226] have been associated with increases in entropy similar to those observed in psychedelic states as well. This increased entropy may allow for the emergence of novel and unconstrained patterns of thought and experience with disruptions in normal patterns of activity potentially leading to altered states of consciousness.

2.6 The ReBUS model as a unified framework for mystical experiences

The ReBUS model posits that psychedelics induce a relaxation of high-level priors or beliefs, allowing for a more unconstrained and flexible state of cognition. This relaxation of priors is thought to be mediated by the activation of 5-HT_{2A} receptors in cortical regions, particularly in

layer five pyramidal neurons, which are involved in the top-down propagation of predictions[88]. The disruption of hierarchical predictive processing leads to a greater influence of bottom-up sensory information, resulting in vivid perceptual experiences, dissolution of self-boundaries, and a sense of unity with the environment during PMEs[33].

2.6.1 ReBUS and the phenomenology of mystical experiences

One can begin to see how ReBUS can be applied to mystical experiences broadly by looking at the phenomenological features of MEs. For example, ego dissolution can be interpreted as the weakening of one's prior beliefs about their "self." The disruption of the internal model of the self and connections to external reality are broken. In the absence of a functional internal model to contrast with sensory input, the distinction between internal and external realities becomes indiscernible, resulting in the sensation of unity. Moreover, the intensity of ego dissolution may be proportional to the degree of disruption in the brain's predictive models of the self. The belief in the oneness of all things and the capability of consciousness of all things following MEs illustrates the consequential belief updating that occurs as a result of ego dissolution. These suggestions cohere with what Lutz *et al*'s proposition that meditation practices may alter predictive processing by reducing the precision of self-related predictions and increasing the precision of sensory predictions, leading to a more vivid and less self-centered experience of the present moment[227]. This aligns well with the ReBUS model. This shift in the balance of predictive processing may underlie the profound changes in self-perception and emotional regulation reported by experienced meditators[228,229].

In some potent MEs, people experience encounters with external entities, most commonly referred to as beings, guides, spirits, aliens, or helpers[146]. These two can be understood through the

lens of the ReBUS model. The relaxation of high-level priors may cause internal cognitive processes to be perceived as external entities. The phenomenon likely involves the activation of neural circuits associated with social cognition and face recognition. In the absence of normal predictive frameworks and faced with unfiltered sensory and interoceptive input, the brain may utilize existing cognitive schemas to interpret these experiences. This could account for reports of encounters with sentient beings or alternate realities during MEs.

This process may involve the recruitment of evolutionarily conserved neural substrates responsible for processing faces, biological motion, and social interactions. The vivid nature of these experiences might result from intense activation of sensory processing areas, including those responsible for color perception and visual pattern recognition, coupled with reduced top-down inhibitory control[230]. Thus, entity encounters during MEs may represent a complex interplay between disrupted reality modeling, heightened bottom-up sensory processing, and the brain's tendency to seek meaningful patterns in ambiguous stimuli, all of which align with the predictions of the ReBUS model.

God Encounters, in particular, may illustrate how the degree of weakened priors influences the experience and interpretation of MEs. In the God encounters study, one of the most striking differences between PME and NME God encounters was that PME participants reported feelings of unity with God, while NME participants maintained feelings of separation. The PME participants who, in this study, reported more complete MEs as measured by the Mystical Experience Questionnaire (MEQ)[75], may have thus experienced a greater disruption of top-down influence on the perceptual experience. This disruption could diminish the influence of preconceived notions and biases, enabling a more open interpretation of the encounter that is less

constrained by existing worldviews[1]. In contrast, NME participants, whose experiences may be less intense or complete, might retain a greater influence of prior beliefs and expectations on their perception of the God encounter. This could explain the higher prevalence of traditional religious terminology in NME reports[75].

Here, the intensity of the mystical experience, as reflected in MEQ scores, may be inversely related to the influence of prior beliefs on the perception and interpretation of the encounter. More complete MEs, associated with greater disruptions in predictive processing, could lead to more flexible and less constrained interpretations of the divine. Further research is needed to test these hypotheses and elucidate the precise relationship between the intensity of MEs, the relaxation of prior beliefs, and the perception of God encounters. Studies directly comparing the phenomenology and neural correlates of PME and NME God encounters in individuals with diverse religious and cultural backgrounds could provide valuable insights into the role of predictive processing in shaping these profound experiences.

2.6.2 ReBUS and belief

In conditions like depression and anxiety, negative beliefs can become pathologically rigid, creating a self-reinforcing cycle that is resistant to change. The ReBUS model posits that psychedelics temporarily disrupt this rigidity by altering the balance between top-down and bottom-up information processing in the brain. This disruption allows for a more flexible and receptive state of cognition, potentially facilitating the revision of maladaptive beliefs and the integration of new perspectives[1].

The profound shifts in beliefs and perspectives reported across different types of MEs suggest a similar process of belief relaxation, and updating may be at work. Long-term meditation

practice and meditation-induced MEs can produce gradual or sudden shifts in perspective. The focused attention and altered state of consciousness in deep meditation may create conditions for belief relaxation similar to those proposed in the ReBUS model. Near-death experiences also often result in major reconfigurations of beliefs. The extreme physiological and psychological state during near-death experiences may induce a ReBUS-like relaxation of prior beliefs, allowing for dramatic updates to one's worldview. Even in cases of unexpected spontaneous MEs, the ReBUS model might explain how a sudden, intense alteration of consciousness could lead to lasting belief changes.

The belief changes observed across these different types of MEs often share common themes, such as increased sense of interconnectedness, reduced fear of death, and shifts in spiritual or metaphysical beliefs. This consistency supports the idea that a common mechanism of belief updating, as proposed in the ReBUS model, may underlie these diverse experiences. Importantly, the ReBUS model also offers an explanation for how these belief changes persist beyond the acute experience. The relaxation of prior beliefs during an ME may create a window of plasticity, allowing for the formation of new neural connections that encode updated beliefs. This process could be supported by neuroplastic changes in the brain, such as increased synaptic plasticity and the formation of new neural connections[231,232].

Importantly, while MEs often lead to positive outcomes, it's crucial to recognize and study potential risks and adverse effects. These may include the exacerbation of pre-existing mental health conditions such as psychosis, the development of persistent delusional beliefs, or the onset of hallucinogen persisting perception disorder (HPPD)[77,142,233]. Some individuals may experience prolonged dissociation, depersonalization, or derealization following intense MEs. Moreover, the

integration of profound mystical experiences into everyday life could be challenging, potentially leading to interpersonal difficulties or existential crises. The ReBUS model can also shed light on potentially problematic outcomes such as delusional or magical thinking. The disrupted predictive processing proposed by ReBUS bears similarities to cognitive patterns observed in conditions where magical thinking and delusions are common[234]. In conditions like schizophrenia and in high-risk populations for schizophrenia, altered predictive processing is evidenced by deficits in tasks such as mismatch negativity[60]. Investigating the neural and cognitive mechanisms underlying both positive and negative outcomes of MEs within the ReBUS framework could inform safer protocols for clinical applications and contribute to our broader understanding of belief formation and revision. Furthermore, in cases where MEs result in adverse outcomes, ReBUS may help explain how the context of mindset and setting during and after MEs, considering the proposed increased sensitization to sensory information, can lead to negative consequences.

Future research should and can investigate the role of altered information processing and the belief changes and therapeutic benefits observed after MEs induced by various methods. By comparing information processing before and/or after psychedelic experiences, meditation training, near-death experiences, and temporal lobe epilepsy-induced MEs, researchers can gain insights into the common mechanisms underlying the transformative potential of these states. Additionally, exploring the relationship between altered information processing and neuroplastic changes in the brain may shed light on how the effects of MEs are sustained over time and contribute to the long-term psychological effects of MEs.

2.6.3 ReBUS and neural correlates of mystical experiences

Altered predictive processing, specifically the weakening of top-down influence and increased bottom-up sensitization, may be an effect of the various neural mechanisms occurring during MEs, such as changes in DMN and FPTN activity, increased functional connectivity between these usually anticorrelated networks, as well as potentially lasting effect on theta and gamma power after MEs. DMN disintegration may reflect a breakdown of rigid self-related beliefs[94]. Altered connectivity patterns could represent the brain's increased flexibility in processing information[192]. Changes in oscillatory activity may reflect this shift in information processing[86]. Increased entropy in brain activity is consistent with the model's prediction of a more flexible, unconstrained state of cognition[30,31] These neural changes, observed across various types of MEs, support the REBUS model's explanation of how diverse induction methods can lead to similar profound alterations in consciousness and belief systems[133].

In conclusion, the predictive processing framework and the ReBUS model offer a compelling hypothesis for understanding MEs, regardless of their induction method. This theoretical framework provides a valuable lens through which researchers can design studies and contextualize findings related to MEs, including those induced by psychedelics, meditation, and near-death experiences. The strength of this approach lies in its ability to generate testable predictions about how alterations in hierarchical predictive coding might lead to the phenomenology and lasting effects associated with MEs. It suggests that by temporarily disrupting normal predictive processing, these experiences may create a more flexible cognitive state that allows for the revision of entrenched beliefs and the integration of new insights. Importantly, this framework aligns well with our current understanding of cortical circuitry and sensory processing,

providing a neurobiologically grounded basis for future investigations. It offers a way to conceptualize how diverse induction methods might converge on similar experiential and transformative outcomes. Moving forward, this hypothesis can guide research across multiple levels of analysis, from computational modeling to neuroimaging and phenomenological studies. It may be particularly valuable in elucidating the neurobiology of spontaneous MEs, which are challenging to capture in real time.

While the predictive processing and ReBUS models show promise, it's crucial to remember that they remain hypothetical frameworks. Further research integrating various methodologies across different types of MEs is needed to rigorously test these ideas and refine our understanding of the mechanisms underlying these profound and transformative experiences.

2.7 Future directions and conclusion

The ReBUS model provides a unifying framework for understanding MEs across various induction methods. This model can be studied at multiple levels of the brain's hierarchical structure, from cellular interactions to large-scale network dynamics, and higher-order cognitive processing. Previous research using EEG and visual deviance detection tasks in our lab has already shown that studying psychedelic experiences at the level of basic visual processing may be a good translational model for researching MEs[32]. Deviance detection tasks such as oddball and saccadic planning paradigms, which involve presenting a series of repetitive stimuli interspersed with infrequent, deviant stimuli, have been used to extensively study predictive processing and mismatch negativity in various contexts[23,27,235,236]. We found that psychedelic experiences shift the balance from top-down to bottom-up information processing, at least in the visual system[32]. Future researchers should expand this research to compare the effects of different MEs on visual

information processing. Furthermore, future research should explore whether similar mechanisms of relaxed priors and increased bottom-up signaling do occur across multiple levels of the cortical hierarchy. This cascade, propagating from sensory processing to higher-order cognition, could explain how perceptual changes during MEs lead to profound shifts in abstract beliefs.

It's crucial to investigate whether alterations in predictive processing persist after the acute ME. Our previous research suggests that psychedelic use altered sensory information processing beyond the acute exposure period[32]. This is further supported by a recent meta-analysis that showed that the "afterglow" effects of PMEs, which include changes in mindfulness, mood, and behavioral flexibility, last up to a month or more[237]. Furthermore, studies have demonstrated that changes in functional connectivity can persist after the acute psychedelic experience[97]. These findings suggest that PMEs may induce a window of plasticity, potentially facilitating long-term changes in brain function and cognition. Future research should investigate whether similar prolonged effects occur in other types of MEs and explore the implications of this extended window of plasticity. By doing so, researchers can draw conclusions about the underlying neural processes that take place during these experiences. This approach is particularly valuable for investigating the neurobiology of spontaneous MEs, like near-death experiences, which are challenging to study in real time due to their unpredictable nature.

Future studies should investigate the interplay between personality traits, individual differences, and brain predispositions in the occurrence and intensity of MEs. Research suggests that certain characteristics, such as openness to experience, absorption, propensity for dissociative symptoms, and magical thinking, may predispose individuals to mystical or spiritual experiences[238–242]. Furthermore, evidence indicates that brain structure and function may differ in

individuals prone to MEs, including increased cortical thickness in the prefrontal cortex and altered neural activity in the parietal lobe[243,244]. This research could inform neurobiological theories about the origins and mechanisms of both naturally occurring mystical experiences (NMEs) and psychedelic-induced mystical experiences (PMEs) and may be particularly crucial for studying the propensity for NMEs in near-death experiences and temporal lobe epilepsy.

A significant challenge in the field is conducting empirical research on NMEs. Future research should explore a wider range of practices that induce MEs, such as kundalini yoga, chanting, and vipassana meditation, in different cultural settings and contexts. Additionally, the role of set and setting across different types of MEs requires further investigation. Understanding how these factors shape the ME could help in developing more effective therapeutic protocols and help us better understand cultural context's impact on MEs. Recent advancements in wireless, portable EEG technology, along with established measures like the MEQ and Hood Mysticism Scale, could facilitate this research.

In this review, we concentrated on PMEs produced by 5-HT_{2A} serotonergic psychedelics. Future studies should explore the similarities and differences between MEs induced by these substances and those induced by other psychoactive compounds like 5-MeO-DMT. This could expand our understanding of the diverse routes to mystical states and their implications.

Finally, longitudinal studies examining the long-term effects of MEs, the effects on belief, psychological well-being, and information processing could provide valuable insights into the enduring impact of these experiences. By pursuing these research directions, we can deepen our understanding of MEs within the ReBUS model and potentially develop more effective therapeutic

interventions based on this model. This comprehensive approach will help unravel the complex nature of mystical experiences and their profound impact on human consciousness and well-being.

The ReBUS model offers a compelling framework for understanding mystical experiences across various induction methods. Conceptualizing MEs as periods of relaxed high-level priors and increased bottom-up information flow provides a mechanistic explanation for their phenomenology, associated belief changes, and underlying neural correlates. Furthermore, the ReBUS model can be used to explore differences in phenomenology based on the strength and duration of MEs, as well as the specific brain regions affected in different types of MEs, potentially explaining the varied subjective experiences across induction methods. The profound nature of MEs, along with their impact on metaphysical beliefs and self-identity, underscores the importance of studying these aspects generally, and specifically in psychedelic science, despite their complexity. The ReBUS model offers a promising framework to bridge scientific inquiry and mystical phenomena without taking a position on the veracity of any particular worldview, allowing for a more comprehensive understanding of psychedelic effects and their therapeutic potential. The ReBUS model opens new avenues for therapeutic interventions and deepens our understanding of consciousness. It provides a roadmap for future research into belief updating mechanisms, neuroplasticity in transformative experiences, and the potential for harnessing these states for personal growth and healing. While further research is needed to rigorously test and refine this model, we propose calling it the "Relaxed Beliefs After Mystical Experiences Model" (ReBAME). The integration of MEs into a predictive processing framework represents a significant step towards a more comprehensive scientific understanding of these profound, often ineffable experiences. Future research guided by this model could contribute to our evolving

understanding of consciousness, belief dynamics, and the role of profound experiences in mental health and well-being.

3 A LASTING IMPACT OF SEROTONERGIC PSYCHEDELICS ON VISUAL PROCESSING AND BEHAVIOR

3.1 Introduction

Serotonergic psychedelic compounds such as psilocybin and lysergic acid diethylamide (LSD) have garnered significant interest in neuropsychiatry for their potential to treat mood, anxiety, and substance use disorders[245,246]. The neurobiological mechanisms underlying these therapeutic effects remain an active area of research[247]. Connecting molecular- and cell-level effects to changes in perception and behavior remains a central goal for psychedelics research as well as for neuropsychiatry as a whole, and requires an integrative understanding at the level of neural circuits and systems neuroscience.

One prevailing systems-level hypothesis, formalized in the Relaxed Beliefs Under Psychedelics (ReBUS) hypothesis[248], posits that psychedelics exert their effects by disrupting predictive processing. Predictive processing refers to a theoretical framework in which internal models of the world are generated and maintained in hierarchical cortical networks to optimize perception, leaning, and action[249,250]. If a sensory input matches the internally held models of the environment ("priors"), neural responses to this expected input are suppressed in sensory cortical pathways via "top-down" modulation (predictions) from higher regions. If instead, sensory input deviates from prior expectation (e.g., an unpredicted stimulus), the responses in sensory cortex are effectively amplified, constituting a sensory "prediction error" that propagates forward in the network to higher cortical areas from the "bottom-up" to revise the internal model.

The ReBUS hypothesis posits that psychedelics reduce the precision of high-level priors and, thereby, reduce the suppressive impact of the top-down, predictive modulation on sensory regions, allowing for larger and more influential bottom-up signals[251]. Through this mechanism,

psychedelics can effectively destabilize pathological beliefs and thought processes that have become over-weighted in individuals with anxiety and depression by allowing for the processing of new sensory data and experiences that challenge these beliefs.

The ReBUS hypothesis and other similar hypotheses (e.g., synthetic surprise[251]) are supported by various lines of work. For example, psychedelics use leads to more realistic and less negatively biased projections of future events – an effect that positively correlates with the therapeutic benefits[245,252,253]. Psychedelics also decrease functional connectivity in distributed brain networks[254], an aspect of increased entropy (a core component of the ReBUS hypothesis)[255]. The model is also supported by the cellular and subcellular actions of psychedelic compounds. 5-HT_{2A} receptors are enriched in layer 5 excitatory pyramidal neurons in the cortex – the neurons that largely send top-down feedback to lower cortical and subcortical brain regions and that are thought to carry the "predictions" in predictive coding theory[250,256,257]. 5-HT_{2A} receptor activation is known to increase spontaneous and asynchronous excitatory postsynaptic currents (EPSCs) in layer 5 neurons[258], perhaps underlying a decrease in "precision" by randomizing activity in top-down cortical projections. Further, psychedelics are known to alter connectivity in these circuits, increasing dendritic spine turnover[259] via changes in synaptic gene expresssion[260], potentially accounting for the lasting therapeutic effects.

While the neural bases of pathological beliefs are difficult to directly measure experimentally (especially at a cellular level), 5-HT_{2A} receptors are expressed cortex-wide, with a particular enrichment in visual cortices[261]. Focus on predictive processing in visual cortices could therefore provide a promising translational strategy. For example, visual oddball paradigms consist of the presentation of a rare stimulus ("deviant") interspersed in a sequence of highly predictable stimuli ("redundants"). In a sense, oddball paradigms generate expectations (or predictions) about

likely stimuli and test how cortical systems respond to violations of these expectations, providing a simplified system to test predictive processing theories[249]. Oddball paradigms translate well to rodents[262], where basic research has confirmed that "deviance detection" (DD) -- enhanced neural responses to contextually deviant stimuli -- follows multiple aspects of predictive processing theory[250], including enhanced DD in feed-forward superficial layers[263–265] that depends on feed-back modulation from higher brain areas[266]. In fact, DD (and one of its electrophysiological analogues "mismatch negativity") served as an example of a "sensory prediction error" in early conceptualizations of predictive processing theory[249].

Past work in humans has shown that psychedelics do alter brain responses in oddball paradigms, but the patterns of effects across studies contain some inconsistencies. Specifically, some studies demonstrate that P300 potentials – a late (300-600ms) event-related EEG signal linked to DD, context updating, and orienting to novel stimuli – are reduced in the auditory[267], tactile[268], and visual domains[269] during an acute trip. The impact of psychedelics on mismatch negativity, an earlier EEG component also related to DD, is mixed[268,270]. This discrepancy may result from comparing brain responses to deviant versus redundant stimuli, which ultimately convolves bottom-up adaptation of the redundant stimulus with genuine DD, rather than comparisons of deviants to a neutral control context[271].

Further, psychedelics also impact the earlier sensory-evoked responses, reducing the strength of measures such as the P100 and N170 in these human EEG studies. Similarly, in mice, the 5-HT_{2A} psychedelic DOI leads to an overall reduction of visually driven responses in primary visual cortex (V1)[272]. Although a disruption in predictive processing under psychedelics is ostensibly in line with ReBUS and related hypotheses, it is unclear how a *general reduction* of all sensory evoked activity, or in the magnitude of prediction errors could be congruent with the

ReBUS framework, which posits that a relaxation or reduction of the suppressive impact of top-down modulation will *enhance bottom-up sensory processing* to support the revision of pathological schema.

One potential resolution may lie in comparing the acute impacts of psychedelic drugs on cortical networks to the lasting impacts. For one, the psychedelic action of 5-HT_{2A} agonists involves temporary and dramatic changes to perception that last between 1 and 12 hours[247], yet the therapeutic effects are curiously long-lived, lasting for weeks at a time even after one dose[273], but do not involve lasting changes in visual perception commensurate to the acute period. A recent meta-analysis demonstrates reliable reports of "afterglow" effects lasting for up to a month (and beyond in many cases), including changes to mindfulness, mood, and behavioral flexibility[274]. One possibility is that psychedelics increase top-down modulation during the acute state in a very general manner (via increased spontaneous EPSCs in layer 5 pyramidal cells[258]) leading to greater suppression of lower cortical regions such as V1, but also increase plasticity among these top-down projecting layer 5 neurons, which could broadly increase their interconnectivity in the days and weeks after the trip[259]. This reorganization could reduce precision in their activity at the ensemble level in a manner that, in the days after the "trip", effectively weakens their top-down impact on sensory processing and enhances bottom-up signaling in cortical networks (and thus, revision of pathological belief structures), as posited by predictive processing theories of psychedelic action.

To test this resolution, we sought to understand whether and how predictive processing is altered in the weeks after psychedelics use. We studied individuals who had voluntarily taken 5-HT_{2A} agonist psychedelics (psilocybin or LSD), recording saccadic latencies to predictable versus deviant target locations (saccadic prediction task; SPT) and electroencephalography (EEG) during

the SPT and a passive visual oddball task. We found that recent psychedelics use mainly reduced the proportion of hyper-fast (putatively pre-cortical[275,276]) responses to targets in predictable locations, while leaving reaction times – and brain responses – to deviant target locations mostly intact. During passive visual processing, recent psychedelics use did not alter responses to contextually deviant or redundant stimuli in an oddball sequence, but did increase the responses to contextually neutral stimuli in a "many standards" control sequence, suggesting an over-generalization of deviance detection and enhanced bottom-up processing in the visual system. These effects were largely correlated with time since acute drug exposure. Passive visual processing-level effects were not present for individuals who had recently taken 5-MeO-DMT, a psychedelic with 100-fold higher 5-HT_{1A} affinity than 5-HT_{2A}[277,278]. Further, we show that similar impacts on predictive processing were present in V1 of mice given DOI, with suppressed DD during the acute phase and recovered DD after 7 days, along with generally augmented responses. Mice also exhibited weaker top-down modulation in V1 from medial prefrontal cortex (anterior cingulate area; ACa), along with enhanced bottom-up drive from V1 to ACa, as measured with multisite electrophysiology and Granger causality analysis. These results are consistent with the hypothesis that psychedelics have a lasting impact on predictive modulation of sensory processing from cortical circuitry. This study outlines a potent translational system for future, deeper investigations into the molecular, cellular, and systems-level mechanisms of psychedelics and their therapeutic effects.

3.2 Results

3.2.1 Recent psychedelics users exhibit fewer short latency "express" saccades to predictably presented targets

Sixteen individuals who had recently used 5-HT2A-recptor agonist psychedelics (PSY group; psilocybin [n=15] or LSD [n=1]) in the past 21 days (range 1 to 21 days) and sixteen age and sex matched comparison subjects (controls or CNT; see Table 2) were recruited for this study. PSY and CNT did not differ in major personality metrics (five-factor model[279]) or risk-taking behaviors, except for a slight increase in health/safety risk taking in the PSY group ($t(30)=2.10$, $p=.04$). Three subjects in the CNT group had used psychedelics previously at some point during their lifetimes, but were not group-level outliers in any of the major effects reported. The PSY group differed from the CNT group in the proportion of subjects using cannabis frequently (>4 times a month; Table 2), but the pattern of all major effects reported did not change when excluding the PSY participants with frequent cannabis use.

First, we administered a saccadic prediction task (SPT)[280,281] to study predictive processing and updating after psychedelics use. The SPT requires subjects to fixate on a central cross (i.e., prestimulus) after which a star-shaped stimulus appears at one of eight locations (Fig. 1A). For the majority of trials (85%), the stimulus appears at a standard (predictable) location and is colored green or purple ("standard" trials). On a subset of trials (15%), the stimulus appears at an "deviant" (unexpected) location. On half of these deviant trials, the stimulus is orange and does not signal a change in probable stimulus location ("deviant-no-update" trials). On the other half of the deviant trials, the stimulus is purple or green and signals a new "standard" stimulus location ("deviant-update" trials). This paradigm allows researchers to assess a) whether and how prior information

about stimulus location affects behavior (i.e., response latencies to stimuli at expected or unexpected locations), and b) how individuals integrate new information to update behavior.

We measured saccades through electrooculograms via two electrodes, placed just below and on the outer canthus of the left eye. Saccadic reaction times for each participant were scored blind to group identity and trial type (see Methods). Overall, participants produced faster saccades to stimuli at standard (predictable) locations than to stimuli at deviant (or unexpected) locations (standard mean/std: 264ms/28ms; deviant: 296ms/31ms; $F^{location}(1,29)=42.4$, $p<.001$). On average, CNT participants produced slightly faster saccades than PSY participants (CNT: 270ms/32ms; PSY: 289ms/33ms; $F^{group}(1,29)=4.69$,$p<.05$), but group differences in mean latency did not vary as a function of stimulus location (standard/expected location vs deviant location; $F^{interaction}(1,29)=.02$, $p=.88$), suggesting that use of prior information guided saccades similarly in both groups – at least at the level of mean latencies.

However, examination of the distributions of response latencies to different trial types suggested otherwise. CNT, but not PSY, participants exhibited different distributions of saccade latencies to the standard location compared to the deviant location (Fig 1C; kstest=.086, $p<.001$), suggesting that CNT participants generated different types of saccades to predictable versus unexpected target locations, while PSY did not (kstest=.046, $p=.16$). CNT and PSY response distributions to the deviant stimulus locations were not different (kstest=.040, $p=.60$), while the CNT response distribution to the standard (expected) location differed dramatically from the PSY distribution (kstest=0.10, $p<.001$).

As illustrated in Fig 1C, CNT participants produced an enriched proportion of short latency responses (<200ms) to targets in the standard location relative to the deviant location. This set of short latency saccades contains two subtypes: anticipatory saccades (ii in Fig. 1B) and express

saccades (iii in Fig. 1B)[282]. Saccades <70ms are considered anticipatory as this is the lower limit of visual afferent innervation of saccade-generating brainstem nuclei, and thus these saccades are non-visually driven[283]. CNT and PSY did not differ in the overall percentage of anticipatory responses (CNT: 2.9%/3.5%; PSY:2.2%/3.2%; $F^{group}(1,29)=0.67$, p=.42), nor was there a group by stimulus location interaction ($F^{interaction}(1,29)=1.34$, p=.26). On the other hand, express saccades are a subpopulation of very fast – *yet visually-driven* (non-anticipatory) – saccades with a mode around ≈110ms, separate from typical response latencies around 200ms[276,282,284]. Such fast responses specifically arise when stimulus location and timing is fixed or highly predictable (typically with a pre-stimulus "gap" interval)[285]. Unlike normal latency saccades, express saccades are not initiated by typical cortical saccade generating circuitry[276,283]. Instead, express saccades arise due to preparatory/pre-stimulus increases in excitability in the midbrain superior colliculus[276,286]. This priming in the superior colliculus motor system depends on pre-stimulus excitatory modulation in a "top-down" manner from cortex –namely frontal eye fields and occipitoparietal regions[276,287,288]. Further, express saccades are known to increase with practice[285], further suggesting that they reflect learning of spatiotemporal stimulus likelihoods. Therefore, express saccade production could be argued to reflect top-down facilitation of motor responses.

We found that the group differences in the proportion of express saccades likely accounted for differences in condition-specific latency distributions mentioned above (Fig. 1C). Specifically, CNT participants produced a greater proportion of express saccades (90ms to 153ms) specifically to the standard stimulus (Fig 1D). When compared with the PSY saccades, CNT saccades include a greater percentage of express saccades to stimuli in the standard location (CNT mean/std: 8.7%/5.9%; PSY: 3.5%/2.7%; $t(29)=3.16$, p<.01), but showed no difference from the PSY group

in express saccades to the deviant location (CNT: 3.4%/3.5%; PSY: 1.6%/2.4%; t(29)=1.63, p=.11; ($F^{interaction}$(1,29)=5.16, p<.05).

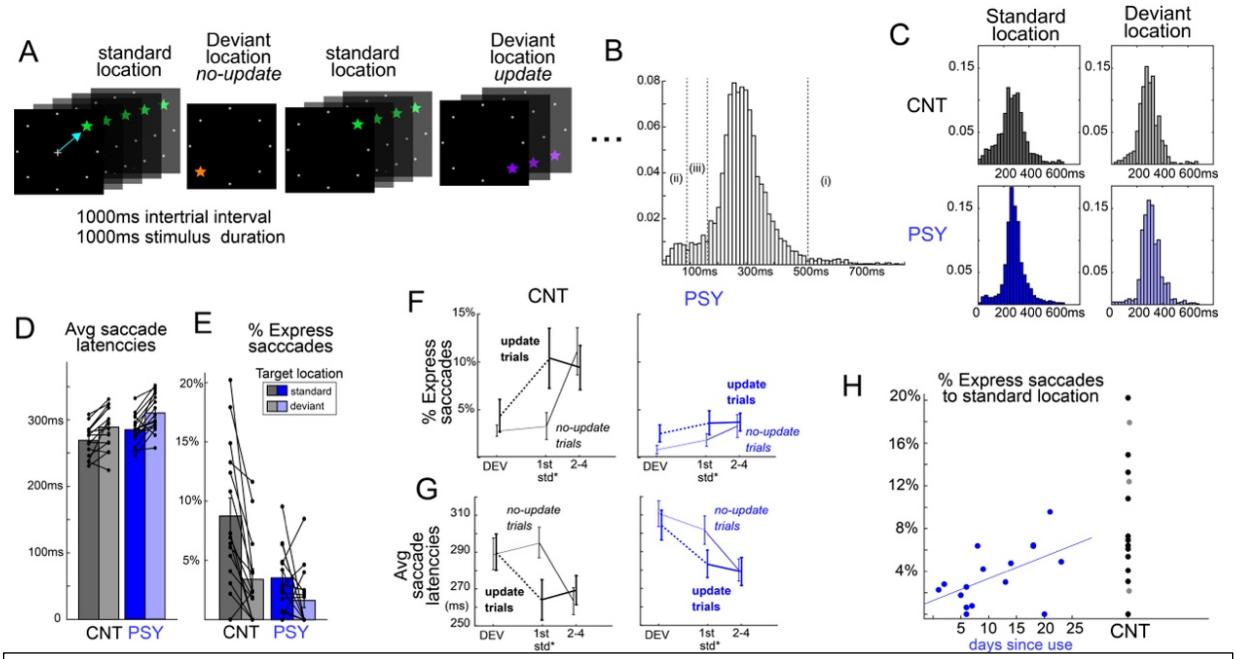

Figure 1: Recent psychedelics use reduces fast latency responses to predictable stimuli. *A) The saccadic prediction task (SPT) involving saccadic targets in standard and deviant locations, which were either informative of the upcoming targets (update) or not (no-update). B) saccade latency histograms across all subjects and trial types, categorized as portions of slow/non-responsive trials (i), putative anticipatory saccades (ii), and fast- or express-saccades (iii). C) Histograms by group and stimulus location. D) Average saccade latencies by group to standard and deviant target locations. E) Percentage of express saccadic responses (between 90 and 153ms) by group and target location. F) Percentage of express saccade responses and G) average saccade latencies for each group as a function of trial-type (x-axis) and deviant type (different lines). H) Percentage of express saccades produced as a function of days since psychedelics use. Gray dots in the CNT group represent individuals with past use of psychedelics, but >11 months prior to the study.*

Excluding these fast latency saccades, CNT and PSY did not differ in their response latencies to stimuli in the standard location (CNT: 282ms/23ms; PSY: 288ms/26ms; t(1,29)=-0.70,p=.48), suggesting recent psychedelics use could specifically weakened top-down (excitatory) modulation brainstem circuitry (superior colliculus), rather than a general slowing of higher-level motor control circuitry. This interpretation is consistent with the fact that the

percentage of express saccades to the standard stimulus was correlated with the time that had passed since the last use of psychedelics (Fig. 1H; $r=.53$, $p<.05$), suggesting that subjects begin to return to typical top-down control of saccadic circuitry after ≈7 days. The SPT also allows for an assessment of how individuals use new information to update their behavioral strategies. The proportion of express saccades was mostly stable to stimuli in the standard location across trials except for stimuli immediately after the "no update" deviant (Fig 1F). Subjects generated significantly fewer express saccades to the standard stimulus immediately after the "no update" deviant compared to the standard after the "update" deviant ($F^{location}(1,29)=11.81$, $p<.01$). Examining mean saccade latencies over all responses, a similar a slowing effect was also present after the "no update" deviant (relative to the "update deviant"; $F^{location}(1,29)=16.89$, $p<.001$), Interestingly, this pattern was present in both groups (Fig. 1G) and did not differ between groups ($F^{interaction}(1,29)=0.76$, $p=.39$).

A slowing effect after the "no update" deviant is highly consistent with past studies using this paradigm and has been interpreted to reflect effects of updating[281]. That is, a) participants in both groups made faster saccades overall to the standard stimulus occurring immediately after the updating deviant, suggesting rapid updating of internal models of probable target locations in both groups, but b) participants erroneously updated their expectations to "no update" deviants, effecting slower responses to the subsequent "standard" stimulus (which recovered quickly).

In sum, these results suggest that predictive processing in the visuomotor system is altered after psychedelics use. These results are nuanced in that overall mean saccade latencies of were faster to the predictable location in both PSY and CNT, but the proportion of very fast saccades (express saccades) to predictable locations was dramatically reduced in PSY. This effect may be explained by examining the multiple effector loops in the human saccadic system. These effector

loops consist of slower volitional saccades involving sensory, motor, and frontal cortical processing of the target and intended movement[283], and fast- or express-saccades that circumvent higher cortical structures due to preparatory (top-down) priming of midbrain saccadic nuclei[276,289] by frontal and parietal eye fields[276,288]. In this framework, our results suggest that psychedelics may leave predictive processing and context updating intact in the former system – higher cortico-cortical circuitry – while reducing top-down modulation in latter system – cortico-subcortical circuitry – effectively eliminating phenomena like express saccades.

3.2.2 Recent psychedelics users show enhanced early EEG responses to predictably presented targets

Past work suggests that fast-regular and express-saccades are produced with limited cortical processing of visual information[289], due to preparatory modulation of retinotopic motor maps in superior colliculus from top-down cortical sources[276,290]. Above, we interpret the lack of express saccades in PSY participants to be driven by the attenuation of such top-down modulation, in line with the ReBUS theory[248]. If this interpretation is true, the CNT group should exhibit smaller cortical responses to stimuli in the standard location than to the deviant location while, the PSY group should show similar cortical responses to the stimulus in the standard location as to the deviant location, as equal cortical involvement is needed in both cases.

We recorded 32 channel electroencephalography (EEG-Biosemi) while subjects completed the SPT. Scalp-EEG is far more sensitive to neural activity from cortical sources than e.g., brainstem nuclei, allowing us to test our hypothesis. Based on averaged event-related responses (ERPs) to stimuli in the time-voltage domain, PSY participants appeared to demonstrate greater cortical responses to all stimuli (Fig. 2A-F). To study trial-type specific activity during this paradigm, we analyzed the EEG activity in the time-frequency domain to increase signal to noise

ratio (as the number of trials was ≈20 for some conditions) and disentangle increases in signal power from phase-alignment across trials[276,291,292].

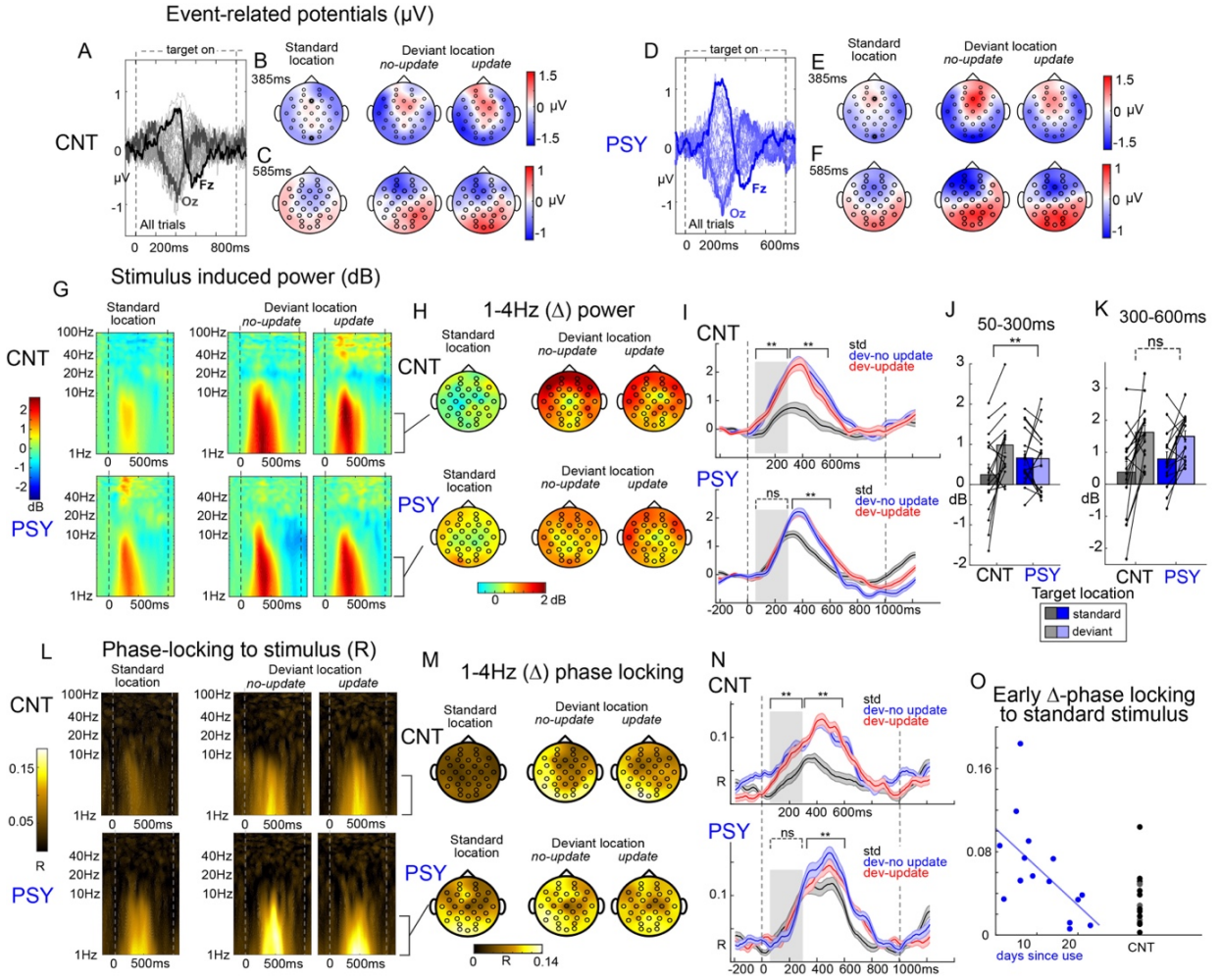

Figure 2: Psychedelics use augments early processing of predictable target stimuli. *A) Butterfly plot of event-related potentials to all stimuli (each line is one of 32 electrodes) averaged across all CNT subjects, locked to target onset, with B,C) averaged topographies from peaks in A. D-F) same as A-C but for PSY. G) Stimulus induced power, averaged over all electrodes, to targets in the standard location and the deviant locations for CNT (top) and PSY (bottom) subjects. H) Topographies showing averaged delta-band power from 50 to 600ms post-stimulus onset. I) Time-course of averaged delta-band power showing J) early time windows (50-300ms) were larger to the deviant targets in the CNT but (below) not in the PSY group. K) Both groups showed significant modulation in the later time window (300-600ms). L-N) same as G-I, but for inter-trial phase locking. O) Correlation of delta-band phase locking across all electrodes during the early period (50-300ms) with days since psychedelics use. **-p<.01*

Consistent with our hypothesis, trial-averaged power (i.e., average single-trial power) to the onset of saccadic targets was much weaker in CNT subjects to stimuli in the standard location as compared to stimuli appearing in deviant locations (Fig. 2G; averaged over all electrodes, 50-600ms post-stim onset), and this was generally true across the scalp in delta (1-4Hz; Fig. 2H; $t(15)=3.65$, $p<.01$), theta, (5-8Hz; $t(15)=3.15$, $p<.01$) and alpha frequencies (9-13Hz; $t(15)=2.35$, $p<.05$). Also as expected, theta and delta differences were absent in PSY for early stages of sensory cortical processing (50-300ms; delta, Fig. 2I,J: $F^{interaction}(1,30)=6.40$, $p<.05$, CNT-$t(15)=3.12$,$p<.01$, PSY-$t(15)=-0.08$, $p=.93$; theta: $F(1,30)=7.85$, $p<.01$, CNT-$t(15)=2.95$, $p<.01$, PSY-$t(15)=-1.02$, $p=.32$).

No group by stimulus location interactions were present for later processing periods, as both PSY and CNT groups demonstrated augmented delta (Fig. 2K; CNT-$t(15)=3.62$, $p<.01$, PSY-$t(15)=3.55$, $p<.01$) and theta power (CNT-$t(15)=2.90$, $p<.05$, PSY-$t(15)=2.63$, $p<.05$) to deviant stimuli. This suggests that later brain responses to contextually deviant and behaviorally important stimuli, i.e., DD, P300, or prediction-error-like signals, were unaffected in PSY participants during this paradigm. While single-trial power may reflect both stimulus-entrained and endogenously-driven neural processing of a stimulus[293,294], inter-trial phase-locking to the onset of sensory stimuli specifically captures stimulus-entrained signals and may better index bottom-up processing of sensory inputs, although it is also modulated by context and attention[295]. Like with single trial power, CNT participants showed increased phase-locking factor (PLF) to stimuli in the deviant locations compared to stimuli in the standard location in delta frequencies (1-4Hz; Fig. 2L-N; $t(15)=4.7$, $p<.001$) and, to a weaker extent, in theta frequencies (5-8Hz; $t(15)=2.38$, $p<.05$), as PLF responses in general were most robust from 1-4Hz. Delta differences were altered in PSY for early stages of sensory cortical processing (50-300ms; delta: $F^{interaction}(1,30)=5.39$, $p<.05$, CNT-

t(15)=3.31,p<.01, PSY-t(15)=-0.50, p=.62; Fig. 2L-N), but not for later stages (300-600ms), again suggesting intact processing of deviant stimuli.

The magnitude of the early (50-300ms) response to the stimulus in the standard location was inversely correlated with the number of days since psychedelics had last been taken (r=-.59, p=.017; Fig. 2O) and with a lower proportion of express saccades across all subjects (r=-.37, p=.03; Fig. S8F), suggesting that these fast saccades to predictably located target stimuli (which were enriched in the CNT group) occurred in the absence of strong bottom-up, cortical processing of the stimuli. This is consistent with the hypothesis posited above and past work[275,276], linking express saccades with more involvement of a faster, sub-cortical effector loop.

Low frequency responses (delta/theta) did not differ between groups for update versus no-update deviants (Fig. 2G-I,L-N), but a trend toward a group by update-type interaction was present in the gamma-band in the CNT group (40-100Hz, 200-600ms Fig. 2G; F(1,30)=2.35, p=.14; Fig. S8C-E), showing greater late gamma power to update trials versus no-update trials. PSY, instead, appeared to show stronger gamma to stimuli in the standard location than the CNT group than to the deviants (Fig. 2G; t(30)=-2.05, p<.05). In both groups, gamma in this time range was mostly right-frontally distributed (Fig. S8E), emerged later than the start of theta and delta-band (Fig. 2G), and was not phase-locked to the onset of the stimulus: all suggesting that it reflected later-emerging endogenous activity, possibly akin to mental processes underlying context updating. However, these effects were highly variable across subjects in both groups, and should be interpreted with caution (Fig. S8D). Indeed, the oculomotor behaviors suggested that context updating was mostly intact in the PSY group (Fig. 1).

In summary, the CNT subjects demonstrated drastically reduced early brain responses to stimuli in standard (expected) locations, relative to stimuli in deviant (unexpected) locations, along

with a higher proportion of express saccades to these targets (Fig. 1E). Because express saccades result from prestimulus "top-down" modulation of midbrain superior colliculi from cortical sources[276,287–290] that effectively reduces the magnitude of (and perhaps the need for) cortical involvement (see Fig. S10 for response-locked EEG)[276], we interpret these results to suggest that CNT show strong top-down influence of their oculomotor behavior in this paradigm. In contrast, in PSY, cortical processing to standard versus deviant locations did not differ in the early processing stages, and this group exhibited much fewer "express saccades" to stimuli in standard locations (Fig. 1). This suggests weakened top-down excitatory modulation of oculomotor circuitry – an effect which scales with recent psychedelics use.

Brain responses in the 300 to 600ms window – the timeframe where DD manifests[262,264,296]– were increased to stimuli in deviant locations in both CNT and PSY participants, suggesting that both groups registered deviance at some level. As sensory prediction errors are theorized to support subsequent learning and update of environmental models (i.e., context updating), this finding is consistent with results in Fig. 1G and H, showing that context updating is also unaltered in saccadic metrics among PSY (Fig. 1GH).

3.2.3 Recent psychedelics users show overgeneralized visual deviance detection

Next, we sought to study visual DD more directly. The SPT is an active saccade task that involves motor preparation and concurrent eye-movements that may have altered visual processing via attentional modulations[297] or which may be convolved with the sensory processing related EEG signal[276], making it difficult to ascertain the impacts on basic visual processing and bottom-up DD. Further, in the SPT, the direct comparison of brain responses to repeated stimuli (the standard stimulus location in this case) to brain responses to rare stimuli (the deviant location) convolves reduced responses to redundancy (e.g., stimulus specific adaptation or repetition suppression) with

enhanced responses to deviance, i.e., DD. A more neutral comparisons condition, where a stimulus is neither contextually redundant nor deviant, is more appropriate for studying DD.

To this end, we presented oriented drifting grating stimuli both in a context where one orientation (e.g., 90 degrees) was contextually redundant (p=.875) and another orientation (e.g., 0 degrees) was contextually deviant (p=.125; "oddball" sequence; ≈3.3 minutes; Fig. 3A) and again in another context where both orientations were equally rare (p=.125) but contextually neutral ("many standard control" sequence; ≈3.3 minutes; Fig. 3A), while subjects maintained fixation on a central cross[266]. In this "many standards control" sequence, brain responses to stimuli should exhibit limited adaptation, but not carry contextual deviance relative to their concurrent context[298], providing a useful contrast to the oddball "deviant" for studying DD.

As expected, subjects showed augmented responses to a stimulus when it was deviant relative to when it was contextually neutral (Fig. 3B-D). These differences were largely present in delta band (3-4Hz; $F^{stimulus}$ (1,28)=25.93, p<.001) and to a lesser degree in the theta-band (5-8Hz; $F^{stimulus}$((1,28)=7.04, p<.05), peaking in occipitoparietal and frontocentral electrodes (Fig. 3C). Other frequency bands did not show strong DD effects. Delta- and theta-band DD is consistent with past work on DD in mice[264], which has shown that this DD signal emerges alongside increased neural firing in layer 2/3 of primary visual cortex (V1) after 225ms.

Past work on the P300 in humans has isolated two scalp-level components – a P3a component, which emerges >250ms post-deviant onset and marks change detection and attentional engagement, and a P3b component, which emerges later and marks context updating and subsequent memory processing[296]. As we focused analyses in the time-frequency domain (in order to enhance signal to noise ratio and to dissociate phase from amplitude to avoid polarity effects across stimuli), we analyzed a time-frequency equivalent DDa (275-400ms) and DDb (400-600ms)

in the delta-band based on this past literature and on the waveforms evident in our group averages (Fig. 3D; the same patterns were present for theta; Fig. S9E)

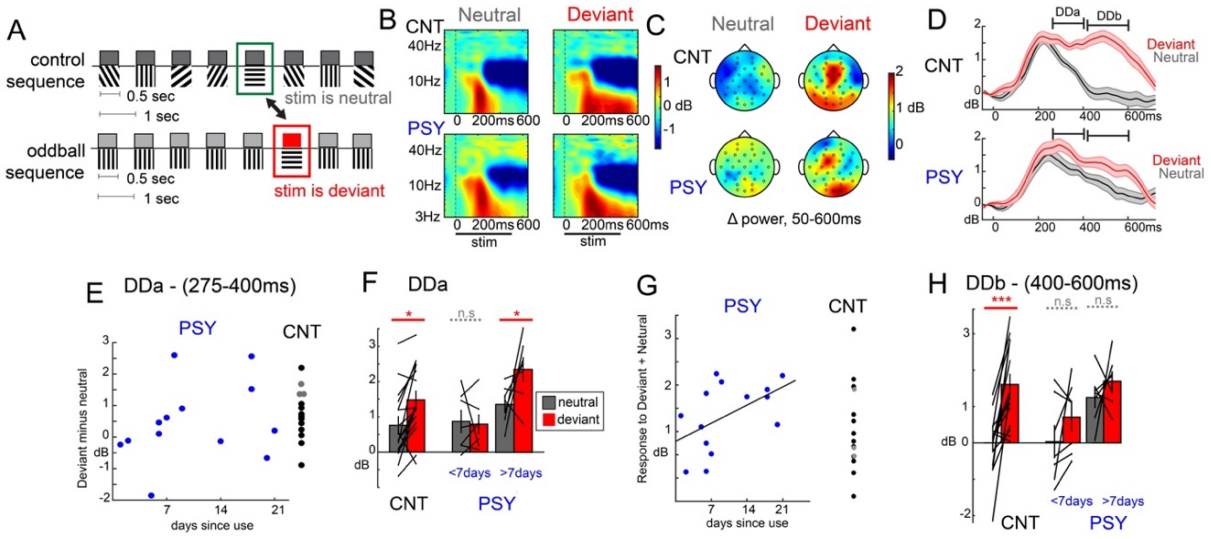

Figure 3:Psychedelics enhance processing of contextually neutral visual stimuli. *A) Visual oddball and many standards control sequence, designed to study evoked responses to the same visual stimuli (full-field, square-wave moving oriented gratings) when they are contextually deviant (bottom) vs neutral (yet equally rare). B) Time-frequency plots of induced power across frontocentral and posterior electrodes evince strong deviance detection (stronger responses to deviant vs neutral) in the delta- (3 to 4Hz) and theta-band (5 to 8Hz). C) Topographic plots of delta power for each group. D) Average induced power over time averaged over frontocentral and posterior electrodes. Analyses focused on an early (275ms to 400ms) and late (400ms to 600ms) time windows termed DDa and DDb. E) Scatterplot of delta power to the deviant minus neutral for DDa period for all subjects vs days since psychedelics use. F) Average delta power for DDa for CNT (individual subjects as single lines) and for the PSY group, split into psychedelics use in the past 7 days vs in the time period between 7 and 24 days. G) Scatterplot of delta power averaged over deviant and neutral stimuli for DDa period for all subjects vs days since psychedelics use. H) Same as F, but for DDb. *p<.05, ***p<.001.*

For the DDa component, there was a strong effect of stimulus type across all subjects ($F^{stimulus}(1,28)=11.33$, $p<.001$), and no apparent group by stimulus-type interaction ($F^{interaction}(1,28)=0.53$, $p=.47$). However, based on the correlations present in the SPT task behavior and brain responses, we investigated whether the time since psychedelics use predicted the DDa response. Although DDa did not significantly correlate with the number of days since psychedelics

use (r=.26, Fig. 3F), the PSY group was much more homogeneous, and lower, in the first week after use as compared to in the 2-3 week range. We split the PSY group in to <7days (n=7; "recent") and >=7 days (n=7; "later"). Interestingly, we observed a loss of DDa compared to CNT for the recent PSY use group ($F^{interaction}(1,21)=5.21$, $p<.05$) but not for the later PSY group ($F^{interaction}(1,21)=0.44$, $p=.51$; Fig. 3F, S3D). There was also group main effect present the later group ($F^{group}(1,21)=4.22$, $p=.052$). That is, while DDa did trend toward returning for the late group (later-$t(6)=2.05$, $p=.08$; recent-$t(6)=0.24$, $p=.81$; CNT- $t(15)=3.88$, $p=.001$), this later use PSY group also exhibited larger responses than CNT in this time window to both contextually neutral and deviant stimuli than the CNT group, consistent with the notion that psychedelics lead to a generalization of DD-like cortical responses across contexts. This overall increased response to all stimuli was strongly correlated to the number of days post psychedelics use, increasing since use ($r=.51$, $p<.05$; Fig. 3G).

For the DDb component, there was also a very strong effect of stimulus type across all subjects ($F^{stimulus}(1,28)=24.82$, $p<.001$), and a group by stimulus-type interaction ($F^{interaction}(1,28)=4.68$, $p<.05$). Splitting into recent vs later PSY suggested that DDb was reduced in both groups (later-$t(6)=1.03$, $p=.35$; recent-$t(6)=1.52$, $p=.18$; CNT- $t(15)=5.04$, $p<.001$; Fig. 3H), with a similar pattern of larger overall responses in the later group (Fig. 3H; S9F).

We also found moderate DDa and DDb effects in phase locking factor (PLF) to visual stimuli for delta (DDa: $F^{stimulus}(1,28)=5.94$, $p<.05$; DDb: $F^{stimulus}(1,28)=14.72$, $p<.001$) and theta bands (DDa: $F^{stimulus}(1,28)=5.38$, $p<.05$; DDb: $F^{stimulus}(1,28)=12.71$, $p<.01$), but no group by stimulus interaction (Fig. S9J-L), even when splitting by recent vs later use. This absence of a PLF effect may result from an overall smaller DD PLF signal in all subjects (CNT and PSY) in a passive (oddball) as compared to an active (SPT) paradigm.

Although we employed the oddball paradigm to study DD, it also provides a platform to study stimulus specific adaptations (SSA) to the redundant stimulus[271]. Past work suggests that SSA is distinct from DD, both in terms of its upstream anatomical emergence[264], circuit mechanisms[262], and pharmacological modulators[299], so we sought to separately examine whether SSA was affected by PSY. However, EEG responses to the redundant stimulus in CNT were largely similar to responses to the neutral stimulus, regardless of frequency band (Fig. S9; $t^{delta}(15)=0.17$, p=.86; $t^{theta}(15)=0.72$, p=.48; $t^{alpha}(15)=0.49$, p=.62; $t^{beta}(15)=0.11$, p=.91; $t^{gamma}(15)=-1.78$, p=.09), suggesting that the parameters of our study were not well suited to capture true SSA. Further, the response to the redundant stimulus in the PSY group was not different from that in the CNT group (Fig. S9Y; $t^{delta}(28)=0.33$,p=.74; $t^{theta}(28)=0.43$, p=.67; $t^{alpha}(28)=0.68$, p=.50; $t^{beta}(15)=0.51$, p=0.61; $t^{gamma}(15)=-1.46$, p=.15).

In sum, visual context processing during the passive oddball paradigm was altered after psychedelics use. The pattern of results (Fig. 3B-D) suggests that PSY did not exhibit weaker brain responses to contextually deviant stimuli (suggesting intact deviance detection), but stronger responses to contextually neutral stimuli, effectively decreasing the deviant versus neutral contrast. This suggests that psychedelics generalize prediction errors to otherwise neutral stimuli, but not to obviously redundant stimuli. SSA has been theorized to reflect passive, bottom-up adaptation to repetition[271], involving mechanisms such as synaptic depression in thalamocortical inputs[264] that are distinct from the top-down predictive suppression that is posited in predictive processing theories. Ostensibly, comparing the redundant to the deviant, as others have in the past[267,268,270], yielded no obvious differences between groups, replicating some past results[270]. This comparison ultimately highlights the importance of utilizing a context-neutral control for studying DD.

3.2.4 Alterations in basic visual predictive processing are specific to 5-HT$_{2A}$ psychedelics

We additionally recruited 12 subjects who had recently (<24 days) taken a different psychedelic compound, 5-MeO-DMT, which is produced in the parotoid glands of the toad species, Incilius alvarius. Like psilocybin and LSD, 5-MeO-DMT involves an intense psychedelic experience involving altered perception, but, unlike psilocybin or LSD, 5-MeO-DMT has a 100-fold higher affinity for 5-HT$_{1A}$ receptors than 5-HT$_{2A}$[278]. This group did not significantly differ from CNT in any demographic, lifestyle, or risk-taking behaviors, and only showed a moderately increased openness compared to the CNT group (D=0.80; Table 3). We focused on the major effects that were different in the PSY group from Figs 1 to 3 and present effects in Fig. S11.

The distribution of saccade latencies to targets in the standard (predictable) location did not statistically differ between the 5-MeO-DMT group and the CNT (kstest=.038, p=.12). Nor did the two groups differ in their distributions of responses to targets in the deviant location (kstest=0.057, p=.28; Fig. S11A). Further, an analysis of the proportion of express latency saccades to the standard vs deviant target locations demonstrated no main effect of group (F(1,25)=0.09, p=.77) or group by location interaction (F(1,25)=0.69, p=.41), suggesting that, unlike the group taking 5-HT$_{2A}$ agonist psychedelics, the 5-MeO-DMT group produced comparable portion of express saccades to spatiotemporally predictable stimuli (Fig. S11C). The proportion of express saccades did not scale with the time since use (Fig. S11D).

However, the lack of group differences in express saccade production could have been driven by two subjects in the 5-MeO-DMT group (Fig. S11D). Consistent with this notion, visual processing of saccadic targets in predictable (standard) versus deviant locations were altered in the 5-MeO-DMT group in a similar manner to the PSY group. Namely, early ($F^{interaction}$(1,26)=7.03

p<.05) but not later delta power ($F^{interaction}(1,26)=1.08$, p=.31) showed group by stimulus location interactions, driven by larger early EEG responses to stimuli in the standard location in the 5-MeO-DMT group relative to the CNT, but relatively normal responses to targets in the deviant location (Fig. S11E-G; also see Fig. S11H-J for PLF). This effect pattern was nearly identical to which was seen in the PSY group (Fig. 2). Overall, this suggests that predictive processing in an active oculomotor task is similarly altered after both types of psychedelic experience. Still, the lack of a clear behavioral difference, and the lack of effects which correlated with time since psychedelics use (Fig. S11D) suggest caution in this interpretation.

Critically, unlike the PSY group, the 5-MeO-DMT group exhibited unaltered predictive processing during a basic – or passive – visual processing task. That is, visual DD was unaltered in the 5-MeO-DMT group relative to CNT during the oddball paradigm (Fig. S11K-P), with strong DD in delta band power for early (275-400ms DDa, $F^{interaction}(1,26)=1.31$, p=.27) and late time periods (400-600ms DDb, $F^{interaction}(1,26)=0.35$, p=.56), and these effects did not significantly correlate with time since psychedelics use (r=0.09 and 0.43, for early and late, respectively).

In summary, similar effects between the two psychedelic groups were on oculomotor processing during the SPT, but not on visual predictive processing in a passive setting. As the oddball paradigm was a passive task, not requiring a coordinated motor output like in the SPT, we interpret the pattern of effects to suggest that, while both psychedelics alter predictive processing in broader sensorimotor and cognitive brain networks (e.g. frontal-eye fields), only 5-HT_{2A} receptor agonist psychedelics (psilocybin and LSD) appeared to alter purely visual predictive processing. This is consistent with the fact that 5-HT_{2A} receptors are enriched in visual cortex, while 5-HT_{1A} receptors have relatively lowest concentration in visual cortex (relative to the rest of

cortex)[261]. Overall, these results suggest that visual processing paradigms may be more appropriate for studying the mechanisms of 5-HT_{2A} agonist psychedelics than other compounds.

We note, however, some caution is warranted in this interpretation. The 5-MeO-DMT group was relatively small (n=12) and not as well matched to the control in terms of age (CNTmean/std=37.4/15.1; PSY=36.8/14.5; vs 5-MeO-DMT=47.2/10.5), and the 5-MeO-DMT group had a longer period since the last use of psychedelics than the PSY group on average (PSY=11.0/7.1; vs 5-MeO-DMT=16.9/7.2). Regardless, none of the principal measures in the current study showed significant age or sex effects in either group (Fig. S11), with the exception of the DDa, which showed a trend level increase in males across all groups ($F(1,38)=3.64$, $p=.064$; Fig. S11G).

3.2.5 5-HT_{2A} receptor agonists alter predictive processing and top-down modulation in primary visual cortex in mice

To test causality more directly and interpret the neurophysiological basis of this finding of altered visual predictive processing after 5-HT_{2A} receptor agonist psychedelics, we used mice, and examined how 2,5-Dimethoxy-4-iodoamphetamine (DOI), a 5-HT_{2A} receptor agonist with established psychedelic properties in both humans and mice[247,272], affected passive V1 processing of context in the animals.

Using the same basic visual oddball paradigm described above and in past work[264,266,300] (Fig. 4A), we recorded local field potentials (LFP) using bipolar electrodes inserted into V1 of mice (Fig. 4B) as previously reported[266]. We quantified stimulus-induced power to full-field moving grating stimuli when stimulus orientations were contextually neutral (i.e., during a many standards control) and when they were contextually deviant (i.e., during an oddball paradigm—Fig. 4D) across three timepoints: before, 30 minutes after (acute or during), and seven days after

(post) subcutaneous injection of 10mg/kg of DOI[272]. We compared these mice to a separate cohort of mice that were injected with the saline vehicle and recorded at the same intervals (Fig. 4E). Groups did not differ in the average locomotion speed or proportion of time locomoting during recordings (Fig. S13). In the saline group (SAL), we found a robust broadband (3- to 40-Hz) DD signal (i.e., stronger responses to deviant versus neutral contexts) in the 250- to 400-ms time range (Fig. 4E,F; Fig. S13; $F^{stim\text{-}type}(1,15)=18.18$, $p<.001$; time ($p=77$) and interval by stimulus-type interactions were not present ($p=.38$)). In the cohort administered DOI, an interval by stimulus-type interaction was present at a trend level ($F^{timeXstim\text{-}type}(1,15)=3.2$, $p=.07$) in a manner that was highly similar to the pattern of effects we saw in humans (Fig. 3). That is, we observed diminished DD shortly after DOI administration ($t(6)=-0.12$, $p=.45$, one-tailed), and DD recovery in the seven days post-DOI ($t(3)=3.38$, $p<.05$ one-tailed; Fig. 4G, H;). Interestingly, DD in this time-range (DDa) in humans after 7 days co-occurred with larger overall responses to all stimuli (Fig. 3F,G). This same pattern was present in the mice ($t(11)=1.94$, $p<.05$, one-tailed), suggesting that the increased cortical responses seen in humans post-psychedelics is present in primary visual cortex. Thus, psychedelics may have a lagged impact on bottom-up processing in cortical systems, in addition to weakened top-down modulation. To more directly test the hypothesis that psychedelics alter the balance of top-down modulation versus bottom-up information processing in the cortex, in favor of enhancing the latter, we also recorded local field potentials from ACa, a region of mouse prefrontal cortex with dense reciprocal connections with V1[301]. Although an exact analogue of a medial prefrontal region reciprocally connected with V1 is not present in primates, this region was chosen based on considerable past work showing a role for this circuit in mice in visual context processing[266,302] and visuospatial attention[303,304], suggesting it serves as a translational strategy to

understand top-down modulation of visual processing. ACa inputs to V1 synapse in layer 1, suggesting that they supply feed-back modulation, and have been demonstrated to be necessary for DD[263,266]

We analyzed phase-phase coherence between ACa and V1 during visual processing, which was maximal in the 1-10Hz range (Fig. S13B-D), as previously reported[266]. ACa-V1 coherence showed a slight decrease during DOI ($t(12)=1.94$, $p<.05$) and a nominal but non-significant decrease in the 7-days post DOI recording ($t(9)=0.83$, $p=.21$). This effect is consistent with recent work showing decreases in functional connectivity in distributed brain networks in humans for weeks after a single dose of psilocybin[59].

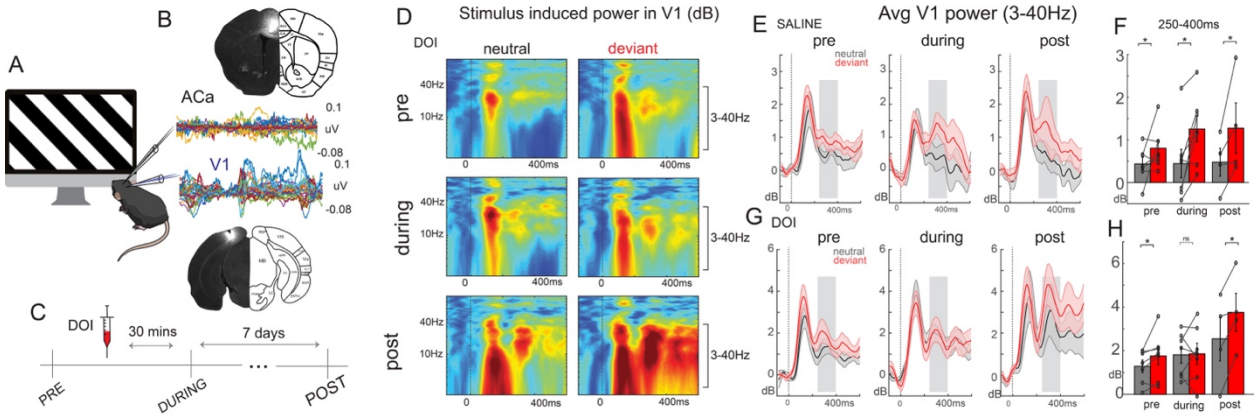

Figure 4: Acute and chronic effects of psychedelics in V1 of mice. *A) Visual oddball and many standards control paradigms were presented to mice while B) local field potentials were recorded in primary visual cortex (V1) and an area of medial prefrontal cortex (anterior cingulate area, ACa) that projects directly to V1. Anatomical slices indicate locations of DiI dye stained electrode placements, and overlapping traces depict LFP recorded on individual trials in a single mouse from ACa or V1. C) Recordings took place before, 30-minutes after (during the acute drug effects), and 7-days after DOI (n=7) or saline (n=7) was injected into mice intraperitonially. D) Time-frequency power plots of stimulus induced activity when a stimulus was contextually neutral (left) and contextually deviant (right) for the DOI group. E) Average power line plots from 3 to 40-Hz for the saline group demonstrates deviance detection pre, during, and 7-days post saline injection. F) Bar plots from the DDa time range in (E). G,H) Same as E and F, but for the DOI group. * p<.05, one-tailed t-test.*

As this circuit is reciprocally connected, we further sought to characterize the directionality of these effects. Specifically, we examined whether top-down (ACa-to-V1) and/or bottom-up (V1-to-ACa) connectivity differed during or after DOI. We utilized a non-parametric Granger causality analysis across frequencies (1-100Hz) to assess directed functional connectivity between these nodes during visual stimulation[305]. Our past work showed that ACa-to-V1 Granger coefficients were generally stronger than V1-to-ACa Granger coefficients in low frequencies during visual processing, suggesting strong top-down modulation in this circuit[266]. Our results here replicate that pattern and demonstrate relatively stable top-down (Fig. 5A,B) and bottom-up Granger causality during and 7-days after saline injection (Fig. 5E,F; Granger coefficients [GC] max-normalized within recordings; all comparisons to baseline $p>.33$). DOI induced a decrease in top-down Granger causality in the delta band (1-4Hz) relative to baseline during the acute drug phase ($t(12)=2.58$, $p=.020$) and a trend-level decrease in the 7-day post recording ($t(9)=1.68$, $p=.06$; Fig. 5C,D). Conversely, DOI induced an increase in bottom-up granger causality in the theta-beta band (5-25Hz) relative to baseline during the acute drug phase ($t(12)=-3.24$, $p=.008$) and in the 7-day post recording ($t(9)=-2.14$, $p=.030$; Fig. 5G,H). Collectively, these results offer more direct evidence of relaxed top-down modulation and enhanced bottom-up processing following psychedelics use.

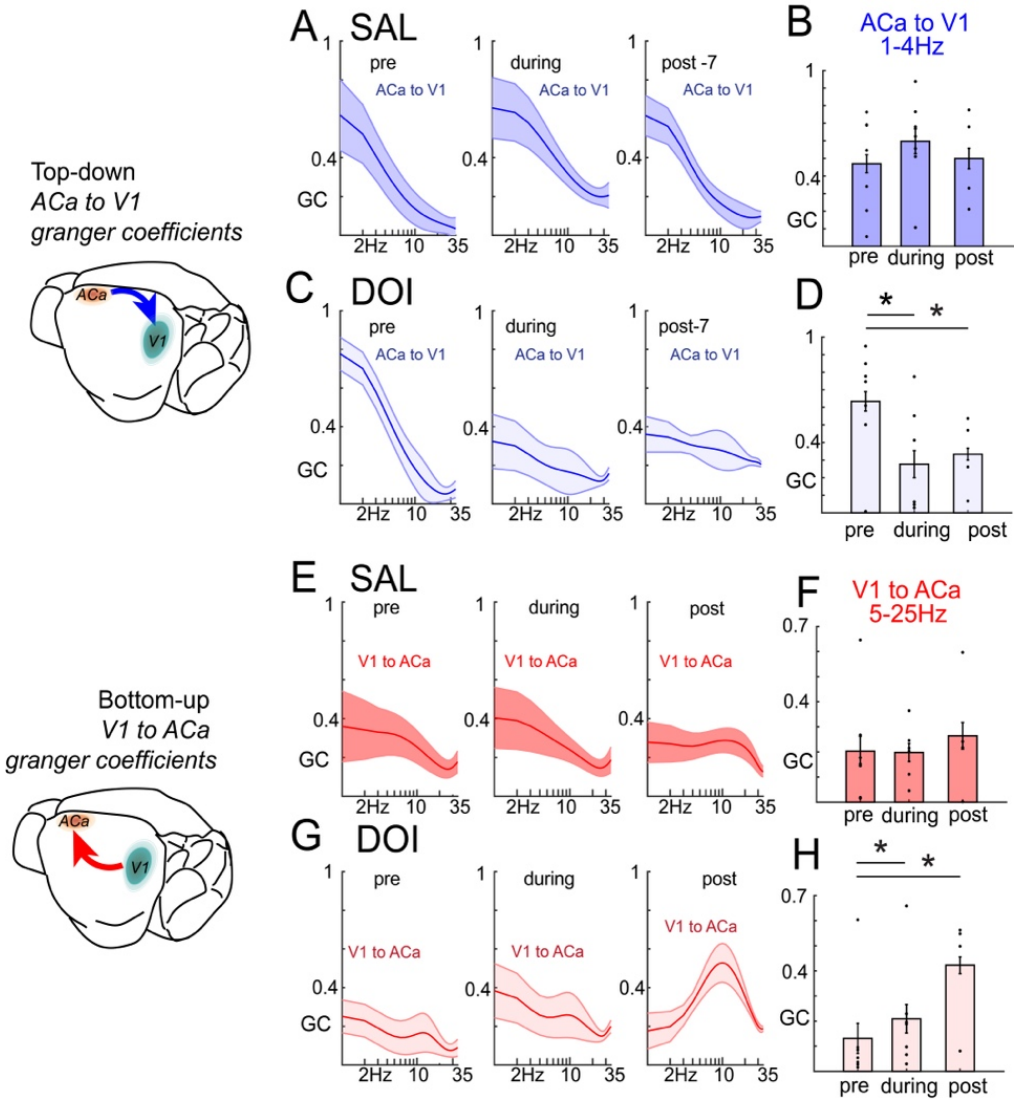

Figure 5: Psychedelics reduce top-down influence and increase bottom-up influence in fronto-sensory visual cortical networks. *A) Granger coefficients (GCs) calculated during the oddball paradigm, quantifying ACa to V1 influence across frequency bands in the pre-, during-, and post-7day time windows relative to saline injection. B) Bar-plot reflecting average ACa-to-V1 GCs for 1-4Hz. C,D) same as A and B, but for the group injected with DOI. E-H) Same as A-D, but for Granger causality in the bottom-up (V1 to ACa) direction, 5-25Hz. *p<.05.*

3.3 DISCUSSION

A principal function of the neocortex is to process sensory data in the context of concurrent and past stimuli and behavioral goals[257,306]. Predictive coding theories provide an

explanation of how such context processing is achieved in hierarchically organized cortical networks: top-down suppression of responses to expected stimuli that are consistent with, and amplification of responses (i.e. prediction errors) to unexpected stimuli that are inconsistent with, internal models of the world[250]. Our results show that 5-HT_{2A} psychedelics alter how visual stimuli are processed in their spatiotemporal and behavioral context. The pattern of effects concord with predictive coding models of context processing[249] and psychedelic action[248].

Specifically, augmented brain responses to contextual deviants (i.e., prediction error-like responses; Fig. 2I, 3F) and rapid response updating to contextually deviant events (Fig. 1H) were ultimately intact in the weeks after psychedelics use, suggesting that individuals could learn and update higher brain regions and behaviors. However, top-down modulation appeared weakened in certain circuits, as evidenced by reduced express saccades (Fig. 1G) and greater involvement of cortex during saccade generation (Fig. 2; Fig. S10), augmented stimulus processing outside of deviant contexts (Fig. 3,4), and direct recordings of the ACa-to-V1 circuit rodents (Fig. 5). This weakened top-down modulation (which is primarily suppressive in cortico-cortical circuitry[303], but excitatory in some cortico-collicular projections[288]) is consistent with the fact that bottom-up processing was stronger after psychedelics use: an effect which was evident in overall larger cortical responses to all stimuli in humans (Fig. 2,3) and mice (Fig. 4) and by direct recordings of functional connectivity in the mouse (Fig. 5). This pattern of effects, and the fact that it persists after the acute period, could help explain the abiding therapeutic power of psychedelics; an

enhanced ability to process and accommodate new information could serve to support the revision of negative schema that have become pathological in some individuals.

Important nuances are present in the temporal pattern of the effects that warrant attention and which both support and help revise existing theories of psychedelic action. Our experiments in both humans and mice suggest some differential short versus longer term impacts of psychedelics use on these functions, as summarized in Fig. 6. Acute (mice) and short-term impacts (<7days in humans) involve weakened responses to contextually deviant stimuli relative to contextually neutral stimuli, suggesting a temporary reduction in prediction errors, consistent with some past work[269], and reduced gain in V1[272]. Longer-term impacts in humans and mice (7 to 24 days) involved a recovery of DD, along with stronger brain responses to all stimuli, suggestive of a generalization of prediction errors to otherwise neutral stimuli[251]. Further, our mouse experiments suggest that 5-HT_{2A} agonists may exert these effects on visual predictive processing by shifting the balance of feed-back (or top-down) and feed-forward (or bottom-up) functional connectivity in the neocortex, reducing the former and enhancing the latter.

Interestingly, our results suggest that this reduction in top-down influence may emerge and recover in a different timescale than the enhancement of bottom-up drive (Fig. 6), implying that they may represent somewhat separate effects of psychedelics, with distinct mechanisms. First, we interpret the decreased proportion of express saccades in PSY to reflect a reduction in top-down modulation. This effect appeared to normalize over weeks (Fig. 1H). Similarly, top-down Granger causality in the mouse seemed to increase slightly over 7 days (Fig. 5C,D). Second, an increase in overall cortical responses actually became more dramatic over time after the psychedelic dose, as evident in the magnitude of DDa and DDb (Fig. 3F-H) and DD in the mouse (Fig. 4D). The bottom-up Granger curve in the post-7 day timeframe also appeared to be stronger than in the acute

timeframe of DOI exposure (Fig. 5G).If these effects, indeed, reflect temporally distinct impacts of psychedelics, this could ultimately carry implications for strategic therapeutic windows. Future theoretical or computational work should explore how this model (Fig. 6) and these results fit into ReBUS and related predictive processing theories of psychedelic action, while experimental work should test whether acute versus sustained effects in feed-forward versus feed-back circuity have distinct molecular, cellular, and structural correlates.

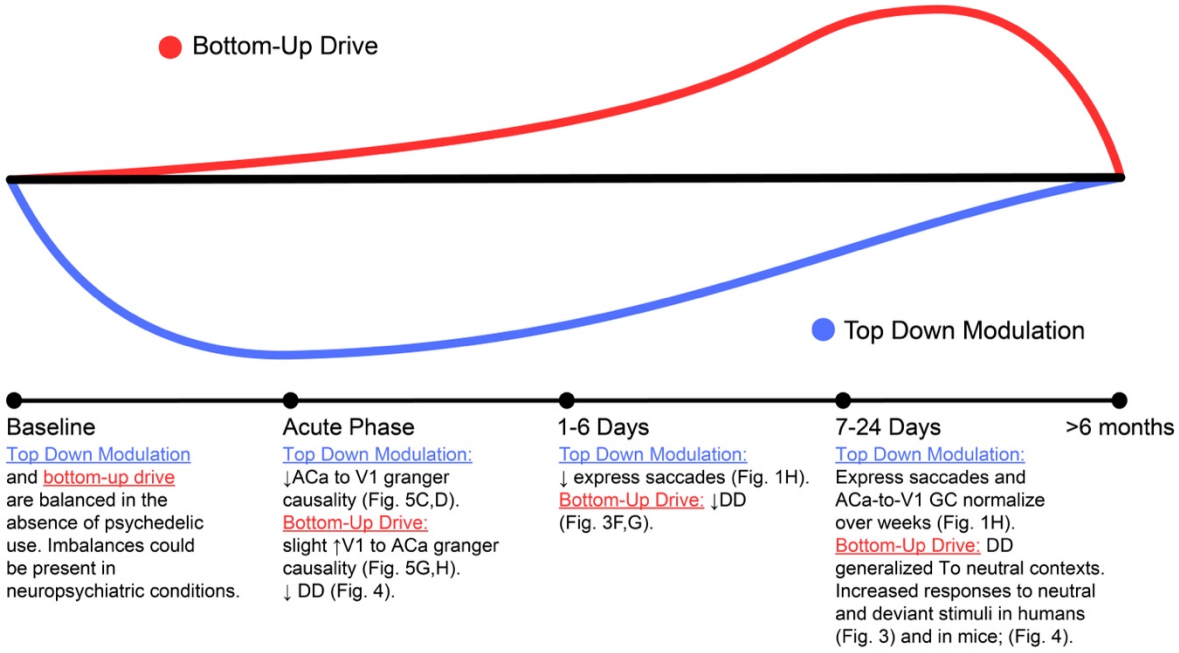

Figure 6: Distinct timescales of impacts of psychedelics on top-down vs bottom-up processing in the visual system. *Hypothesized timescales of impacts of psychedelics on visual processing in the oddball paradigm and oculomotor preparation and response generation. Effects summarized from figures above. Model is hypothetical, intended to provide guidance for future work. Return to baseline after 6 months is based on a) three control subjects who took psychedelics >11 months prior and b) Seigel et al 2024[10].*

The effects of psychedelics on saccadic behavior have not been thoroughly characterized to our knowledge. We identified alterations in saccadic behavior due to recent psychedelics use that were robust and correlated to the time since psychedelics use (Fig. 1H), yet which carried

some nuance that has implications for which brain circuitry is most impacted by 5-HT_{2A} agonists in the longer term. More generally, how serotonin directly modulates saccadic circuitry is not fully known. The superior colliculus (SC) receives projections from the dorsal, medial, and pontine raphe nuclei[307], but has relatively low expression of the 5-HT_{2A} subtype[308], especially when compared to cortex[261]. As 5-HT_{2A} receptors are enriched particularly in layer 5 pyramidal neurons[258], which project subcortically[257], this provides a plausible mechanism through which serotonin and serotonin-like compounds may alter the predictive circuits that give rise to express saccades[250,276,289].

Interestingly, we found that simple SSA – or reduced responses to a redundant stimulus – were not altered after PSY (Fig. S9). This could account for past negative results in mismatch negativity studies that compared the deviant to the redundant stimulus[270]. In our study, the primary effect of PSY on oddball processing is not in reducing responses to the deviant relative to a redundant (the classic "mismatch negativity" comparison), but in augmenting responses to a non-repetitive stimulus that is not technically deviant in its context (i.e. the neutral).

A number of limitations are present in the current study that should be addressed in future work. The human portion of our study was a retrospective between-subjects design. Although groups were matched on age, sex, and personality metrics, the PSY group had mildly increased health/safety risk taking and marijuana usage (Table 2). Importantly, excluding frequent marijuana users did not change the pattern of effects, most effects identified correlated with time-since psychedelics use, and the subsequent mouse experiments also helped to further establish a causal relationship between psychedelics use and cortical processing. Future work should validate our findings and include multiple timepoints from the same individuals, with random assignment and tight control of psilocybin dose (which was also missing from our study).

While our study focuses on visual processing as a model system, we hypothesize that similar mechanisms of relaxed priors and increased bottom-up signaling may occur across multiple levels of the cortical hierarchy. This cascade, propagating from sensory processing to higher-order cognition, could explain how perceptual changes lead to profound shifts in abstract beliefs, including those related to the self-perception and worldview. Future study is needed to connect these basic sensory changes to therapeutic effects – in time and in mechanism. If the two phenomena are connected, the saccadic and electrophysiological measures presented here could represent useful biomarkers for testing drug effects in animal models.

Table 2: Demographic data, personality scores, and risk-taking among control and recent psychedelics-users.

	Control Group	**Psychedelic Users**	**Statis**	**p-value**
Subjects	16	16	-	-
Age (years)	37.44 ± 15.082	36.81 ± 14.520	t(30) = -0.119	$p = 0.906$
Sex	6 Male; 10 Female	7 Male; 9 Female	$\chi^2(1) = 0.130$	$p = 0.719$
Race	11 White (non-Hispanic) 2 Hispanic or Latino 2 Black or African American 1 Asian	13 White (non-Hispanic) 2 Hispanic or Latino 0 Black or African American 1 Asian	$\chi^2(3) = 2.167$	$p = 0.539$
Education Level	3 High School Degree 8 Associate or Bachelor's Degree 5 Advanced Degree	5 High School Degree 5 Associate or Bachelor's Degree 6 Advanced Degree	$\chi^2(2) = 1.283$	$p = 0.526$
Marijuana Use	15 Never Used / Infrequent User 1 Frequent User	9 Never Used / Infrequent User 7 Frequent User	$\chi^2(1) = 6.00$	*$p = 0.014$**
Days Since Last Psychedelic Use	-	11.06 ± 7.10 (range: 1–23)		
OCEAN Assessment Personality Traits				
Openness	29.563 ± 5.240	31.063 ± 5.066	t(30) = 0.823	$p = 0.417$
Contentiousness	27.875 ± 8.461	26.625 ± 6.010	t(30) = 0.485	$p = 0.634$
Extraversion	23.063 ± 7.550	27.063 ± 8.520	t(30) = 1.406	$p = 0.170$
Agreeableness	34.125 ± 3.500	35.375 ± 3.649	t(30) = 0.989	$p = 0.331$
Neuroticism	24.688 ± 7.631	25.063 ± 9.469	t(30) = 0.123	$p = 0.903$
DOSPERT Risk-Taking Domains				
Ethical	11.250 ± 3.715	13.438 ± 7.071	t(30) = 1.096	$p = 0.282$
Financial	15.125 ± 7.032	19.000 ± 6.623	t(30) = 1.604	$p = 0.119$
Health/Safety	18.250 ± 6.266	23.188 ± 6.969	t(30) = 2.107	$p = 0.043$*
Recreational	22.563 ± 9.654	26.188 ± 9.239	t(30) = 1.085	$p = 0.287$
Social	33.563 ± 4.953	33.313 ± 6.322	t(30) = 0.125	$p = 0.902$

Group values represent means, +/- standard deviations.

3.4 METHODS

3.4.1 Humans

All experimental procedures were approved by the Georgia State University Institutional Review Board (IRB) and were carried out in accordance with their guidelines. Participants were recruited through advertisements posted on university bulletin boards, social media platforms, and

in local psychedelic community groups. Eligibility criteria included adults aged 18 or older with no history of autism spectrum disorders, bipolar disorder, schizophrenia, current major depressive episodes, or substance abuse, excluding nicotine. Participants filled out a detailed questionnaire to ensure suitability for study participation. Participants provided informed consent and were compensated $30 for their participation in the study.

The study cohort comprised 47 individuals, divided into a control group and a psychedelic group. The control group consisted of 16 participants (6 male, 10 female), who had no recent (within 30 days) history of psychedelic use. The psychedelic group included 31 participants who had used psychedelics within 30 days prior to their participation in this study. This group was further subdivided based on the type of psychedelic used. The PSY subgroup consisted of 16 participants, with 15 taking mushrooms (7 male, 8 female) and 1 (male) taking LSD. Another subgroup comprised 12 participants (5 male, 7 female) who inhaled Incilius alvarius toad toxin. 5-MeO-DMT is considered to be the primary compound present that is responsible for the toxin's psychoactive effects.

Dosage information for psilocybin, LSD, or 5-MEO-DMT was unattainable, as potency of the drugs used could not be ascertained directly, but participants were pre-screened to exclude those who only took sub-perceptual microdoses. All doses reported were judged as moderate to high. Additionally, within the psychedelic group, 3 out of 16 participants identified as non-binary. Due to the small number of participants in this category, statistical analysis on gender was not feasible. Consequently, gender was excluded from the comparative analysis, although effects of sex and age on all major group differences were analyzed (Fig. S12).

3.4.1.1 Saccadic Prediction Task:

The saccadic prediction task[280,281] was conducted in a darkened room where participants were seated 100cm away from an LCD monitor (19-27 inches, 60Hz refresh rate). This task involved visual stimuli in the form of differently colored stars (2.46 degrees of visual angle in diameter), each appearing at one of eight designated spots 8 degrees from fixation on a circular layout. Participants were instructed to initially fixate on a central cross displayed on the screen for 1000ms, followed by shifting their gaze to the star, which appeared for the subsequent 1000ms at one of the eight spots. Each of the 142 trials per run was classified into three types, differentiated by the color of the star: 'expected' trials featured a green or purple star appearing in a predictable sequence at the same location; 'deviant-update' trials involved a green or purple star appearing unexpectedly at a new location, signaling participants to update their expectations; and 'deviant-no-update' trials, indicated by an orange star, appeared unexpectedly but did not require a change in expectation for future star locations. This color-coding scheme was not described to participants prior to the task, but allowed them to learn the significance of each color and to anticipate whether an update in expectation was necessary. Participants completed two consecutive runs for a total duration of nine minutes and forty-seven seconds.

3.4.1.2 Human Visual Oddball Paradigm:

The visual oddball paradigm was presenting using Psychopy in a darkened room where participants were seated 100cm away from an LCD monitor (19-27 inches, 60Hz refresh rate). Square-wave gratings (12.75”x12.75” squares; 18.18 degrees of visual angle) were presented at 100% contrast and 2.0 cycles per degree, drifting at two cycles per second lasting 500ms, with a randomly jittered 450-550ms inter stimulus interval (black screen). We presented three separate sequences – each consisting of 200 trials and lasting ≈200 seconds.

The many standards control sequence was composed of eight orientations (degree angles: 30º, 45º, 60º, 90º, 120º, 135º, 150º, and 180º) that were presented in random order. The oddball sequence consisted of a repetitive sequence of one stimulus ("redundant", either 0º, or 90º degree angles, presented 87.5% of the time), randomly interrupted by a stimulus of a different orientation ("deviant", 90º, or 0º degree angles, presented 12.5% of the time). In a subsequent sequence, the redundant stimulus was "flipped" to become the deviant, and vice versa ("oddball flip"); thus, we can assess responses to the stimulus context (i.e., in what context a stimulus is shown) rather than stimulus features (i.e., what orientation a stimulus is).

3.4.1.3 *EEG recordings and data processing:*

EEG recordings and data processing were conducted using a 32-channel BioSemi ActiveTwo EEG system. Participants were fitted with a BioSemi 32-channel cap, arranged according to the 10-20 system for electrode placement. EEG data were recorded with a sampling rate of 500 Hz, using a band-pass filter of 0.16 Hz and a lowpass filter at 200 Hz. Reference electrodes were placed 1 cm to the right of Cz (later average referenced) and the ground electrode was positioned at 1 cm to the left of Cz. Impedance was tested prior to each run (SPT1, SPT2, Control run, Oddball, Oddball flip), and kept below 10kΩ for each electrode.

Data preprocessing was performed using Besa Research software (Gräfelfing, Germany) as previously described[276,309–311]. Data were average referenced and noisy channels were interpolated (two or fewer per run). Eye-blinks and saccades were identified using Independent Components Analyses (ICA) and removed from the EEG data as previously described[276,309–311]. Individual trial data was then isolated for subsequent analysis (-700 to 1500ms pre- vs post-stimulus onset for SPT runs; -375ms to 875ms pre- to post-stimulus onset for oddball runs). SPT trials were excluded if there was no saccade, or if there was a saccade 300ms prior to the stimulus

in order to ensure adequate processing of early stimulus evoked activity. Data was baseline-corrected (-200 to 0 ms pre-stimulus onset) and averaged for plotting event related potentials (Fig. 2A-F), which was done mainly for descriptive purposes. The primary analyses of all human and mouse data were done in the time-frequency domain in Matlab (Mathworks, Natick, MA, USA), using the EEGLAB toolbox[312].

Individual trial data for each electrode was converted to the time-frequency domain with a modified morelet wavelet approach with 100 evenly spaced wavelets from 1 to 100 Hz (for SPT) or 3 to 100Hz (for oddball, as stimuli were only 500ms long, activity < 2Hz is difficult to interpret), linearly increasing in length from 1 to 25 cycles per wavelet, applied every 10ms. Stimulus-induced power spectra was computed as decibels relative to the pre-stimulus baseline (-200 to 0ms) for each frequency, timepoint, electrode, trial, condition, and participant, and averaged over trials to yield time-frequency power plots for each electrode, condition, and participant. Comparisons were carried out using traditional frequency bands (delta: 1-4Hz, theta: 5-8Hz, alpha: 9-14Hz, beta: 15-25Hz, gamma1: 26-40Hz, gamma2: 40-100Hz) and on time windows based on maximal time and time-frequency responses in the grand average plots, as described in the results. For the SPT task, signals were averaged over all electrodes, as task related brain activity was largely scalp-wide (See Fig. 2H). For the oddball paradigm, we focused on visuoparietal electrodes (Oz, O1, O2, PO1, PO2, P3, P4) and frontocentral electrodes (FCz, Cz, FC1, FC2, C1, C2) as a) this is where the maximal effects were seen for DD (Fig. 3C) and b) these electrodes are standard for capturing P300 and mismatch signals in visual oddball tasks. The number of trials used for each trial type was equated across conditions for the SPT (n=40 for standard and deviant locations) and for the oddball (n=20 for neutral, deviant, and redundant). We excluded neutral stimuli that were preceded by orientations <30degrees of difference to avoid effects of carryover

stimulus specific adaptation from the previous stimulus. The third redundant in each sequence was analyzed for supplemental analyses.

Additionally, intertrial phase locking (phase-locking factor, or PLF) was analyzed for the SPT task in order to help isolate brain activity that was locked to stimulus onset (i.e., and not convolved with e.g., response preparation). PLF was calculated, as previously described[311], by dividing the complex results of the above described wavelet analysis by their absolute values for each electrode, timepoint, frequency, participant, trial, and condition. The resulting values were averaged across trials, with the absolute value of this result yielding the PLF or R-statistic, which is bound between 0 and 1 (1 indicating perfect phase alignment across trials). In non-phaselocked (or phase-randomized) data, R-values vary depending on the number of trials involved in the calculation and can be baseline corrected using previously described mathematical approaches[294,311], as they were done in this study.

3.4.1.4 Saccade scoring:

Eye movements were measured using two additional facial electrodes (BioSemi) placed 1cm below and beside the outer canthus of the left eye (Fig. S7A). All saccades were manually scored using routines written in the host lab. Scoring focused on the onset of the first saccade after the onset of each stimulus and used a combination of each electrode and the average of their absolute value. Each run and subject was scored by at least 2 scorers, blinded to group membership or trial type. In the case where discrepancies were present (lower than .85 inter-rater reliability for a given subject, across all trials; or greater than 20ms difference between trial), a third scorer was included. Scores were averaged between the two closest estimates. Trials without clear saccades in the 800ms after stimulus onset, or with saccades present in the 300ms prior to trial onset were not scored and were excluded from EEG analysis as well. In the end, all but one subject had greater

than 75% of trials included with greater than .85 inter-rater reliability. This subject was excluded from behavioral analysis but included in EEG analyses. The proportion of trials excluded did not differ between groups, t(29)=1.46,p=.16). An automated scoring procedure, which converted signals to smoothed first-derivatives and automatically determined thresholds from fitting 2 to 5 distributions of values across all trials, revealed nearly identical overall results. Saccades with latencies >500ms were rare (<3.12% overall) and did not differ between groups (F^{group}(1,29)=0.5; p=.48) or show a group by stimulus location interaction ($F^{interaction}$ (1,29)=0.14; p=.71). As such slow responses could reflect task disengagement, we excluded them from subsequent analyses. Saccades with latencies greater than 90ms and less than 153ms were considered express saccades based on i) past literature[276], ii) neuroanatomy[282,283], iii) group-level histograms (Fig. 1B), and iv) 1.96 standard deviations (i.e., 2-tailed p<.05) below the grand group average (153ms).

3.4.2 Mice

3.4.2.1 *Animals and Surgeries:*

All animals were housed in the Georgia State animal facility under the supervision of the researchers and the Georgia State University (GSU) Division of Animal Resources. All experiments were performed under the approval of the institutional animal care and use committee (IACUC) at GSU. Adult C57BL/6 mice, n = 14, age range from P63 to P124 (from Jackson Laboratories) were used. Mice were weaned at P21-25 and group housed (max 5 mice per cage) separated by sex. They were maintained at a 12/12 light/dark cycle with food and water available *ad libitum*. Both female (n=4,2 for saline and DOI groups) and male mice (n=3,5) were included. Animals were anesthetized using 3% isoflurane, maintained at 1-2% isoflurane, and received pre and post care medication appropriately (5 mg/kg carprofen, IP). Small 0.2mm craniotomies were performed at mouse V1 (coordinates from bregma: X =-2mm, Y = -2.92mm) and ACa (X=0.3mm,

Y=0.6mm) and bipolar electrodes were implanted in each region, targeting layer 2/3 (200µm below the pial surface), and grounded at an adjacent skull surface. Prior to insertion, electrodes were submerged in DiI dye for post-hoc anatomical validation. During the same surgery session, a titanium head-plate was secured at the mouse head to allow for their fixation to the imaging apparatus. Head-fixation and visual stimulation habituation was performed three days following the surgery, in increments of 5-minute sessions each day (5 minutes for day one, 10 minutes for day 2, and 15 minutes for day 3), in which the visual stimuli were presented only once (many standards control run). This was done to acclimate the mouse to head-fixation and to reduce movement during recordings. Recordings took place after the seventh day post-surgery.

3.4.2.2 Mouse Visual Oddball Paradigm:

Visual stimuli were presented on a computer monitor (19-inch diameter, 60Hz refresh rate) at a 45-degree angle from the animal axis, approximately 15cm from the mouse's eyes, using the Psychophysics Toolbox on MATLAB (Mathworks) while the mouse was head-fixed to table. Visual stimuli consisted of black and white, full-field square-wave gratings at approximately 0.08 cycles per degree, drifting at 2 cycles per second, each presented for 500ms and separated from one another by 450-550ms of black screen. The oddball paradigm and many standards control sequences were the same as used for humans, described above.

3.4.2.3 LFP recordings and data processing

The mouse was head-fixed to the recording apparatus and free to move on a manual treadmill during recordings. Mice were monitored by the experimenter to ensure that they were awake and not in clear distress or discomfort during all recordings. Insulated cables were connected to the implanted electrodes and plugged into a differential amplifier (Warner instruments, DP-304A, high-pass: 0 Hz, low-pass: 500 Hz, gain: 1K, Holliston, MA, USA).

Amplified signals were passed through a 60 Hz noise cancellation machine (Digitimer, D400, Mains Noise Eliminator, Letchworth Garden City, UK), which, instead of filtering creates an adaptive subtraction of repeating signals which avoids phase delays or other forms of waveform distortion that can result from standard bandstop filters. Electrophysiological activity was recorded using the Prairie View software. Locomotion was recorded with a rotary encoder embedded in the treadmill and connected to the computer as an analogue input. Mice did not differ as function of group or condition in locomotion (Fig. S13). Further, more than 75% of the mice locomoted less than 5% of the time, so analysis of visual processing as a function of locomotion was not feasible. At least two previous studies[264,266] have shown that the visual oddball paradigm does not evoke reliable changes in locomotion or other facial motor variables (e.g., whisking) in mice. Three mice in each group showed loss of signal in the post-7 time period (i.e., no visually evoked response, and/or very low signal/noise) and were excluded from further analyses, leaving seven pre-, seven during, and four post-7-day mice for each condition.

3.4.2.4 Drug administration:

Drug administration (DOI or saline) took place after two sets of baseline recordings (two control, two oddball/oddball-flip combinations). This was the “pre” condition. Saline or DOI ((R)(−)-DOI hydrochloride, from Sigma-Aldrich, D153) was injected (10mg/kg[272], subcutaneously; 100µl) after the first recordings. The mouse was allowed to rest in its home cage in the 30-minute wait time, and then it was refixed to the recording setup for an identical set of visual stimulation sequences. This was the “during” condition. It was then returned to its home cage and the animal facility. After 7 days, a final recording was conducted after the mouse was acclimated to the setup for >30minutes. This was the “post-7” condition.

3.4.2.5 *Local field potential signal processing and analysis:*

Trials with excessive signal (>≈5 std devs) in either V1 and ACa were manually excluded (between 0 and 10 for each mouse). Analyses focused on presentations of the same stimulus (0 or 90 degrees) in the neutral vs deviant context (control vs oddball). Analyses were combined across both orientations, as LFP responses in mouse V1 do not exhibit significant orientation selectivity[313]. Ongoing data were converted to the time-frequency domain with the same approach described above. Statistical analyses focused on comparisons between neutral and deviant stimulus induced power from delta to gamma1 frequency band, in the 250ms to 400ms period post stimulus onset, most similar to DDa in the human results. This frequency and time-window selection was based on the main deviant vs neutral differences in the grand averaged responses across all mice and conditions, and differs from the human effect window due to the fact that the human signal is a scalp measurement, which integrates activity across a large scale brain network (and thus, captures both early (DDa) and later (DDb) deviance detection), while the mouse LFP is a highly local signal to V1.

Interregional phase synchrony was quantified by taking the phase difference for each frequency (1-100 Hz) between ACa and V1 for all measurements from 100ms pre- to 100ms post-stimulus offset (separately for control, redundant, and deviant trials) and calculating the 1-circ variance (R-statistic) of these lags. For analyzing the directionality of interregional connectivity, we carried out a non-parametric Granger causality-based approach in the time-frequency domain [266,305] as implemented in the Fieldtrip toolbox[314]. This analysis examined lagged spectral covariance between regions for each direction (ACa to future-V1 vs V1 to future-ACa) for each frequency 1-100Hz. We focused on a time-lag of 10ms based on similar studies of long-range brain connectivity[266,315]. The resulting value is a Granger coefficient (GC) reflecting the spectral

covariance in between the signal from one region and the lagged signal from the other region. GCs were normalized to the maximum across frequencies and directions for each recording and combined between the control and oddball sequences. Analyses and plots focused on 1 to 35Hz, as higher frequencies showed small values across mice.

3.4.3 Statistical analyses:

For saccade analyses, we used Komologrov-Smirnov tests on mean-centered saccade distributions, collapsed over all participants in each group, to test for differences in latency distributions. We used mixed ANOVAs on saccade latency and proportion of express saccades, with GROUP as a between-subjects factor (CNT, PSY or 5-MEO-DMT) and LOCATION as a within-subjects factor (standard, deviant). For SPT task EEG activity, we used mixed ANOVAs on early and late time period power and PLF, with GROUP as a between-subjects factor (CNT, PSY or 5-MEO-DMT) and LOCATION as a within-subjects factor (standard, deviant). For both saccades and EEG data during the SPT, we focused analyses on the second through fourth standards in the sequence in order to equate the number of trials across conditions and avoid updating effects (see Fig. 1F,G). For oddball task EEG activity, we used mixed ANOVAs on DDa (275-400ms) and DDb (400-600ms) time period power, with GROUP as a between-subjects factor (CNT, PSY or 5-MEO-DMT) and STIMULUS context as a within-subjects factor (neutral, deviant). Significant interactions were followed up with paired or two-sample t-tests with two-tailed significance.

To compare oddball processing in mice, we carried out a mixed ANOVA on power DDa time-periods, coherence, or GC with TIME as a between-subjects factor (pre-, during-, and 7-days-post). Significant interactions were followed up with two-sample t-tests with one-tailed

significance (as the direction of effects was hypothesized a priori based on the human results and/or the ReBUS hypothesis).

3.5 Supplemental Methods:

This section provides an overview of the supplemental behavioral assessments we used to compare – and better match -- our experimental groups. We focused on personality factors and risk-taking behaviors. Each participant was administered a computerized version of the Domain-Specific Risk-Taking (DOSPERT) scale and the OCEAN personality assessment following the EEG data collection.

3.5.1 DOSPERT Scale

The 30-item DOSPERT scale, a comprehensive tool designed to evaluate risk-taking attitudes and behaviors across different domains (e.g., financial, health/safety, recreational, ethical, and social), was utilized to assess participants' propensity for risk-taking. This scale comprises 6 items, rated on a Likert scale, for each domain. For each item, participants were asked the likelihood that they would engage in the activity on a seven-point scale, ranging from extremely unlikely (with a numeric value of 1) to extremely likely (with a numeric value of 7). Responses were summed across each domain to calculate domain scores for risk-taking behavior. Two-sample independent t-tests were used to investigate potential differences in risk-taking behavior between our control group (CNT) and recent 5-HT_{2A} psychedelic users (PSY). We identified only a difference in Health/Safety risk taking between CNT and PSY (Table 2). We also repeated this for the 5-MeO-DMT group, comparing to CNT. No group differences were identified (Table S1).

3.5.2 OCEAN Model Assessment

A 50-item survey version of the five factor model of personality[279], also known as the OCEAN model (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism) was employed to assess for group differences in personality traits of our participants. This model is well established and provides a robust framework for understanding personality.

Two-sample independent t-tests were used to investigate potential differences in each of the 5 factors between our control group (CNT) and recent 5-HT_{2A} psychedelic users (PSY). We identified no significant group differences between CNT and PSY (Table 2). We also repeated this for the 5-MeO-DMT group, comparing to CNT. We found a modest group difference in openness, with the 5-MeO-DMT group showing slightly more openness to experience (Table 3).

Table 3: Demographic data, personality scores, and risk-taking among control and recent 5-MeO-DMT-users.

	Control Group	5-MeO-DMT Users	Statistics	p-value
Subjects	16	12	-	-
Age (years)	37.44 ± 15.082	47.17 ± 10.49	t(26) = 2.636	$p = 0.117$
Sex	6 Male; 10 Female	7 Male; 5 Female	$\chi^2(1)= 0.050$	$p = 0.823$
Race	11 White (non-Hispanic) 2 Hispanic or Latino 2 Black or African American 1 Asian	9 White (non-Hispanic) 2 Hispanic or Latino 1 Black or African American 0 Asian	$\chi^2(3)= 0.982$	$p = 0.806$
Education Level	3 High School Degree 8 Associate or Bachelor's Degree 5 Advanced Degree	3 High School Degree 5 Associate or Bachelor's Degree 4 Advanced Degree	$\chi^2(2)=0.237$	$p = 0.888$
Marijuana Use	15 Never Used / Infrequent User 1 Frequent User	9 Never Used / Infrequent User 3 Frequent User	$\chi^2(1)= 0.197$	$p = 0.161$
Days Since Last Psychedelic Use	-	16.92 ± 7.24 (range: 4-27)	-	-
OCEAN Assessment Personality Traits				
Openness	29.56 ± 5.240	33.75 ± 3.571	t(26) = 2.379	$p= 0.025$*
Contentiousness	27.87 ± 8.461	27.17 ± 10.143	t(26) = -0.201	$p = 0.842$
Extraversion	23.06 ± 7.550	26.58 ± 6.708	t(26) = 1.280	$p = 0.212$
Agreeableness	34.12 ± 3.500	32.42 ± 4.122	t(26) = -1.185	$p = 0.247$
Neuroticism	24.68 ± 7.631	25.91 ± 8.928	t(26) = 0.528	$p = 0.698$
DOSPERT Risk-Taking Domains				
Ethical	11.25 ± 3.715	10.33 ± 4.097	t(26) = 0.618	$p = 0.542$
Financial	15.12 ± 7.032	13.68 ± 5.331	t(26) = 0.600	$p = 0.554$
Health/Safety	18.25 ± 6.266	15.75± 7.200	t(26) = -0.980	$p = 0.336$
Recreational	22.56 ± 9.654	23.92± 10.004	t(26) = 0.362	$p = 0.720$
Social	33.56 ± 4.953	34.58± 5.089	t(26) = 0.533	$p = 0.598$

Group values represent means, +/- standard deviations.

3.5.3 Supplemental figures

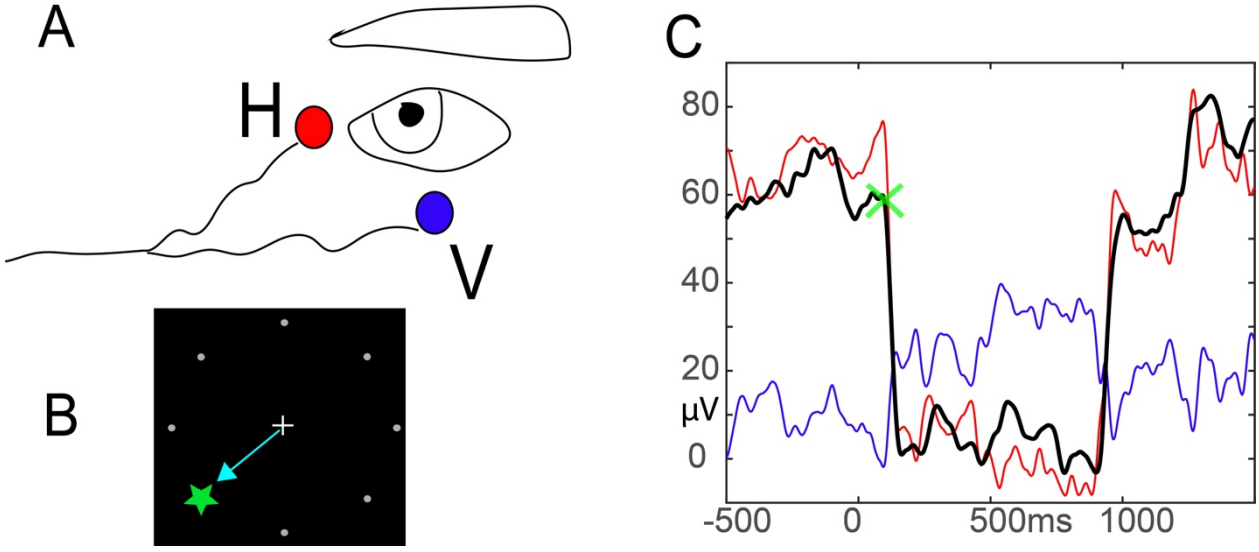

Figure S7: Electrooculography (EOG). *A) Surface electrodes were placed <1cm to the left of the outer canthi of the right eye and <1cm below the right eye. B) example trial, where a stimulus appears in one of 8 locations. C) Example EOG from one subject. The sum of the absolute values of the two EOGs were plotted for each trial and used to score the onset of each saccade (green X).*

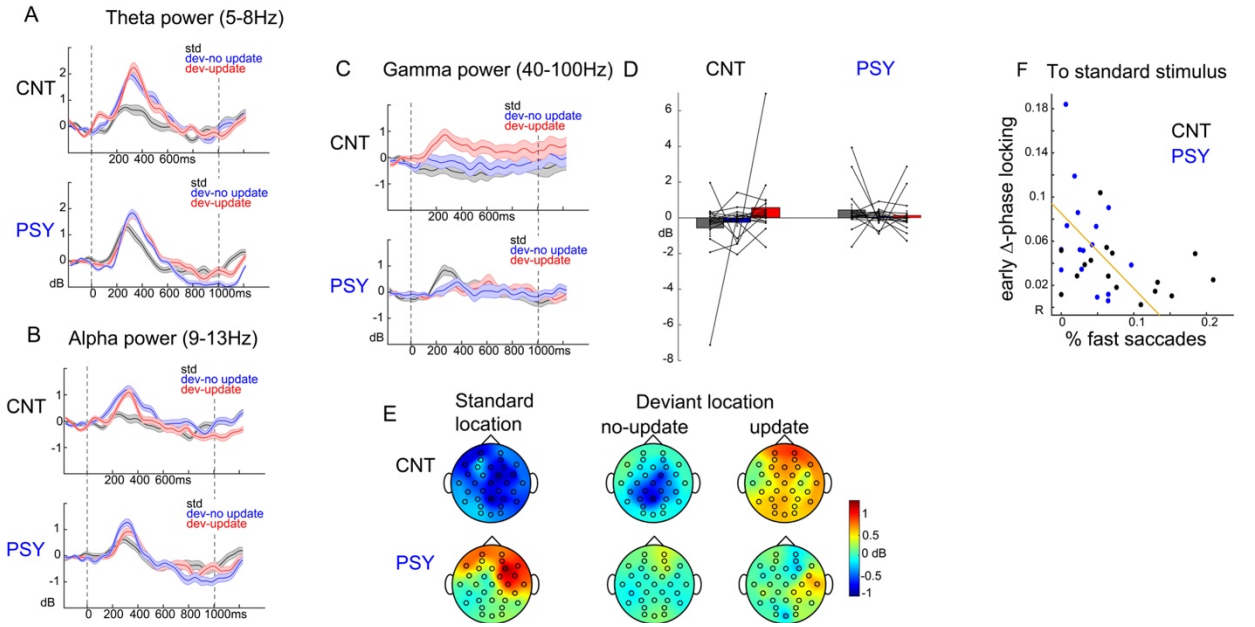

Figure S8: Other frequency band effects during the Saccadic Prediction Task. *A) Average theta power and B) alpha power across all electrodes demonstrates similar effects as delta (in figure 2). C) Gamma power plots (all electrodes) suggest increased power for update-deviants in the CNT group, and increased gamma power for the predictable targets in the PSY group, D) but these effects are likely driven by outliers in both groups (all electrodes, 200 to 600ms post stimulus onset). E) Topographic plot of gamma power from 200 to 600ms post stimulus onset. F) Phase locking factor plotted against the proportion of express/fast saccades. Fit line is for all subjects.*

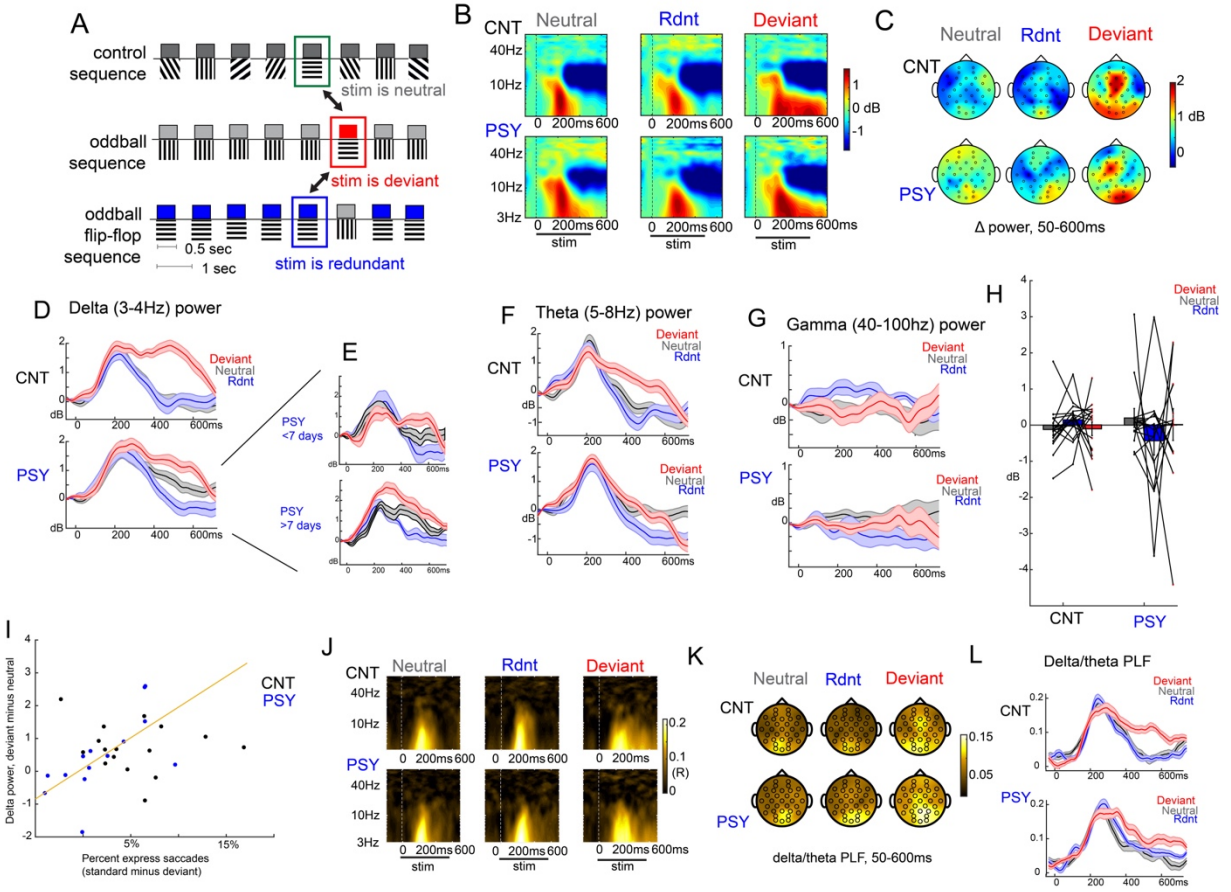

Figure S9: supplemental oddball analyses -- other frequency bands, redundant processing/SSA, and inter-trial phase locking. *A) Schematic of oddball paradigm, showing how the addition of a flip-flopped oddball paradigm allows analysis of stimulus specific adaptation (SSA), or altered responding to a sequentially repeated stimulus. (B-D) are partially reproduced from figure 3, in order to show the response to the stimulus in the redundant context, as compared to deviant and neutral. B) Power spectra from fronto-central and visuoparietal electrodes, demonstrating similar group-level responses to the redundant and neutral stimuli across all frequency bands for CNT subjects. C) Topographic plots of power for the delta band, from 50 to 600ms post stimulus onset. D) Delta power averaged across fronto-central and visuoparietal electrodes. E) Same as (D) but with the PSY group split into subgroups depending on time since psychedelics use. F-G) Same as D, but for theta and gamma power. H) Scatter plot of average gamma power from 50 to 600ms post stimulus onset, showing an overall null effect in the context of high heterogeneity across subjects. I) DDa (deviant minus neutral; from figure 3) plotted against proportion of express saccades to predictable stimulus location (standard; from figure 1). J-L) same as B-D, but for inter-trial phase locking factor (PLF, R-values). No significant stimulus by group interactions were present for theta or delta frequencies, for DDa or DDb time ranges.*

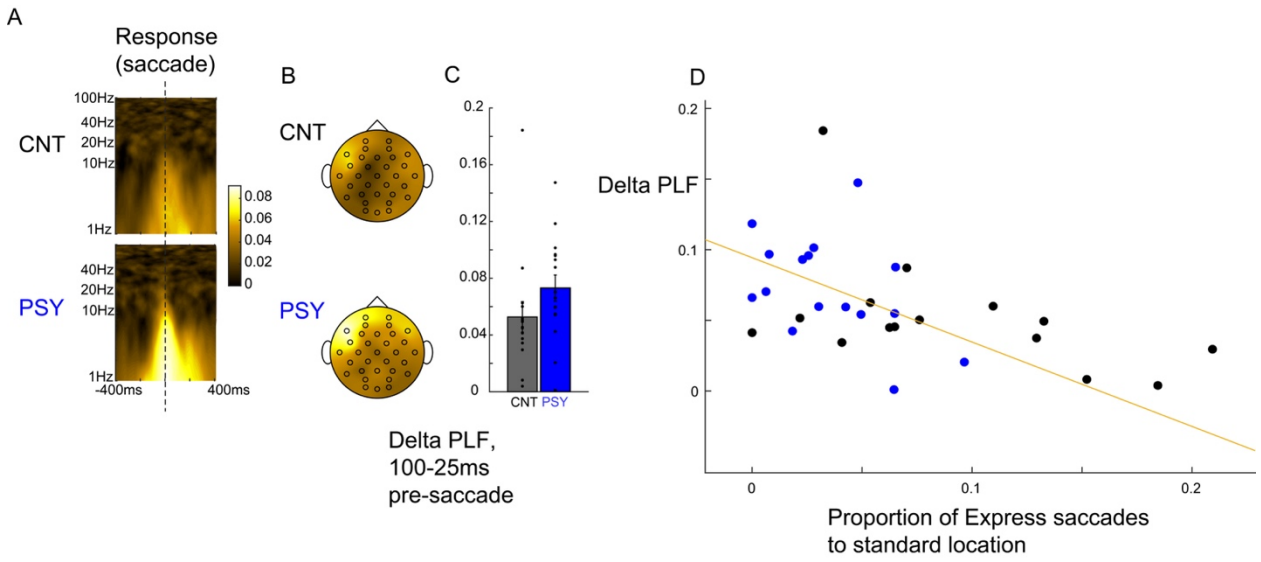

Figure S10: Response-locked EEG activity (phase locking factor) to the onset of the saccade. *A) Phase locking-factor was calculated across trials to stimuli in standard locations, using the onset of saccades, rather than the stimulus appearance, as the reference point in time. This was done separately for each of the 8 stimulus locations (to eliminate differences in phase distributions across the scalp during saccades with opposite or orthogonal directions), and then averaged together within subject to generate a global response-locked PLF spectrum. This was not generated for the deviant trials, as there were <4 trials for each condition for each location across subjects. Trials with latencies >90ms and <500ms were used. B) Scalp topographies of delta band (1-4Hz) PLF in the 100-25ms prior to saccade onset. This time window was chosen based on Hamm et al J Neurosci 2010, which also showed that express saccades involved less response-locked cortical activity in the leadup to saccade generation. C) There was a statistical trend toward this response being larger in PSY across frontal electrodes, who showed fewer express saccades than CNT ($t(30)=-1.75$, $p=.09$). D) This activity was significantly correlated ($r=.44$, $p<.05$) with the proportion of express saccades generated across subjects*

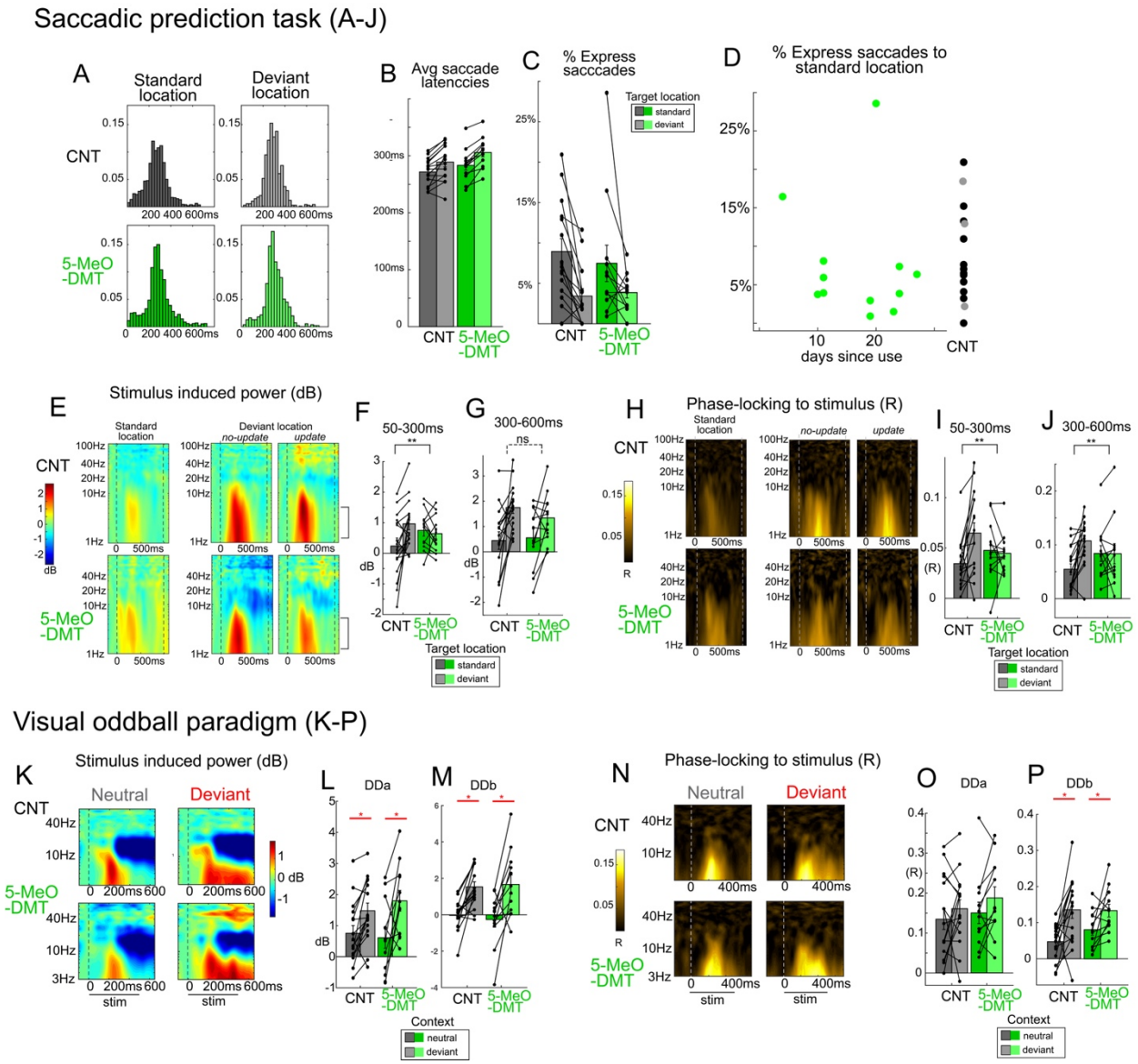
Saccadic prediction task (A-J)
A
Standard location
Deviant location
CNT
5-MeO -DMT
B
Avg saccade latenccies
C
% Express sacccades
Target location
standard
deviant
D
% Express saccades to standard location
days since use
E
Stimulus induced power (dB)
F
50-300ms
G
300-600ms
ns
H
Phase-locking to stimulus (R)
no-update
update
I
J
Visual oddball paradigm (K-P)
K
Stimulus induced power (dB)
Neutral
Deviant
stim
L
DDa
M
DDb
N
Phase-locking to stimulus (R)
O
P
Context
neutral
deviant

Figure S11: 5-MeO-DMT: *A) Twelve participants who recently took 5-MeO-DMT, a psychedelic with much greater affinity for the 5-HT_{1A} receptor than 5-HT_{2A}, displayed overall similar saccadic latency distributions to control subjects (CNT) to standard (predictable) and deviant targets. B) Like the PSY group (i.e., the group taking psychedelics with highest affinity for 5-HT_{2A} receptors [psilocybin and LSD]), there was a trend toward the 5-MeO-DMT group showing slightly slower latencies overall (figure S4B), but this effect was not statistically significant ($F(1,25)=1.84$, $p=.19$) and did not show a group by stimulus location interaction ($F(1,25)=0.78$, $p=.39$). C) Bar plot demonstrating percentage of express saccades generated to standard and deviant locations. The 5-MeO-DMT group did not statistically differ from CNT, and D) proportion of express saccades did not correlate with the number of days since psychedelic drugs were last taken. Two clear outliers in the 5-MeO-DMT group are apparent, with the rest of the group showing similar effects to the PSY group (figure 1). E) Stimulus induced power to the onset of targets in the predictable location was smaller than to targets in the deviant locations in the CNT group for both F) early (pre/perisaccade activity) and G) later time ranges. As was seen in PSY (figure 2), this difference was not present in the 5-MeO-DMT group for the early time window. H) Phase locking factor plots for each condition for each group and I, J) Corresponding barplots show a group by stimulus location interaction for early PLF ($F^{interaction}(1,26)=6.98$, $p<.05$) and later PLF ($F^{interaction}(1,26)=9.18$, $p<.05$), driven by largely similar responses across contexts for the 5-MeO-DMT group, while the CNT group showed smaller phase locking to stimuli in predictable (standard) locations. In contrast, (K-P) the 5-MeO-DMT group showed no group level differences or trends suggesting altered passive visual deviance detection in the oddball paradigm. K) Time-frequency plots of stimulus induced power averaged across fronto-central and visuoparietal electrodes, along with L) bar plots for the Dda period (275ms to 400ms) and M) the DDb period (400ms to 600ms). N-P) Same as K-L, but for phase locking factor. **$p<.01$, *$p<.05$.*

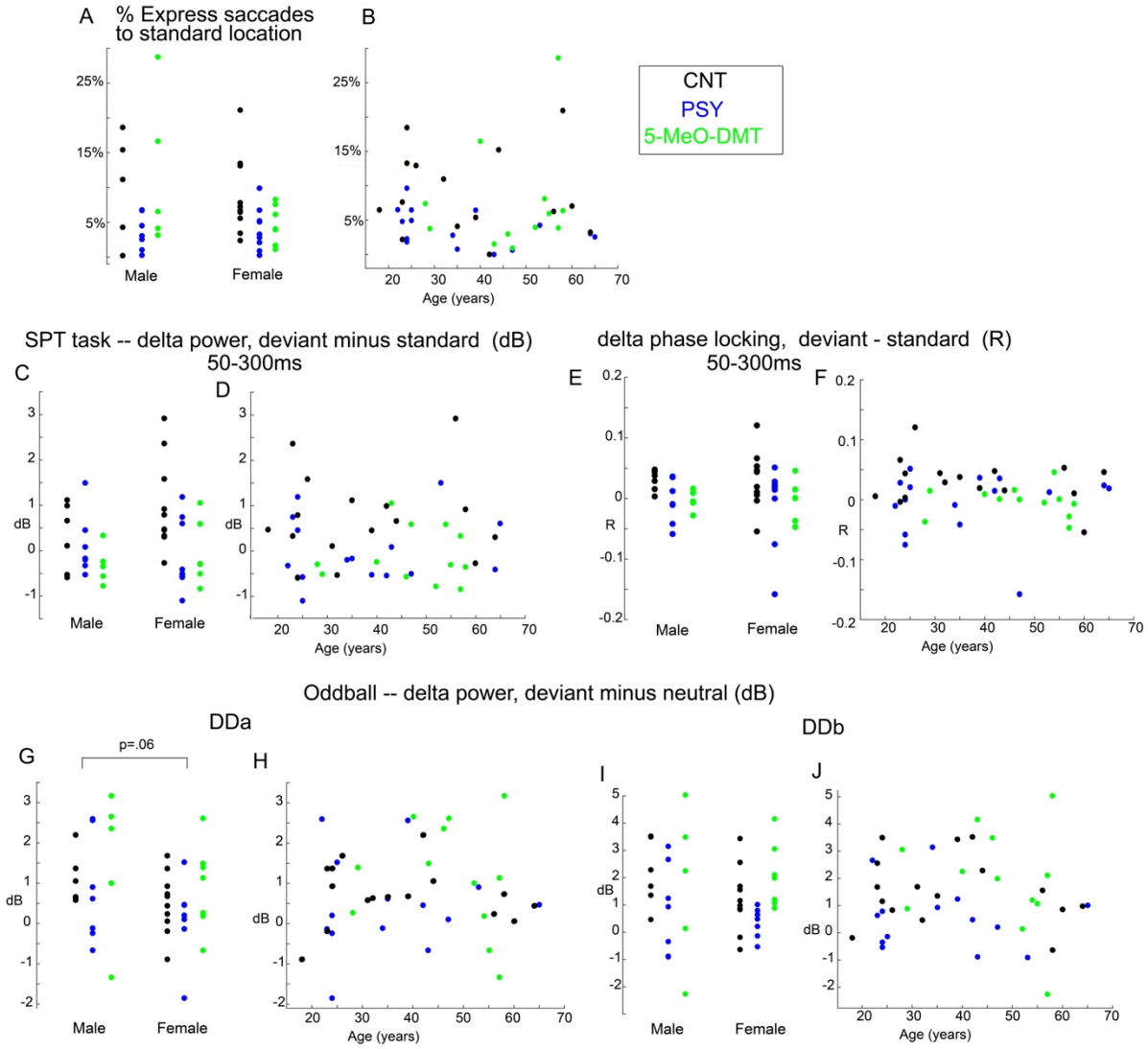

Figure S12: Age and sex effects. *A) Percent of saccades that were express plotted as a function of sex and B) age for each group. C) Delta power (all electrodes) to the onset of standard vs deviant targets during the saccade task (which differed between PSY and CNT (figure 2) and 5-MeO-DMT (figure S4)), plotted as a function of sex and D) age for each group. E-F) same as (C), but for phase locking factor. G) Delta power (frontocentral and visuoparietal electrodes) during the DDa period (deviance detection period 275ms to 400ms; which differed only between PSY and CNT (figure 3)) plotted as a function of sex and H) age. I-J) Same as G, H, but for the later DDb (deviance detection period 400 to 600ms). All correlations with age were r<-.2 and r>.2. None of these effects showed clear sex differences, except for DDa (G), which showed a trend toward being larger in males—a trend that was similar across groups.*

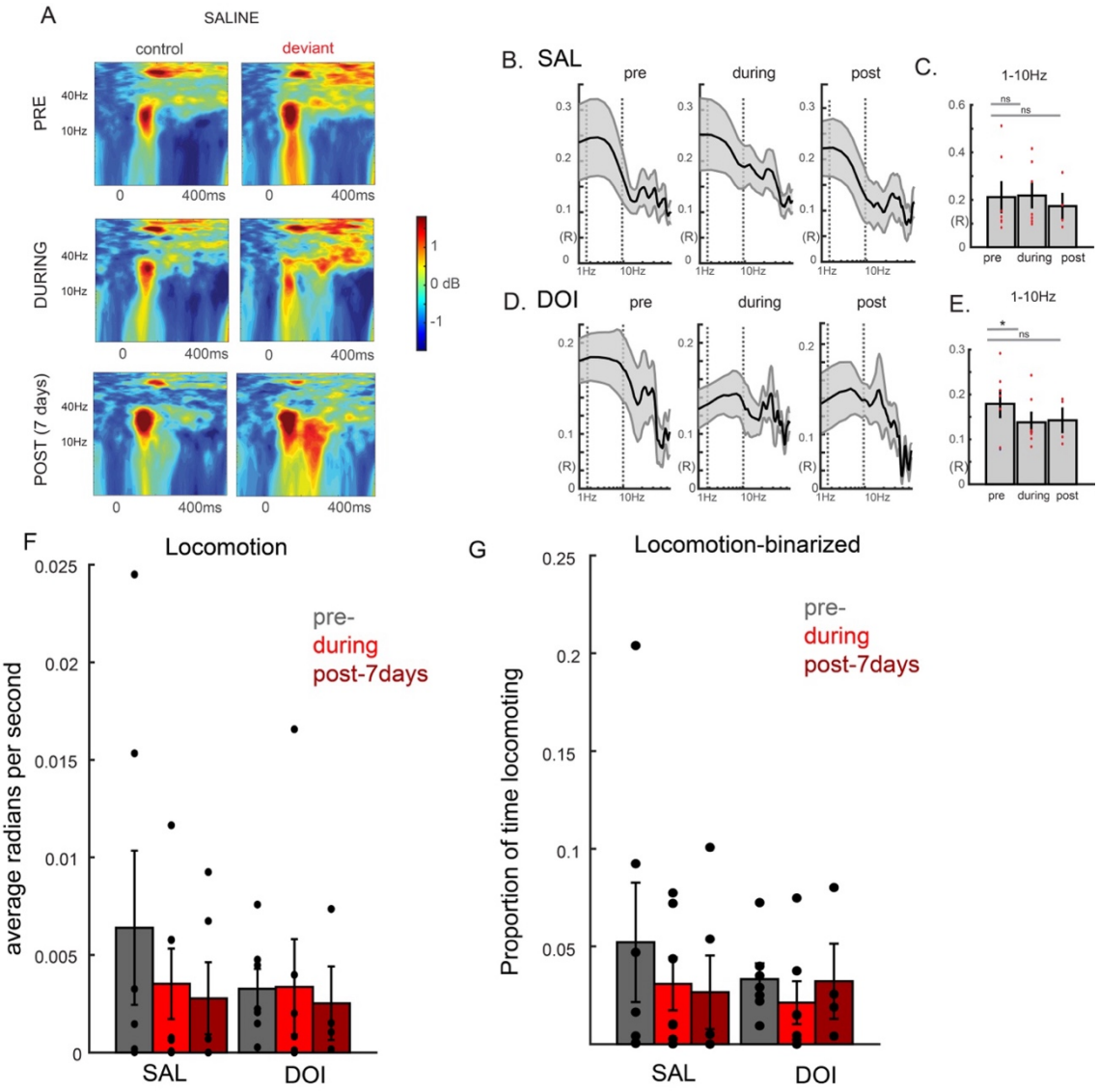

Figure S13: Supplementary LFP and behavioral analyses. *A) Time-frequency power plots of stimulus induced activity when a stimulus was contextually neutral (left) and contextually deviant (right) for the Saline group. Accompanies figure 4D. Deviance detection signals are present in the 3 to 40Hz range in all three conditions. B) Line-plots of phase-phase coherence between ACa and V1 during the oddball paradigm for the SAL group, along with C) bar/scatter plots, reflecting averages of the 1-10Hz coherence for each mouse. D, E) same as B,C, but for the DOI group. F) Average locomotion speed and G) proportion of time running during lfp recodings for each group. * p<.05, two-tailed t-test.*

4 DISTINCT EEG DYNAMIC FUNCTIONAL CONNECTIVITY PATTERNS FOLLOWING 5-HT$_{1A}$ AND 5-HT$_{2A}$ PSYCHEDELIC USE.

4.1 Introduction

Serotonergic 5-HT$_{2A}$ psychedelics such as psilocybin and lysergic acid diethylamide (LSD) have emerged as promising treatments for psychiatric disorders such as depression and anxiety, with therapeutic effects persisting weeks after a single dose[9]. The 'relaxed beliefs under psychedelics' (ReBUS) model posits that these psychedelics work by increasing bottom-up drive versus top-down modulation in information processing[1]. In doing so they loosen or 'relax' high-level beliefs, including ingrained biases that have become pathological[1]. Chapter 3 of this dissertation focused on task-related sensory processing and behavior, providing support for the ReBUS model at the systems level. For example, we showed that 5-HT$_{2A}$ psychedelic use enhances deviance detection to contextually neutral targets, treating them as if they are contextually deviant. In contrast, we found that 5-MeO-DMT use, a 5-HT$_{1A}$ agonist, did not produce alterations in deviance detection. In this chapter we further elucidate the distinct effects of 5-HT$_{1A}$ and 5-HT$_{2A}$ psychedelics by examining their impact on resting-state entropy and global dynamic functional connectivity, beyond the acute exposure period. Both of these measures have been implicated in the ReBUS model[1].

During the acute 5-HT$_{2A}$ psychedelic experience increased neural entropy, or signal complexity, has been consistently observed in the literature[29,33,93,100]. However, to our knowledge, the effects of 5-MeO-DMT on neural entropy remain unexplored. This high neural entropy observed during the acute 5-HT$_{2A}$ psychedelic experience is associated with the breakdown of segregated network activity structures[30,31]. Increased entropy is thought to underly the relaxation of high-level beliefs and promote cognitive flexibility[30,31]. One of the most commonly used

methods for measuring neural entropy in the psychedelic literature is known as 'Lempel-Ziv Complexity' (LZc)[33,100], which assesses the temporal complexity of neural signals[33,316]. Recent research by Siegel et al. found that Normalized Global Spatial Complexity (NGSC), a similar, but distinct measure of spatial entropy, was only transiently increased during the acute psychedelic exposure period[98]. However, the persistence of increased temporal entropy beyond the acute phase, particularly as measured by LZc, remains largely unexplored. This gap in the literature motivated our investigation of LZc in the post-acute period following psychedelic use. By examining LZc after the acute effects have subsided, we aim to understand whether the increased neural temporal entropy associated with psychedelics persists beyond the acute phase.

Global functional connectivity analyses asses overall connectivity patterns without focusing on specific localized regions, providing a comprehensive view of the brain's integrated network functioning[317]. However, recent studies have revealed discrepancies in the effects of 5-HT_{2A} psychedelics on global connectivity patterns. Some studies suggest that 5-HT_{2A} psychedelics' increase global functional connectivity[94,185], indicating enhanced communication between brain regions that are typically not strongly synchronized and desynchronization within segregated networks. Together this leads to a more integrated and less differentiated network of neural communication[2,185]. Daws et al.[2] found that psilocybin therapy for depression was associated with this increase in global integration up to 3 weeks post-treatment, correlating with symptom improvement.

However, recent research by Siegel et al.[98] challenges this view, demonstrating that 5-HT_{2A} psychedelic use leads to global desynchronization and disruptions in normal connectivity patterns, rather than a simple increase in global connectivity. They observed that whole-brain functional connectivity had mostly returned to baseline within 3 weeks, with only specific persistent changes,

such as decreased connectivity between the anterior hippocampus and default mode network[98]. These discrepancies highlight the complexity of 5-HT_{2A} psychedelics effects on brain function, particularly in the post-acute phase.

The desynchronization and disruption of normal connectivity patterns observed in psychedelic states may drive neuroplasticity. This burst of plasticity, involving a neurotrophic cascade, appears to be crucial for the rapid antidepressant-like effects seen in animal models[318,319]. By temporarily altering brain network dynamics, psychedelics may create a window of heightened plasticity, allowing for the reorganization of neural circuits and the integration of new information. However, more nuanced approaches are needed to understand the persisting effects of 5-HT_{2A} psychedelics on brain network dynamics in humans in this potential window of plasticity.

Importantly, these network effects of appear to be 5-HT_{2A} receptor-dependent[184]. However, because of the lack of research on 5-MeO-DMT, it is unclear whether similar effects may be produced through 5-HT_{1A} agonism. This gap is significant given the unique phenomenological experiences reported with 5-MeO-DMT, which are often less visually driven and can include "white-out experiences" reminiscent of amnesia or a void-like state[221]. Despite these distinct subjective effects, 5-MeO-DMT may hold therapeutic potential similar to other psychedelics[223]. Interest in 5-MeO-DMT's therapeutic potential is growing and Phase 1 and 2 clinical trials have shown therapeutic potential for treatment-resistant depression. While promising, large-scale clinical trials have yet to be completed to evaluate its safety and efficacy[320].

Static connectivity measures, which assume stable connectivity patterns over time, fail to capture the dynamic nature of brain network activity. This limitation is particularly significant for studying the effects of psychedelics. Previous research has shown that global functional

connectivity is in fact, not stable over time. Rather, psychedelic states are characterized by rapidly changing and increased variability in brain activity patterns[29,93,321] compared to controls. More sensitive measures that can account for temporal variability, to better understand the neurobiology of psychedelic states, are needed. This variability may extend beyond the acute psychedelic experience. A recent meta-analysis[237] reports reliable "afterglow" effects, including changes to mindfulness, mood, and behavioral flexibility. These afterglow effects which last up to a month, suggesting underlying neural changes persist beyond the acute treatment period[237]. Moreover, individuals can experience sudden, intense reactivations of the psychedelic experience in the days and weeks following 5-MeO-DMT use[322]. Despite these findings, few studies have examined the dynamic, temporal effects of 5-HT_{2A} and 5-HT_{1A} psychedelics on brain network activity after the acute exposure period, highlighting a crucial gap in our understanding.

Dynamic functional connectivity (dFC) analyses are capable of capturing temporal fluctuations in functional connectivity, and can allow for the identification of distinct ‘states’ of neural connectivity within the observed signal. In dFC analyses, 'states' refer to distinct, recurring patterns of neural connectivity that emerge and dissolve over the time course of an EEG recording session[101]. Unlike static functional connectivity, which assumes a single, stable pattern of connectivity throughout the recording, dFC recognizes multiple states, each characterized by a unique configuration of functional connectivity. These states represent snapshots of the brain's dynamic functional organization, offering a more nuanced view of brain network dynamics.

This study aims to elucidate the lasting impacts of 5-HT_{2A} and 5-HT_{1A} psychedelics on brain network dynamics utilizing dFC analyses of electroencephalography (EEG) recordings gathered from three groups: control participants, individuals who have recently used 5-HT_{2A}

psychedelics (psilocybin or LSD), and individuals who have recently used the 5-HT_{1A} psychedelic 5-MeO-DMT (< 3 weeks). To measure dFC, we chose EEG due to its excellent temporal resolution. This approach allows for more robust capture of rapid changes in functional connectivity compared to fMRI, while also enabling us to analyze connectivity patterns across different frequency bands[101]. EEG's high temporal precision makes it particularly well-suited for characterizing the dynamic nature brain activity following psychedelic use[323].

We utilize the weighted Phase Lag Index (wPLI) to assess both full spectral analysis and specific frequency bands of dynamic connectivity[324]. wPLI quantifies the consistency of phase differences between two electrophysiological signals, emphasizing non-zero phase lags to mitigate volume conduction effects. It weights phase differences according to their magnitude, providing a robust measure of functional brain connectivity that minimizes the impact of noise and near-zero phase lag interactions[324].

We assess three measures which characterize how participants remained in particular states: proportion of time spent in each state, mean dwell time in each state, and the number of transitions between states. Additionally, we visualize each of the distinct connectivity states for each group and each frequency band of interest.

We hypothesize that the 5-HT_{2A} psychedelic group would spend a higher proportion of time in global hyper-connectivity states compared to controls. This sustained presence in hyper-connectivity states may facilitate enhanced communication and integration across diverse brain regions[93]. We also hypothesize that the 5-HT_{2A} psychedelic group would exhibit more frequent state transitions, indicating greater network variability or flexibility, which may be associated with enhanced cognitive flexibility and therapeutic outcomes[102].

Additionally, given the distinct pharmacological profile of 5-MeO-DMT, we expect to observe unique patterns of functional connectivity in this group. Because 5-HT_{1A} receptor agonism inhibits some of the effects of 5-HT_{2A} psychedelics[325,326], and agonism at 5-HT_{1A} receptors is contrasting to 5-HT_{2A} receptor agonism[327–329] we expect to see some opposing results between the two psychedelic groups such as less time in hyper-connected states. Comparing these two groups would provide insight 5-MeO-DMT's unique mechanism of action. By employing a dFC approach, our study seeks to elucidate the mechanisms underlying the lasting psychedelic-induced changes in brain function, contributing to a more comprehensive understanding of their therapeutic potential.

4.2 Methods

Ethical Approval: All experimental procedures were approved by the Georgia State University Institutional Review Board (IRB) and were carried out in accordance with their guidelines. Participants were recruited through advertisements posted on university bulletin boards, social media platforms, and in local psychedelic community groups. Eligibility criteria included adults aged 18 or older with no history of autism spectrum disorders, bipolar disorder, schizophrenia, current major depressive episodes, or substance abuse, excluding nicotine. Participants filled out a detailed questionnaire to ensure suitability for study participation. Participants provided informed consent and were compensated $30 for their participation in the study.

The study cohort comprised 42 individuals, divided into a control group, a Psilocybin/LSD group, and a 5-MeO-DMT group. The psilocybin/LSD group (5-HT_{2A} psychedelics) included 13 participants (6 male, 7 female) who had used psilocybin and 1 (male) who had used LSD within

30 days prior to their participation in this study. The 5-MeO-DMT group (5-HT_{1A} psychedelic) comprised 12 participants (5 male, 7 female) who used inhaled Incilius alvarius toad toxin. 5-MeO-DMT is considered to be the primary compound present that is responsible for the toxin's psychoactive effects. The control group consisted of 16 age and sex matched participants (6 male, 10 female), who had no recent (within 365+ days) history of psychedelic use. See table 4 for detailed demographic data. Dosage information for psilocybin, LSD, or 5-MEO-DMT was unattainable, as potency of the drugs used could not be ascertained directly, but participants were pre-screened to exclude those who only took sub-perceptual microdoses. All doses reported were judged as moderate to high.

Table 4: Participant demographic and substance use characteristics.

	Control Group	**Psilo/LSD Users**	**5-MeO-DMT Users**	**Statistics**	**p-value**
Subjects	16	14	12	-	-
Age (years)	37.44 ± 15.08	35.71 ± 13.21	47.17 ± 10.49	F(2, 39) = 2.75	***p* = 0.08**
Sex	6 Male; 10 Female	7 Male; 7 Female	5 Male; 7 Female	$x^2(2) = .486$	$p = 0.784$
Race	11 White (non-Hispanic) 2 Hispanic/Latino 2 Black/African American 1 Asian	11 White (non-Hispanic) 2 Hispanic/Latino 0 Black/African American 1 Asian	9 White (non-Hispanic) 2 Hispanic/Latino 1 Black/African American 0 Asian	$x(6) = 2.66$	$p = 0.85$
Education Level	3 High School Degree 8 Associate or Bachelor's Degree 5 Advanced Degree	4 High School Degree 4 Associate or Bachelor's Degree 6 Advanced Degree	3 High School Degree 5 Associate or Bachelor's Degree 4 Advanced Degree	$x^2(4) = 1.47$	$p = 0.83$
Marijuana Use	15 Never Used / Infrequent User 1 Frequent User	8 Never Used / Infrequent User 6 Frequent User	9 Never Used / Infrequent User 3 Frequent User	$x^2(2) = 5.53$	***p* = 0.06**
Days since Psychedelic Use	-	10.43± 7.33 (range: 1–23)	16.92 ± 7.24 (range: 4–27)	t(24) = -2.26	***p* = 0.033***

Group values represent means, +/- standard deviations.

4.2.1 Resting-State EEG recordings and processing:

EEG data were recorded in a controlled environment with moderate temperature, moderate humidity, good ventilation, and electromagnetic insulation. Participants were instructed to open eyes for 5 minutes. Participants were seated approximately 40 inches away from an LCD monitor

(19-27 inches, 60Hz refresh rate). Participants were instructed to fixate on a small white cross in the center of a blank black screen.

EEG recordings and data processing were conducted using a 32-channel BioSemi ActiveTwo EEG system. Participants were fitted with a BioSemi 32-channel cap, arranged according to the 10-20 system for electrode placement. The EEG data were recorded with a sampling rate of 500 Hz, using a band-pass filter of 0.16 Hz and a lowpass filter at 200 Hz. Reference electrodes were placed 1 cm to the right of Cz (later average referenced) and the ground electrode was positioned at 1 cm to the left of Cz. Independent Component Analysis (ICA) was used to isolate ocular and muscular artifacts for subsequent removal. The cleaned EEG data were then segmented into 1-second epochs.

4.2.2 Weighted Phase Lag Index:

Let X and Y be time series with length T. The weighted phase lag index (wPLI)[324] measures how differences in the phase angle between X and Y tend to be positively or negatively distributed along an imaginary axis of the complex plane. Standard PLI is defined as:

$$PLI(X,Y) = \left| \frac{\sum_{t=1}^{T} sign\left(imag\left(S_{xy,t}\right)\right)}{T} \right|$$

where S_{xy} is the cross-spectral density of X and T at time T. While PLI is insensitive to zero-lag interactions, noise and other confounds can be introduced via volume conduction.

The wPLI, defined as:

$$wPLI(X,Y) = \left| \frac{\sum_{t=1}^{T} \left|imag\left(S_{xy,t}\right)\right| sign\left(imag\left(S_{xy,t}\right)\right)}{\sum_{t=1}^{T} \left|imag\left(S_{xy,t}\right)\right|} \right|$$

addresses the limitation of PLI by scaling phase angle differences by their distance from the real line. PLI and wPLI both utilize only the imaginary part of the cross-spectral density, and are robust

to noise when compared to other FC metrics like coherence or Pearson's correlation coefficient. For this work, we focus only on wPLI, leveraging the robustness to noise and volume conduction established in the literature[324].

4.2.3 Dynamic Functional Connectivity:

Dynamic functional connectivity was assessed using a sliding window approach, with windows of 5 seconds duration and 1-second overlap, following the precedent in Chen et al.[101]. Connectivity within each window was quantified using the weighted Phase Lag Index (wPLI). dFC analysis was conducted across the entire frequency spectrum (full spectral analysis) and within individual frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta/low-gamma (13–39 Hz), and high gamma (40–100 Hz). Analyzing individual frequency bands is crucial as each band is associated with distinct neurophysiological processes and modes of neural communication.

To perform temporal segmentation, k-means clustering was performed on the wPLI connectivity windows within each band to identify distinct brain states. This clustering approach allows for a data-driven association of related connectivity windows, and while it is just one method for determination of states, it is established in the functional connectivity literature[330–333]. The optimal number of clusters of K=5 was determined using the elbow criterion, which evaluates the variance explained by clusters and identifies the point at which adding more clusters yields diminishing returns. For computational efficiency, the elbow criterion was evaluated on a subset of exemplar windows computed for each participant representing local maxima of the standard deviation computed over windows. Different values of K between 2 and 16 were evaluated, with K=5 determined to be the optimal number according to the elbow criterion using the silhouette

score[334] and Davies-Bouldin index[335]. Each exemplar clustering was initialized randomly 10 times and the result with the best silhouette score was taken. The resulting states from the clustering of exemplar windows were then utilized to initialize the clustering of the full set of windows. K-Means was implemented using the scikit-learn package (v0.24.2) in Python 3.9.12.

Following K-Means clustering, the identified brain states were characterized by the following measures: proportion time, mean dwell time and number of transitions. Proportion time for state *k* is measured as the total time that a participant spends within that state divided by the total number of windows in the recording. Mean dwell time is computed as the average duration that a particular state was maintained before transitioning to another state. Finally, the number of transitions quantifies the total number of transitions between different states, reflecting the stability and dynamism of the brain's connectivity patterns. To characterize significant differences in the Proportion Time, Mean Dwell Time, and Number of Transitions between groups we performed two-sample T-Tests and report the results in figures 14-17.

4.2.4 Lempel-Ziv Complexity:

Lempel-Ziv Complexity (LZC) is a measure of the complexity of a time series, capturing the degree of randomness and the number of distinct patterns within the data[33,100]. LZC quantifies how difficult it is to compress a given signal, with more complex signals resulting in higher LZC values[33]. Following the precedent in Timmerman et al.[33], to analyze the LZC, the continuous resting-state recordings were segmented into 3-second epochs, corresponding to 1500 samples per epoch at the 500 Hz sampling rate. This segmentation allowed for the examination of signal complexity over short, consistent time windows.

Each epoch underwent the following additional preprocessing steps. First, the data were linearly detrended and standardized by subtracting the mean and dividing by the standard deviation for each channel, ensuring that the analysis was not influenced by amplitude differences across channels or epochs. Next, the Hilbert transform was applied to each standardized epoch to obtain the amplitude envelope of the EEG signal. A binary string representation was then generated by comparing the amplitude envelope to its mean value, with samples above the mean encoded as '1' and those below the mean encoded as '0'. To compute LZc, the binary string was shuffled to create a surrogate dataset, and LZc was calculated as the ratio of the compression length of the original binary string to that of the shuffled string, quantifying the complexity of the EEG signal with higher values indicating greater complexity.

4.3 Results

4.3.1 Differential dynamic functional connectivity characteristics between 5-HT_{2A} and 5-HT_{1A} psychedelic users in full spectral analysis.

In the full spectral analysis of global dFC, no significant differences were observed between the control group and the psychedelic groups overall (Fig.14). However, specific differences were noted between the 5-MeO-DMT and psilocybin/LSD groups. The 5-MeO-DMT group spent a greater proportion of time in the lowest connectivity state (State 1), with a median proportion time of .51 compared to .25 in the psilocybin/LSD group ($t(24) = -2.53$, $p = 0.018$) (Fig. 14A-B). Additionally, the 5-MeO-DMT group had a longer mean dwell time in this state (3.87 seconds vs. 2.69 seconds for the psilocybin/LSD group; $t(24) = -2.11$, $p = 0.046$) (Fig. 14C). Using Pearson correlation coefficient, we found no significant correlation between days since last psychedelic use and proportion time in this state for the 5-MeO-DMT group ($r= 0.440$, $p=0.152$) or for the psilocybin/LSD group ($r=-0.007$, $p = 0.981$).

Conversely, the psilocybin/LSD group spent more time in medium connectivity states 2 and 3, with a median proportion time of .49 compared to .38 in the 5-MeO-DMT group in state 2 and ($t(24) = 2.37$, $p = 0.026$) a median proportion time of .20 compared to .05 in the 5-MeO-DMT

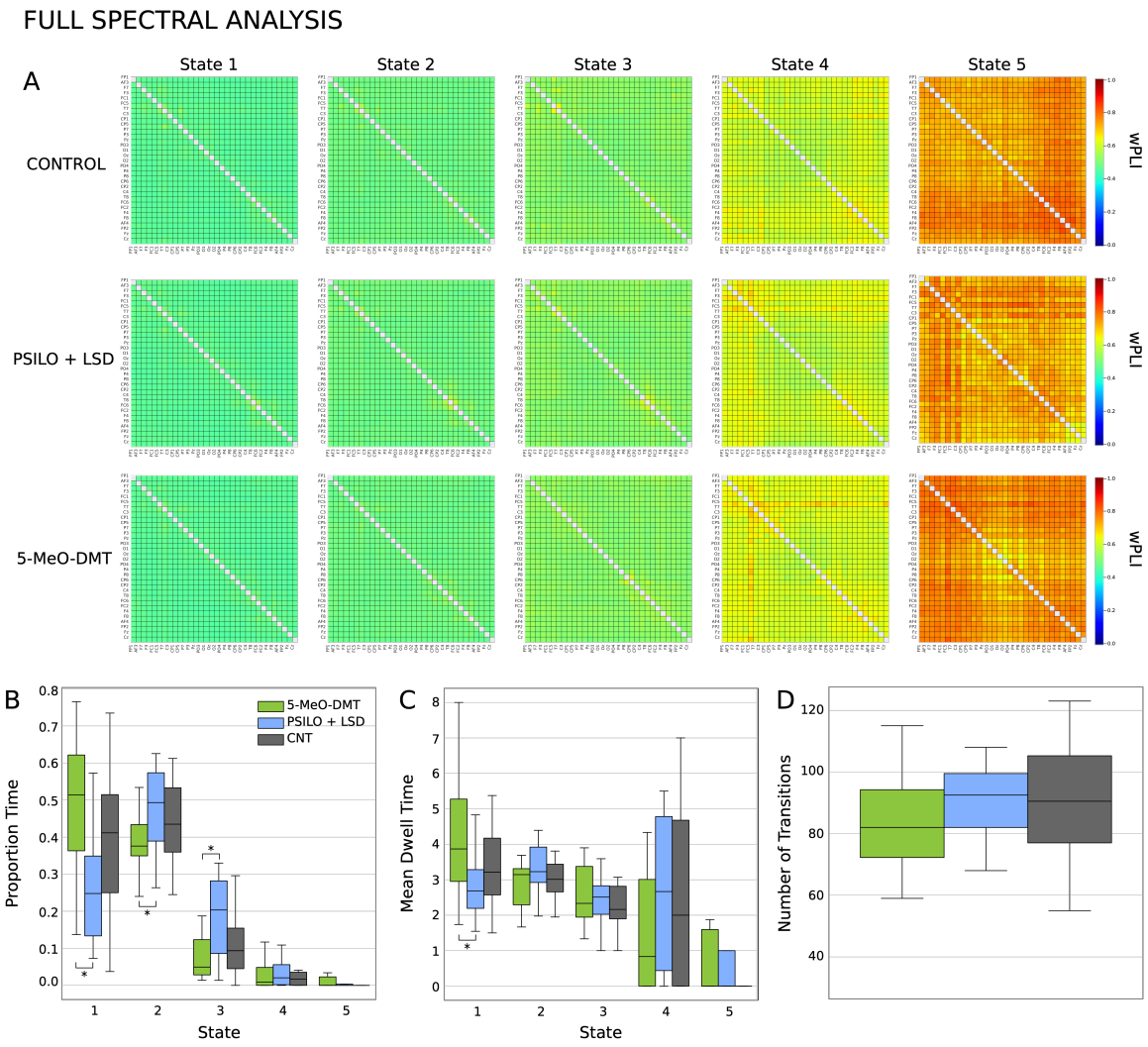

Figure 14: Full spectral analysis of the differences in dynamic functional connectivity characteristics between groups. *A) Group-specific matrices show functional connectivity patterns across five states. The color intensity indicates the strength of weighted Phase Lag Index (wPLI) connectivity values. B) Mean proportion of time spent in each state, showing significant differences between psychedelic groups in states 1-3. C) Mean dwell time spent in each state showed significant difference between psychedelic groups in state 1. D) Number of transitions between states did not significantly vary across groups. Error bars represent standard error of the mean (SEM). * Indicates $p < .05$.*

group in state 3 (t(24) = 2.42, p = 0.024) (1B). See table 5 for comprehensive list of mean connectivity values and standard deviations for each identified connectivity state discussed above.

4.3.2 Differential dynamic functional connectivity characteristics in theta, alpha, and beta/low-gamma bands between 5-HT_{2A} and 5-HT_{1A} psychedelic users, and controls.

Next, we analyzed differences in frequency band-specific global connectivity patterns. We examined the following frequency bands: delta (1-4 Hz), theta (5-8 Hz), alpha (9-14 Hz), beta/low-gamma (15-39 Hz), and high-gamma (40-100 Hz). For each band, we identified five distinct states. Significant differences in proportion time, mean dwell time, or number of transitions were observed in the theta (Fig. 15), alpha (Fig. 16), and beta/low-gamma (Fig. 17) frequency ranges. Consequently, we focus our following analysis on these three frequency bands.

4.3.2.1 Theta Band (5-8Hz)

In the theta frequency band (5-8Hz), the psilocybin/LSD group spent more time in the highest connectivity state (state 1), with a median proportion time of .08 compared to .03 in the 5-MeO-DMT group (t(24) = 2.72, p = 0.012) and .06 in the control group (t(28) = -2.16, p = 0.039) (Fig. 15A-B). The psilocybin/LSD group also exhibited a longer mean dwell time in this state (2.38 seconds vs. 1.63 seconds; t(24) = 2.35, p = 0.027) compared to the 5-MeO-DMT group (Fig. 15C). Pearson correlation coefficient analysis revealed no significant correlation between days since last psychedelic use on proportion time in state 1 for the psilocybin/LSD group (r=-0.121, p=0.681) or the 5-MeO-DMT group (r=0.083, p=0.798).

Conversely, the 5-MeO-DMT group spent significantly more time in the lowest connectivity state (State 3), with a median proportion time of .44 compared to .28 in the psilocybin/LSD group (t(24) = -2.44, p = 0.023), and in state 4 with a median proportion time of

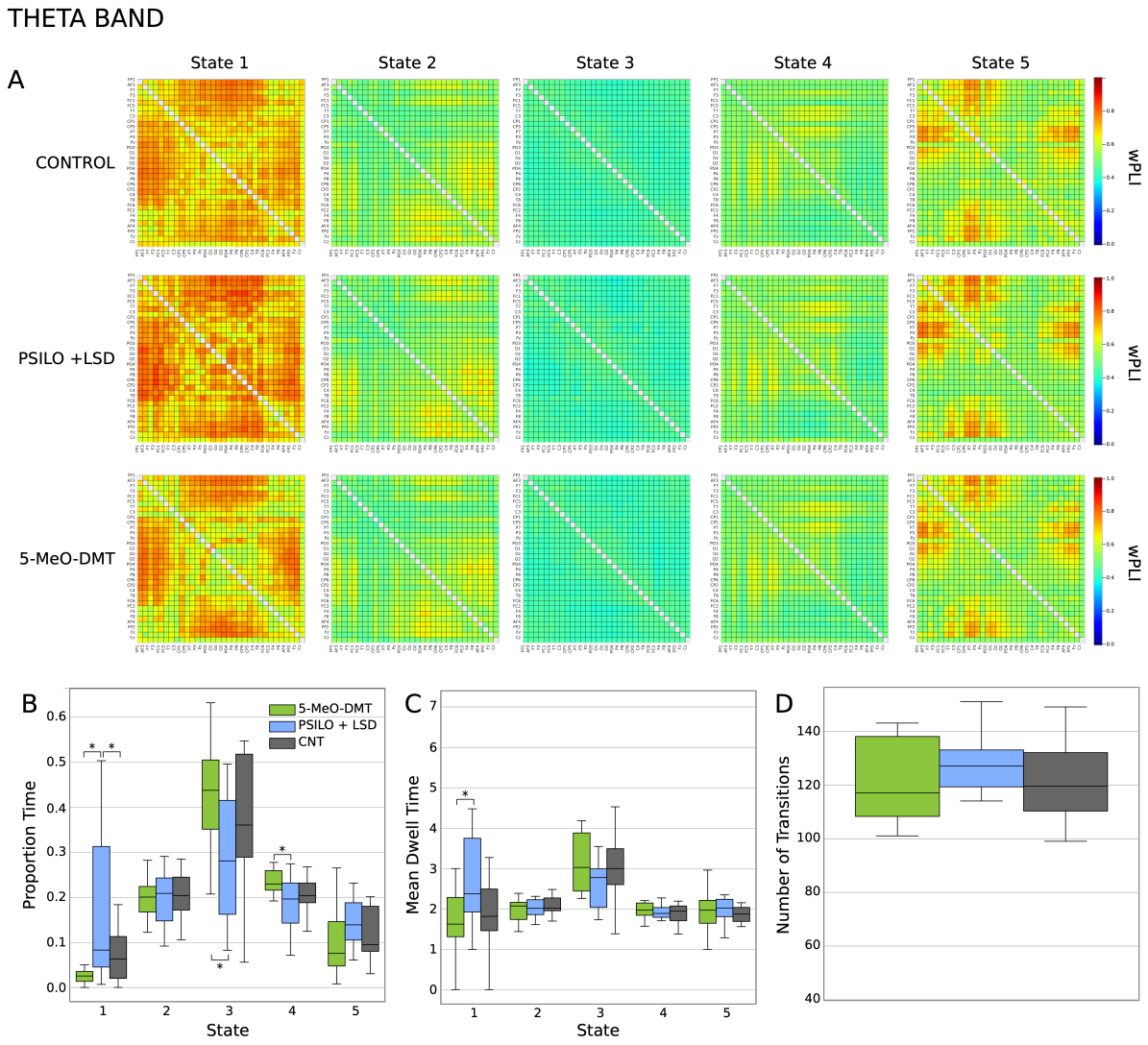

Figure 15: Dynamic functional connectivity characteristics in the theta band. *A) Group-specific dFC matrices for each state in the theta band. B) Mean proportion of time spent in each state, showing significant differences between psychedelic groups in states 1, 3, and 4. C) Mean dwell time spent in each state showed significant difference between psychedelic groups in state 1. D) Number of transitions between states did not significantly vary across groups. Error bars represent standard error of the mean (SEM). * Indicates p < .05.*

.23 compared to .20 in the psilocybin/LSD group (t(24) = -2.67, p = 0.014) (Fig. 15B). Again, we found no significant correlation between days since last psychedelic use on proportion time in this state (state 4) for the 5-MeO-DMT group (r=-0.242, p=0.449) or psilocybin/LSD group (r=0.360, p=0.206).

4.3.2.2 Alpha Band (9-14Hz)

In the alpha frequency band, the 5-MeO-DMT group exhibited a similar pattern of spending more time in the lowest connectivity state (State 2), with a median proportion time of .43 compared to .27 in the psilocybin/LSD group (t(24) = -2.21, p = 0.037) (Fig 3A-B). They also had

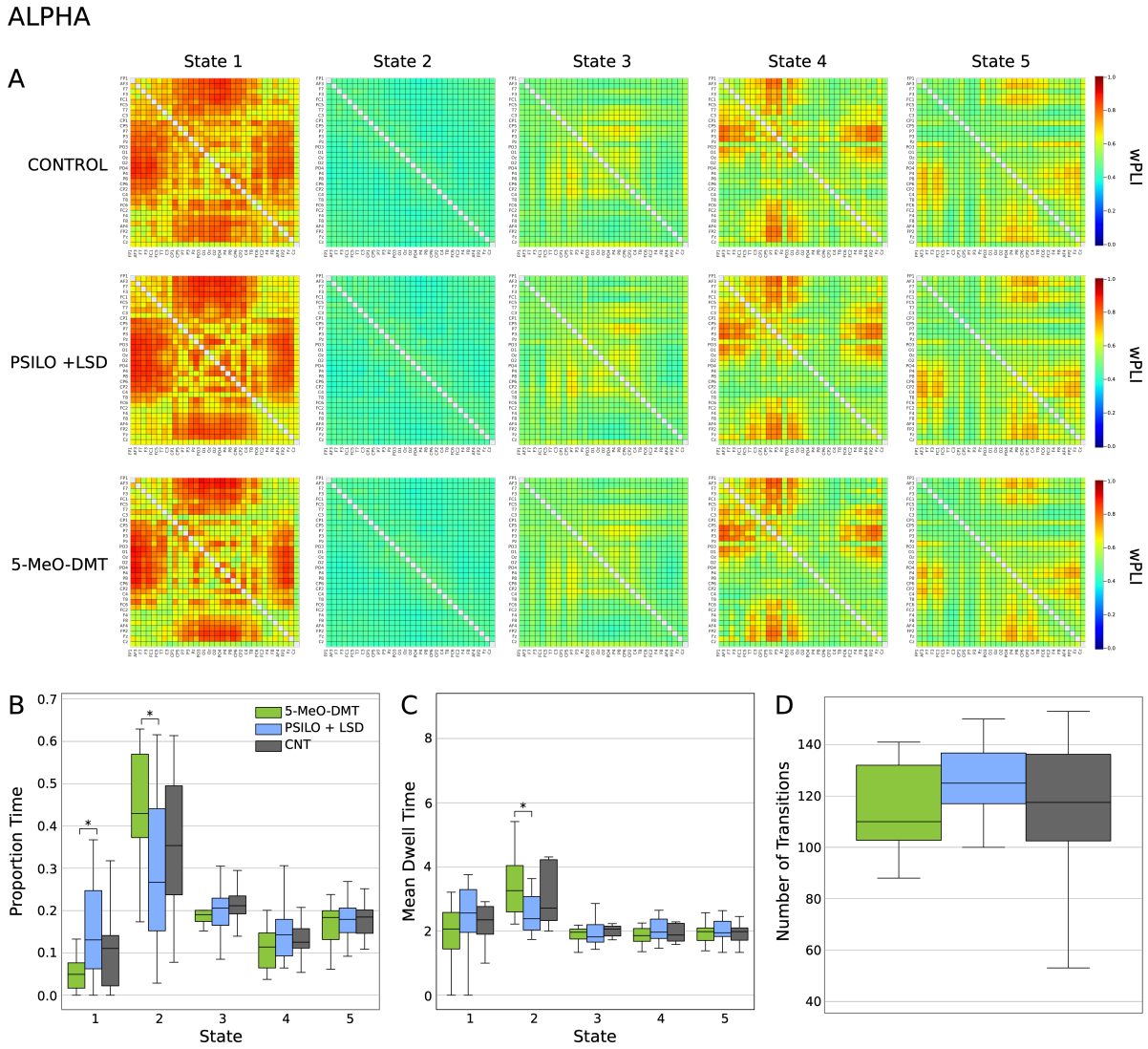

Figure 16: Dynamic functional connectivity characteristics in the alpha band. *A) Group-specific connectivity matrices for each state in the theta band. B) Mean proportion of time spent in each state, showing significant differences between psychedelic groups in states 1-2. C) Mean dwell time spent in each state showed significant difference between psychedelic groups in state 2. D) Number of transitions between states did not significantly vary across groups. Error bars represent standard error of the mean (SEM). * Indicates p < .05.*

a longer mean dwell time in this state, with a median of 3.26 seconds versus 2.38 seconds for the psilocybin/LSD group (t(24) = -2.17, p = 0.040) (Fig. 16C). We found no significant correlation between days since last psychedelic use on proportion time in this state (state 2) for the 5-MeO-DMT group (r=-0.076, p=0.814) or psilocybin/LSD group (r=0.403, p=0.153). Conversely, the psilocybin/LSD group spent more time in the highest connectivity state (state 1), with a median proportion time of .13 compared to .05 in the 5-MeO-DMT group (t(24) = 2.16, p = 0.041) (Fig 16A-B). again, we found no correlation between days since last psychedelic use on proportion time in this state (state 1) for the psilocybin/LSD group (r=-0.321, p=0.264) or the 5-MeO-DMT group (r=-0.053, p=0.871).

4.3.2.3 Beta/Low-Gamma Band (15-39Hz)

In the beta/low-gamma frequency band (15-39Hz), the 5-MeO-DMT group again spent more time in the lowest connectivity state (state 5), with a median proportion time of .42 compared to .22 in the psilocybin/LSD group (t(24) = -2.55, p = 0.018) (Fig.4A-B). The 5-MeO-DMT group also had a longer mean dwell time in this state; 3.08 seconds vs. 2.14 seconds for the psilocybin/LSD group (t(24) = -3.39, p = 0.002). The control group also had a longer mean dwell time than the psilocybin/LSD group (median = 2.72 seconds; (t(28) = 2.25, p = 0.033) (Fig. 17C). The psilocybin/LSD spent more time in a medium connectivity state (state 4), with a median proportion time of .15 compared to .07 in the 5-MeO-DMT group (t(24) = 2.37, p = 0.026) (Fig. 17B).

Additionally, the control group showed a longer mean dwell time in a medium connectivity state (state 1), with a median of 2.27 seconds compared to 2.04 seconds in the 5-MeO-DMT group (t(26) = 2.25, p = 0.033) (Fig. 17C). Additionally, the psilocybin/LSD group exhibited more frequent transitions between states compared to both the 5-MeO-group and control group, with a

median of 131.5 transitions compared to 113.5 in the 5-MeO-DMT group ($t(24) = 2.58$, $p = 0.017$) and 118 in the control group ($t(28) = -2.14$, $p = 0.041$) (Fig. 17D). To determine whether this effect correlated with the number of days since last psychedelic use, we used Pearson's correlation

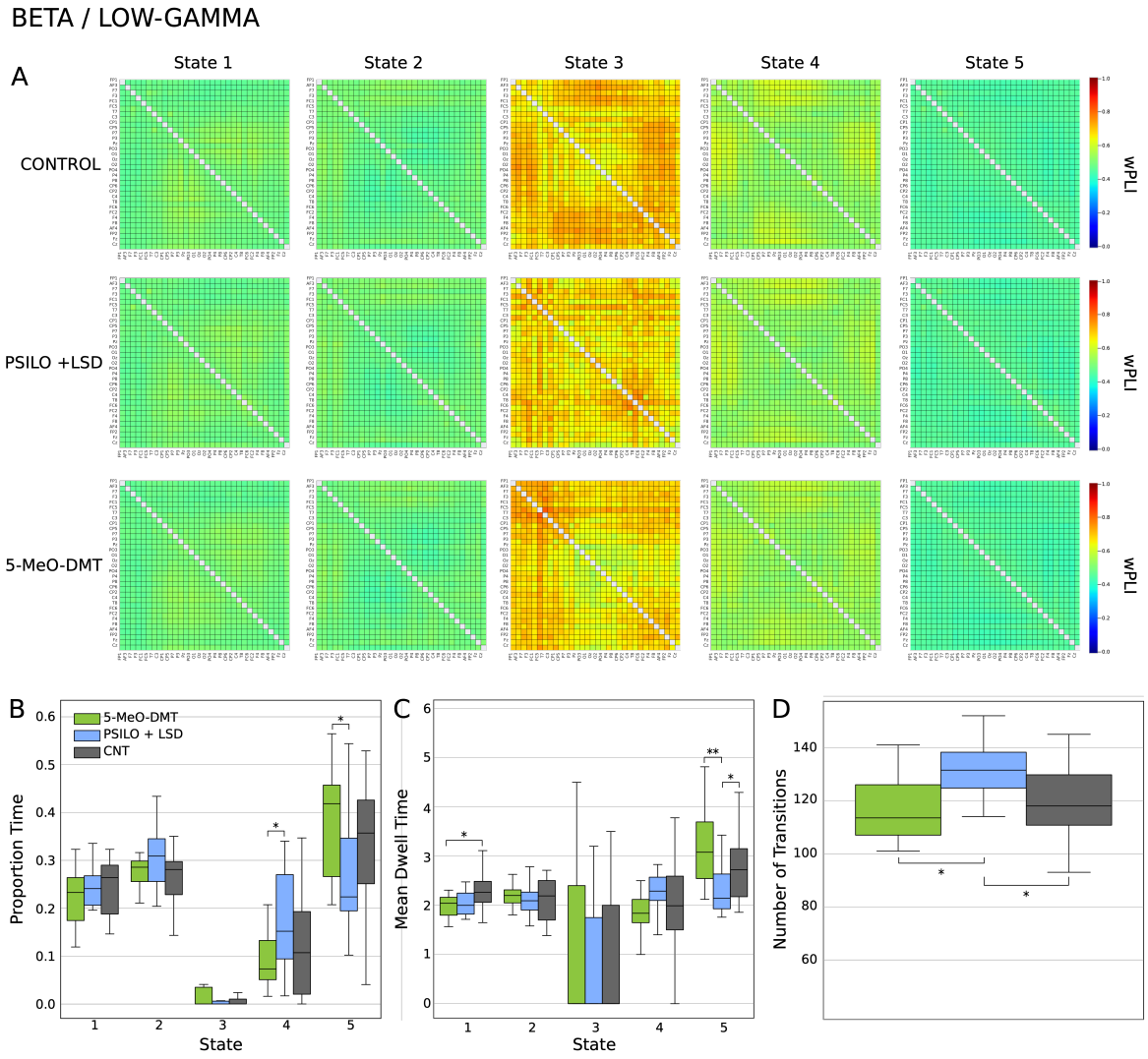

Figure 17: Dynamic functional connectivity characteristics in the beta/low-gamma band. *A) Group-specific connectivity matrices for each state in the theta band. B) Mean proportion of time spent in each state, showing significant differences between psychedelic groups in states 4-5. C) Mean dwell time spent in each state showed significant difference between 5-MeO-DMT users and controls in state one and all three groups in state 5. D) Psilocybin/LSD users also had significantly a greater number of transitions between states compared to 5-MeO-DMT users and controls. Error bars represent standard error of the mean (SEM). * Indicates $p < .05$. **Indicates $p < .005$.*

coefficient. We found no significant correlation between days since last psychedelic use and number of transitions for the psilocybin/LSD group (r=-0.041, p=0.142). Similarly, no significant correlation was observed for the 5-MeO-DMT group (r=-0.083, p=0.80).

We did observe one significant effect in delta frequency range (1-3hz) with the 5-MeO-DMT group spending significantly more time in lowest connectivity state with a median proportion time of .23 compared to .19 in the control group (t(26) = -2.25, p = 0.033).

4.3.3 Lempel-Ziv Complexity not altered in weeks following 5-HT$_{2A}$ and 5-HT$_{1A}$ psychedelic use.

Additionally, examined whether entropy, measured by Lempel-Ziv Complexity (LZc), was altered in our groups, given previous research showing increased entropy during psychedelic experiences. However, the LZc analysis did not reveal any significant differences between the control, 5-MeO-DMT, and psilocybin/LSD groups. Despite the observed differences in dFC across various states and frequency bands, the overall complexity of the EEG signals, as quantified by LZc, was comparable across all groups (Fig. 18). Furthermore, Pearson correlation coefficient

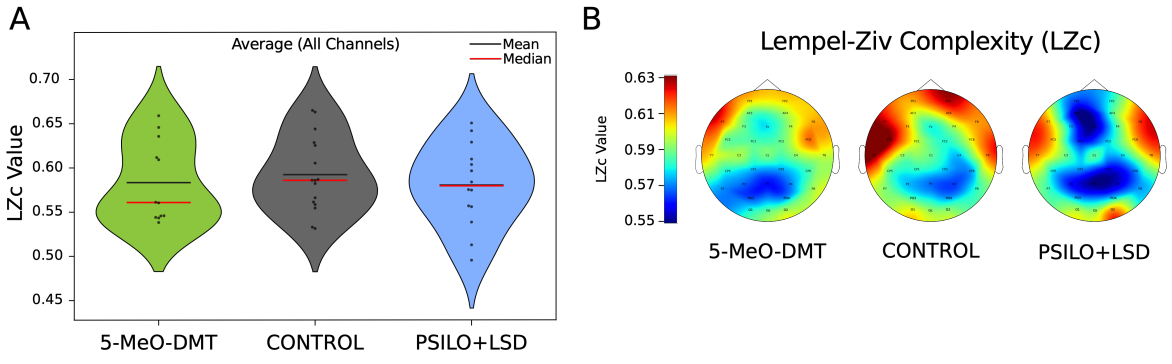

Figure 18: Lempel-Ziv Complexity between groups. *A) Violin Plots: Distributions of LZC values across EEG channels for 5-MeO-DMT users, control participants, and Psilocybin/LSD users. The black line represents the mean, and the red line indicates the median LZC value. B) Topographical Maps: Spatial distribution of LZC values for each group, with color scales indicating LZC from low (blue) to high (red). These maps show regional differences in neural signal complexity among the groups.*

analysis revealed no significant effect of days since last psychedelic use on mean LZc score in the 5-MeO-DMT (r=-0.31, p=0.328) and the psilocybin/LSD group (r=0.06, p=0.843).

Table 5: Comprehensive table of mean connectivity values across frequency bands and states. *Mean connectivity values and standard deviations for each sensor pair in the identified connectivity state across different frequency bands (full spectral analysis, theta, alpha, beta/low-gamma) are presented for the control, psilocybin/LSD, and 5-MeO-DMT user groups. This table provides a detailed comparison of the dFC characteristics across both neural frequency bands and user groups*

Frequency Band	State	Control (Mean ± SD)	Psilo/LSD Users (Mean ± SD)	5-MeO-DMT Users (Mean ± SD)
Full Spectral Analysis	**1**	0.4647 ± 0.0083	0.4661 ± 0.0094	0.4640 ± 0.0075
(1-100Hz)	**2**	0.4878 ± 0.0079	0.4889 ± 0.0101	0.4867 ± 0.0076
	3	0.5194 ± 0.0132	0.5190 ± 0.0138	0.5232 ± 0.0115
	4	0.6041 ± 0.0239	0.6051 ± 0.0270	0.6176 ± 0.0231
	5	0.7437 ± 0.0298	0.7226 ± 0.0361	0.7466 ± 0.0350
Theta	**1**	0.6905 ± 0.0490	0.7157 ± 0.0588	0.6651 ± 0.0702
(5-8hZ)	**2**	0.5348 ± 0.0508	0.5413 ± 0.0512	0.5298 ± 0.0516
	3	0.4379 ± 0.0172	0.4382 ± 0.0219	0.4371 ± 0.0195
	4	0.5177 ± 0.0429	0.5219 ± 0.0454	0.5127 ± 0.0430
	5	0.5863 ± 0.0614	0.5826 ± 0.0721	0.5794 ± 0.0628
Alpha	**1**	0.7182 ± 0.0739	0.7241 ± 0.0814	0.6840 ± 0.0989
(9-14Hz)	**2**	0.4393 ± 0.0193	0.4417 ± 0.0222	0.4389 ± 0.0192
	3	0.5266 ± 0.0515	0.5282 ± 0.0506	0.5205 ± 0.0470
	4	0.5912 ± 0.0760	0.5911 ± 0.0807	0.5820 ± 0.0843
	5	0.5572 ± 0.0629	0.5658 ± 0.0654	0.5538 ± 0.0648
Beta/Low Gamma	**1**	0.4951 ± 0.0204	0.4963 ± 0.0178	0.4935 ± 0.0192
(15-39Hz)	**2**	0.4865 ± 0.0201	0.4883 ± 0.0197	0.4862 ± 0.0194
	3	0.6863 ± 0.0353	0.6679 ± 0.0393	0.6674 ± 0.0435
	4	0.5439 ± 0.0283	0.5371 ± 0.0249	0.5429 ± 0.0193
	5	0.4517 ± 0.0111	0.4555 ± 0.0130	0.4503 ± 0.0113

4.4 Discussion

This study utilized EEG to investigate the effects of 5-HT_{2A} psychedelics (psilocybin and LSD) and the 5-HT_{1A} psychedelic 5-MeO-DMT on brain network dynamics. We conducted both a full spectral analysis and frequency band-specific analyses. Significant group differences were observed in the theta (5-8 Hz), alpha (9-14 Hz), and beta/low-gamma (15-39 Hz) frequency bands, as well as the full spectral analysis. We observed only one significant effect in the delta (1-4 Hz) frequency range and none in the high-gamma (40-100Hz) range. With this approach we hoped to gain valuable insights into the nuanced effects of psychedelic use on functional connectivity across the brain, emphasizing the potential of EEG-based methodologies in capturing the brain's complex network dynamics.

While we observed several significant differences between the psychedelic groups, few of these differences extended to comparisons with the control group. Where differences were observed, controls often fell between the two psychedelic groups, highlighting the distinct effects of 5-HT_{2A} and 5-HT_1 psychedelics. For instance, in the theta band, the psilocybin/LSD group spent more time in high-connectivity states compared to both 5-MeO-DMT users and controls. Distinct and opposing patterns emerged between the psychedelic groups, conforming with our expectations: the 5-MeO-DMT group spent more time in the least globally connected states, particularly in the theta, alpha, beta/low-gamma bands and full spectral analysis, whereas the psilocybin/LSD group spent more time in the most hyper-connected states, particularly in the theta frequency band which is associated with long-range communication[336], and alpha frequency band, which is associated with top-down cognitive control and attention [337]. This is particularly interesting given the hallmark effects of decreased alpha band oscillatory power during

psychedelic states which is often interpreted as a reduction in the brain's "top-down" control mechanisms[1,86,177].

Additionally, in the beta/low-gamma band (15-39Hz) the psilocybin/LSD group showed a greater number of transitions between states compared with the 5-MeO-DMT users and controls. This frequency range is associated with inter-regional communication and cognitive processing[338]. Thus, the increased transitions suggest enhanced neural flexibility and integration[102], consistent with static FC research indicating that psilocybin promotes a more interconnected and dynamic brain network state. Together, this tendency toward hyper-connected theta and alpha band states and increased number of beta/low-gamma state transitions in the psilocybin/LSD group might indicate a more integrated brain network, potentially linked to enhanced cognitive flexibility and emotional processing facilitated by these substances, beyond the acute exposure period[237].

The 5-MeO-DMT group's tendency to occupy less connected states, particularly in the theta, alpha, beta/low-gamma bands and full spectral analysis, may reflect its different mechanism of action at the receptor level, possibly involving more localized network dynamics. This propensity to inhabit broad hypo-connectivity suggests less synchronized activity across widespread brain regions. This pattern may be related to the unique pharmacological profile of 5-MeO-DMT, which includes significant agonism at 5-HT_{1A} receptors, known for their inhibitory effects on cortical excitability. Consequently, this may result in less inter-regional communication and a more fragmented or simplified neural network state compared to the hyper-connectivity observed with 5-HT_{2A} psychedelics.

Additionally, previous mouse research in our lab showed that 5-HT_{2A} receptor agonism, weakens top-down modulation while indirectly enhancing bottom-up sensory processing[32]. This

is primarily due to the high concentration of 5-HT_{2A} receptors in cortical layer 5, where top-down connections originate[24]. Activation of these receptors increases cortical excitability and spontaneous activity in layer 5 pyramidal neurons, disrupting normal top-down control[339]. As a consequence of this disrupted top-down modulation, bottom-up sensory processing becomes relatively enhanced[32]. Importantly, 5-HT_{2A} receptors are more prevalent in visual cortex[88], which may explain the intensified visual experiences associated with 5-HT_{2A} psychedelics. In contrast, 5-MeO-DMT, primarily acts as a 5-HT_{1A} receptor agonist, which tends to inhibit cortical neuronal activity[184]. 5-HT_{1A} receptors are more concentrated in regions like the raphe nuclei, hippocampus, and prefrontal cortex[340]. This distinct receptor profile likely contributes to the unique phenomenological effects of 5-MeO-DMT, though the specific mechanisms require further investigation. These differences in receptor distribution and activation help explain the distinct neural and psychological experiences elicited by different psychedelics. These findings also highlight the complexity of psychedelics' impacts on brain function and connectivity, underscoring the need for further research, especially concerning 5-MeO-DMT's potential link to epileptiform activity and its unique phenomenological effects[221]. Understanding these differences could provide critical insights into the safety and mechanisms of action of these substances. These findings, while preliminary, reveal distinct effects of 5-HT_{2A} and 5-HT_{1A} psychedelics on brain network dynamics. The observed differences align with the unique pharmacological profiles of these substances and may relate to their distinct subjective effects. Further investigation is warranted to fully elucidate the implications of these connectivity patterns and their relationship to the varied phenomenological experiences associated with different psychedelics.

4.4.1 Limitations

Although our findings are intriguing, there are a number of limitations to this study to be addressed in future work. First, there is a gap in the age between groups, with the 5-MeO-DMT group being slightly older (47.17 ± 10.49 versus 37.44 ± 15.08 for controls and 35.71 ± 13.21 for psilocybin/LSD users). This may have had an influence on findings presented in this paper, particularly counteracting any effects of 5-MeO-DMT use on increasing network variability, as measured by number of transitions. However, this age range is still that of stable adulthood and most age effects are fairly minor at this age in the static connectivity literature[341,342]. The effect of age on dFC is an active area of research[343], and in future work we plan to study the effect of this potential confound and contribute to this growing body of literature.

Additionally, the psilocybin/LSD group had a higher proportion of frequent marijuana users compared to the other two groups, which could confound the results (table 2). As with age, the effects of frequent marijuana use on dFC not well studied in the literature; however, static FC studies have shown that frequent marijuana use does have complex and lasting impact on global functional connectivity[344]. Thus, future work investigating this potential confound would not only solidify our results here, but contribute to understanding the interaction with frequent marijuana use and dFC.

The interval between the last psychedelic use and the EEG recording was different between the 5-MeO-DMT group (16.92 ± 7.24 days) and psilocybin/LSD group (10.43 ± 7.33 days). Our previous research has shown that psychedelic use temporal effects on top-down versus bottom-up information processing[32]. Thus, the temporal effects observed in dFC may be altered based on the

period since psychedelic use, which suggests an intriguing path for future studies studying how dFC patterns may change during the period following the user's trip.

Together the factors discussed above highlight important areas of future dFC research. Future work should validate our findings and include multiple timepoints from the same individuals, with random assignment and tight control of dose (which was also missing from our study).

4.4.2 Future directions

Our study of the effect of psychedelics on patterns in dFC suggests several intriguing paths for future work. While the limitations addressed above suggest obvious paths for studying demographic effects or long-term variations in brain network dynamics following psychedelic use, our work provides additional possible extensions in the form of future study designs, methodological extensions to dFC, and comparisons to other connectivity metrics. For example, future research is needed to directly assess the link between dFC characteristics and cognitive flexibility and belief-revision after psychedelic use. Additionally future work should aim to address the relationship between the observed measures of increased entropy during the acute treatment period and the long-term effects on dFC observed here. Together, these experiments could provide empirical evidence to support a largely theoretical framework explaining psychedelics' effects on neural activity and how these effects lead to increases in cognitive flexibility and the reconfiguration of pathological beliefs.

While the wPLI connectivity metric addresses the limitations of normal PLI, or real-valued metrics like Pearson correlation or coherence, a number of alternative methods for studying

connectivity in EEG recordings exist in the literature[345]. First, functional connectivity in EEG is not limited to PLI-based metrics and has also been studied with other non-parametric methods like the phase locking value[346] or with parametric methods like structural equation modeling[347] which impose an apriori theoretical model for connectivity. Furthermore, effective connectivity metrics such as Transfer Entropy[348] and Mutual Information have been used to study potential causal relationships in EEG[324], particularly regarding signal complexity during and after the psychedelic experience[349]. An intriguing future direction for this work would involve a comparison of wPLI-based dynamic connectivity with other functional and effective connectivity approaches.

For determining the window size in dFC, we have followed precedent in the literature by selecting a window length of 5 seconds; however, as with the epoch length in static connectivity[350] it is well established in the EEG literature that the size of a window for sliding window analyses may affect the resulting dynamics observed in connectivity[351]. The obvious next direction for this choice in our work is to systematically study the effect of window size on our analysis. Additionally, a future extension of the methods taken in this work may utilize state of the art approaches for an adaptive window size[352].

In this work, we use K-Means clustering to detect states from wPLI windows. The selection of the number of clusters (K) for K-means clustering, though guided by the elbow criterion, remains a qualitative decision. Future studies can explore alternative clustering methods, such as Hierarchical Clustering and DBSCAN[353], which do not require pre-determining the number of clusters. Additionally, some of the assumptions of K-Means such as the dependence on Euclidean distance or assumption of a relatively spherical distribution within clusters may lead to bias in the determination of states. Other clustering methods such as Gaussian Mixture Models may help with

this, but still require a predetermination of the number of states like K-Means or the selection of other hyper-parameters which may affect clustering results. Importantly, no comprehensive comparison of different clustering methods has been performed for dynamic functional connectivity in EEG or other modalities. This and other dFC studies utilizing clustering methods would benefit immensely from future work studying the various effects different methods can have on dynamic functional connectivity.

4.4.3 Conclusion

These preliminary findings emphasize the distinct impacts of different types of psychedelics on dFC. Despite the unique phenomenological effects of 5-MeO-DMT, such as "whiteouts" and reexperiencing phenomena, research on its mechanisms of action remains limited. This, coupled with the promising potential of 5-MeO-DMT as a therapeutic agent highlights the need for further investigation. It is hoped that this study encourages a more comprehensive exploration of 5-MeO-DMT's unique mechanisms and supports a balanced approach to researching the therapeutic potential of psychedelics overall.

5 DISCUSSION

Neuroscience investigates the brain and behavior across multiple levels of analysis, from molecular interactions to large-scale cognitive processes. This dissertation explores the lasting impact of psychedelic use at multiple levels across this hierarchy, examining changes in cortical network dynamics, sensory processing, and conscious experience. The findings described herein show that psychedelic use induces changes in sensory processing and dynamic functional connectivity that persist beyond the acute exposure period.

A key insight emerging from this work is that 5-HT_{2A} psychedelics shift the balance from top-down to bottom-up information processing, particularly within the visual system. These alterations unfold across distinct timescales, with differential temporal effects on top-down and bottom-up drive. Notably, we found evidence for a generalization of prediction errors, providing a potential neural basis for the heightened sense of novelty and salience often reported after psychedelic experiences. This aligns with subjective reports of psychedelic users experiencing a sense of "seeing the world anew" or finding renewed wonder in a contextually redundant environment.

This research in full extends the ReBUS model, suggesting a framework of "relaxed beliefs after psychedelic use" that may explain both the acute and enduring effects of psychedelics on perception and cognition. By demonstrating lasting changes in predictive processing within the visual system, our work provides a translational model for understanding how psychedelics might influence higher-order cognitive processes and belief structures. This chapter explores the potential implications of these findings on understanding the trade-offs between uncertainty reduction and perceptual richness, the potential cascading effects on higher-order cognition and

belief, and the importance of context, matrix and integration in shaping the outcomes of psychedelic experiences.

5.1 The cost of reducing uncertainty

The Free Energy Principle, proposed by Karl Friston, posits that biological systems, including the brain, strive to minimize free energy - a measure of surprise or uncertainty[25]. This principle has been crucial for our evolutionary survival, allowing us to conserve energy in order to predict and respond efficiently to environmental threats and opportunities. By continually updating internal models of the world, organisms can better anticipate future states and optimize their behaviors accordingly[1,25].

However, in modern, safe environments, the brain's hyper-efficient processing may be excessive. This efficiency may lead to a kind of perceptual and cognitive "autopilot" where familiar stimuli and experiences are processed with reduced conscious awareness, potentially contributing to a less vibrant perception of the world. Psychedelics may offer an opportunity to recalibrate this balance by temporarily disrupting information processing and increasing uncertainty. While this disruption can be therapeutically beneficial in addressing pathologically rigid beliefs in conditions like depression, our findings indicate broader implications for perception and cognition in psychiatrically healthy individuals as well.

5.1.1 The afterglow period

The ‘afterglow’ following psychedelic experiences is a phase lasting several weeks and is characterized by persistent alterations in perception, mood, and cognition[237]. Our research provides a neural basis for the afterglow phase. A key finding of the research presented in chapter 3 is the generalization of prediction errors during the afterglow periods. In this period, contextually neutral stimuli – that are neither predictable nor deviant – generate prediction errors, unlike in typical

brain states where responses to neutral stimuli are suppressed. This suggests that 5-HT_{2A} psychedelics may weaken overgeneralized predictions that suppress responses to neutral stimuli. This altered sensory processing allows individuals to experience their environment with renewed novelty and richness enabling a fresh perspective on familiar experiences and awareness of stimuli usually filtered out to conserve energy.

This window of enhanced perception is finite. Our findings suggest that over time, the brain gradually returns to its baseline state of information processing. This transient state of altered information processing offers value beyond engraining new beliefs but presents a unique opportunity to extend present-awareness and rich perceptual experiences into everyday life. This shift towards a more attentive state of mind aligns with documented therapeutic benefits of present-focused attention [354,355]. The challenge lies in incorporating this heightened awareness into everyday life as the brain minimizes free energy overtime. This refers to the brain's tendency to reduce uncertainty by constructing and refining internal models of the world. According to the free energy principle, the brain continually works to minimize the difference between its predictions and actual sensory inputs, theoretically aiming to reach a state where it can predict incoming information with 100% accuracy. This process leads to more efficient but potentially less flexible information processing, potentially diminishing the heightened perceptual awareness experienced during the afterglow period.

There may be potential methods for extending this present-awareness beyond the afterglow such as mindfulness meditation[354]. Research on combining psychedelic use with mindfulness practices already shows promising results in enhancing and potentially prolonging positive outcomes[140]. Furthermore, as discussed in chapter two, certain types of meditation and breath-work may lead to similar shifts in top-down bottom-up processing that we observed after

psychedelic use. However, future research should specifically investigate whether mindfulness practices can prolong present-focused awareness. Without active maintenance, the enhanced perceptual richness diminishes, metaphorically leading one to "walk right past the roses," forgetting their once-vivid sensory experiences.

5.2 Cascading effects on higher-order cognition

While our study focuses on visual system as a model for studying the impact of psychedelics on information processing, we hypothesize that similar mechanisms of relaxed priors and increased bottom-up signaling may occur across multiple levels of the cortical hierarchy. This cascade, propagating from sensory processing to higher-order cognition, could explain how perceptual changes lead to profound shifts in abstract beliefs.

A key area for future research is the impact of psychedelics on abstract beliefs within this framework, including those related to self-perception and worldview. Studies suggest that psychedelic experiences can significantly alter self-perception[97,356]. These changes may include increased openness and cognitive flexibility, reduced egocentricity and enhanced connection to others, improved self-awareness, heightened sense of agency, and positive shifts in self-concept.

To systematically study these phenomena within the predictive processing framework, researchers could adapt existing paradigms that probe self-related cognition. For example, tasks could compare participants' predictions of their own actions, sense of agency, decision-making, and cognitive performance or traits against objective measures. These approaches would allow researchers to directly measure the accuracy of self-related predictions and examine how individuals update their self-models in response to prediction errors. By applying these methods before and after psychedelic experiences, we can quantify changes in self-perceptions. This approach could reveal how psychedelics may "relax" rigid self-beliefs, allowing for the integration

of new information and the how self-remodeling may contribute to the therapeutic effects of psychedelics.

The results of Chapter 3 regarding 5-MeO-DMT, which has a higher affinity for 5-HT_{1A} receptors than psilocybin and LSD, presents a more complex picture of the effects on sensory processing, with similar alterations to saccade production, but unaltered deviance detection[222]. This complexity is further highlighted in Chapter 4, where we observed contrasting effects of 5-MeO-DMT use and 5-HT_{2A} psychedelic use on dynamic functional connectivity. Specifically, 5-MeO-DMT users exhibited a preference for less connected brain states, while 5-HT_{2A} psychedelic users spent more time in globally connected states and increased transitions between states. This may be attributed to the differential distribution of serotonin receptor subtypes across the cortex. While 5-HT_{1A} and 5-HT_{2A} receptors are both widely distributed throughout the context, 5-HT_{2A} receptors are particularly concentrated in the visual cortex[222]. This distinction might explain why 5-MeO-DMT is less associated with visual hallucinations and more often described as producing a "white out" experience[223].

Despite the absence of vivid visual effects, 5-MeO-DMT experiences are frequently reported as profoundly mystical, often characterized by a subjective impression of a void, amnesia, ego dissolution, and a sense of unity with the divine[221], as discussed at length in chapter 2. Our less definitive results with 5-MeO-DMT in visual processing paradigms indicate that the visual cortex may be a more potent translational system for investigating 5-HT_{2A} agonists like psilocybin and LSD.

To bridge the gap between our findings on visual processing and the proposed higher-order self-changes, future studies should aim to examine both aspects within the same experimental design. Such an approach would allow us to directly correlate alterations in sensory processing

with changes in self-perception and other higher-order cognitive functions. Additionally, extending this research to include other psychedelics like 5-MeO-DMT would provide valuable insights into how spatial distribution and receptor variation in the serotonergic system influences and plays a role in both low-level sensory processing and higher-order cognitive changes.

By comparing the effects of various psychedelics on both information processing across the cortical hierarchy, we can develop a more comprehensive understanding of how these substances affect the brain. This approach could help elucidate the mechanisms underlying the therapeutic potential of different psychedelic compounds and potentially guide the development of more targeted interventions for specific mental health conditions.

5.2.1 Context, matrix, and integration in psychedelic assisted therapy

Set and setting" refers to the internal state (set) and external environment (setting) that influence the effects of the experience. "Set" includes the user's mindset, expectations, and mood, while "setting" encompasses the physical environment and social context in which one uses psychedelics[78]. The role of context, the set and setting, in shaping psychedelic experiences, the consequential belief changes, and their therapeutic outcomes has gained significant attention in recent research. The importance of context is supported by research on set and setting in determining the contents of one's subjective experience[12,13] and studies on suggestibility during psychedelic states[357,358]. Recent literature has further refined our understanding of contextual factors by introducing the concept of "microclimates" - distinct subcultural environments that mediate between broad cultural contexts and individual experiences. These microclimates, such as specific therapeutic, spiritual, or artistic settings, can produce characteristic patterns of psychedelic effects and interpretations, highlighting the complex interplay between cultural, subcultural, and individual factors in shaping psychedelic experiences[359]. Our findings in chapter 3, which show

increased sensitivity to bottom-up information during the psychedelic experience, shed light on the underlying mechanisms that make environmental context so crucial in producing the subjective psychedelic experience.

However, our findings also suggest that context may play a crucial role in shaping the revision of beliefs *beyond the acute exposure period*. Our results, particularly the generalization of prediction errors after the acute exposure period point to a protracted window of plasticity. Our research on dynamic functional connectivity, presented in chapter 4, further supports this idea of altered information processing following 5-HT_{2A} (psilocybin and LSD) psychedelic use. We found that 5-HT_{2A} psychedelic users spent more time in globally hyper-connected brain states than 5-MeO-DMT users. 5-HT_{2A} psychedelic users also exhibited more transitions between states compared to both 5-MeO-DMT users and control participants. These patterns of hyperconnectivity and increased state transitions are associated with greater cognitive flexibility[102], potentially aligning with the notion of relaxed beliefs and enhanced bottom-up processing during the afterglow period.

In this afterglow window, new beliefs are formed but as this window closes, new beliefs are solidified. Thus, the concept of "set and setting," which traditionally applies to the preparation for and immediate context of psychedelic experiences, may be equally crucial after the acute effects have worn off. This idea was first proposed by Betty Eisner as the concept of "matrix," defined as "the environment from which the subject comes: the environment surrounding the subject before and after the session, and the larger environment to which the subject returns"[360]. Of particular interest is the environment someone returns to after their psychedelic experience. The potential for psychedelics to have long-term positive benefits may be heavily dependent on this matrix period. This presents both an opportunity and a challenge: while it allows for the

consolidation of positive changes and insights gained during the psychedelic experience, it also means that individuals may be more vulnerable to negative influences in their environment.

5.2.2 Integration

The importance of context after the psychedelic experience – and the abiding impacts on bottom-up and top-down processing in the days and weeks after a dose -- highlights an opportunity for integration therapy. Integration, in the context of psychedelic-assisted therapy, refers to the process of making sense of, working through, and incorporating the insights and experiences gained during a psychedelic session into one's daily life. This process is gaining increasing recognition in the literature as a critical component of psychedelic therapy[361].

Integration therapy can take various forms, including individual psychotherapy sessions, group therapy, mindfulness practices, creative expression, and nature-based activities. The goal is to help individuals process their experiences, derive meaningful insights, and translate these insights into tangible changes in their lives[361].

Research suggests several factors may influence the longevity of psychological benefits from psychedelic experiences. These include the quality and intensity of the psychedelic experience itself, the integration practices following the experience, ongoing lifestyle changes and psychological work, and individual biological and psychological factors[362–365]. While psychedelics show promise for long-lasting effects on conditions like depression, more research is needed to fully understand the factors that influence the duration of benefits and how to optimize long-term outcomes. In fact it’s unclear in the current literature how long the therapeutic benefits of psychedelics last, with large variability across studies with some showing that psychedelics can produce antidepressant effects lasting weeks, months, or with some individuals reporting even longer-lasting benefits[17,72,366]. Integration therapy and a supportive matrix, in conjunction with

psychedelic use, may play a vital role in determining the efficacy of psychedelic therapy beyond the therapeutic window. Conversely, returning to abusive or unsupportive environments during this period could potentially reinforce or negative beliefs. This aspect of psychedelic therapy requires further study to fully understand its implications and to develop best practices for post-session care.

In conclusion, the concepts of context, matrix, and integration underscore the complex interplay between psychedelic experiences and the environments in which they occur and are processed. Future research should focus on optimizing the matrix and integration processes to enhance and prolong the therapeutic benefits of psychedelic experiences, potentially leading to more effective and lasting treatments for a range of mental health conditions.

5.3 The debate on subjective effects and therapeutic benefits

There is ongoing debate in the field regarding whether the subjective effects of psychedelics are necessary for their therapeutic benefits. The results of our literature review suggests that the subjective experience may indeed play a crucial role by providing context for belief changes, particularly those related to self-perception. As discussed in Chapter 2 regarding mystical experiences, the content and quality of the psychedelic experience can significantly influence subsequent belief changes.

Martin and Sterzer agree that we cannot leave alterations in the sense of self to random chance[105]. Instead, the subjective experience may guide the direction and strength of changes in self-perception[105]. This aligns with our findings on the importance of context in shaping psychedelic outcomes[83]. Crucially, we propose that the context after the acute phase is particularly vital for guiding belief revision, especially regarding the self. Thus, the period following the

immediate psychedelic experience, marked by increased bottom-up drive, may be just as important than the acute phase itself in terms of shaping and solidifying healthy changes in self-perception and other beliefs.

It's worth noting that even in studies where context is not explicitly controlled, therapeutic benefits are often observed in conditions like depression[367]. This may be because depressed individuals tend to hold overly pessimistic views of reality[19]. Thus, most post-trip environments are likely to be more positive than depressed individuals' pre-existing beliefs, unless they return to particularly negative situations. The post-acute context provides a critical window for reinforcing and integrating the insights gained during the psychedelic experience. Additionally, the psychedelic experience often provides a detached perspective, allowing individuals to view their lives more objectively even after the acute effects have subsided, and this new perspective can be further developed and consolidated in the days and weeks following the experience[154].

While some argue that the subjective "trip" may not be necessary and that neuroplasticity alone could account for therapeutic effects, the results of our literature review suggest that both the experiential component and the environment after the experience add crucial context[169]. Our experiments in Chapters 3 and 4 provide potential mechanisms for these effects, demonstrating lasting changes in information processing and functional connectivity. The feelings of unity and ego dissolution commonly reported during psychedelic experiences may guide subsequent belief changes, but it is the integration process in the post-acute phase that likely cements these changes. These altered beliefs are then potentially encoded into mental models during the critical period of heightened plasticity following the experience, with the post-acute context playing a pivotal role in shaping the nature and persistence of these changes[232].

In conclusion, while the debate continues, our literature review supports the idea that both subjective effects during the acute phase and the context following it play significant roles in determining the outcomes of psychedelic experiences. The acute subjective experience appears to provide initial context for the interpretation of the experience and the subsequent revision of beliefs. These beliefs are likely solidified during the "afterglow" period, and these changes in beliefs, particularly those regarding self-perception, seem to play a crucial role in the therapeutic outcomes of psychedelic use. However, this hypothesis requires empirical validation at multiple stages of the psychedelic experience and beyond.

5.4 Final remarks

The research presented in this dissertation suggests that psychedelics have profound and lasting effects on perception and cognition. By examining changes in visual processing this work provides a translational model for understanding how 5-HT_{2A} psychedelics may influence higher-order cognitive processes and belief structures. The findings suggest a shift from top-down to bottom-up information processing in the days and weeks following a 5-HT_{2A} psychedelic dose, with a generalization of prediction errors that may underlie the heightened sense of novelty often reported after psychedelic use. This aligns with the proposed "relaxed beliefs after psychedelic use" framework, offering a mechanistic explanation for both acute and enduring effects[1]. Importantly, the research conforms with a previously posited role of context, integration, and the post-acute matrix period[83,360] in shaping therapeutic outcomes. As the field of psychedelic research continues to evolve, this work provides a foundation for future studies to explore how these substances may be optimally used to promote lasting positive changes in mental health and well-being. By bridging neuroscientific investigation with phenomenological experience, this

dissertation contributes to our understanding of consciousness, perception, and the potential for psychedelics to catalyze belief revision.

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