Psychedelic Vision

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For Huxley Swanson

Abstract

The visual effects of psychedelic drugs are well-known but not well understood. In this dissertation, I investigate psychedelic visual phenomenology. I provide evidence and analysis to argue that psychedelics selectively impact contextual modulation at multiple levels of mental function. I report preliminary results of two experiments from a pilot study, in which we measured contrast surround suppression in humans under the psychedelic drug psilocybin, using psychophysical and EEG event-related potential (ERP) methods. We found that psilocybin enhanced perceptual surround suppression, and strengthened surround suppression of neural responses, compared with placebo. The results support the hypothesis that psychedelics enhance contextual modulation in visual processes, which has theoretical as well as practical implications for psychedelic therapy, cognitive neuroscience, and philosophy.

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Introduction

"Vision is a fundamental component of the human conscious experience. Consequently, an accurate characterization of where and how hallucinogens, such as psilocybin, influence different stages of visual perception could be beneficial on a number of counts."

–Olivia Carter et al. (2004), "Psilocybin impairs high-level but not low-level motion perception"

Background

Psilocybin, mescaline, lysergic acid diethylamide (LSD), and N,N-dimethyltryptamine (DMT) (see Figure 1) fall into a class of drugs which is (still) officially named *hallucinogens*, a name which emphasizes their perceptual effects.[1] The visual effects (termed 'psychedelic visuals') are by far the most "notorious", "prominent," (Aday et al. 2021) and "famous" (Kometer and Vollenweider 2016; Vollenweider and Preller 2020; Letheby 2021) psychoactive properties of these drugs. Visual phenomena, which "are the most frequent and robust features of the psychedelic experience" (Vollenweider and Preller 2020), dominate first-person narrative accounts of psychedelic phenomenology, and have a robust dose-response on psychometric instruments that measure the subjective effects of LSD (Schmid et al. 2015; Liechti, Dolder, and Schmid 2017; Holze et al. 2020, 2022), DMT (Strassman et al. 1994; Pallavicini et al. 2021), and psilocybin (Hasler et al. 2004; Studerus et al. 2010; Carbonaro, Johnson, and Griffiths 2020; Hirschfeld and Schmidt 2021; Holze et al. 2022). Changes in visual perception are often the first to be noticed as the drug takes effect and can be the last effects to remain after all other psychedelic effects have subsided (Klüver 1926; Hofmann 1980). In modern illicit markets, visuals continue to serve as a subjective benchmark for the authenticity, quality, and potency of psychedelic drug material (see, e.g., Weasel 1994), and are among the top effects that motivate self-administration of these drugs (Carbonaro, Johnson, and Griffiths 2020). Historically, visual (and visionary) effects of psychedelics were and are highly regarded in many human societies (Schultes 1969; Schultes, Hofmann, and Rätsch 2006; Carod-Artal 2015; Richards 2015; George et al. 2021)—"in such societies hallucinations are often cherished and regarded as potentially valuable for the individual and the culture" Wallace (1959).

By the late nineteenth century, medical doctors and scientists began publishing their 'discoveries' of the visual effects of psychedelic plants, mostly in the form of first-person reports after observing the effects on their own minds (Lewin 1894, 1927; Prentiss and Morgan 1895; Mitchell 1896; Ellis 1898). Systematic investigation of

[1] Abraham (1996, 287) explains: "The term *hallucinogen* while unduly emphasizing perceptual effects connotes by convention their effects on emotion and cognition as well."

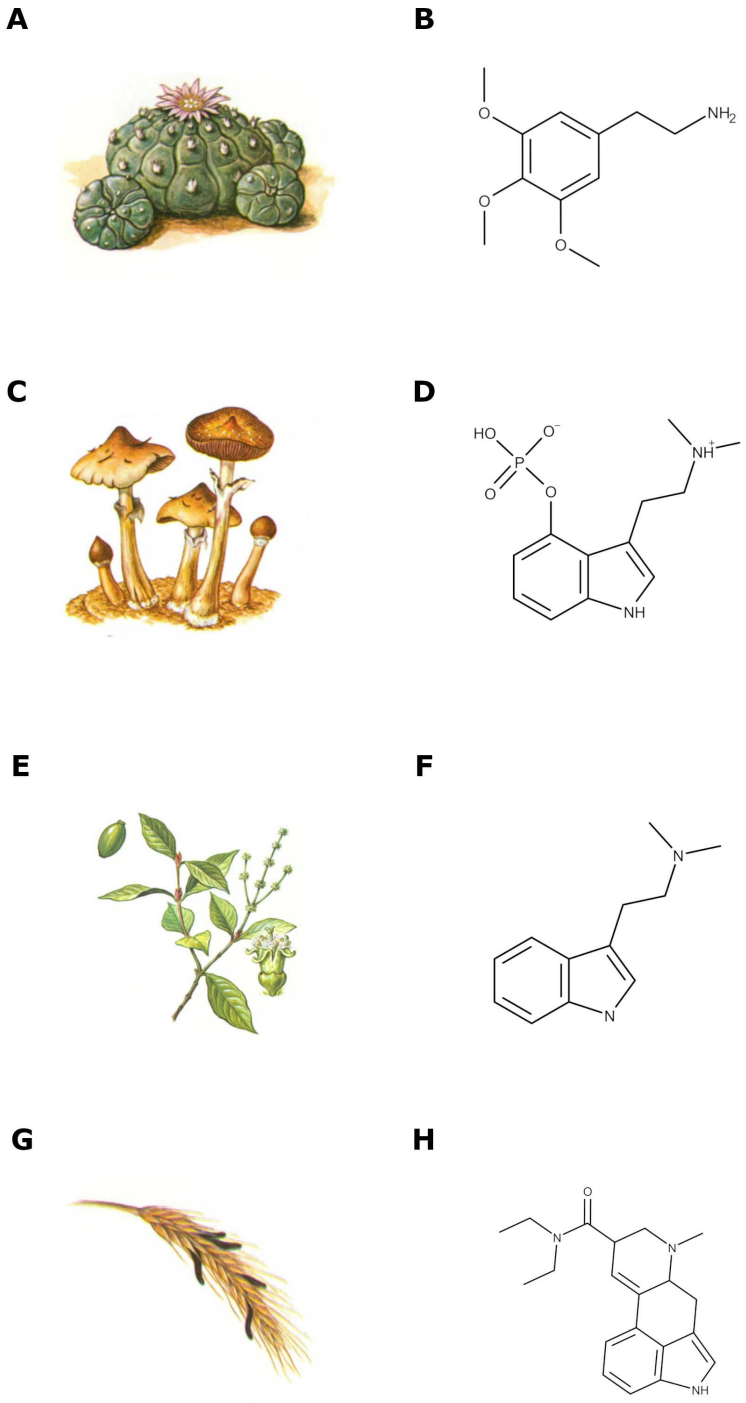

Figure 1: The classic psychedelic drugs and their natural sources. *Lophophora williamsii* (peyote; **A**) is one of dozens of species of cacti that produce the phenethylamine mescaline (**B**). *Psilocybe cubensis* (**C**) is one of more than a hundred species of fungi that produce the tryptamine psilocybin (**D**). *Psychotria viridis* (**E**) is one of hundreds of species of plants and animals (including humans) that produce the tryptamine N,N-dimethyltryptamine (DMT; **F**). LSD (**H**) is a synthetic molecule derived from *Claviceps purpurea* (**G**). Illustrations by Elmer W. Smith (Schultes and Smith 1976).

psychedelics from the standpoint of visual neuroscience began with Knauer and Maloney (1913) who inspired Klüver (1926, 1928, 1966) to investigate the visual effects of mescaline using the methods of psychophysics. However, this early visual research became less common as other research into the therapeutic and psychotomimetic potential of these drugs, which began with Beringer (1927) and continued through the 1960s (Stoll 1947; Sandison 1954; Osmond 1957; Cohen 1965; Leary, Litwin, and Metzner 1963; Grof 1976) until *all* U.S. based psychedelic research ceased as a result of the Controlled Substances Act of 1970, and did not resume until the early 1990s (i.e., Strassman et al. 1994; Spitzer et al. 1996).

Recently, psychedelics are (once again) attracting significant scientific and public interest. However, not all subjective effects of psychedelics have received equal levels of attention: visual effects appear to be largely ignored and downplayed in the current academic arena, where the focus has shifted to emotional effects, mystical experience, and the ways in which these drugs affect the sense of self (Letheby 2021). This is unsurprising, as visual 'hallucinogenic' effects have featured prominently in anti-hallucinogen propaganda rhetoric and sensationalist media, not just since the War on Drugs, but dating back to the Inquisition and Christian colonialism (Carod-Artal 2015; George et al. 2021; Collins 2018). Moreover, early psychiatry labeled these drugs as *psychotomimetic*—psychosis mimicking—in part because of their visual effects.

To date, systematic investigation of psychedelic visuals remains underdeveloped (Abraham 1996; Aday et al. 2021). This situation has created knowledge gaps in our understanding of how psychedelic drugs affect the mind. Most studies pre-1970 do not meet current methodological standards—controls, blinding, standardization, statistical techniques, transparency, reporting, etc.—making it problematic to draw conclusions from this body of work. Furthermore, the technical tools available to neuroscientists circa 1900–1970 were only in their infancy. For example, techniques for identifying Event Related Potentials (ERP) in electroencephalography (EEG) recordings were developed only in 1964 (Walter et al. 1964), so by the time psychedelic research halted in 1970 virtually no studies had investigated the impact of psychedelics on visual ERPs (Aday et al. 2021). Meanwhile, neuroscience progressed over the 70's, 80's and 90's

while the neuroscience of psychedelic drugs remained stuck in the 1960s. Furthermore, there have been several *theoretical* advances in the cognitive sciences during this time. Theories provide prediction, explanation, understanding (Thagard 2009), allowing researchers "to generate and vet ideas prior to full experimental testing" (Abbott 2008). Moreover, theorizing facilitates conceptual and computational models (Kay 2017) that guide researchers in making inferences, deductions, and conclusions from available data. Consequently, our understanding of psychedelic drugs must now catch up on decades of maturation in the cognitive sciences. The inverse is also true: the cognitive sciences have missed out on the use of psychedelics as research tools—"The study of psychedelics also provides an important—and neglected—source of data for understanding the neural basis of consciousness" (Bayne and Carter 2018, 6)

Psychedelic effects are varied and complicated, emerging in all modalities of perception, impacting multiple cognitive processes, sometimes fundamentally altering the sense of self and producing mystical experiences. Because of this, scientific attempts to understand psychedelics can be complicated and daunting. In this dissertation I adopt an approach that I believe can provide scope and parsimony to investigating psychedelic effects; namely, examine their effects on open-eyed visual perception. Visual perception is a central feature of human subjective experience (Crick 1998) and is perhaps the most well-characterized and extensively studied functions of the human mind. We can leverage this platform of knowledge to understand how psychedelics work. Psychedelics reliably cause subjects to report alterations in the subjective appearance of low-level visual features (e.g., colors, textures, angles, motion) as well as higher-level visual properties (objects, faces, scenes). Presently we know that serotonin (5-HT) receptor agonism at 5-HT_{2A} and 5-HT_{1A} receptor sites is required for psychedelic molecules to have visual effects (Glennon, Titeler, and McKenney 1984; Halberstadt 2015; Vollenweider and Smallridge 2022). Thus, by investigating the visual effects, we can learn much about how psychedelics work more generally, and perhaps also about the functional neuromodulatory role of serotonin in everyday visual perception.

Research Problem

Existing literature on low-level visual effects of psychedelics includes contradictory findings. Early-era researchers found significant changes in discrimination thresholds for various low-level visual features (Aday et al. 2021). However, these early studies "seem to contradict recent models of psychedelic effects which argue that low-level processes are largely unaffected by the drugs" (Aday et al. 2021). This is one of several examples where findings conflict regarding the effect of psychedelics on fundamental visual processes. Psychedelics impact performance on some visual tasks but not others (Carter et al. 2004; Gouzoulis-Mayfrank et al. 2002; Barrett et al. 2018; Kometer et al. 2011). Furthermore, performance on 'catch-trials' is largely comparable to placebo, suggesting that psychedelics do not cause whole-scale visual impairment or complete perceptual chaos, but rather *selectively* impact only some aspects of visual function. Thus, carefully designed psychophysical paradigms might elucidate the nature of this selectivity. Yet very few experiments using such paradigms have been carried out.

Klüver (1928) reported that under mescaline "Very pronounced simultaneous contrast is found," yet no further investigations have measured contrast perception under psychedelic drugs. A visual illusion known as apparent contrast surround suppression (Ejima and Takahashi 1985; Snowden and Hammett 1998; Schallmo and Murray 2016) is an important paradigm in visual neuroscience because it elucidates *contextual modulation*—how perceptual and neural responses to a target stimulus are altered by the presence of contextual cues (surrounding stimuli) (Heeger 1992; Carandini, Heeger, and Senn 2002; Angelucci et al. 2002; Webb et al. 2005; Schwartz, Hsu, and Dayan 2007; Coen-Cagli, Kohn, and Schwartz 2015; Schallmo et al. 2018; Schallmo, Kale, and Murray 2019). An investigation of surround suppression under peak effects of a psychedelic drug could thus shed light on how psychedelics impact this important visual function.

The lack of research pairing psychedelics with contextual modulation paradigms like surround suppression is thus a considerable knowledge gap. The neuromodulatory mechanisms underpinning visual surround suppression remain unknown (Schwartz,

Hsu, and Dayan 2007; Schallmo et al. 2018). The hypothesis that surround suppression is underpinned by the neuromodulator molecule gamma-aminobutyric acid (GABA) was pursued but has not found significant empirical support (Read et al. 2015; Schallmo et al. 2018; Schach, Surges, and Helmstaedter 2021). Surround suppression has also been probed using drugs that activate acetylcholine receptors (Gratton et al. 2017; Kosovicheva et al. 2012; Nguyen et al. 2018); dopamine receptors (Gratton et al. 2017), and noradrenaline receptors (Gratton et al. 2017). However, drugs that bind to *serotonin* receptors—including the classic psychedelics—have not been investigated for their impact on surround suppression in humans.

This knowledge gap reaches into psychiatry. Weaker (attenuated) visual surround suppression has been measured in patients with major depressive disorder (MDD) (Golomb et al. 2009; Salmela et al. 2021), a difference that normalized somewhat as MDD symptoms went into remission (Salmela et al. 2021). The neuromodulatory correlates of weakened surround suppression in MDD are unknown. Furthermore, the links between serotonin and MDD are widely assumed but not well understood (Cowen and Browning 2015; Carhart-Harris and Nutt 2017). Psilocybin-assisted therapy has rapid and enduring antidepressant effects in MDD patients (Davis et al. 2021; Ross et al. 2016; Griffiths et al. 2016; Carhart-Harris, Bolstridge, et al. 2018; Gukasyan et al. 2022) but its therapeutic mechanisms are under debate (Letheby 2021; Yaden and Griffiths 2020). Taken together, knowing the impact of a classic psychedelic molecule on visual surround suppression could thus address multiple knowledge gaps in our understanding of the links between contextual modulation, serotonin, visual surround suppression, MDD, and the antidepressant mechanisms of psychedelic-assisted therapy.

Research Aims

In this dissertation I aim to address some of the gaps in our understanding of how psychedelic drugs impact visual processes with both empirical and theoretical contributions. First, I aim to address the disconnect between the theories that guided early-era psychedelic research pre-1970 and the theories being developed in current

cognitive science. Second, I aim to address the absence of focused theoretical analysis of psychedelic *visual* phenomena. Third and finally, I aim to address the lack of empirical research into visual contrast perception and surround suppression under psychedelic drugs.

My specific research objectives are:

1. To examine and compare theoretical explanations of psychedelic drug effects, past and present.
2. To taxonomize and analyze the phenomenology of psychedelic visuals.
3. To measure the impact of a psychedelic drug on visual contrast perception and surround suppression in humans.

Each research objective is driven by a corresponding research question.

1. What is the best explanation of psychedelic drug effects to date?
2. Do psychedelic drugs affect contextual modulation in visual processes?
3. Does psilocybin impact contrast perception and surround suppression in humans?

Significance

This work is significant because it elucidates the possible mechanisms by which psychedelic drugs alter mental functions. Understanding these mechanisms has the potential to improve our understanding of how the nervous system supports everyday mental functions, which can aid our understanding of causes of—and treatments for—mental health disorders.

There are currently several important clues in the puzzle of understanding mental health. Psychedelics have therapeutic benefits but the mechanisms are not well understood. Reduced contextual modulation on visual tasks has been found in certain mental health disorders but the reasons for this are unclear. Psychedelics impact visual processes via serotonin signaling but we do not know why. Mental health disorders are linked to serotonin signaling but the mechanisms have not been elucidated. Here, I use empirical and analytical methods to investigate the links

between visual processes, contextual modulation, serotonin, and psychedelic drugs. The practical and pragmatic usefulness of this investigation is twofold. First, a better understanding of how psychedelics shift the brain's mode of processing might help psychiatry understand why this shift has therapeutic benefits, and how to optimize these benefits. Second, the focus of the work is to understand why psychedelic drugs produce visual effects, which has direct application to visual neuroscience. Probing visual function pharmacologically with serotonergic psychedelics has the potential to facilitate understanding of how vision itself works, which might provide insights into the causes of visual abnormalities, including those associated with certain mental health diagnoses.

Taken together, the above points illustrate how my aim of understanding psychedelic visuals has the potential to advance understanding of other psychedelic effects, the possible mechanisms of psychedelic therapies, and the neuromodulatory functions that underpin everyday vision. Such advances in knowledge could contribute to improvements in our understanding of sensory impairments, mental health disorders, and their treatments.

Cognitive Science

This is a dissertation for the degree of PhD in the field of *Cognitive Science*, a field that has been interdisciplinary since its beginnings (Miller 2003; Brook 2007), founded on the explicit goal of integrating psychology, linguistics, neuroscience, computer science, anthropology and philosophy (see Figure 2). My contribution leverages three of these disciplines—namely, psychology, neuroscience, and philosophy—to investigate a phenomenon of interest (psychedelic visuals) that is appropriate for the domain of cognitive science. Psychedelics alter neural activity (neuroscience), leading to changes in perception and cognition (psychology, philosophy, artificial intelligence), as well as patterns of language and semantic meaning (linguistics). Furthermore, cultures around the globe have valued and used psychedelics for a wide variety of purposes since prehistoric times (anthropology), and their implications for our understanding

of perception, mind, spirituality, and ethics are significant (philosophy). Finally, their impact on human behavior and neural dynamics lends itself to computational modeling (computer science, machine learning, artificial intelligence).

Thus, by investigating psychedelic visuals from the field of cognitive science, I am addressing "the need and potential benefit of incorporating the expertise and interests of the relatively independent fields of psychopharmacology, vision science, and mental health in future research into perception and consciousness" (Carter, Pettigrew, et al. 2005).

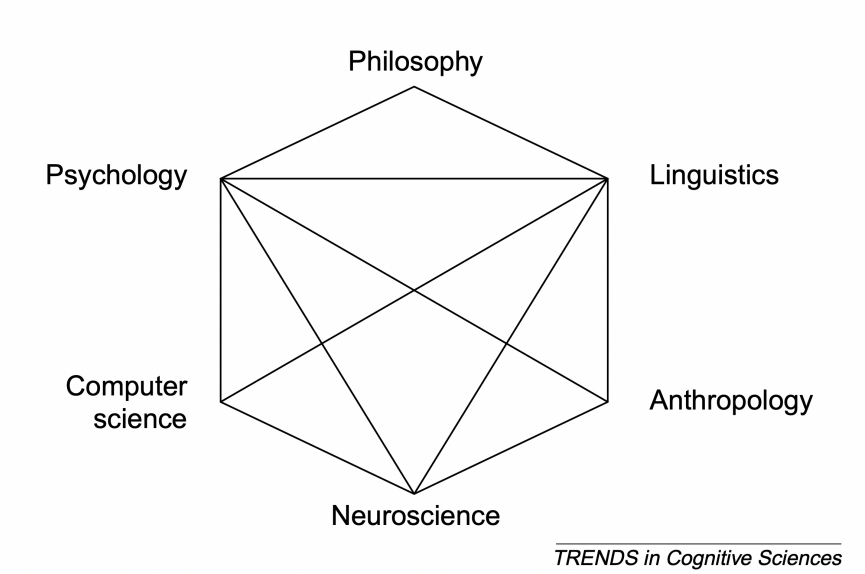

Figure 2: "The six fields are connected in a hexagon. Each line in the figure represented an area of interdisciplinary inquiry that was well defined in 1978 and that involved the tools of the two disciplines it linked together" (Miller 2003).

Limitations

The experiments in Chapters 3 and 4 were from a pilot phase of a study and included a very limited number of participants (n = 6). This small sample size limits the statistical power and conclusions that can be drawn from them. Our inclusion criteria required all participants to have at least one previous personal experience with psilocybin—we excluded drug-naive candidates—which raises the possibility that our findings will

not generalize to first-time drug-naive individuals. Another limitation somewhat unique to psychedelic research is the issue of placebo blinding—even if the study has a 'double-blind placebo-controlled' design, the drastic effects of the psychedelic drug (or lack thereof) can become obvious to everyone involved, thus breaking the blind. We cannot rule out the possibility that participants knew which drug they had received by the time they completed the experimental tasks.

This work combines empirical and analytical methods together to investigate a single phenomenon, creating a system of checks and balances. The psychophysics keeps the neuroimaging connected to the phenomenology, while the neuroimaging keeps the psychophysics connected to the brain. The empirical work keeps the theoretical and philosophical work honest and on-track. The theoretical work guides the empirical work and vice versa. The philosophical work gives the scientific work purpose and keeps the science aware of its own inconsistencies and limitations.

Structure

In this section I briefly introduce each chapter, organized by research objectives described above.

Objective 1

As stated above, my research objective **1** is: *To examine and compare theoretical explanations of psychedelic drug effects, past and present.* The corresponding research question is *What is the best explanation of psychedelic drug effects to date?* Chapter 1 addresses these with an in-depth literature review, historical perspectives, and conceptual analyses of existing theories.

Chapter 1

In Chapter 1 I provide a literature review and historical survey of psychedelic research since 1895. I emphasize the conceptual themes through which early 20th-century researchers interpreted their findings, and I link concepts from these early theories to

current models from cognitive neuroscience. This chapter was originally published *March 2nd, 2018* (Swanson 2018), as a Review Article in the journal *Frontiers in Pharmacology*, part of the special issue research topic "Psychedelic Drug Research in the 21st Century." The published manuscript is available open access under its DOI: 10.3389/fphar.2018.00172. It has been reprinted here exactly as published.

Research Objective 2

Research objective **2** of this dissertation is: *To taxonomize and analyze the phenomenology of psychedelic visuals.* The corresponding research question is: *Do psychedelic drugs affect contextual modulation in visual processes?* Chapter 2 addresses this research objective with a phenomenological-functional analysis of psychedelic visuals.

Chapter 2

In Chapter 2 I narrow the scope and focus on the effects that psychedelics have on visual perception with eyes open (known as 'open-eye visuals' or OEVs). I use examples from the literature to describe the subjective phenomenology of OEVs and then classify them into basic categories. I then analyze this phenomenology and ask what might cause them considering what we know about everyday visual processing. I argue that OEVs might stem from drug-induced hypersensitivity in contextual modulation, the process that produces common visual illusions when the stimuli contain certain contextual cues. I support this argument with interpretations of empirical evidence from previous studies with psychedelics and perceptual tasks. I further argue that psychedelics might produce hypersensitivity to contextual cues in non-visual areas of cognitive processing, and that the general state of what I call 'hypercontextual modulation' might have therapeutic benefits. This chapter was written as an invited chapter (under review) to be included in a forthcoming edited volume *Philosophical Perspectives on the Psychedelic Renaissance* from Oxford University Press (Letheby and Gerrans, n.d.).

Research Objective 3

Research objective **3** of this dissertation is: *To measure the impact of a psychedelic drug on visual contrast perception and surround suppression in humans.* The corresponding research question is: *Does psilocybin impact contrast perception and surround suppression in humans?* Chapters 3 and 4 address this objective with two experiments that measured how psilocybin impacted the perceptual and neural responses to stimuli designed to induce visual center-surround interactions in humans.

Chapter 3

Chapter 3 reports results from a pilot study with a small number of participants (n = 6) who performed a contrast-matching task under peak effects of a 25mg (high) dose of psilocybin in a double-blind, randomized, placebo-controlled psychophysical experiment. The stimuli in this task were designed to induce and measure contrast surround suppression, a form of contextual modulation in visual contrast perception in which illusory (suppressed) contrast is perceived when a stimulus is surrounded by higher-contrast (surround) stimuli. We found that psilocybin increased the strength of the surround suppression illusion under psilocybin compared with placebo. Furthermore, the magnitude of this increase was 'feature-selective', as the difference between psilocybin and placebo was greatest when the target stimulus appeared within a surround that had parallel orientation. This finding is consistent with the arguments I make in chapter 2 that psychedelic effects result from hypersensitivity to contextual cues.

Chapter 4

Chapter 4 reports results from a second experiment completed by the same participants in the same study as Chapter 3. We obtained electroencephalography (EEG) signals as the participants viewed stimuli designed to induce and measure surround suppression in neural responses to visual stimuli as measured by event-related potential (ERP) techniques. We found that responses to the target stimulus showed greater surround

suppression under psilocybin compared with placebo. Moreover, like our psychophysical findings, the effect of psilocybin on ERP surround suppression was greatest when the surround stimulus had parallel orientation. This finding mirrors our psychophysical findings, and further supports the arguments in Chapter 2 that the visual system becomes hypersensitive to contextual cues under psychedelic drugs.

Chapter 1

Unifying theories of psychedelic drug effects

"Hallucinogens sit at the crossroads of the mind-brain interaction."

–Henry David Abraham (1996, 294) "The Pharmacology of Hallucinogens"

ABSTRACT

In this chapter I review theories of psychedelic drug effects and highlight key concepts which have endured over the last 125 years of psychedelic science. First, I describe the subjective phenomenology of acute psychedelic effects using the best available data. Next, I review late 19th-century and early 20th-century theories—*model psychoses theory, filtration theory*, and *psychoanalytic theory*—and highlight their shared features. I then briefly review recent findings on the neuropharmacology and neurophysiology of psychedelic drugs in humans. Finally, I describe recent theories of psychedelic drug effects which leverage 21st-century cognitive neuroscience frameworks—*entropic brain theory, integrated information theory*, and *predictive processing*—and point out key shared features that link back to earlier theories. I identify an abstract principle which cuts across many theories past and present: psychedelic drugs perturb universal brain processes that normally serve to constrain neural systems central to perception, emotion, cognition, and sense of self. I conclude that making an explicit effort to investigate the principles and mechanisms of psychedelic drug effects is a uniquely powerful way to iteratively develop and test unifying theories of brain function.[1]

1.1 Introduction

Lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), psilocybin, and mescaline—the 'classic' psychedelic drugs—can produce a broad range of effects in perception, emotion, cognition, and sense of self. How do they do this? Western science began its 'first wave' of systematic investigations into the unique effects of mescaline 125 years ago. By the 1950s, rising interest in mescaline research was expanded to include drugs like DMT, LSD, and psilocybin in a 'second wave' of psychedelic science. Because of their dramatic effect on the character and contents of subjective awareness, psychedelic drugs magnified the gaps in our scientific understanding of how brain chemistry relates to subjective experience (see Evarts 1957; Purpura 1968). Huxley (1954, 12) commented that our understanding circa 1954 was "absurdly inadequate" and amounted to a mere "clue" that he hoped would soon develop into a more

[1] Originally published *March 2nd, 2018* (Swanson 2018), as a Review Article in the journal *Frontiers in Pharmacology*, part of the special issue research topic "Psychedelic Drug Research in the 21st Century." The published manuscript is available open access under the DOI: 10.3389/fphar.2018.00172.

robust understanding. "Meanwhile the clue is being systematically followed, the sleuths—biochemists, psychiatrists, psychologists—are on the trail" (Huxley 1954, 12). A 'third wave' of psychedelic science has recently emerged with its own set of sleuths on the trail, sleuths who now wield an arsenal of 21st-century scientific methodologies and are uncovering new sets of clues.

Existing theoretical hurdles span five major gaps in understanding. The first gap is that we do not have an account of how psychedelic drugs can produce such a broad diversity of subjective effects. LSD, for example, can produce subtle intensifications in perception—or it can completely dissolve all sense of space, time, and self. What accounts for this atypical diversity?

The second gap is that we do not understand how pharmacological interactions at neuronal receptors and resulting physiological changes in the neuron lead to large-scale changes in the activity of neural populations, or changes in brain network connectivity, or at the systems-level of global brain dynamics. What are the causal links in the multi-level pharmaco-neurophysiological chain?

The third gap is that we do not know how psychedelic drug-induced changes in brain activity—at any level of description—map onto the acute subjective phenomenological changes in perception, emotion, cognition, and sense of self. This kind of question is not unique to psychedelic drugs (i.e., Crick and Koch 1998; Tononi and Edelman 1998) but our current understanding of psychedelic drug effects clearly magnifies the disconnect between brain science and subjective experience.

Fourth, there is a gap in our understanding of the relationships between psychedelic effects and symptoms of psychoses, such as perceptual distortion, hallucination, or altered self-reference. What is the relationship between psychedelic effects and symptoms of chronic psychotic disorders?

Fifth and finally, there is a gap in our clinical understanding of the process by which psychedelic-assisted therapies improve mental health (Carhart-Harris and Goodwin 2017). Which psychedelic drug effects (in the brain or in subjective experience) enable clinical improvement? How?

Scientific efforts to understand diverse natural phenomena aim to produce a single

theory that can account for many phenomena using a minimal set of principles. Such theories are sometimes called *unifying theories*. Not everyone agrees on the meaning of 'unification' or 'unifying theory' in science.[2] Morrison (2000) observed that, although theory unification is a messy process which may not have discernible universal characteristics, historically successful unifying scientific theories tend to have two common features: (1) a *formalized framework* (quantitative mathematical descriptions of the phenomena) and (2) *unifying principles* (abstract concepts that unite diverse phenomena). On this conception, then, a unifying theory of psychedelic drug effects would offer a single formalized (mathematical or computational) framework capable of describing diverse psychedelic phenomena using a minimal set of unifying principles. Unfortunately, the survey of literature in this review does not locate an existing unifying theory of psychedelic drug effects. It does, however, highlight enduring abstract principles that recur across more than a century of theoretical efforts. Furthermore, it reviews recent formalized frameworks which, although currently heterogeneous and divergent, hint at the possibility of a quantitative groundwork for a future unifying theory.

The field of cognitive neuroscience offers formalized frameworks and general principles designed to track and model the neural correlates of perception, emotion, cognition, and consciousness. These broad frameworks span major levels of description in the brain and attempt to map them onto behavioral and phenomenological data. Corlett et al. (2009, 516) argue that until this is done "our understanding of how the pharmacology links to the symptoms will remain incomplete." Montague et al. (2012, 1) argue that 'computational psychiatry' can remedy the "lack of appropriate intermediate levels of description that bind ideas articulated at the molecular level to those expressed at the level of descriptive clinical entities." Seth (2009, 50) argues that "computational and theoretical approaches can facilitate a transition from correlation to explanation in consciousness science" and explains how a recent LSD, psilocybin, and ketamine study (Schartner et al. 2017) was motivated by a need to elucidate descriptions at intermediate levels somewhere between pharmacology and phenomenol-

[2]For example, see Kitcher (1981, 1989), Friedman (1983), and Morrison (2000).

ogy: "We know there's a pharmacological link, we know there's a change in experience and we know there's a clinical impact. But the middle bit if you like, what are these drugs doing to the global activity of the brain, that's the gap we're trying to fill with this study" (quoted in Osborne 2017). Taken together, the above quotations point to an emerging sense that cognitive neuroscience frameworks can address gaps in our understanding of psychedelic drug effects.

In this chapter I review theories of psychedelic drug effects. First, making an effort to clearly define the target explananda, I review the acute subjective phenomenological properties of psychedelic effects as well as long-term clinical outcomes from psychedelic-assisted therapies. Second, I review theories from first-wave and second-wave psychedelic science—*model psychoses theory, filtration theory*, and *psychoanalytic theory*—and identify core features of these theories. Third, I review findings from recent neurophysiological research in humans under psychedelic drugs. Finally, I review select 21st-century theories of psychedelic effects that have been developed within cognitive neuroscience frameworks; namely, *entropic brain theory, integrated information theory*, and *predictive processing*. My analysis of recent theoretical efforts highlights certain features, first conceptualized in 19th- and 20th-century theories, which remain relevant in their ability to capture both the phenomenological and neurophysiological dynamics of psychedelic effects. I describe how these enduring theoretical features are now being operationalized into formalized frameworks and could serve as potential unifying principles for describing diverse psychedelic phenomena.

1.2 Psychedelic Drug Effects

There are dozens of molecules known to cause psychedelic-like effects (Schultes and Hofmann 1973; Shulgin and Shulgin 1997). This review focuses only on a limited set of drugs dubbed 'classical hallucinogens' or 'classic psychedelics' which are: LSD, DMT, psilocybin, and mescaline[3] (Nichols 2016). Importantly, there are qualitative inter-drug

[3]Ayahuasca contains DMT but is importantly different from pure DMT (McKenna, Towers, and Abbott 1984).

differences between the effects of the four classic psychedelic drugs (Strassman et al. 1994; Hasler et al. 2004; Studerus, Gamma, and Vollenweider 2010; Schmid et al. 2015; Liechti, Dolder, and Schmid 2017). Drug dosage is a primary factor in predicting the types of effects that will occur Liechti, Dolder, and Schmid (2017). Effects unfold temporally over a drug session; onset effects are distinct from peak effects and some effects have a higher probability of occurring at specific timepoints over the total duration of drug effects (Masters and Houston 1966; Preller and Vollenweider 2016). Furthermore, effects are influenced by non-drug factors traditionally referred to as *set and setting*, such as personality, pre-dose mood, drug session environment, and external stimuli (Figure 1.1) (Leary, Litwin, and Metzner 1963; Studerus et al. 2012; Hartogsohn 2016; Carhart-Harris and Nutt 2017).

The above variables, while crucial, do not completely prohibit meaningful characterization of general psychedelic effects, as numerous regularities, patterns, and structure can still be identified (Masters and Houston 1966; Grinspoon and Bakalar 1979; Preller and Vollenweider 2016). Indeed, common psychedelic effects can be reliably measured using validated psychometric instruments consisting of self-report questionnaires and rating scales (Strassman et al. 1994; Dittrich 1998; Dittrich, Lamparter, and Maurer 2010; Riba, Rodríguez-Fornells, et al. 2001; Studerus, Gamma, and Vollenweider 2010, 2010; Maclean et al. 2012; Turton, Nutt, and Carhart-Harris 2014; Barrett, Johnson, and Griffiths 2015; Nour et al. 2016) though some of these rating scales may be in need of further validation using modern statistical techniques (Bouso et al. 2016). Items from these rating scales are wrapped in 'scare quotes' in the following discussion in an effort to characterize the subjective phenomenology of psychedelic effects from a first-person perspective. An example of rating scale results is given in (Figure 1.2).

1.2.1 Perceptual Effects

Perceptual effects occur along a dose-dependent range from subtle to drastic. The range of different perceptual effects includes perceptual intensification, distortion, illusion, mental imagery, elementary hallucination, and complex hallucination (Klüver 1928; Kometer and Vollenweider 2016; Preller and Vollenweider 2016). Intensifications

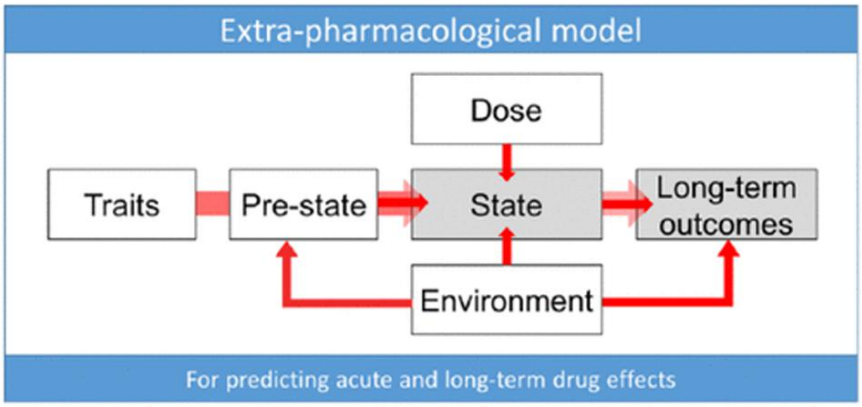

Figure 1.1: 'Extra-pharmacological' factors that can determine psychedelic drug effects (Carhart-Harris and Nutt 2017). "*Trait* factors may be biological [e.g., receptor polymorphisms (Ott 2007)] or psychological in nature [e.g., personality (MacLean, Johnson, and Griffiths 2011) or suggestibility (Carhart-Harris et al. 2015)]. The *pre-state* refers to such things as anticipatory anxiety, expectations and assumptions (which account for so-called 'placebo' and 'nocebo' effects), and readiness to surrender resistances and 'let go' to the drug effects (e.g., see Russ and Elliott 2017). In the context of psychedelic research, the pre-state is traditionally referred to as the 'set' (Hartogsohn 2016). *State* refers to the acute subjective and biological quality of the drug experience and may be measured via subjective rating scales or brain imaging (see Roseman, Nutt, and Carhart-Harris 2017). *Dose* relates to the drug dosage—which may be a critical determinant of state (Griffiths et al. 2011; Nour et al. 2016)—as well as long-term outcomes (see Roseman, Nutt, and Carhart-Harris 2017). *Environment* relates to the various environmental influences. In the context of psychedelic research this is traditionally referred to as 'setting' (Hartogsohn 2016). We recognize that the environment can be influential at all stages of the process of change associated with drug action. The *long-term outcomes* may include such things as symptoms of a specific psychiatric condition such as depression—measured using a standard rating scale (Carhart-Harris, Bolstridge, et al. 2016) as well as relatively pathology-independent factors such as personality (MacLean, Johnson, and Griffiths 2011) and outlook" (Carhart-Harris and Nutt 2017, 1097).

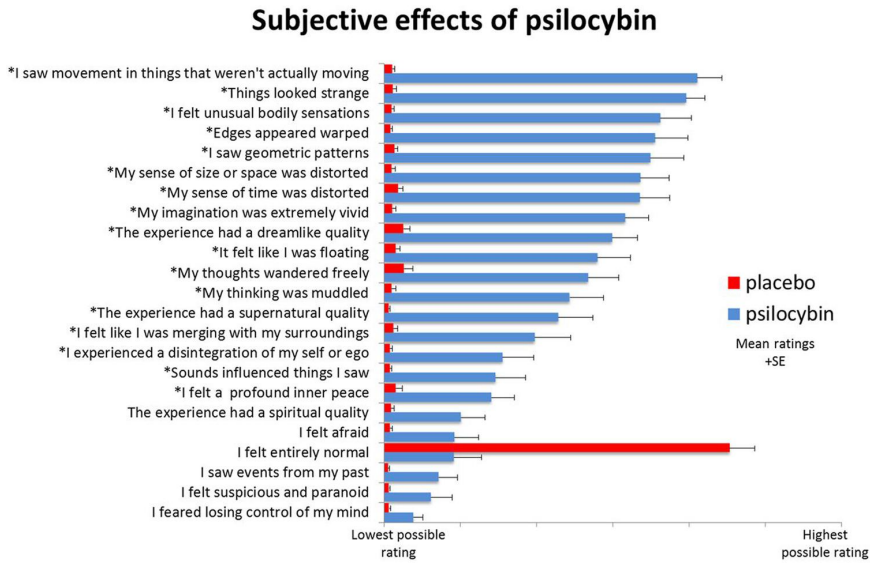

Figure 1.2: Subjective rating scale items selected after psilocybin (blue) and placebo (red) ($n = 15$) (Muthukumaraswamy et al. 2013). "Items were completed using a visual analog scale format, with a bottom anchor of 'no, not more than usually' and a top anchor of 'yes, much more than usually' for every item, with the exception of 'I felt entirely normal,' which had bottom and top anchors of 'No, I experienced a different state altogether' and 'Yes, I felt just as I normally do,' respectively. Shown are the mean ratings for 15 participants plus the positive SEMs. All items marked with an asterisk were scored significantly higher after psilocybin than placebo infusion at a Bonferroni-corrected significance level of $p < 0.0022$ (0.5/23 items)" (Muthukumaraswamy et al. 2013, 15176).

of color saturation, texture definition, contours, light intensity, sound intensity, timbre variation, and other perceptual characteristics are common (Kometer and Vollenweider 2016; Kaelen et al. 2018). The external world is experienced as if in higher resolution, seemingly more crisp and detailed, often accompanied by a distinct sense of 'clarity' or 'freshness' in the environment (Hofmann 1980; Huxley 1954; Díaz 2010; Kometer and Vollenweider 2016). Sense of meaning in percepts is altered, e.g., 'Things around me had a new strange meaning for me' or 'Objects around me engaged me emotionally much more than usual' (Studerus, Gamma, and Vollenweider 2010).

Perceptual distortions and illusions are extremely common, e.g., 'Things looked strange' or 'My sense of size and space was distorted' or 'Edges appeared warped' or 'I saw movement in things that weren't actually moving' (Dittrich 1998; Muthukumaraswamy et al. 2013). Textures undulate in rhythmic movements, object boundaries warp and pulsate, and the apparent sizes and shapes of objects can shift rapidly (Kometer and Vollenweider 2016). Controlled psychophysical studies have measured various alterations in motion perception (Carter et al. 2004), object completion (Kometer et al. 2011), and binocular rivalry (Frecska, White, and Luna 2004; Carter et al. 2007).

In what are known as *elementary hallucinations*—e.g., 'I saw geometric patterns'—the visual field can become permeated with intricate tapestries of brightly colored, flowing latticework and other geometric visuospatial 'form constants' (Klüver 1928; Siegel and West 1975; Kometer and Vollenweider 2016). In *complex hallucinations* visual scenes can present elaborate structural motifs, landscapes, cities, galaxies, plants, animals, and human (and non-human) beings (Shanon 2002; Studerus, Gamma, and Vollenweider 2010; Carhart-Harris et al. 2015; Kaelen et al. 2016; Preller and Vollenweider 2016; Kraehenmann, Pokorny, Vollenweider, et al. 2017). Complex hallucinations typically succeed elementary hallucinations and are more likely at higher doses (Kometer and Vollenweider 2016; Liechti, Dolder, and Schmid 2017) especially under DMT (Strassman et al. 1994; Shanon 2002). Both elementary and complex hallucinations are more commonly reported behind closed eyelids ('closed eye visuals'; CEVs) but can dose-dependently occur in full light with eyes open ('open eye visuals'; OEVs) (Kometer and Vollenweider 2016). CEVs are often described as vivid

mental imagery. Under psychedelic drugs, mental imagery becomes augmented and intensified—e.g., 'My imagination was extremely vivid'—and is intimately linked with emotional and cognitive effects (Carhart-Harris et al. 2015; Preller and Vollenweider 2016). "Sometimes sensible film-like scenes appear, but very often the visions consist of scenes quite indescribable in ordinary language, and bearing a close resemblance to the paintings and sculptures of the surrealistic school" (Stockings 1940, 31). Psychedelic mental imagery can be modulated by both verbal (Carhart-Harris et al. 2015) and musical (Kaelen et al. 2016) auditory stimuli. Synaesthesia (Ward 2013) has been reported, especially visual phenomena driven by auditory stimuli—'Sounds influenced the things I saw'—but classification of these effects as 'true' synaesthesia is actively debated (Sinke et al. 2012; Brogaard 2013; Luke and Terhune 2013; Terhune et al. 2016).

Somatosensory perception can be drastically altered—e.g., 'I felt unusual bodily sensations'—including body image, size, shape, and location (Savage 1955; Klee 1963; Preller and Vollenweider 2016). Sense of time and causal sequence can lose their usual linear cause-effect structure making it difficult to track the transitions between moments (Heimann 1963; Wittmann et al. 2007; Wackermann et al. 2008; Studerus, Gamma, and Vollenweider 2010; Schmid et al. 2015).

Overall the perceptual effects of psychedelics are extremely varied, multimodal, and easily modulated by external stimuli. Perceptual effects are tightly linked with emotional and cognitive effects.

1.2.2 Emotional Effects

Emotional psychedelic effects are characterized by a general intensification of feelings, increased (conscious) access to emotions, and a broadening in the overall range of emotions felt over the duration of the drug session. Psychedelics can induce unique states of euphoria characterized by involuntary grinning, uncontrollable laughter, silliness, giddiness, playfulness, and exuberance (Preller and Vollenweider 2016). Negatively experience emotions—e.g., 'I felt afraid' or 'I felt suspicious and paranoid'—are often accompanied by a general sense of losing control, e.g., 'I feared losing control of my

mind' (Strassman 1984; Johnson, Richards, and Griffiths 2008; Barrett, Johnson, and Griffiths 2017). However, the majority of emotional psychedelic effects in supportive contexts are experienced as positive (Studerus, Gamma, and Vollenweider 2010; Schmid et al. 2015; Carhart-Harris, Kaelen, et al. 2016; Belser et al. 2017; Watts et al. 2017). Both LSD and psilocybin can bias emotion toward positive responses to social and environmental stimuli (Kometer et al. 2012; Carhart-Harris, Kaelen, et al. 2016; Dolder et al. 2016; T. Pokorny et al. 2016). Spontaneous feelings of awe, wonder, bliss, joy, fun, excitement (and yes, peace and love) are also consistent themes across experimental and anecdotal reports (Huxley 1954; Kaelen et al. 2015; Preller and Vollenweider 2016; Belser et al. 2017). In supportive environments, classic psychedelic drugs can promote feelings of trust, empathy, bonding, closeness, tenderness, forgiveness, acceptance, and connectedness (Dolder et al. 2016; Belser et al. 2017; Carhart-Harris et al. 2017; T. Pokorny et al. 2017; Watts et al. 2017). Emotional effects can be modulated by all types of external stimuli, especially music (Bonny and Pahnke 1972; Shanon 2002; Kaelen et al. 2015, 2018).

1.2.3 Cognitive Effects

Precise characterization of cognitive psychedelic effects has proven enigmatic and paradoxical (Shanon 2002; Carhart-Harris, Kaelen, et al. 2016). Acute changes in the normal flow of linear thinking—e.g., 'My thinking was muddled' or 'My thoughts wandered freely'—are extremely common (Hasler et al. 2004; Studerus, Gamma, and Vollenweider 2010). This is reflected in reduced performance on standardized measures of working memory and directed attention (Carter, Burr, et al. 2005; Vollenweider et al. 2007); however, reductions in performance have been shown to occur less often in individuals with extensive past experience with the drug's effects (Bouso et al. 2013). Crucially, cognitive impairments related to acute psychedelic effects are dose-dependent (Wittmann et al. 2007). Extremely low doses, known as *microdoses*, have been anecdotally associated with improvements in cognitive performance (Waldman 2017; Wong 2017) "a claim that urgently requires empirical verification through controlled research" (Carhart-Harris and Nutt 2017, 1103). Theoretical attempts to

account for the reported effects of microdosing have yet to emerge in the literature and therefore present an important opportunity to future theoretical endeavors.

Certain cognitive traits associated with creativity can increase under psychedelics (Sessa 2008; Baggott 2015) such as divergent thinking (Kuypers et al. 2016), use of unlikely language patterns or word associations (Natale et al. 1978), expansion of semantic activation (Spitzer et al. 1996; Family et al. 2016), and attribution of meaning to perceptual stimuli (Liechti, Dolder, and Schmid 2017; Preller et al. 2017) especially musical stimuli (Kaelen et al. 2015, 2018; Atasoy, Roseman, et al. 2017; Barrett, Preller, et al. 2017). Primary-process thinking (Rapaport 1950)—a widely validated psychological construct (Arminjon 2011) associated with creativity (Suler 1980)—is characterized phenomenologically by "image fusion; unlikely combinations or events; sudden shifts or transformations of images; and contradictory or illogical actions, feelings, or thoughts" (Kraehenmann, Pokorny, Aicher, et al. 2017, 2). Psilocybin and LSD have been shown to increase primary-process thinking (Martindale and Fischer 1977; Natale, Dahlberg, and Jaffe 1978; Family et al. 2016; Kraehenmann, Pokorny, Aicher, et al. 2017) as well as the subjective bizarreness and dreamlike nature of mental imagery associated with verbal stimuli (Carhart-Harris et al. 2015; Kraehenmann, Pokorny, Vollenweider, et al. 2017). Cognitive flexibility (or 'loosening' of cognition) and optimism can remain for up to 2 weeks after the main acute drug effects have dissipated (Carhart-Harris, Kaelen, et al. 2016). Furthermore, long-term increases in creative problem-solving ability (Sweat, Bates, and Hendricks 2016) and personality trait openness (MacLean, Johnson, and Griffiths 2011; Lebedev et al. 2016) have been measured after just one psychedelic experience.

1.2.4 Ego Effects and Ego Dissolution Experiences

Klüver (1926, 513) observed that under peyote "the line of demarcation drawn between 'object' and 'subject' in normal state seemed to be changed. The body, the ego, became 'objective' in a certain way, and the objects became 'subjective'." Similar observations continued throughout first-wave and second-wave psychedelic science (Beringer 1927; Klüver 1928; Savage 1955; Eisner and Cohen 1958; Klee 1963; Leary, Metzner, and

Alpert 1964; Grof 1976). Importantly, effects on sense of self and ego occur along a dose-dependent range spanning from subtle to drastic (Letheby and Gerrans 2017; Millière 2017). Subtle effects are described as a 'softening' of ego with increased insight into one's own habitual patterns of thought, behavior, personal problems, and past experiences; effects which were utilized in 'psycholytic' psychotherapy (Grof 1980). Drastic ego-effects, known as *ego dissolution[4], are described as "the dissolution of the sense of self and the loss of boundaries between self and world" (Millière 2017, 1)—e.g., 'I felt like I was merging with my surroundings' or 'All notion of self and identity dissolved away' or 'I lost all sense of ego' or 'I experienced a loss of separation from my environment' or 'I felt at one with the universe' (Dittrich, Lamparter, and Maurer 2010; Nour et al. 2016; Millière 2017). These descriptions resemble non-drug 'mystical-type' experiences (James 1902; Huxley 1945; Stace 1960; Forman 1998; Baumeister and Exline 2002); however, the extent of overlap here remains an open question (Hood 2001; Maclean et al. 2012; Barrett and Griffiths 2017; Millière 2017; Winkelman 2017). Ego dissolution is more likely to occur at higher doses (Griffiths et al. 2011; Studerus, Gamma, and Vollenweider 2010; Studerus et al. 2012; Liechti, Dolder, and Schmid 2017). Furthermore, certain psychedelic drugs cause ego dissolution experience more reliably than others; psilocybin, for example, was found to produce full ego dissolution more reliably compared with LSD (Liechti, Dolder, and Schmid 2017). Ego dissolution experiences can be driven and modulated by external stimuli, most notably music (Carhart-Harris, Muthukumaraswamy, et al. 2016; Atasoy, Roseman, et al. 2017; Kaelen et al. 2018). Interestingly, subjects who experienced 'complete' ego dissolution in psychedelic-assisted therapy were more likely to evidence positive clinical outcomes (Griffiths et al. 2008, 2016; Majić, Schmidt, and Gallinat 2015; Ross et al. 2016; Roseman, Nutt, and Carhart-Harris 2017) as well as long-term changes in life outlook and the personality trait openness (MacLean, Johnson, and Griffiths 2011; Carhart-Harris, Kaelen, et al. 2016; Lebedev et al. 2016).

[4]Variously termed 'ego disintegration,' 'ego loss,' and 'ego death.' For a comprehensive review, see Millière (2017).

1.2.5 Clinical Efficacy and Long-Term Effects

Mescaline-assisted therapies showed promising results during first-wave psychedelic science (Beringer 1927; Rouhier 1927) and this trend continued through second-wave psychedelic research on LSD-assisted therapies (Sandison and Whitelaw 1957; Cohen and Eisner 1959; Pahnke 1966; Grof 1976). Recent studies have produced significant evidence for the therapeutic utility of psychedelic drugs in treating a wide range of mental health issues (Tupper et al. 2015; Lieberman and Shalev 2016; Carhart-Harris and Goodwin 2017), including anxiety and depression (Grob et al. 2011; Gasser et al. 2014; Carhart-Harris, Bolstridge, et al. 2016; Carhart-Harris, Bolstridge, et al. 2018; Dos Santos et al. 2016; Griffiths et al. 2016; Ross et al. 2016), obsessive-compulsive disorder (Moreno et al. 2006), and addiction (Michael P. Bogenschutz and Johnson 2016) to alcohol (Michael P. Bogenschutz et al. 2015) and tobacco (Johnson et al. 2014). In many clinical studies, ego-dissolution experience has correlated with positive clinical outcomes (Griffiths et al. 2008, 2016; Majić, Schmidt, and Gallinat 2015; Ross et al. 2016; Roseman, Nutt, and Carhart-Harris 2017).

Remarkably, as mentioned above, a single psychedelic experience can increase optimism for at least 2 weeks after the session (Carhart-Harris, Kaelen, et al. 2016) and can produce lasting changes in personality trait openness (MacLean, Johnson, and Griffiths 2011; Lebedev et al. 2016). A study of regular (weekly) ayahuasca users showed improved cognitive functioning and increased positive personality traits compared with matched controls (Bouso et al. 2015). Interestingly, these outcomes may expand beyond sanctioned clinical use, as illicit users of classic psychedelic drugs within the general population self-report positive long-term benefits from their psychedelic experiences (Carhart-Harris and Nutt 2010), are statistically less likely to evidence psychological distress and suicidality (Hendricks et al. 2015; Argento et al. 2017), and show an overall lower occurrence of mental health problems in general (Krebs and Johansen 2013).

1.2.6 Summary

The above evidence demonstrates the broad diversity of acute subjective effects that classic psychedelic drugs can produce in perceptual, emotional, and cognitive domains. Unique changes in sense of self, ego, body image, and personal meaning are particularly salient themes. How do these molecules produce such dramatic effects? What are the relationships between acute perceptual, emotional, cognitive, and self-related effects? What is the link between acute effects and long-term changes in mental health, personality, and behavior? Theories addressing these questions emerged as soon as Western science recognized the need for a scientific understanding of psychedelic drug effects beginning in the late 19th century.

1.3 19th and 20th Century Theories of Psychedelic Drug Effects

The effects described above are what captured the interest of first-wave and second-wave psychedelic scientists, and the theories they developed in their investigations have two central themes. The first theme is the observation that psychedelic effects share descriptive elements with symptoms of psychoses, such as hallucination, altered self-reference, and perceptual distortions. This theme forms the basis of *model psychoses theory* and is what motivated the adoption of the term 'psychotomimetic' drugs. The second theme is the observation that psychedelic drugs seem to expand the total range of contents presented subjectively in our perceptual, emotional, cognitive, and self-referential experience. This theme forms the basis of *filtration theory* and is what motivated the adoption of the term 'psychedelic' drugs. A third theoretical account uses *psychoanalytic theory* to address the expanded range of mental phenomena produced by psychedelic drugs as well as the shared descriptive elements with symptoms of psychoses. The next section reviews these themes along with their historically associated theories before tracing their evolution into third-wave (21st-century) psychedelic science.

1.3.1 Model Psychoses Theory

When (Lewin 1894, 1927) 'discovered'[5] the peyote cactus, his reports caught the attention of adventurous 19th-century scientists like (Prentiss and Morgan 1895; Mitchell 1896; Ellis 1898), who promptly obtained samples and began consuming the cactus and observing its effects on themselves. When Heffter (1898) isolated mescaline from the peyote cactus and Späth (1919) paved the way for laboratory synthesis, scientists began systematically dosing themselves (along with their colleagues and students) with mescaline and publishing their findings in medical journals (Knauer and Maloney 1913; Klüver 1926; Beringer 1927; Rouhier 1927; Guttmann 1936; Stockings 1940). Klüver (1926), intrigued by the approach of Knauer and Maloney (1913), ingested peyote at the University of Minnesota Psychological Laboratory and, after the effects had taken hold, completed standard psychophysical measures. Klüver (1926, 502) argued that systematic investigations into the neural mechanisms of mescaline effects would help neurology "elucidate more general questions of the psychology and pathology of perception." However, it was the pathology aspect, not the general psychology questions, which became the dominant focus of ensuing mescaline research paradigms.

Model psychoses theory began long before any of the classic psychedelic drugs became known to Western science. Moreau (1845) linked hashish effects with mental illness and Kraepelin (1892) founded "pharmacopsychology" by dosing himself and his students with various psychoactive drugs in the laboratory of Wilhelm Wundt (Müller, Fletcher, and Steinberg 2006; Schmied, Steinberg, and Sykes 2006). These scientists hoped to study psychotic symptoms using drugs to induce 'model psychoses' (1) in themselves, to gain first-person knowledge of the phenomenology of psychotic symptoms by "administering to one another such substances as will produce in us transitory psychoses" (Knauer and Maloney 1913, 426; see also Guttmann 1936), and (2) in normal research subjects, allowing for laboratory behavioral observations

[5] An unnamed JAMA book reviewer critically notes that "it is interesting that attention had not been paid by American scientists to this intoxicant used by the Mexican Indians until a European called attention to it" (Beringer 1927).

on how the symptoms emerge and dissipate. Kraepelin and colleagues attempted to model psychoses using many drugs—"tea, alcohol, morphine, trional, bromide, and other drugs"—yet Kraepelin's pupils (Knauer and Maloney 1913, 426) argued that these drugs unfortunately "produce mental states which have little similarities to actual insanities" and argued instead that *mescaline* was unique in its ability to truly model psychoses. The dramatic subjective effects of mescaline invigorated the model psychoses paradigm. Growing demand for the ideal chemical agent for model psychoses eventually motivated Sandoz Pharmaceuticals to bring LSD to market in the 1940s.[6]

Importantly, model psychoses theory was not initially a theory of drug effects; it was an idealistic paradigm for researching psychoses that was already in use before Western science 'discovered' classic psychedelic drugs. Nonetheless, it seeded the idea that psychedelic effects themselves could be explained in terms of psychopathology and motivated a search for common neural correlates. The founding figures of neuropharmacology were driven by questions regarding the relationship between psychoactive drugs and endogenous neurochemicals (see Abramson 1956). The putative psychoses-mimicking effects of LSD and mescaline inspired the idea that psychotic symptoms might be caused by a "hypothetical endotoxin" (Osmond 1957, 422) or some yet-unknown endogenous neurochemical gone out of balance (Osmond and Smythies 1952; Abramson 1956; Himwich 1959). The discovery that LSD can antagonize serotonin led to the hypothesis that the effects of LSD are serotonergic and simultaneously to the historic hypothesis[7] that serotonin might play a role in regulating mental function (Gaddum 1953; Gaddum and Hameed 1954; Woolley and Shaw 1954; Shaw and Woolley 1956; Green 2008).

At the 1955 *Second Conference on Neuropharmacology* the whole class of drugs was dubbed *psychotomimetic* (Abramson 1956). Interestingly, the word *mimetic* means to

[6]A marketing team at Sandoz Pharmaceuticals sent free samples of LSD to physicians around the world and inside each package was a pamphlet which read: "By taking Delysid [LSD] himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease" (Hofmann 1980, 47).

[7]In this sense LSD catalyzed the neuroscientific revolution of serotonin neurochemistry (Nichols 2016) and crystallized the emergence of the field of neuropharmacology.

"imitate" "mimic" or "exhibit mimicry" which is the act of *appearing* as something else—for example, when one species mimics the appearance or behavior of another (e.g., the non-venomous bullsnake rattles its tail against dry leaves to *mimic* a venomous rattlesnake). Psychoto*mimetic* drug effects, on this literal reading of the term, would merely mimic or imitate—appear as if they are—psychoses. However, to mimic is not to model.[8] A model intends to capture important structural or functional principles of the entity or phenomena that it models. A mimic, by contrast, merely creates the illusion that it possesses the properties it mimics. Thus, the term *psychotomimetic* implies that the effects of these drugs merely resemble psychoses but do not share functional or structural properties in their underlying biology or phenomenology. Nonetheless, LSD and mescaline were used as *models* to investigate psychotic symptoms. Yet the scientific utility of drug models hinges on our understanding of the mechanisms underpinning the drugs' effects; we still need a theory of how psychotomimetic drugs work. A subtle explanation-explananda circularity can come into play here, in which psychoses are explained using drug models yet the drug effects are explained using theories of psychoses. Further complicating the matter is the clear difference between *acutely induced* drug effects and the gradual development of a *chronic* mental illness (Osmond and Smythies 1952). This cluster of conceptual challenges poured fuel on the flaming debates about the merits of drug-induced model psychoses, which in 1957 had already "smoldered for nearly 50 years" (Osmond 1957, 421). An additional conceptual challenge was the fact that mescaline had for years shown promise in *treating* psychopathologies (Beringer 1927; Rouhier 1927) and LSD was gaining popularity for pharmaceutically enhanced psychotherapy (Sandison and Whitelaw 1957; Eisner and Cohen 1958; Cohen and Eisner 1959). Model psychoses theory needed to explain how it was the case that drugs putatively capable of inducing psychotic symptoms could simultaneously be capable of treating them—what Osmond (1957, 420) termed the "hair of the dog" problem. In fact, to this day "the apparent paradox by which the same compound can be both a model of, and yet a treatment for, psychopathology

[8]In fact, in the terminology of biological science, a *model* is "an organism whose appearance a mimic imitates" (Merriam-Webster 2017).

has never been properly addressed" (Carhart-Harris, Kaelen, et al. 2016, 2) Taken together, the above cluster of conceptual challenges drove Osmond (1957) to doubt his own prior work on model psychoses (Hoffer, Osmond, and Smythies 1954; i.e., Osmond and Smythies 1952) and he declared 'psychotomimetic' an outmoded term, arguing that the effects of these drugs could not be captured wholly in terms of psychopathology. "If mimicking mental illness were the main characteristic of these agents, 'psychotomimetics' would indeed be a suitable generic term. It is true that they do so, but they do much more" (Osmond 1957, 429).

1.3.2 Filtration Theory

Osmond (1957) argued that the 'psychotomimetic' class of drugs needed a more appropriate name. "My choice, because it is clear, euphonious, and uncontaminated by other associations, is *psychedelic*, mind-manifesting" (Osmond 1957, 429). But how exactly should we understand psychedelic effects as 'mind-manifesting'? Osmond's nomenclature legacy was directly influenced by his friend Aldous Huxley, who described the core idea to Osmond in the following personal letter dated April 10, 1953 (Huxley 1953, 29):

> Dear Dr. Osmond,
>
> . . .
>
> It looks as though the most satisfactory working hypothesis about the human mind must follow, to some extent, the Bergsonian model, in which the brain with its associated normal self, acts as a utilitarian device for limiting, and making selections from, the enormous possible world of consciousness, and for canalizing experience into biologically profitable channels. Disease, mescaline, emotional shock, aesthetic experience and mystical enlightenment have the power, each in its different way and in varying degrees, to inhibit the function of the normal self and its ordinary brain activity, thus permitting the 'other world' to rise into consciousness.
>
> *Yours sincerely*,
>
> *Aldous Huxley*

Huxley's letter can help unpack the intended 'mind-manifesting' etymology of Osmond's new term *psychedelic*. Huxley saw the biological function of the brain as a "device" engaged in a continuous process of *elimination and inhibition* to sustain the

"normal self" of everyday waking experience to maximize adaptive fit. Huxley's choice metaphor for visualizing this was the *cerebral reducing valve* (Figure 1.3).

Figure 1.3: Aldous Huxley's "cerebral reducing valve." On the 'inlet' (right) side of the cerebral reducing valve is a vast ocean of all possible perceptual, emotional, and cognitive experiences. On the 'outlet' (left) side is our moment-to-moment stream of experience in normal waking life. Mechanisms inside the valve 'reduce' the character and contents of experience, 'canalizing' the ocean of possible experience into a more limited stream of waking consciousness aimed at maximum biological utility.

"What I have called the cerebral reducing valve [is a] normal brain function that limits our mental processes to an awareness, most of the time, of what is biologically useful" (Huxley 1956, 121). Huxley (1961, 193) argued that this "normal brain function" emerges developmentally during the course of psychological maturity, so for a period during childhood, before the cerebral reducing valve has fully developed, "there is this capacity to live in a kind of visionary world." Once the valve is fully developed, however, normal waking life becomes restricted to a "world fabricated by our everyday, biologically useful and socially conditioned perceptions, thoughts and feelings" (Huxley 1961, 214).

Huxley borrowed the core idea from 19th-century *filtration theory* accounts of various mental phenomena (see Marshall 2005): "According to filtration theorists, consciousness is ordinarily kept narrow by biological and psychological selection processes that exclude a great deal of subconscious material" (Marshall 2005, 233). Filtration theorists include founding figures of psychopharmacology (Kraepelin 1892), psychology (James 1890), and parapsychology (Myers 1903), along with early 20th-century philosophers Bergson (1911, 1931) and Broad (1923). Bergson (1931) applied his own filtration framework to drug effects in his brief response to James' (1882) glowing descriptions of what it is like to inhale nitrous oxide. James' peculiar state of mind, explained Bergson, should be thought of as a latent potential of the brain/mind, which nitrous oxide simply "brought about materially, by an inhibition of what inhibited it, by the removing of an obstacle; and this effect was the wholly negative one produced by the drug" (Bergson 1931). Huxley picked up Bergson's line of thinking and eventually convinced Osmond that it was important to reflect this principle in scientific descriptions of the effects of LSD and mescaline. Smythies (1956, 96) also subscribed to this idea, stating that "mescaline may be supposed to inhibit that function in the brain which specifically inhibits the mescaline phenomena from developing in the sensory fields."

Thus, Osmond's (1957) proposed name-change—*psychedelic*—was intended to capture the spirit of filtration theory. In this new descriptive model, *psyche* (mind) *delic* (manifesting) drugs manifest the mind by inhibiting certain brain processes which normally maintain their own inhibitory constraints on our perceptions, emotions, thoughts, and sense of self. Osmond (1957) and Huxley (1954) both found this principle highly applicable to their own direct first-person knowledge of what it is like to experience the effects of mescaline and LSD—the expanded range of feelings, intensification of perceptual stimuli, vivid vision-like mental imagery, unusual thoughts, and expanding (or dissolving) sense of self and identity.

Osmond argued that his 'mind-manifesting' description had further theoretical virtues that could address the conceptual challenges of model psychoses theory and improve our understanding of (1) the diverse range of psychedelic effects, (2) their

relationship to psychotic symptoms, and (3) their role in psychedelic-assisted therapies. First, the pharmacological disruption of hypothetical inhibitory brain mechanisms that normally attenuate internal and external stimuli suggested that the kinds of effects produced by the drug would depend on the kinds of stimuli in the system, which is consistent with the diverse range of effects on multiple perceptual modalities, emotional experience, and cognition.

Second, the brain's selective filtration mechanisms, while evolutionarily adaptive and biologically useful, could develop pathological characteristics in two fundamentally distinct ways. First, a chronically *overactive* filter limits too much of the mind, causing a rigid, dull, neurotic life in which mental contents become overly restricted to "those enumerated in the Sears-Roebuck catalog which constitutes the conventionally 'real' world" (Huxley 1953, 30). Second, a chronically *underactive* or 'leaky' filter places too few constraints on the mind and allows too much 'Mind at Large' to enter conscious awareness, potentially resulting in perceptual instability, cognitive confusion, or hallucination. This picture helped Huxley and Osmond understand the relationship between psychedelic phenomena and psychotic phenomena: temporarily opening the cerebral reducing valve with psychedelics could produce mental phenomena that resembled symptoms of chronic natural psychoses precisely because both were the result of (acute or chronic) reductions in brain filtration mechanisms.

Third and finally, filtration theory addressed the paradoxical "hair of the dog" issue—why drugs that 'mimic' psychoses can aid psychotherapy—which, as described in the previous section, was a conceptual challenge for model psychoses theory. The solution to the paradox was in the filtration theory idea that psychedelic drugs temporarily 'disable' brain filtration mechanisms, which could allow patients and therapists to work outside of the patient's everyday (pathological) inhibitory mechanisms. Thus, filtration theory offered a way to understand psychedelic effects that was consistent with both their psychotomimetic properties and their therapeutic utility.

Osmond and Huxley argued that filtration theory concepts were fully consistent with the subjective phenomenology, psychotomimetic capability, and therapeutic efficacy of psychedelic drugs. However, it remains unclear exactly *what it is* that

the brain is filtering and consequently *what it is* that emerges when the filter is pharmacologically perturbed by a psychedelic drug. According to Huxley, LSD and mescaline "inhibit the function of the normal self and its ordinary brain activity, thus permitting the '*other world*' to rise into consciousness" (Huxley 1953, 29; emphasis mine). Huxley (and Bergson) spoke of the brain as a device that filters the *world* and when the filter is removed we experience 'more' of reality. Osmond's 'mind-manifesting' (*psyche*) (*delic*) name, by contrast, suggests that these drugs permit latent aspects of *mind* to rise into conscious awareness. So which is it? Do psychedelic drugs manifest latent aspects of *mind* or of *world*? How we answer this question will crucially determine our ontological and epistemological conclusions regarding the nature of psychedelic experience. Huxley and Osmond did not make this clear. Huxley seems to favor the position that psychedelic experience reveals a wider ontological reality and grants epistemic access to greater truth. Osmond's view, on which these drugs reveal normally hidden aspects of mind, seems less radical, more compatible with materialist science, and less epistemically and ontologically committed. Still, if mind provides us with access to world, then lifting restrictions on mind could in principle expand our access to world. This important point resurfaces in section 1.5.3 below.

1.3.3 Psychoanalytic Theory

Freud (1895) developed an elaborate theoretical account of mental phenomena which, like filtration theory, placed great emphasis on inhibition mechanisms in the nervous system.[9] Freud divided the psyche into two fundamentally distinct modes of activity: *the primary process* and *the secondary process* (Freud 1895, 1940). In the primary process, the exchange of "neuronal energy" is "freely mobile" and its psychological dynamics are characterized by disorder, vagueness, conceptual paradox, symbolic imagery, intense emotions, and animistic thinking (Freud 1940, 164). In the secondary process, by contrast, the exchange of neuronal energy is "bound" and its psychological dynamics are characterized by order, precision, conceptual consistency, controlled

[9]Huxley was overtly critical of Freud, yet Huxley's cerebral reducing valve is strikingly similar to Freud's ego (see Benton 2016 for a comparison of Freud and Bergson).

emotions, and rational thinking (Freud 1895, 1940). Freud (1895) hypothesized that the secondary process is maintained by an organizing neural "mass" called the ego which "contains" and exerts control over the primary process by binding primary process activity into its own pattern of activity.[10] Freud hypothesized that secondary process neural organization, sustained by the ego, is required for certain aspects of perceptual processing, directed attention, reality-testing, sense of linear time, and higher cognitive processes (Freud 1895, 1940). When Freud's ego is suppressed, such as during dream sleep, wider worlds of experience can emerge, but secondary process functions are lost. The secondary process and its supporting neural organizing pattern—the ego—emerges during ontogenetic development and solidifies with adult maturity: "A unity comparable to the ego cannot exist from the start; the ego has to be developed" (Freud 1915, 77). Furthermore, pathological characteristics can emerge when Freud's ego restricts either *too much* or *too little* of the primary process.

Freud himself was apparently uninterested in psychedelic drugs and instead emphasized dreams as "the royal road to a knowledge of the unconscious activities of the mind" (Freud 1900, 769). Nonetheless, psychedelic drugs produce dream*like* visions and modes of cognition that feature symbolic imagery, conceptual paradox, and other hallmark characteristics of the primary process (Carhart-Harris and Friston 2010; Kraehenmann, Pokorny, Aicher, et al. 2017; Sanz and Tagliazucchi 2018). How did other psychoanalytic theorists describe psychedelic drug effects? The core idea is that psychedelic drugs interfere with the structural integrity of the ego and thereby reduce its ability to suppress the primary process and support the secondary process (Grof 1976). This 'frees' the primary process which then spills into conscious awareness, resulting in perceptual instability, wildly vivid imagination, emotional intensity, conceptual paradox, and loss of usual self-boundaries. Due in part to the close resemblance

[10] "The secondary process is characterized by a bound state in the neurone, which though there is a high cathexis, permits only a small current. ... Now the ego itself is a mass like this of neurones which hold fast to their activity—are, that is in a bound state and this surely can only happen as a result of the effect they have on one another. We can therefore imagine that a perceptual neurone which is active with attention is as a result temporarily, as it were, taken up into the ego and is now subject to the same binding of its energy as are all the other ego neurones ... This bound state, which combines high activity with small current, would thus characterize processes of thought mechanically" (Freud 1895, 368).

between psychedelic effects and primary process phenomena, psychoanalytic theory became the framework of choice during the mid 20th-century boom in psychedelic therapy (Sandison 1954; Sandison and Whitelaw 1957; Cohen 1965; Grof 1976; Merkur 1998). Psychedelic ego effects, which range from a subtle loosening to a complete dissolution of ego boundaries, were found to be great tools in psychotherapy because of their capacity to perturb ego and allow primary process phenomena to emerge (Sandison 1954, 509).

But *how* do psychedelic drugs disrupt the structure of the ego? Freud hypothesized that the organizational structure of ego rests upon a basic perceptual schematic of the body and its surrounding environment. Perceptual signals are continuously 'bound' and integrated into the somatic boundaries of the ego. Savage (1955) speculated that the LSD's perceptual effects and ego effects are tightly linked. "LSD acts by altering perception. Continuous correct perception is necessary to maintain ego feeling and ego boundaries. ... *Perception determines our ego boundaries.* ... disturbances in perception caused by LSD make it impossible for the ego to integrate the evidence of the senses and to coordinate its activities ..." (Savage 1955, 14). Klee (1963) expanded Savage's insights into a set of hypotheses aimed at elucidating the neurobiological mechanisms of a Freudian 'stimulus barrier' and its dissolution under LSD:

> Such barriers would presumably consist of processes limiting the spread of excitation between different functional areas of the brain. The indications are that LSD, in some manner, breaks down these stimulus barriers of which Freud spoke. *Nor is this merely a figure of speech.* There is some reason to suspect that integrative mechanisms within the central nervous system (CNS) which handle inflowing stimuli are no longer able to limit the spread of excitation in the usual ways. We might speculate that LSD allows greater energy exchanges between certain systems than normally occurs, without necessarily raising the general level of excitation of all cortical and subcortical structures (Klee 1963, 465; emphasis mine).

Freud hypothesized that ego is sustained by a delicate balance of 'neuronal energy' which critically depends on integrative mechanisms to process inflowing sensory stimuli and to 'bind' neural excitation into functional structures within the brain. Psychedelic drugs, according to Savage and Klee, perturb integrative mechanisms that normally bind and shape endogenous and exogenous excitation into the structure of the ego. As

we will see below, Klee's ideas strongly anticipate many neurophysiological findings (Alonso et al. 2015; Tagliazucchi et al. 2016; Schartner et al. 2017) and theoretical themes (Carhart-Harris and Friston 2010; Letheby and Gerrans 2017) from 21st-century psychedelic science.

1.3.4 Summary

From the above analysis of first-wave and second-wave theories I have identified four recurring theoretical features which could potentially serve as unifying principles. One feature is the hypothesis that psychedelic drugs inhibit a core brain mechanism that normally functions to 'reduce' or 'filter' or 'constrain' mental phenomena into an evolutionarily adaptive container. A second feature is the hypothesis that this core brain mechanism can behave pathologically, either in the direction of too much, or too little, constraint imposed on perception, emotion, cognition, and sense of self. A third feature is the hypothesis that psychedelic phenomena and symptoms of chronic psychoses share descriptive elements because they both involve situations of relatively *unconstrained* mental processes. A fourth feature is the hypothesis that psychedelic drugs have therapeutic utility via their ability to temporarily inhibit these inhibitory brain mechanisms. But how are these inhibitory mechanisms realized in the brain?

1.4 Neuropharmacology and Neurophysiological Correlates of Psychedelic Drug Effects

Klee recognized that his above hypotheses, inspired by psychoanalytic theory and LSD effects, required neurophysiological evidence. "As far as I am aware, however, adequate neurophysiological evidence is lacking ... The long awaited millennium in which biochemical, physiological, and psychological processes can be freely correlated still seems a great distance off" (Klee 1963, 466, 473). What clues have recent investigations uncovered?

A psychedelic drug molecule impacts a neuron by binding to and altering the

conformation of receptors on the surface of the neuron (Nichols 2016). The receptor interaction most implicated in producing classic psychedelic drug effects is agonist or partial agonist activity at serotonin (5-HT) receptor type 2A (5-HT_{2A}) (Nichols 2016). A molecule's propensity for 5-HT_{2A} affinity and agonist activity predicts its potential for (and potency of) subjective psychedelic effects (Glennon, Titeler, and McKenney 1984; McKenna et al. 1990; Halberstadt 2015; Nichols 2016; Rickli et al. 2016). When a psychedelic drug's 5-HT_{2A} agonist activity is intentionally blocked using 5-HT_{2A} *antagonist* drugs (e.g., ketanserin), the subjective effects are blocked or attenuated in humans under psilocybin (Vollenweider et al. 1998; Kometer et al. 2013), LSD (Kraehenmann, Pokorny, Aicher, et al. 2017; Kraehenmann, Pokorny, Vollenweider, et al. 2017; Preller et al. 2017), and ayahuasca (Valle et al. 2016). Importantly, while the above evidence makes it clear that 5-HT_{2A} activation is a necessary (if not sufficient) mediator of the hallmark subjective effects of classic psychedelic drugs, this does not entail that 5-HT_{2A} activation is the sole neurochemical cause of all subjective effects. For example, 5-HT_{2A} activation might trigger neurochemical modulations 'downstream' (e.g., changes in glutamate transmission) which could also play causal roles in producing psychedelic effects (Nichols 2016). Moreover, most psychedelic drug molecules activate other receptors in addition to 5-HT_{2A} (e.g., 5-HT_{1A}, 5-HT_{2C}, dopamine, sigma, etc.) and these activations may importantly contribute to the overall profile of subjective effects even if 5-HT_{2A} activation is required for their effects to occur (Ray 2010, 2016).

How does psychedelic drug-induced 5-HT_{2A} receptor agonism change the behavior of the host neuron? Generally, 5-HT_{2A} activation has a depolarizing effect on the neuron, making it more excitable (more likely to fire) (Andrade 2011; Nichols 2016). Importantly, this does not necessarily entail that 5-HT_{2A} activation will have an overall excitatory effect throughout the brain, particularly if the excitation occurs in inhibitory neurons (Andrade 2011). This important consideration (captured by the adage 'one neuron's excitation is another neuron's inhibition') should be kept in mind when tracing causal links in the pharmaco-neurophysiology of psychedelic drug effects.

In mammalian brains, neurons tend to 'fire together' in synchronized rhythms

known as *temporal oscillations* (brain waves). MEG and EEG equipment measure the electromagnetic disturbances produced by the temporal oscillations of large neural populations and these measurements can be quantified according to their *amplitude* (power) and *frequency* (timing) (Buzsáki and Draguhn 2004). Specific combinations of frequency and amplitude can be correlated with distinct brain states, including waking 'resting' state, various attentional tasks, anesthesia, REM sleep, and deep sleep (Tononi and Koch 2008; Atasoy, Deco, et al. 2017). In what ways do temporal oscillations change under psychedelic drugs? MEG and EEG studies consistently show *reductions* in oscillatory power across a broad frequency range under ayahuasca (Riba et al. 2002, 2004; Schenberg et al. 2015; Valle et al. 2016), psilocybin (Muthukumaraswamy et al. 2013; Kometer et al. 2015; Schartner et al. 2017), and LSD (Carhart-Harris, Muthukumaraswamy, et al. 2016; Schartner et al. 2017). Reductions in the power of alpha-band oscillations, localized mainly to parietal and occipital cortex, have been correlated with intensity of subjective visual effects—e.g., 'I saw geometric patterns' or 'My imagination was extremely vivid'—under psilocybin (Kometer et al. 2013; Muthukumaraswamy et al. 2013; Schartner et al. 2017) and ayahuasca (Riba et al. 2004; Valle et al. 2016). Under LSD, reductions in alpha power still correlated with intensity of subjective visual effects but associated alpha reductions were more widely distributed throughout the brain (Carhart-Harris, Muthukumaraswamy, et al. 2016). Furthermore, ego-dissolution effects and mystical-type experiences (e.g., 'I experienced a disintegration of my "self" or "ego" ' or 'The experience had a supernatural quality') have been correlated with reductions in alpha power localized to anterior and posterior cingulate cortices and the parahippocampal regions under psilocybin (Muthukumaraswamy et al. 2013; Kometer et al. 2015) and throughout the brain under LSD (Carhart-Harris, Muthukumaraswamy, et al. 2016).

The concept of *functional connectivity* rests upon fMRI brain imaging observations that reveal temporal correlations of activity occurring in spatially remote regions of the brain which form highly structured patterns (brain networks) (Buckner, Andrews-Hanna, and Schacter 2008). Imaging of brains during perceptual or cognitive task performance reveals patterns of functional connectivity known as *functional networks*;

e.g., control network, dorsal attention network, ventral attention network, visual network, auditory network, and so on. Imaging brains in taskless resting conditions reveals *resting-state functional connectivity* (RSFC) and structured patterns of RSFC known as resting state networks (RSNs; Deco, Jirsa, and McIntosh 2011). One particular RSN, the default mode network (DMN; Buckner, Andrews-Hanna, and Schacter 2008), increases activity in the absence of tasks and decreases activity during task performance (Fox and Raichle 2007). DMN activity is strong during internally directed cognition and a variety of other 'metacognitive' functions (Buckner, Andrews-Hanna, and Schacter 2008). DMN activation in normal waking states exhibits 'inverse coupling' or anticorrelation with the activation of task-positive functional networks, meaning that DMN and functional networks are often mutually exclusive; one deactivates as the other activates and vice versa (Fox and Raichle 2007).

In what ways does brain network connectivity change under psychedelic drugs? First, functional connectivity between key 'hub' areas—mPFC and PCC—is reduced. Second, the 'strength' or oscillatory power of the DMN is weakened and its intrinsic functional connectivity becomes disintegrated as its component nodes become decoupled under psilocybin (Carhart-Harris, Erritzoe, et al. 2012; Carhart-Harris et al. 2013), ayahuasca (Palhano-Fontes et al. 2015), and LSD (Carhart-Harris, Muthukumaraswamy, et al. 2016; Speth et al. 2016). Third, brain networks that normally show anticorrelation become active simultaneously under psychedelic drugs. This situation, which can be described as increased *between-network* functional connectivity, occurs under psilocybin (Carhart-Harris, Erritzoe, et al. 2012; Carhart-Harris et al. 2013; Roseman et al. 2018; Tagliazucchi et al. 2014), ayahuasca (Palhano-Fontes et al. 2015), and especially LSD (Carhart-Harris, Muthukumaraswamy, et al. 2016; Tagliazucchi et al. 2016). Fourth and finally, the overall repertoire of explored functional connectivity motifs is substantially expanded and its informational dynamics become more diverse and entropic compared with normal waking states (Tagliazucchi et al. 2014, 2016; Alonso et al. 2015; Lebedev et al. 2016; Viol et al. 2016; Atasoy, Roseman, et al. 2017; Schartner et al. 2017). Notably, the magnitude of occurrence of the above four neurodynamical themes correlates with subjective intensity of psychedelic effects

during the drug session. Furthermore, visual cortex is activated during eyes-closed psychedelic visual imagery (Araujo et al. 2012; Carhart-Harris, Muthukumaraswamy, et al. 2016) and under LSD "the early visual system behaves 'as if' it were receiving spatially localized visual information" as V1-V3 RSFC is activated in a retinotopic fashion (Roseman et al. 2016, 3036).

Taken together, the recently discovered neurophysiological correlates of subjective psychedelic effects present an important puzzle for 21st-century neuroscience. A key clue is that 5-HT_{2A} receptor agonism leads to desynchronization of oscillatory activity, disintegration of intrinsic integrity in the DMN and related brain networks, and an overall brain dynamic characterized by increased between-network global functional connectivity, expanded signal diversity, and a larger repertoire of structured neurophysiological activation patterns. Crucially, these characteristic traits of psychedelic brain activity have been correlated with the phenomenological dynamics and intensity of subjective psychedelic effects.

1.5 21st-Century Theories of Psychedelic Drug Effects

How should we understand the growing body of clues emerging from investigations into the neurodynamics of psychedelic effects? What are the principles that link these thematic patterns of psychedelic brain activity (or inactivity) to their associated phenomenological effects? Recent theoretical efforts to understand psychedelic drug effects have taken advantage of existing frameworks from cognitive neuroscience designed to track the key neurodynamic principles of human perception, emotion, cognition, and consciousness. The overall picture that emerges from these efforts shares core principles with filtration and psychoanalytic accounts of the late 19th and early 20th century. Briefly, normal waking perception and cognition are hypothesized to rest upon brain mechanisms which serve to suppress entropy and uncertainty by placing various *constraints* on perceptual and cognitive systems. In a 'selecting' and 'limiting'

fashion, neurobiological constraint mechanisms support stability and predictability in the contents of conscious awareness in the interest of adaptability, survival, and evolutionary fitness. The core hypothesis of recent cognitive neuroscience theories of psychedelic effects is that these drugs interfere with the integrity of neurobiological information-processing constraint mechanisms. The net effect of this is that the range of possibilities in perception, emotion, and cognition is dose-dependently expanded. From this core hypothesis, cognitive neuroscience frameworks are utilized to describe and operationalize the quantitative neurodynamics of key psychedelic phenomena; namely, the diversity of effects across many mental processes, the elements in common with symptoms of psychoses, and the way in which temporarily removing neurobiological constraints is therapeutically beneficial.

This section is organized according to the broad theoretical frameworks informing recent theoretical neuroscience of psychedelic effects: *entropic brain theory, integrated information theory*, and *predictive processing*.

1.5.1 Entropic Brain Theory

Entropic Brain Theory (EBT; Carhart-Harris et al. 2014) links the phenomenology and neurophysiology of psychedelic effects by characterizing both in terms of the quantitative notions of entropy and uncertainty. Entropy is a quantitative index of a system's (physical) disorder or randomness which can simultaneously describe its (informational) uncertainty. EBT "proposes that the quality of any conscious state depends on the system's entropy measured via key parameters of brain function" (Carhart-Harris et al. 2014, 1). Their hypothesis states that hallmark psychedelic effects (e.g., perceptual destabilization, cognitive flexibility, ego dissolution) can be mapped directly onto elevated levels of entropy/uncertainty measured in brain activity, e.g., widened repertoire of functional connectivity patterns, reduced anticorrelation of brain networks, and desynchronization of RSN activity. More specifically, EBT characterizes the difference between psychedelic states and normal waking states in terms of how the underlying brain dynamics are positioned on a scale between the two extremes of order and disorder—a concept known as 'self-organized criticality' (Beggs

and Plenz 2003). A system with high order (low entropy) exhibits dynamics that resemble 'petrification' and are relatively inflexible but more stable, while a system with low order (high entropy) exhibits dynamics that resemble 'formlessness' and are more flexible but less stable. The notion of 'criticality' describes the transition zone in which the brain remains poised between order and disorder. Physical systems at criticality exhibit increased transient 'metastable' states, increased sensitivity to perturbation, and increased propensity for cascading 'avalanches' of metastable activity. Importantly, EBT points out that these characteristics are consistent with psychedelic phenomenology, e.g., hypersensitivity to external stimuli, broadened range of experiences, or rapidly shifting perceptual and mental contents. Furthermore, EBT uses the notion of criticality to characterize the difference between psychedelic states and normal waking states as it "describes cognition in adult modern humans as 'near critical' but 'sub-critical'—meaning that its dynamics are poised in a position between the two extremes of formlessness and petrification where there is an optimal balance between order and flexibility" (Carhart-Harris et al. 2014, 12). EBT hypothesizes that psychedelic drugs interfere with 'entropy-suppression' brain mechanisms which normally sustain sub-critical brain dynamics, thus bringing the brain "closer to criticality in the psychedelic state" (Carhart-Harris et al. 2014, 12).

Entropic Brain Theory further characterizes psychedelic neurodynamics using a neo-psychoanalytic framework proposed in an earlier paper by Carhart-Harris and Friston (2010, 1265) where they "recast some central Freudian ideas in a mechanistic and biologically informed fashion." Freud's primary process (renamed "primary consciousness") is hypothesized to be a high-entropy brain dynamic which operates at criticality, while Freud's secondary process (renamed "secondary consciousness") is hypothesized to involve a lower-entropy brain state which sustains a sub-critical dynamic via a key neurobiological entropy-suppression mechanism—the ego—which exerts an organizing influence in order to constrain the criticality-like dynamic of primary consciousness. EBT argues that these ego functions have a signature neural footprint; namely, the DMN's intrinsic functional connectivity and DMN coupling of medial temporal lobes (MTLs) in particular. Furthermore, EBT argues that DMN/ego develops ontoge-

netically in adult humans and plays an adaptive role in which it sustains secondary consciousness and associated metacognitive abilities (Shimamura 2000; Fleming, Dolan, and Frith 2012) along with an "integrated sense of self" (Carhart-Harris et al. 2014, 9).

Importantly, this hypothesis maps onto the subjective phenomenology of psychedelic effects, particularly ego dissolution. As psychedelics weaken the oscillatory power and intrinsic functional connectivity of the DMN, the normally constrained activity of subordinate DMN nodes—MTLs in particular—becomes "freely mobile" allowing the emergence of more uncertain (higher entropy) primary consciousness. This view, based on Freudian metapsychology, is also consistent with filtration accounts, like those of Bergson and Huxley, who hypothesized that psychedelic drug effects are the result of a pharmacological *inhibition* of inhibitory brain mechanisms. EBT recasts these theoretical features using the quantitative terms of physical entropy and informational uncertainty as measured via "the repertoire of functional connectivity motifs that form and fragment across time" (Carhart-Harris et al. 2014, 1). In normal waking states, the DMN *constrains* the activity of its cortical and subcortical nodes and prohibits simultaneous co-activation with TPNs. By interfering with DMN integration, psychedelics permit a larger repertoire of brain activity, a wider variety of explored functional connectivity motifs, co-activation of normally mutually exclusive brain networks, increased levels of between-network functional connectivity, and an overall more diverse set of neural interactions.

Carhart-Harris et al. (2014) point out a number of implications of EBT. First, they map the feelings of 'uncertainty' that often accompany psychedelic effects onto the fact that a more entropic brain dynamic is the information-theoretic equivalent to a more 'uncertain' brain dynamic. "Thus, according to the entropic brain hypothesis, just as normally robust principles about the brain lose definition in primary states, so confidence is lost in 'how the world is' and 'who one is' as a personality" (Carhart-Harris et al. 2014, 16).

Second, like Huxley's cerebral reducing valve and Freud's ego, EBT argues that the DMN's organizational stronghold over brain activity can be both an evolutionary

advantage *and* a source of pathology. "It is argued that this entropy-suppressing function of the human brain serves to promote realism, foresight, careful reflection and an ability to recognize and overcome wishful and paranoid fantasies. Equally however, it could be seen as exerting a limiting or narrowing influence on consciousness" (Carhart-Harris et al. 2014, 7). Carhart-Harris et al. (2014) point out that neuroimaging studies have implicated increased DMN activity and RSFC with various aspects of depressive rumination, trait neuroticism, and depression. "The suggestion is that increased DMN activity and connectivity in mild depression promotes concerted introspection and an especially diligent style of reality-testing. However, what may be gained in mild depression (i.e., accurate reality testing) may be offset by a reciprocal decrease in flexible or divergent thinking (and positive mood)" (Carhart-Harris et al. 2014, 10).

Third, consistent with both psychoanalytic and filtration theory, is the notion that psychedelic drugs' capacity to temporarily weaken, collapse, or disintegrate the normal ego/DMN stronghold underpins their therapeutic utility. "Specifically, it is proposed that psychedelics work by dismantling reinforced patterns of negative thought and behavior by breaking down the stable spatiotemporal patterns of brain activity upon which they rest" (Carhart-Harris et al. 2014, 1).

Fourth and finally, EBT sheds light on the shared descriptive elements between psychedelic effects and psychotic symptoms by characterizing both in terms of elevated levels of entropy and uncertainty in brain activity which lead to a "regression" into primary consciousness. The collapse of the organizing effect of DMN coupling and anticorrelation patterns, according to EBT, point to "system-level mechanics of the psychedelic state as an exemplar of a regressive style of cognition that can also be observed in REM sleep and early psychosis" (Carhart-Harris et al. 2014, 5)

Thus, EBT formulates all four of the theoretical features identified in filtration and psychoanalytic accounts, but does so using 21st-century empirical data plugged into the quantitative concepts of entropy, uncertainty, criticality, and functional connectivity. EBT hints at possible ways to close the gaps in understanding by offering quantitative concepts that link phenomenology to brain activity and pathogenesis to therapeutic mechanisms.

1.5.2 Integrated Information Theory

Integrated Information Theory (IIT) is a general theoretical framework which describes the relationship between consciousness and its physical substrates (Oizumi, Albantakis, and Tononi 2014; Tononi 2004, 2008). While EBT is already loosely consistent with the core principles of IIT, Gallimore (2015) demonstrates how EBT's hypotheses can be operationalized using the technical concepts of the IIT framework. Using EBT and recent neuroimaging data as a foundation, Gallimore develops an IIT-based model of psychedelic effects. Consistent with EBT, this IIT-based model describes the brain's continual challenge of minimizing entropy while retaining flexibility. Gallimore formally restates this problem using IIT parameters: brains attempt to optimize the give-and-take dynamic between *cause-effect information* and cognitive flexibility. In IIT, a (neural) system generates cause-effect information when the mechanisms which make up its current state *constrain* the set of states which could casually precede or follow the current state. In other words, each mechanistic state of the brain: (1) limits the set of past states which could have causally given rise to it, and (2) limits the set of future states which can causally follow from it. Thus, each current state of the mechanisms within a neural system (or subsystem) has an associated *cause-effect repertoire* which specifies a certain amount of cause-effect information as a function of how stringently it constrains the unconstrained state repertoire of all possible system states. Increasing the entropy within a cause-effect repertoire will in effect constrain the system less stringently as the causal possibilities are expanded in both temporal directions as the system moves closer to its unconstrained repertoire of all possible states. Moreover, increasing the entropy within a cause-effect repertoire equivalently increases the uncertainty associated with its past (and future) causal interactions. Using this IIT-based framework, Gallimore (2015) argues that, compared with normal waking states, psychedelic brain states exhibit higher entropy, higher cognitive flexibility, but lower cause-effect information (Figure 1.4).

Neuroimaging data suggests that human brains exhibit a larger overall repertoire of neurophysiological states under psychedelic drugs, exploring a greater diversity of states

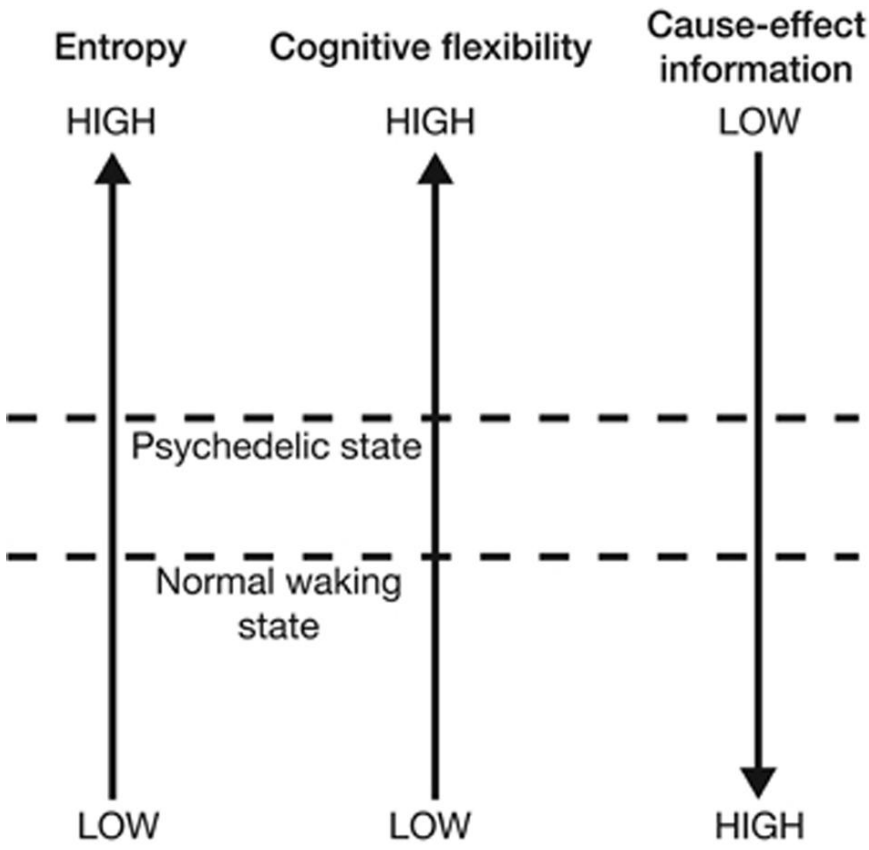

Figure 1.4: "Increasing neural entropy elevates cognitive flexibility at the expense of a decrease in the cause-effect information specified by individual mechanisms" (Gallimore 2015, 10).

in a more random fashion. For example, in normal waking states, DMN activity 'rules out' the activity of TPNs, and vice versa, due to their relatively strict anticorrelation patterns. Brain network anticorrelation generates cause-effect information because it places constraints on the possible causal interactions within and between brain mechanisms; for example, DMN-TPN anticorrelation patterns 'rule out' the DMN activity in the presence of activated TPNs. However, psychedelic drugs 'dissolve' DMN-TPN (and other) network anticorrelation patterns, which permits simultaneous activation of brain networks which are normally mutually exclusive. The cause-effect repertoire of brain mechanisms thus shifts closer to the unconstrained repertoire of all possible past and future states. This has the effect of "increasing the probability of certain states from zero or, at least, from a very low probability" (Gallimore 2015, 7). Therefore the subjective contents perception and cognition become more diverse, more unusual, and less predictable. This increases flexibility but decreases precision and control as the subjective boundaries which normally demarcate distinct cognitive concepts and perceptual objects dissolve. Gallimore leverages IIT in an attempt unify these phenomena under a formalized framework.

However, as Gallimore notes, "this model does not explain how neural entropy is increased by (psychedelic drugs), but predicts consequences of the entropy increase revealed by functional imaging data" (Gallimore 2015, 7). How do psychedelic drugs increase neural entropy?

1.5.3 Predictive Processing

The first modern brain imaging measurements in humans under psilocybin yielded somewhat unexpected results: *reductions* in oscillatory power (MEG) and cerebral blood flow (fMRI) correlated with the intensity of subjective psychedelic effects (Carhart-Harris, Erritzoe, et al. 2012; Muthukumaraswamy et al. 2013). In their discussion, the authors suggest that their findings, although surprising through the lens of commonly held beliefs about how brain activity maps to subjective phenomenology, may actually be consistent with a theory of brain function known as the *free energy principle* (FEP; Friston 2010).

> In one model of global brain function based on the free-energy principle (Friston 2010), activity in deep-layer projection neurons encodes top-down inferences about the world. Speculatively, if deep-layer pyramidal cells were to become hyperexcitable during the psychedelic state, information processing would be biased in the direction of inference—such that implicit models of the world become spontaneously manifest—intruding into consciousness without prior invitation from sensory data. This could explain many of the subjective effects of psychedelics (Muthukumaraswamy et al. 2013, 15181).

What is FEP? "In this view, the brain is an inference machine that actively predicts and explains its sensations. Central to this hypothesis is a probabilistic model that can generate predictions, against which sensory samples are tested to update beliefs about their causes" (Friston 2010). FEP is a formulation of a broader conceptual framework emerging in cognitive neuroscience known as *predictive processing*[11] (PP; A. Clark 2013). PP has links to *bayesian brain hypothesis* (Knill and Pouget 2004), *predictive coding* (Rao and Ballard 1999), and earlier theories of perception and cognition (MacKay 1956; Neisser 1967; Gregory 1968) dating back to Helmholtz (1867) who was inspired by Kant (1787) (see Swanson (2016)). At the turn of the 21st century, the ideas of Helmholtz catalyzed innovations in machine learning (Dayan et al. 1995), new understandings of cortical organization (Mumford 1992; Friston 2005), and theories of how perception works (Kersten and Yuille 2003; Lee and Mumford 2003).

PP subsumes key elements from these efforts (see Clark, 2013) to describe a universal principle of brain function captured by the idea of *prediction error minimization* (PEM; Hohwy 2013). What does it mean to say that the brain works to minimize its own prediction error? Higher-level areas of the nervous system (i.e., higher-order cortical structures) generate top-down synaptic 'predictions' aimed at matching the expected bottom-up synaptic activity at lower-level areas, all the way down to 'input' activity at sense organs. Top-down signals encode a kind of 'best guess' about the most likely (hidden)[12] causes of bodily sensations. In this multi-level hierarchical

[11] See also A. Clark (2015) and Wiese and Metzinger (2017) for introductory reviews conceptual overviews.

[12] The causes of our bodily sensations cannot be directly observed by the brain: an organism's brain is 'skull-bound' (Hohwy 2013) and limited to a 'view from inside the black box' (A. Clark 2013).

cascade of neural activity, high-level areas attempt to 'explain' the states of levels below via synaptic attempts to *inhibit* lower-level activity—"high-level areas tell lower levels to 'shut up' " (Kersten, Mamassian, and Yuille 2004, 297). But lower levels will not 'shut up' until they receive top-down feedback (inference) signals that adequately fit (explain) the bottom-up (evidence) signals. Mismatches between synaptic 'expectation' and synaptic 'evidence' generate *prediction error signals* which 'carry the news' by propagating the 'surprise' upward to be 'explained away' by yet higher levels of hierarchical cortical processing anatomy (see A. Clark 2015). This recurrent neural processing scheme approximates (empirical) Bayesian inference (Friston et al. 2007) as the brain continually maps measured bodily effects to different sets of possible causes and attempts to select the set of possible causes that can best 'explain away' the measured bodily effects. Crucially, the sets of possible causes must be *narrowed* in order for the system to settle on an explanation (Tenenbaum et al. 2011). Prior constraints which allow the system to narrow the hypothesis space are known as 'inductive biases' or *priors* (Kemp, Perfors, and Tenenbaum 2007; Tenenbaum et al. 2011; A. Clark 2013). Efforts in Bayesian statistics and machine learning have demonstrated that improvements in inductive capabilities occur when priors are linked in a multi-level hierarchy, with "not just a single level of hypotheses to explain the data but multiple levels: hypothesis spaces of hypothesis spaces, with priors on priors" (Tenenbaum et al. 2011, 1282). Certain priors in the hierarchy, known as 'hyperpriors' (Friston, Lawson, and Frith 2013) or 'overhypotheses' (Goodman 1983; Kemp, Perfors, and Tenenbaum 2007) are more abstract and allow the system to 'rule out' large swaths of possibilities, drastically narrowing the hypothesis space, making explanation more tractable (Blokpoel, Kwisthout, and Rooij 2012). For example, the brute constraints of space and time act as hyperpriors; e.g., prior knowledge "that there is only one object (one cause of sensory input) in one place, at a given scale, at a given moment," or the fact that "we can only perform one action at a time, choosing the left turn or the right but never both at once" (A. Clark 2013, 196).

Thus, PP states that brains are neural generative models built from linked hierarchies of priors where higher levels continuously attempt to 'guess' and explain activity

at lower levels. The entire process can be characterized as the agent's attempt to *optimize* its own internal model of the sensorium (and the world) over multiple spatial and temporal scales (Friston 2010).

Interestingly, PP holds that our perceptions of external objects recruit the same synaptic pathways that enable our capacity for *mental imagery, dreaming, and hallucination*. The brain's ability to 'simulate' its own 'virtual reality' using internal (generative) models of the world's causal structure is thus crucial to its ability to perceive the external world. "[A] fruitful way of looking at the human brain, therefore, is as a system which, even in ordinary waking states, constantly hallucinates at the world, as a system that constantly lets its internal autonomous simulational dynamics collide with the ongoing flow of sensory input, vigorously dreaming at the world and thereby generating the content of phenomenal experience" (Metzinger 2003).

How do psychedelic molecules perturb predictive processing? If normal perception is a kind of 'controlled hallucination' (see A. Clark 2015) where top-down simulation is constrained by bottom-up sensory input colliding with priors upon priors, then, as the above quotation from (Muthukumaraswamy et al. 2013) suggests, psychedelic drugs essentially cause perception to be *less controlled* hallucination. The idea is that psychedelic drugs perturb the (learned and innate) prior constraints on internal generative models. Via their 5-HT_{2A} agonism, psychedelic drugs cause hyperexcitation in layer V pyramidal neurons, which might cause endogenous simulations to 'run wild' so that awareness becomes more imaginative, dreamlike, and hallucinatory. This hypothesis could in principle still be consistent with observed *reductions* in brain activity under psychedelics; recall from above that, in PP schemes, the higher-level areas 'explain away' lower-level excitation by *suppressing it with top-down inhibitory signals*. "Here, explaining away just means countering excitatory bottom-up inputs to a prediction error neuron with inhibitory synaptic inputs that are driven by top-down predictions" (Friston 2010, 130).

How does PP tie into filtration theories and psychoanalytic accounts? Carhart-Harris, Leech, et al. (2012) link Huxley with Friston to interpret their initially surprising fMRI scans of humans under psilocybin (see also Zizo 2013). One objection

to this linkage might be that Huxley often describes psychedelic opening of the cerebral reducing valve as revealing more of the *world*. At first glance this seems at odds with the above PP account of psychedelic effects, which describes psychedelic drugs causing rampant *internal* simulations of reality, not revealing more of the external world. However, this apparent tension might be resolved in light of *active inference*, a key principle of FEP (Friston 2010). Active inference shows how internal models do not merely generate top-down (inference) signals but also shape the *sampling* and *accumulation* of bottom-up sensory (evidence) signals. "In short, the agent will selectively sample the sensory inputs that it expects. This is known as active inference. An intuitive example of this process (when it is raised into consciousness) would be feeling our way in darkness: we anticipate what we might touch next and then try to confirm those expectations" (Friston 2010, 129). The principle of active inference hints at a resolution to the apparent tensions between Osmond's 'mind-manifesting' model and Huxley's 'world-manifesting' model. Psychedelics manifest *mind* by perturbing prior constraints on internal generative models, thereby expanding the possibilities in our inner world of feelings, thoughts, and mental imagery. Importantly, this could also manifest normally ignored aspects of *world* by altering active inference, which would in effect expand the sampling of sensory data to include samples that are normally routinely 'explained away.' Potentially, this understanding goes some way in explaining the perception-hallucination continuum of psychedelic drug effects (reviewed above) as it shows how perceptual *intensifications*, on the one hand, and *distortions and hallucinations*, on the other hand, could both be caused by a synaptic disruption of hierarchically linked priors in internal generative models.

The brief speculative remark by (Muthukumaraswamy et al. 2013) is not the only PP-based account of psychedelic drug effects. The PP framework describes a recurrent back-and-forth give-and-take between colliding top-down and bottom-up signals, where internal models serve to shape experience and experience serves to build internal models, so this leaves room for rival PP-based accounts that diverge regarding where exactly the psychedelic drug perturbs the system. For example, increased top-down activity could be the result of pharmacological hyperactivation of top-down

synaptic transmission; yet equally plausible is the hypothesis that increased top-down activity is a *compensatory response* to pharmacological attenuations or distortions of bottom-up signal.

For example, Corlett et al. (2009, 521) hypothesize that LSD hallucinations result from "noisy, unpredictable bottom-up signaling in the context of preserved and perhaps enhanced top-down processing." In contrast to the PP-based account outlined above, which focuses on changes to top-down signals, the strategy of Corlett, Frith, and Fletcher (2009) is to map various psychedelic effects to disturbances of top-down *and/or* bottom-up signals. The issue of what is primary and what is compensatory illustrates the vast possibilities in the hypothesis space of PP-based accounts.

While most PP-based accounts point to changes in top-down signaling, even within this hypothesis space there are contrasting conceptions of exactly how psychedelic molecules perturb top-down processing. Briefly, these differing hypotheses include: (1) *hyperactivation* or *heavier weighting* of top-down signaling (Muthukumaraswamy et al. 2013; described above), (2) *reduced* influence of signals from higher cortical areas (Carhart-Harris and Friston 2010; McKenna and Riba 2015), (3) interference with *multisensory integration* processes and PP-based binding of sensory signals (Carhart-Harris and Friston 2010; Letheby and Gerrans 2017; Millière 2017), and (4) changes in the *composition* and *level of detail* specified by top-down signals (Pink-Hashkes, Rooij, and Kwisthout 2017).

Carhart-Harris and Friston (2010) argue that the Freudian conception of ego, with its organizing influence over the primary process, is consistent with PP descriptions of higher-level cortical structures predicting and suppressing the excitation in lower levels in the hierarchy (i.e., limbic regions). Freud hypothesized that the secondary process binds, integrates, and organizes the 'lower' and more chaotic neural activity of the primary process into the broader and more cohesive composite structure of the ego. Carhart-Harris and Friston (2010) argue that when large-scale intrinsic networks become dis-integrated, the activity at lower levels can no longer be 'explained away' (suppressed) by certain higher-level systems, causing conscious awareness to take on hallmark characteristics of the primary process. In normal adult waking states,

networks based in higher-level areas can successfully predict and explain (suppress and control) the activity of lower level areas. "In non-ordinary states, this function may be perturbed (e.g., in the case of hallucinogenic drugs, through actions at modulatory post-synaptic receptors), compromising the hierarchical organization and suppressive capacity of the intrinsic networks" (Carhart-Harris and Friston 2010, 1274).

Similar PP-based theories of psychedelic ego dissolution have been proposed without invoking Freud (Letheby and Gerrans 2017; Millière 2017). PP posits that the brain explains self-generated stimuli by attributing its causes to a coherent and persisting entity (i.e., the self), much like how it predicts and explains external stimuli by attributing their causes to coherent and persisting external objects (see also Limanowski and Blankenburg 2013; M. Allen and Friston 2016). Letheby and Gerrans (2017) use the PP framework to recast the psychoanalysis-based theories of LSD ego effects proposed by Savage (1955) [13] and Klee (1963) described in Section 1.3.3. The core idea is that psychedelic drugs interfere with processes that bind and integrate stimuli according to probabilistic estimates of how relevant the stimuli are to the organism's (self) goals. Letheby and Gerrans (2017, 7) point out that ego dissolution under psychedelic drugs is correlated with the desynchronization (reductions in intrinsic functional connectivity) of brain networks implicated in "one aspect or another of self-representation"—specifically the salience network (SLN) and the DMN (Tagliazucchi et al. 2016). This causes an 'unbinding' of stimuli that are normally processed according to self-binding multisensory integration mechanisms. "Attention is no longer guided exclusively by adaptive and egocentric goals and agendas; salience attribution is no longer bound to personal concern" (Letheby and Gerrans 2017, 6). This description echoes Huxley's cerebral reducing valve "in which the brain with its associated *normal self*, acts as a utilitarian device for limiting, and making selections from, the enormous possible world of consciousness, and for canalizing experience into biologically profitable channels" (Huxley 1953, 29; emphasis mine). Letheby and Gerrans' PP-based account elucidates how psychedelic drugs could perturb the brain's

[13] "Disturbances in perception caused by LSD make it impossible for the ego to integrate the evidence of the senses and to coordinate its activities . . . " (Savage 1955, 14).

"associated normal self" preventing the usual self-binding of internal and external stimuli.

Pink-Hashkes et al. (2017, 2907) argue that under psychedelic drugs "top-down predictions in affected brain areas break up and decompose into many more overly detailed predictions due to hyper activation of 5-HT_{2A} receptors in layer V pyramidal neurons." Pink-Hashkes, Rooij, and Kwisthout (2017) state that when internal generative models are described as categorical probability distributions rather than Gaussian densities (Friston et al. 2015; Kwisthout, Bekkering, and Rooij 2017), "the *state space granularity* (how detailed are the generative models and the predictions that follow from them) is crucial" Kwisthout and Rooij (2015). Categorical predictions that are less detailed will 'explain' more bottom-up data (because they cover more ground) and thus produce less prediction error. Categorical predictions that are more detailed, by contrast, will carry less precision and thus potentially generate more prediction error (Kwisthout and Rooij 2015; Kwisthout, Bekkering, and Rooij 2017). Pink-Hashkes et al. (2017, 2908) propose that psychedelic drugs cause brain structures at certain levels of the cortical hierarchy to issue more detailed (less abstract) 'decomposed' predictions that "fit less data than the 'usual' broad prediction." They argue that many psychedelic effects stem from the brain's attempts to *compensate* for these decomposed top-down predictions as it responds to the increase in prediction errors that result from overly detailed predictions.

In summary, the current state of PP-based theories of psychedelic effects reveals a divergent mix of heterogeneous ideas and conflicting hypotheses. Do psychedelic molecules perturb top-down (feedback) signaling, or bottom-up (feedforward) signaling, or both? Do the subjective phenomenological effects result from direct neuropharmacological changes or compensatory mechanisms responding to pharmacological perturbations? Yet there seems to be a core intuition that transcends the conceptual variance here: psychedelic drugs (somehow) interfere with established priors that normally constrain the brain's internal generative models.

Predictive processing-based accounts, consistent with EBT and IIT (and filtration and psychoanalytic accounts), propose that psychedelic drugs disrupt neural mecha-

nisms (priors on internal generative models) which normally constrain perception and cognition. Perturbing priors causes subjective phenomenology to present a wider range of experiences with increased risk of perceptual instability and excessive cognitive flexibility. As prior constraints on self and world are loosened, the likelihood of psychosis-like phenomena increases. At the same time, novel thinking is increased and the brain becomes more malleable and conducive to therapeutic cognitive and behavioral change.

1.6 Conclusion

The four key features identified in filtration and psychoanalytic accounts from the late 19th and early 20th century continue to operate in 21st-century cognitive neuroscience: (1) psychedelic drugs produce their characteristic diversity of effects because they perturb adaptive mechanisms which normally constrain perception, emotion, cognition, and self-reference, (2) these adaptive mechanisms can develop pathologies rooted in either too much or too little constraint (3) psychedelic effects appear to share elements with psychotic symptoms because both involve weakened constraints (4) psychedelic drugs are therapeutically useful precisely because they offer a way to temporarily inhibit these adaptive constraints. It is on these four points that EBT, IIT, and PP seem consistent with each other and with earlier filtration and psychoanalytic accounts. EBT and IIT describe psychedelic brain dynamics and link them to phenomenological dynamics, while PP describes informational principles and plausible neural information exchanges which might underlie the larger-scale dynamics described by EBT and IIT. Certain descriptions of neural entropy-suppression mechanisms (EBT), cause-effect information constraints (IIT), or prediction-error minimization strategies (PP, FEP) are loosely consistent with Freud's ego and Huxley's cerebral reducing valve.

In surveying the literature for this review I can confidently conclude that 21st-century psychedelic science has yet to approach a unifying theory linking the diverse range of phenomenological effects with pharmacology and neurophysiology while tying these to clinical efficacy. However, the historically necessary ingredients for

successful theory unification—formalized frameworks and unifying principles (Morrison 2000)—seem to be taking shape. Formal models are an integral part of 21st-century neuroscience (Forstmann et al. 2011) where they help to describe natural principles in the brain and aid explanation and understanding (Kay 2017).[14] Here I have reviewed a handful of formalized frameworks—EBT, IIT, PP—which are just beginning to be used to account for psychedelic effects. I have also highlighted the fact that all of the accounts reviewed here, from the 19th-century to the 21st-century, propose that psychedelic drugs inhibit neurophysiological constraints in order to produce their diverse phenomenological, psychotomimetic, and therapeutic effects.

Why should we pursue a unified theory of psychedelic drug effects at all? To date, theories of brain function and mind in general have resisted the kind of unification that has occurred in other areas of science (Huang 2008; Edelman 2012). Because the human brain has evolved disparate and complex layers under diverse environmental circumstances, many doubt the possibility of and debate the merits of seeking 'grand unified theories' (GUTs) of brain function. "There is every reason to think that there can be no grand unified theory of brain function because there is every reason to think that an organ as complex as the brain functions according to diverse principles" (M. L. Anderson and Chemero 2013, 205). Indeed, Anderson and Chemero (2013, 205) caution that "we should be skeptical of any GUT of brain function" and charge that PP in particular, when taken as a unified theory as outlined by (A. Clark 2013), "threatens metaphysical disaster."

Given these understandable critical reservations about seeking after GUTs of brain function (and therefore any truly unifying theory of psychedelic drug effects), it is perhaps safer to aspire for theories that feature "broad explanatory frameworks" and offer "conceptual breadth" allowing us to "paint the big picture" (Edelman 2012). PP and FEP, at the very least, offer a broad explanatory framework that emcompasses a large swath of perceptual and cognitive phenomena (Huang 2008; Friston 2010; A. Clark 2015). Psychedelic drugs offer a unique way to iteratively develop and

[14]This remains true regardless of the outcome of healthy debates about the nature and proper use of models in science (Frigg and Hartmann 2017).

test such big-picture explanatory frameworks: these molecules can be used to probe the links between neurochemistry and neural computation across multiple layers of neuroanatomy and phenomenology. Meeting the challenge of predicting and explaining psychedelic drug effects is the ultimate acid test for any unified theory of brain function.

Chapter 2

Psychedelic visuals in context

"If we analyze the visual phenomena produced by mescaline ... the same mechanisms may be operative, no matter whether an object is perceived, imagined, or hallucinated. The mescaline experiments demonstrate, therefore, that we must go beyond the level of visual hallucinations to determine hallucinatory constants. In fact, we must even go beyond the visual mechanisms that cut across distinctions between perception, imagery, and hallucination and raise the question whether similar mechanisms are operative in nonvisual spheres."

—Heinrich Klüver (1942), *Mechanisms of Hallucinations*

"A psychedelic experience is a period of intensely heightened reactivity to sensory stimuli from within and without."

—Ralph Metzner and Timothy Leary (1967), "On programming psychedelic experiences"

ABSTRACT

The visual effects of psychedelic drugs are well-known but not well understood. Here, I situate psychedelic visual phenomenology within the context of what we know about everyday visual perception. I describe three types of open-eye visuals (OEVs)—common alterations to external visual appearances under psychedelic drugs—and argue that they are caused by hypersensitivity to contextual cues. I provide evidence and analysis to support the notion that psychedelics selectively impact contextual modulation processes at multiple levels of mental function. I then apply this idea to explain both visual and non-visual effects, and how they might link to therapeutic benefits. I note that contextual modulation can be modeled by a canonical neural computation known as divisive normalization. Finally, I explore the practical implications of these ideas for psychedelic therapy, cognitive neuroscience, and philosophy.[1]

2.1 Introduction

Some researchers argue that subjective psychedelic effects are entirely epiphenomenal to the therapeutic mechanisms of psychedelic therapy—i.e., play no role whatsoever—and hope to firmly demarcate the therapeutic benefits from all acute subjective effects (Hesselgrave et al. 2021; McClure-Begley and Roth 2022; Berg et al. 2022; Cao et al. 2022). Others disagree, arguing that mystical-type experiences (Yaden and Griffiths 2020) or experiences of enhanced existential insight (Letheby 2021) are critically involved in engendering beneficial outcomes. Amidst this recent bout of attention on subjective psychedelic phenomenology, *visual effects* have been overlooked. This is surprising, as the visual effects "are the most frequent and robust features of the psychedelic experience" (Vollenweider and Preller 2020) for which these drugs are "famous" (Kometer and Vollenweider 2016; Vollenweider and Preller 2020; Letheby 2021). Rating scale items that measure visual changes have consistent dose-response relative to other effects under lysergic acid diethylamide (LSD) (Schmid et al. 2015; Liechti, Dolder, and Schmid 2017; Holze et al. 2020, 2022), N,N-dimethyltryptamine (DMT) (Strassman et al. 1994; Pallavicini et al. 2021), and psilocybin (Hasler et al.

[1]This chapter was written as an invited chapter (under review) to be included in a forthcoming edited volume *Philosophical Perspectives on the Psychedelic Renaissance* from Oxford University Press (Letheby and Gerrans, n.d.).

2004; Studerus et al. 2010; Carbonaro, Johnson, and Griffiths 2020; Hirschfeld and Schmidt 2021; Holze et al. 2022).

Considering their central place in psychedelic experiences, along with the central role that visual perception itself plays in everyday human mental function, understanding the visual effects of psychedelics should be central to understanding how psychedelics impact the mind. Yet visuals remain relatively under-examined in recent discussions. At best, their role is treated as *vehicular*—that is, as 'vehicles' that deliver the properly therapeutic psychological experiences. For example, although Letheby (2021) acknowledges that the emotional shifts and psychological insights that occur during psychedelic therapy sessions "are often deeply intertwined with perceptual alterations" (Letheby 2021, 47), he nonetheless argues that

> perceptual experiences such as listening to music or visual imagery assume importance *insofar* as they act as a vehicle for experiences of this [psychological insight] kind. Thus, although perceptual and emotional/existential/noetic changes are intertwined, the importance of the former often derives greatly from their intertwinement with the latter (Letheby 2021, 46–47)

This sentiment is not uncommon; recently, visual effects have been sidelined by some authors either as epiphenomenal or as mere means to an end. This is unsurprising, as Anglo-European cultures have long devalued and demonized drug-induced visual alterations, treating 'hallucinations' as a sign of pathology (in psychiatry) and epistemic failure (in philosophy); symptomatic of a more general "negative attitude toward any distortion of normal sensory and cognitive perception" (Wallace 1959), dating back at least to the Inquisition and Christian colonialism.[2] Psychiatry labeled psychedelic effects as 'psychotomimetic' partly because of their visual effects. The War on Drugs appealed to cultural fear of hallucination in anti-drug (echoing anti-witch) propaganda rhetoric (Curtis and Texas Alcohol Narcotics Education 1968 is an early example). Thus, the downplaying of visual effects in contemporary discussions might be an (unconscious) effort to avoid the cultural stigma and negative bias associated with visual hallucinations.

[2]I thank Dr. Kathryn Swanson for illuminating the thematic similarities here. Her insights are supported by Carod-Artal (2015) and George et al. (2021), as well the perspectives found in Collins (2018).

By contrast, visual effects continue to be central to the ritualistic use of psychedelics by indigenous cultures around the world, who place high value on the visual effects of DMT-containing ayahuasca, mescaline-containing cacti, and psilocybin-containing mushrooms (Schultes 1969; Schultes, Hofmann, and Rätsch 2006; GebhartSayer 1985; Carod-Artal 2015; George et al. 2021). As Hartogsohn (2017) notes, "in such societies hallucinations are often cherished and regarded as potentially valuable for the individual and the culture" (see also Wallace 1959). Furthermore, in modern illicit markets, visual effects continue to be a subjective benchmark of the authenticity, quality, and potency of psychedelic drug material (see, e.g., Weasel 1994) and are among the top effects that account for human self-administration of classic psychedelics (Carbonaro, Johnson, and Griffiths 2020).

Here, I address three knowledge gaps in our current understanding of psychedelic visuals. First, with a few notable exceptions (Klüver 1928; Kometer and Vollenweider 2016; Aday et al. 2021), analysis of psychedelic visuals is lacking relative to non-visual effects. Even where visuals are addressed, attention tends to focus on *closed-eye* visuals (CEVs)—visual imagery that occurs behind closed eyelids, in the 'mind's eye', akin to imagination but with extra vivacity and force (Erowid 1995; Swanson 2018), which have been subdivided into 'elementary' and 'complex' (Stoll 1947; Dittrich 1998; Studerus, Gamma, and Vollenweider 2010; Kometer and Vollenweider 2016; Swanson 2018). In comparison, there have been fewer analyses of *open-eye* visuals (OEVs)—psychedelic alterations of external visual perception. Here, I introduce a taxonomy to classify three distinct types of *OEVs*: (1) enhancements, (2) transformations, and (3) overlays. Following Klüver (1942), I demonstrate how examining OEV phenomenology offers insights into how psychedelics affect mental functions.

Second, relatively few accounts attempt to *explain why and how* psychedelics affect visual perception, as contrasted with, for example, the care that has gone into accounts aimed at explaining ego dissolution (Letheby and Gerrans 2017; Millière 2017). Existing accounts that *do* address visuals lack compelling explanations for the *particular* phenomenology of OEVs. For example, the thalamic gating model (Vollenweider and Smallridge 2022) might account for "sensory overload", but this

notion falls short of explaining why OEVs have the particular phenomenology that they do. Similarly, predictive processing accounts that explain OEVs as resulting from disrupted Bayesian priors—"decomposed predictions" (Pink-Hashkes, Rooij, and Kwisthout 2017) or "relaxed beliefs" (Carhart-Harris and Friston 2019)—do not explain why OEVs involve only certain kinds of visual alterations: If psychedelics interrupted *all* visual 'priors' then we would expect complete perceptual chaos, which does not capture the phenomenology of OEVs.

The third knowledge gap I address here is our lack of understanding of how psychedelic visuals link, if at all, to therapeutic mechanisms. Are visuals entirely epiphenomenal to therapeutic mechanisms, or do they play a causal role in the therapeutic process? If they play no role, then why do drugs that cause OEVs also have therapeutic benefits?

Visual perception is perhaps the most well-characterized and extensively studied mental function in psychology and neuroscience. Moreover, visual experiences dominate debates in philosophy compared to other sense modalities. Our efforts to understand psychedelic drugs can advantageously leverage this foundation of knowledge. Psychedelic OEVs can serve as specimens of the way in which psychedelics affect this important aspect of the mind. We can analyze psychedelic visual phenomenology from the platform of existing knowledge about everyday visual perception. Conversely, psychedelics offer pharmacological probes for understanding everyday visual perception (Carter, Burr, et al. 2005; Bayne and Carter 2018). Visual effects are thus 'low-hanging fruit' waiting to be harvested in service of improving our understanding of how psychedelic drugs affect our minds.

In this chapter, I situate psychedelic visual phenomenology within the context of what we know about everyday perceptual and cognitive functions. I think of this approach as a phenomenological-functional analysis. Starting with an informal taxonomic classification of some common OEV phenomenology, I describe a canonical principle that I argue captures the essence of many types of psychedelic visuals, which I call *hypercontextual modulation* (HCM). OEVs, I argue, are ordinary visual context effects 'on drugs'—drugs that I argue cause hypersensitivity to sensory contextual cues

even at the lowest levels of visual processing. From OEVs I apply the notion of HCM to non-visual psychedelic effects in cognition such as expanded semantic activation and symbolic thinking. I note that contextual modulation can be modeled by a canonical neural computation known as divisive normalization, which might provide a plausible neurocomputational account of HCM under psychedelic drugs. Finally, I cash out the notion of HCM to arrive at some practical implications for psychedelic therapy, cognitive neuroscience, and philosophy.

2.2 What it's like to see OEVs

Here, I introduce a general taxonomy that distinguishes three kinds of OEV phenomenology commonly reported under classic psychedelics. Importantly, my analysis is restricted to what are conventionally known as 'classic' psychedelic molecules: LSD, DMT, mescaline, and psilocybin. The following OEVs are reliably induced by these drugs.

2.2.1 Enhancements

Even at low doses, the first detectable visual changes are often subtle 'enhancements' in the ordinary visual field; e.g., edges appear sharper, textures more pronounced, hues intensified. These changes are what I call *enhancement* OEVs. They are commonly measured by rating scale items such as "Change in visual distinctiveness" and "Change in brightness of objects in room" (Strassman et al. 1994; Carbonaro et al. 2018). Visual enhancements were noted in a 1914 issue of *Science* magazine in a report from a botanist who inadvertently consumed a psilocybin-containing mushroom species.

> ... objects took on peculiar bright colors ... Real objects at this time appeared in their true forms, but if colored they assumed far more intense or vivid colors than natural; dull red becoming brilliant red, etc. (Verrill 1914, 409)

In 1925, neuroscientist Heinrich Klüver ingested peyote at the Psychological Laboratory at the University of Minnesota and noted that "there was a general increase in brightness; most colors seemed to be more deeply saturated" (Klüver 1926)

and subsequently collected numerous descriptions of enhancement OEVs from the literature of the time.

> With respect to colors, there are frequently changes in brightness and saturation ... the objects appear more solid than ever, the surface colors are more sharply defined ... Small differences in hue and brightness of real objects are often noticed. ... An enhancement of contrast phenomena seems to be the rule. Very pronounced simultaneous contrast is found; the contours of the objects become sharp and well-defined. ... Objects normally seen in two dimensions may appear tridimensional in the mescal state. Tridimensional objects may seem still more voluminous than usual. ... Human faces seem to undergo certain changes ... the features become more sharply defined (Klüver 1928).

Díaz (2010) refers to these phenomena as *dishabituation of perception*: "The ordinary visual scene looks new, and everything seems as if seen for the first time. Textures or colors are fascinating and are perceived as much more intense." Huxley (1954) describes how the ordinary textures looked to his eyes under mescaline.[3] "Those folds in the trousers—what a labyrinth of endlessly significant complexity! And the texture of the gray flannel—how rich, how deeply, mysteriously sumptuous!"

Enhancement OEVs persist through the duration of the drug effects, often outlasting other effects (Dittrich 1998; Díaz 2010; Kometer and Vollenweider 2016; Preller and Vollenweider 2018). "The following day ... after a period of sleep, there was still a great sensitivity to colors, but visions could not be detected with closed or open eyes" (Klüver 1926). Albert Hofmann, the inventor of LSD, noted that enhancement OEVs remained the morning after taking LSD at 4:20 in the afternoon the day before.

> When I later walked out into the garden, in which the sun shone now after a spring rain, everything glistened and sparkled in a fresh light. The world was as if newly created. All my senses vibrated in a condition of highest sensitivity, which persisted for the entire day (Hofmann 1980).

2.2.2 Transformations

What I call *transformation*[4] *OEVs* involve changes to the spatial properties or *form* of objects—i.e., their perceived shape, size, and distance. Rating scales measure this type

[3] Check out Letheby (2021) for more fun with this quote.

[4] My term 'transformation OEVs' follows Klüver's (1928, 34) remark that such effects are "what may be called a 'visionary transformation' of the object." I prefer this term to terms 'pseudohallucination', 'distortions' or 'illusions' used elsewhere to describe the phenomena (Hofmann 1980; Dittrich 1998; Kometer and Vollenweider 2016; Preller and Vollenweider 2018; Vollenweider and Preller 2020).

of OEV with items such as “Room looks different”, “My sense of size and space was distorted”, “Things in my surroundings appeared smaller or larger”, “Edges appeared warped”, “I saw movement in things that weren’t actually moving”, and “With eyes open visual field vibrating or jiggling” (Dittrich 1998; Strassman et al. 1994; Studerus, Gamma, and Vollenweider 2010; Muthukumaraswamy et al. 2013; Carbonaro et al. 2018; Hirschfeld and Schmidt 2021; Holze et al. 2022; Lawrence et al. 2022).

Regarding size transformations, objects can appear either larger (macropsia) or smaller (micropsia) than normal (Kometer and Vollenweider 2016).

> The changes in the apparent size of real objects require special consideration. To illustrate [from documented cases of mescaline experiences]: “When I moved my hand towards me, it got enormous and bulky forms” ... “I looked out of the window and was particularly surprised at the changes in the size of the houses ... they seemed to have grown” ... “The branches [of a tree] became longer and shorter” (Klüver 1928).

Relatedly, Klüver reports from his own peyote experience how “Standing near a corner of the room, the walls ... seemed to move towards me” (Klüver 1926). Similarly, Huxley remarks that under mescaline “the perspective looked rather odd, and the walls of the room no longer seemed to meet in right angles” (Huxley 1954). These reports highlight how transformation OEVs involve visual shifts in apparent distance and perspective.

Huxley, describing a staple transformation OEV, notes that he looked at flowers in a vase and “seemed to detect the qualitative equivalent of breathing ...” (Huxley 1954). Note that visually ‘breathing’ involves both movement *and* change of shape (take a deep breath now, observe your chest, and it will both move and change shape). Klüver characterized these as “the apparent movement of stationary objects,” but also used descriptions that entail changes in object shape—“undulating movements ... movements which change the contours and dimensions of the object” (Klüver 1928, 41). “Looking at the radiator in the room, its divisions seemed to move rhythmically” (Klüver 1926). Hofmann (under LSD) reported seeing both “continuous motion” and changes in the shape of the inanimate objects he looked at.

> Everything in my field of vision wavered and was *distorted as if seen in a curved mirror*. ... My surroundings had now *transformed* themselves ... the familiar

> objects and pieces of furniture ... were in continuous motion, animated, as if driven by an inner restlessness (Hofmann 1980, emphasis mine).

Similar phenomenology has been noted under psilocybin, an early example being again from the 1914 *Science* magazine.

> I noticed that the irregular figures on the wall-paper seemed to have creepy and crawling motions, contracting and expanding continually, though not changing their forms; finally they began to project from the wall and grew out toward me from it with uncanny motions (Verrill 1914, 409).

2.2.3 Overlays

The final species of OEV phenomena I taxonomize here are what I call *overlays*: geometric patterns that infuse the external visual scene. Often compared to decorative patterns found on rugs, tapestries, and wallpaper, overlay OEVs appear as a layer, on top of, or 'covering' ordinary objects. Rating scales capture overlay OEVs quite explicitly: "Room overlaid with visual patterns" (Strassman et al. 1994; Carbonaro et al. 2018). Klüver observed OEV overlays when he looked at the walls of the room under peyote.

> (Eyes open): the walls covered with squares (about 2 x 2 cm): shadowy dark contours. The corners of the squares: red jewels (three-dimensional). This design followed by similar mostly more complicated designs in various colors. Sometimes not sure whether the phenomena are localized at the distance of the walls (Klüver 1926).

As the effects climaxed, the overlays intensified. "(Eyes open): impossible to look at the walls without seeing them *covered* with visionary phenomena. Various designs ... visionary phenomena on the walls" (Klüver 1926, emphasis mine). Klüver (1928) later compiled descriptions from other subjects:

> "transparent oriental rugs, but infinitely small" seen for example on the surface of the soup at lunch time ... "wallpaper designs" ... "countless rugs with such magnificent hues and such singular brilliancy" ... localized on the walls, on the floor or *wherever the subject happens to look* (Klüver 1928 emphasis mine).

Klüver notes that "The visionary phenomena ... lasted until retiring and could always be seen in the dark room with open eyes" (Klüver 1926). After spending

time staring at his overlay-covered walls, Klüver went on to develop a taxonomy of OEV overlay phenomenology that identifies four fundamental types of patterns that he called "form constants"; namely, (1) lattices (checkerboards, honeycombs and triangles), (2) tunnels, (3) spirals and (4) cobwebs (Klüver 1928). Klüver argued that OEV overlays seen under psychedelic drugs "are upon close examination nothing but variations of these form-constants" (Klüver 1928).

Overlay OEVs are common with all classic psychedelics. The following description of viewing the night sky under psilocybin uses the term 'overlay' as well as 'enhancement':

> Visual acuity is enhanced to the point where the sky becomes three-dimensional. ... Electromagnetic fields ebb and flow, much like a hyperactive *aurora borealis*. ... Overlaying this display of splendor are colorful, dancing, geometrical fractals of infinite complexity (Stamets 1996).

2.3 Hypercontextual modulation in psychedelic vision

Everyday visual perception involves cascades of *contextual modulation*: each perceived element of a visual scene is shaped by the spatial context (the other visual elements) in which it is situated. Spatial *context effects* occur when the perceived properties of a target element change based on the properties of neighboring elements (Schwartz, Hsu, and Dayan 2007). Visual illusions demonstrate how perceived visual properties can be altered simply by changing *contextual cues*, without changing the physical attributes of the target stimulus. Consider the classic context effects presented in Figure 2.1. In such cases, "the origin of the illusory effects is not based on physical distal or physical proximal differences of target objects, but on the differences in their contexts" (Todorović 2020). Indeed, more than a century of psychophysical studies has established that "the perception of, and neurophysiological responses to, a target input depend strongly on both its spatial context (what surrounds a given object or feature) and its temporal context (what has been observed in the recent past)" (Schwartz, Hsu, and Dayan 2007). Figure 2.2 presents the exact same target stimuli used in Figure 2.1 without the contextual cues. The term *contextual modulation* refers to the

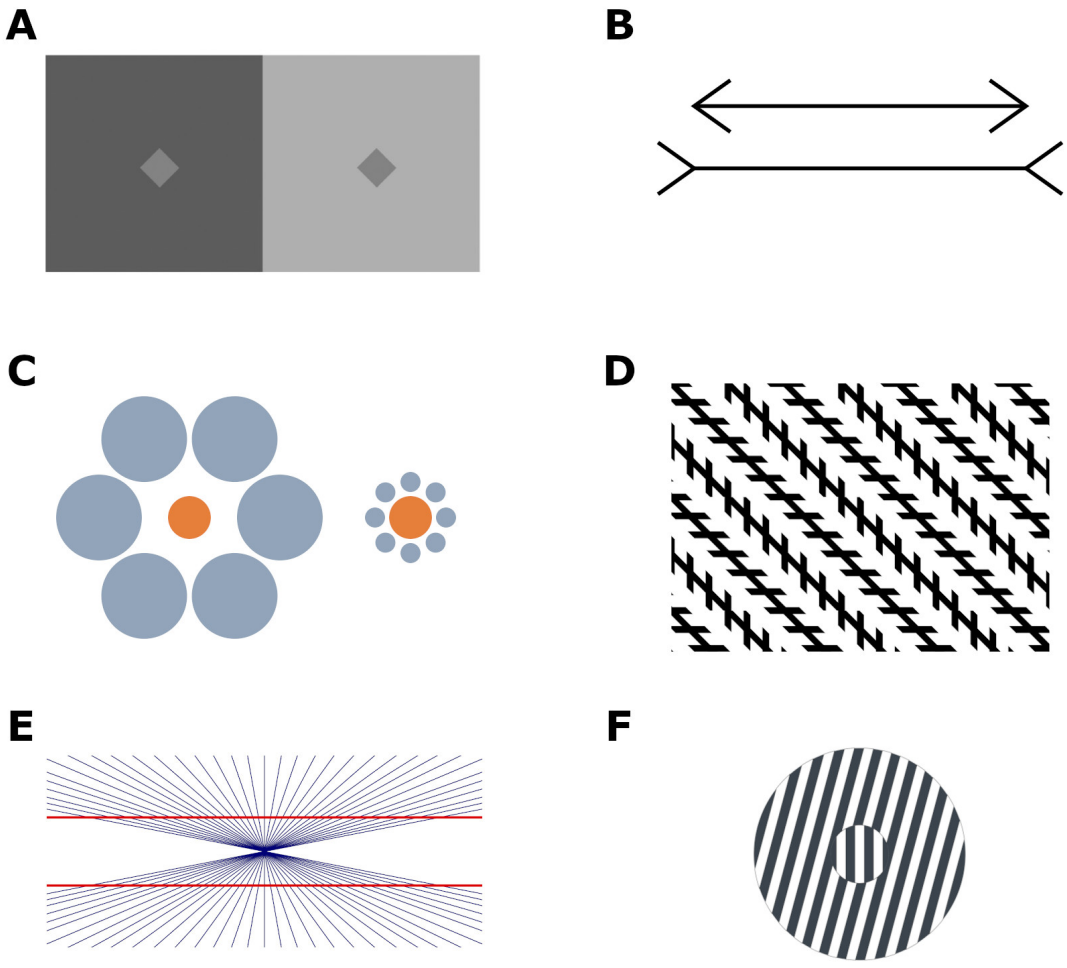

Figure 2.1: Examples of (spatial) visual context effects. **A**: The two diamonds have the same shade of grey, but appear to have different shades (Chevreul 1860). **B**: The top and bottom horizontal lines are the same length, but the bottom line appears longer (Müller-Lyer 1889). **C**: The two (orange) central circles are the same size, but the right one looks larger (Ebbinghaus 1902; Titchener 1905). **D** All strips have the same orientation, but appear slanted in different directions (Zöllner 1860). **E**: The two horizontal (red) lines are straight, but appear slightly curved (Hering 1861). **F** The stripes in the center circle are completely vertical, but appear slightly tilted (Gibson and Radner 1937). Figure 2.2 shows the same target stimuli without the contextual cues.

processes by which contextual stimulus cues influence the perceived properties of a target stimulus. For our purposes here, the specific neural mechanisms of contextual modulation are irrelevant. All that is required is that contextual modulation *occurs in perception*, as demonstrated in Figures 2.1 and 2.2.

The key insight of this section is that psychedelics might produce OEVs *by inducing hypersensitive contextual modulation*. I motivate this analytically with a thought experiment, followed by phenomenological and psychophysical evidence.

2.3.1 Thought experiment

Imagine that some fictional drug could selectively enhance contextual modulation. Under this drug, the apparent contrast of the diamonds in Figure 2.1 **A** would diverge *even more*—that is, the background shades (contextual cues) would have a *greater* effect on the perceived shades of the diamonds (target stimulus). By inducing *hyper*contextual modulation—amplified modulatory effects of contextual cues—the drug would exaggerate perceived differences in line length (**B**), circle size (**C**), line orientation (**D**; **F**), and curvature (**E**). Importantly, under this fictional drug, it is only the *magnitude of influence of contextual cues* that is impacted—i.e., without the contextual cues, (Figure 2.2) the drug would have less influence on percepts of the target stimuli.

Now, imagine further that the *strength* of these drug-amplified contextual modulations *varied from one frame to the next*, perhaps due to its pharmacokinetics, causing a 'rubber-banding' effect, where each moment the contextual modulation was stronger, then weaker, then stronger, relative to the previous moment.[5] The net phenomenology, I argue, would be exactly the kind of "breathing" (Huxley 1954), "wavering" (Hofmann 1980), "undulating movements" (Klüver 1926) seen in transformation OEVs. Our fictional drug would be able to produce transformation OEVs solely by enhancing

[5]Alternatively, the context provided by the visual scene at one moment might unduly influence the next scene as eye movements occur. The phenomenon of 'tracers' or 'trails'—lingering afterimages in moving objects—is consistent with the notion that hypersensitive temporal contextual modulation occurs under psychedelics. In essence, the context of an object being at position A is carried over into the next frame due to hypercontextual modulation of the previous frame. Thanks to Michael-Paul Schallmo for raising this possibility.

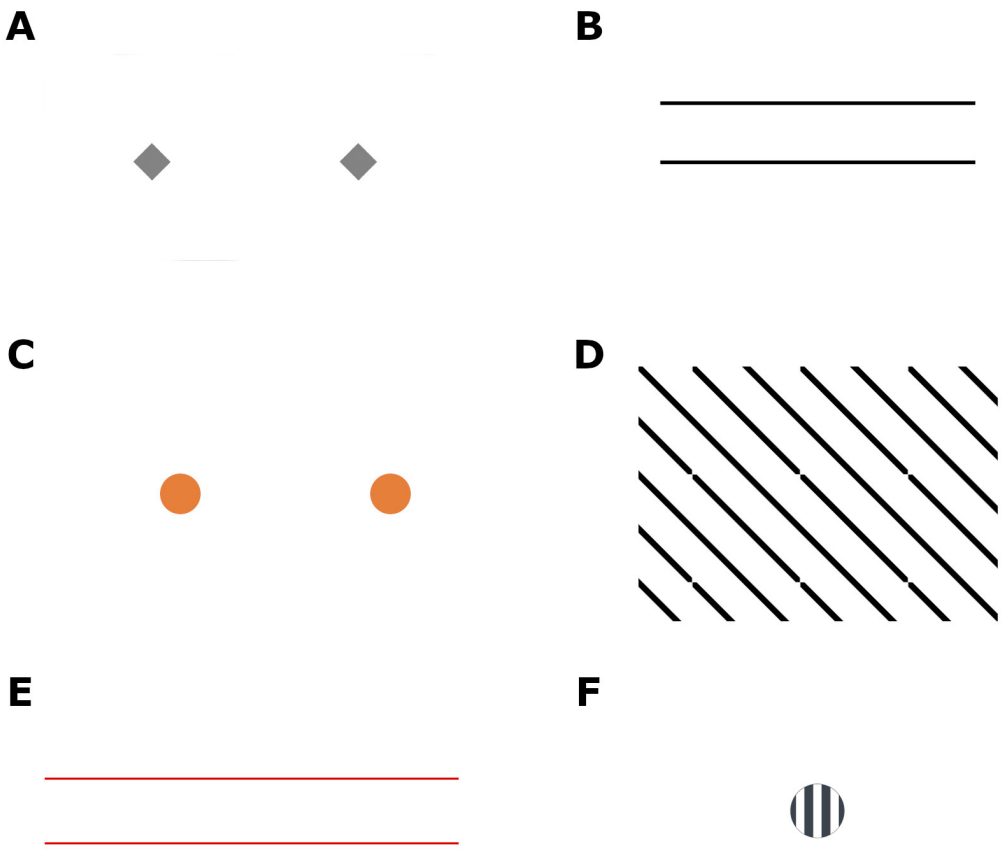

Figure 2.2: The exact same target stimuli from Figure 2.1 but without the contextual cues. **A**: The two diamonds have the same shade of grey. **B**: The top and bottom horizontal lines are the same length. **C**: The two (orange) central circles are the same size. **D** All strips have the same orientation. **E**: The two horizontal (red) lines are straight. **F** The stripes in the center circle are completely vertical. Figure 2.1 shows how contextual cues can alter the appearance of these stimuli.

the contextual modulation that occurs when you look at Figure 2.1. Furthermore, your overall visual field would have *richer variations* among its elements, akin to enhancement OEVs, just as the target stimuli in Figure 2.1 have more variation than they do in Figure 2.2.

I argue that common psychedelic OEVs can be accounted for by what I call *hypercontextual modulation* (HCM) in visual perception. The central notion is that psychedelics could cause OEVs by amplifying the visual processes by which perception of the target stimuli in Figure 2.2 are transformed by the contextual cues as in Figure 2.1.

2.3.2 OEV phenomenology as HCM

Consider that psychedelics increase scores on the rating scale item 'Things in my surroundings appeared smaller or larger', phenomena known as micropsia and macropsia (Kometer and Vollenweider 2016). In normal vision, the apparent sizes of objects are perceived *in relation to the spatial context of the visual scene*—an effect illustrated by the moon illusion (Berkeley 1709; Hershenson 2013), in which the apparent size of the moon changes depending on its position in the sky. Thus, if psychedelics caused HCM—i.e. disproportionate modulatory responses to contextual cues that ordinarily determine perceived size and shape—we would expect shifts in the apparent size of objects, as seen in transformation OEVs. Interestingly, transformation OEVs are often restricted to only some objects in the visual scene—e.g., some objects might appear to move or 'breathe', while others simultaneously remain static and appear normal, consistent with my claim that OEVs stem from a selective impact on contextual modulation processes rather than whole-scale distortions of the entire visual stream.

> It is theoretically interesting that the occurrence of apparent movements in the mescal state depends to a certain extent on the nature of the stimuli. ... objects which together with their surroundings form an optical "whole" and which are so to speak definitely anchored in optical respects are less likely to move than those which seem to be detached from their backgrounds; objects the contours of which "suggest" movement are more likely to move than those with definite, well-marked contours ... (Klüver 1928, 42–43)

The context effects in Figure 2.1 match well to transformation OEVs. In a state

of HCM, a greater-than-usual effect of cues seen in Figure 2.1 **B**/**C** could lead to "The branches [of a tree] became longer and shorter" (Klüver 1928). Hypersensitivity to cues that modulate line orientation (panels **D**/**F**) could lead to "the walls of the room no longer seemed to meet in right angles" (Huxley 1954). Amplification of the modulation seen in panel **E** could lead to "my field of vision wavered and was distorted as if seen in a curved mirror" (Hofmann 1980).

The same logic applies to enhancement OEVs. As seen in Figure 2.1 panel **A**, amplified contextual modulation could produce intensification of colors, heightened vivacity, and finer detail by increasing simultaneous contrast effects. Indeed, Klüver (1928) observed that under mescaline "Very pronounced simultaneous contrast is found." In everyday perception, contextual cues modulate many low-level visual features,[6] including perceived luminance (Adelson 2000; B. L. Anderson and Winawer 2005), contrast (Ejima and Takahashi 1985; Chubb, Sperling, and Solomon 1989; Cannon and Fullenkamp 1991; Snowden and Hammett 1998), and orientation (Zöllner 1860; Fraser 1908; Goddard, Clifford, and Solomon 2008; Qiu, Kersten, and Olman 2013; Clifford 2014), which underpin the perception of textures. Enhancement OEV phenomenology is thus consistent with the notion that psychedelics cause HCM at the lowest levels of visual processing.

Does HCM help us understand overlay OEVs? Klüver (1928) suggests that the 'form constants' in these OEVs arise from intrinsic functions of visual anatomy, and Bressloff et al. (2002) build on this idea in an anatomical-computational account suggesting that the "mechanisms that generate geometric visual hallucinations are closely related to those used to process edges, contours, surfaces, and textures." Speculatively, the geometric patterns seen in overlay OEVs are proto-elements of these higher-level visual features, which might become 'orphaned' or 'detached' from any objects. In a state of HCM, low-level visual processes might generate *extra*

[6]Indeed, like in visual perception, contextual modulation is pervasive in auditory perception of both speech (Stilp 2019) and music, where contextual interactions between loudness, pitch, and timbre (Melara and Marks 1990; Marozeau and Cheveigné 2007; Borchert, Micheyl, and Oxenham 2011; E. J. Allen and Oxenham 2014; Wang, Kreft, and Oxenham 2015) determine perceived auditory qualities. Enhanced subjective fidelity of auditory percepts under psychedelics, captured by the rating scale item "Sounds in room sound different" (Strassman et al. 1994), could thus plausibly be explained by HCM.

proto-elements of edges, contours, surfaces, and textures in (hyper)response to various (low-level) contextual cues, resulting in overlay OEVs. Indeed, there is evidence that the earliest/lowest visual areas generate proto-elements of naturalistic textures (Freeman et al. 2013; Ziemba et al. 2016). Thus, it is plausible that overlay OEVs result from hyper-recruitment of the response patterns in these early visual areas, causing them to produce an overabundance of textures like those found in the natural world.[7]

In summary, I propose that HCM is critically involved in all major types of OEVs induced by classic psychedelics. The defining phenomenological features of enhancement OEVs, transformation OEVs, and overlay OEVs are exactly the kinds of perceptual consequences we might expect to see if the visual system became hypersensitive to contextual cues at multiple levels. So far, I have provided a phenomenological-functional analysis supporting HCM as the cause of OEVs. I next present supporting empirical evidence from studies that asked participants to complete psychophysical tasks under psychedelics.

2.3.3 Psychedelic psychophysics

To support my argument that OEVs are hypercontextual modulations, I need psychophysical evidence that psychedelics *selectively* impact how contextual cues are processed; i.e., that a measured percept is *not* significantly impacted by the drug when significant context-modulating cues are absent from the stimulus, such as in Figure 2.2. Indeed, evidence indicates that visual performance is largely preserved under psychedelic drugs, *unless the stimuli are designed to elicit strong contextual modulation*. For instance, Barrett et al. (2018) found no significant differences in performance on the Penn Line Orientation Test (PLOT) (Moore et al. 2015) under psilocybin, a task that does not trigger significant contextual modulation at the level of perception that it measures.[8]

[7] Thanks to Michael-Paul Schallmo for providing the extra neuroscience references on this point.

[8] "The participant is shown two lines on the computer screen that differ in length and orientation, and must press a button to rotate one of the lines until its orientation (angle relative to a horizontal line) is the same as the other (nonrotating) line" (Moore et al. 2015).

Further evidence can be found in Carter et al. (2004), who designed two motion detection tasks—one "local motion" task, and one "global motion" task—and compared task performance under psilocybin versus placebo. Psilocybin had no impact on the local motion task, but significantly impacted the global motion task. Importantly, *contextual cues remained fixed across trials* on the local motion task. The global motion task, by contrast, presented contextual cues in the form of randomly moving (non-target) dots intermixed with the target dots, so that the visual context varied across trials. Psilocybin significantly impacted performance on this task. Furthermore, "a number of subjects commented that subjectively the global motion task became harder [under psilocybin] *due to an increased salience of the randomly moving dots*" (Carter et al. 2004, emphasis mine). In a different study that measured the influence of contextual cues on visual attention, Gouzoulis-Mayfrank et al. (2002) found that psilocybin significantly increased the influence that visual cues had on performance on the covert orienting of attention task (COVAT), consistent with the notion of HCM.

Taken together, these studies support HCM because they indicate that task performance is largely preserved under psilocybin on tasks (and on 'catch trials') that do not invoke or measure context effects, while performance is significantly impacted on tasks that induce contextual modulation. This data squares nicely with the notion that psychedelics selectively impact contextual modulation to produce OEVs. Note that the notion of HCM suggests an empirical research programme for future studies in psychedelic psychophysics, with testable hypotheses, which could confirm, disprove, or amend the notion that psychedelic visual effects stem from HCM.

2.3.4 Divisive normalization, serotonin, and psychedelics

The link between everyday context effects and psychedelic visuals is a phenomenological-functional insight that stands on its own, regardless of any proposed account of the neural mechanisms by which psychedelic drugs might amplify contextual modulation. Nonetheless, a computation known as *divisive normalization* (DN) stands out in current neuroscience as a successful neurocomputational account of context effects (Heeger 1992; Schwartz, Hsu, and Dayan 2007; Carandini and Heeger 2011; Schallmo

et al. 2018; Louie and Glimcher 2019; Aqil, Knapen, and Dumoulin 2021), so it is worth exploring whether it could be used to model psychedelic visuals. DN is a mathematical operation that, when used to model neural activity,

> scales the activity of a given neuron *by the activity of a larger neuronal pool*. This nonlinear transformation *introduces an intrinsic contextual modulation into information coding*, such that the selective response of a neuron to features of the input is scaled by other input characteristics. This contextual modulation allows the normalization model to capture a wide array of neural and behavioral phenomena not captured by simpler linear models of information processing" (Louie and Glimcher 2019, emphasis mine).

In the simplest terms, DN models how one neuron's activity is influenced by (contextual) activity in other neurons. Classic visual context effects can be modeled with DN (Schwartz, Hsu, and Dayan 2007; Louie and Glimcher 2019; Aqil, Knapen, and Dumoulin 2021), including surround suppression and enhancement of perceived contrast (Xing and Heeger 2001), visual salience (Itti and Koch 2000; Coen-Cagli, Dayan, and Schwartz 2012), object boundaries (Zhou and Mel 2008; Walshe and Geisler 2020), and motion (Quaia, Optican, and Cumming 2017; Schallmo et al. 2018). I suggest here that DN might capture how psychedelics alter these visual features to produce OEVs.

Is it neurobiologically plausible that psychedelics might alter DN computations to cause HCM in visual perception? Indeed, DN responses in early visual cortex have recently been linked to serotonergic (5-HT) neuromodulation in mouse models (Michaiel, Parker, and Niell 2019; Azimi et al. 2020). The findings of Azimi et al. (2020) provide preliminary evidence that serotonergic signaling is the neuromodulatory substrate by which neurons implement DN-like mechanisms to scale their activity.

> 5-HT_{1A} receptors promote divisive suppression of spontaneous activity, while 5-HT_{2A} receptors act divisively on visual response gain and largely account for normalization of population responses over a range of visual contrasts in awake and anesthetized states. Thus, 5-HT input provides balanced but distinct suppressive effects on ongoing and evoked activity components across neuronal populations (Azimi et al. 2020).

All classic psychedelic drugs agonize 5-HT_{2A} receptors (Glennon, Titeler, and McKenney 1984; Halberstadt 2015; Vollenweider and Smallridge 2022). We know

that this agonism is is critically involved in engendering psychedelic effects because the effects can be blocked by blocking 5-HT_{2A} agonism (i.e., by co-administering the drug ketanserin, a selective 5-HT_{2A} *ant*agonist) under psilocybin, LSD, and DMT in humans (Vollenweider et al. 1998; Kometer et al. 2011, 2012; Valle et al. 2016; Preller et al. 2017; Barrett, Preller, et al. 2017; Kraehenmann, Pokorny, Aicher, et al. 2017). Importantly, there is also evidence (Strassman 1995; T. Pokorny et al. 2016; Lawn et al. 2022) "suggesting a modulatory effect of the 5-HT_{1A}R system on 5-HT2-mediated psychedelic effects" (Vollenweider and Smallridge 2022). As noted above, Azimi et al. (2020) found that 5-HT_{2A} *and* 5-HT_{1A} might serve to *balance* different components of the DN computation in mice. Thus, the same 5-HT_{1A}/5-HT_{2A} activity that is critical for psychedelic visuals has also been implicated in supporting DN computations that accurately model visual context effects.

A question arises: How would the computational structure of DN need to be altered to yield the *hyper*contextual modulation that I argue underpins psychedelic effects? A normalization model "computes a ratio between the response of an individual neuron and the summed activity of a pool of neurons" (Carandini and Heeger 2011) such that "the selective response of a neuron to features of the input is scaled by other input characteristics" (Louie and Glimcher 2019). Roughly, the kind of HCM seen in OEVs might arise if the normalization pool were broadened such that the output of each neuron was computed in relation to responses from a larger-than-usual pool of neurons, the net effect being greater-than-usual contextual modulation.[9]

Importantly, my proposal that DN might model psychedelic OEVs is broadly consistent with existing theories based on hierarchical predictive coding (Corlett, Frith, and Fletcher 2009; Pink-Hashkes, Rooij, and Kwisthout 2017; Letheby and Gerrans 2017; Swanson 2018; Carhart-Harris and Friston 2019) insofar as predictive coding and DN computations are not mutually exclusive (Marino 2022; Srinivasan, Laughlin, and Dubs 1982). However, HCM and DN have advantages over existing Bayesian accounts for two reasons. First, DN is more parsimonious than predictive processing; it can yield understanding without requiring us to grasp the whole lot of

[9]My full treatment of this idea is forthcoming as a neurocomputational modeling paper.

esoteric neurocomputational concepts positied by hierarchical predictive processing.[10] Second, as mentioned in Section 2.1, while predictive processing accounts do make some attempt to explain OEVs—"such as seeing walls breathing" (Carhart-Harris and Friston 2019)—they do not offer principled reasons why walls so commonly appear to "breathe" rather than, say, crumble, catch fire, or morph into pink rats. For instance, Carhart-Harris and Friston (2019) argue that psychedelics 'relax' the normally heavily-weighted belief (or Bayesian prior) that "walls don't breathe" thus permitting the percept of breathing walls to emerge. But if psychedelics work this way, why would they not also 'relax' all sorts of other perceptual priors that normally constrain our perception of corporeal properties? Presumably 'relaxed beliefs' at such a fundamental level would cause complete perceptual chaos, which is not the case under classic psychedelics, as psychophysical studies readily show. By comparison, the notion of HCM can explain 'breathing' OEVs in terms of hypersensitivity to contextual cues, causing exaggeration of the same context effects known to operate at multiple levels in everyday visual perception, known to induce illusory curvature (Hering 1861), line orientation (Zöllner 1860; Gibson and Radner 1937), and size (Ebbinghaus 1902; Müller-Lyer 1889)—as seen in Figure 2.1.

Finally, DN is a "canonical computation"—an information processing strategy repeated "across brain regions and modalities to apply similar operations to different problems" (Carandini and Heeger 2011). Indeed, DN can model the contextual modulation involved in multisensory integration (Ohshiro, Angelaki, and DeAngelis 2011), visual attention (Reynolds and Heeger 2009), and value-coding on decision-making tasks (Louie et al. 2014; Louie and Glimcher 2019), all of which also happen to be impacted by psychedelics.[11] It is plausible that psychedelics produce their effects

[10]Such concepts include top-down/bottom-up hierarchical message-passing, unconscious perceptual inference, Bayesian priors, probability density functions, precision-weighting of prediction error, free-energy minimization, or a neurocomputation-specific notion of "relaxed beliefs" (e.g., Carhart-Harris and Friston 2019).

[11]While decision-making has not been studied under psychedelics, Metzner and Leary (1967) anecdotally observe that it "can lead to interminable distracting deliberations." Furthermore, the 5D-ASC includes the items "I felt incapable of making even the smallest decision" and "I had difficulties in distinguishing important from unimportant" (Dittrich 1998). Potentially, normalization models of decision-making (Louie et al. 2014) might be able to model how psychedelics cause "interminable distracting deliberations."

by impacting a canonical computation, given the cross-modal effects of psychedelics across perception and cognition. A DN model of psychedelic effects could be highly appealing for these reasons.

2.4 HCM, multisensory integration, and cognition

Next, I apply the idea of HCM beyond OEVs to explain other common psychedelic effects in modalities that have also been modeled with DN.

2.4.1 Audio-visual context effects

Auditory stimuli influence visual percepts in unusual ways under psychedelics, measured by the rating scale items 'Sounds seemed to influence what I saw', 'Shapes seemed to be changed by sounds or noises', and 'The colors of things seemed to be altered by sounds or noises' (Studerus, Gamma, and Vollenweider 2010). Anecdotally, Hofmann noted these effects in his early experiences with LSD. "It was particularly remarkable how every acoustic perception, such as the sound of a door handle or a passing automobile, became transformed into optical perceptions" (Hofmann 1980). This phenomenology is consistent with the general idea of HCM. In everyday perception, auditory sensations provide contextual cues that can influence visual percepts (McGurk and MacDonald 1976; Shams, Kamitani, and Shimojo 2000) and may even enhance deficient visual abilities (Caclin et al. 2011).

Consistent with this idea, psychedelics can amplify responses to contextual cues in musical stimuli (Bonny and Pahnke 1972; Barrett, Preller, et al. 2017), captured by the rating scale item "Increase in the beauty and significance of music" (Carbonaro et al. 2018), which can manifest as increased CEVs (Kaelen et al. 2016), emotions (Kaelen et al. 2015), and perceived meaning (Preller et al. 2017). One subject describes what it is like to listen to music under LSD as follows.

> The most beautiful array of fabrics and trimmings in fantastic inter-weaving of designs and in delicate colors of pastel to more intense in hue followed the inter-weaving movements of the music—visualizations of the voice timbre—ever

> changing in complex and unusual ways ... When the music stopped, the flow of imagery stopped (Bonny and Pahnke 1972, 71–74).

Musical stimuli provide a rich source of abstract, ambiguous, open-ended auditory cues, especially instrumental music, which is preferred over lyrical music for evoking meaningful associations under psychedelics (Barrett, Robbins, et al. 2017; Kaelen et al. 2018). Enhanced responses to music under psychedelics is thus plausibly due to HCM, where the contextual cues in music might produce greater-than-usual modulations of emotions (Kaelen et al. 2015), mental imagery (Kaelen et al. 2016), and meaning (Preller et al. 2017). Indeed, in everyday auditory perception, interactions between contextual cues determine perceived auditory qualities such as loudness, pitch, and timbre (Melara and Marks 1990; Marozeau and Cheveigné 2007; Borchert, Micheyl, and Oxenham 2011; E. J. Allen and Oxenham 2014; Wang, Kreft, and Oxenham 2015) and aid auditory scene analysis (Lewicki et al. 2014), semantic salience, and perceptual 'pop out' of meaningful sounds (Auerbach and Gritton 2022). Thus, augmentation of these everyday contextual modulation processes might explain why music has peculiar auditory *and* visual phenomenology under psychedelics.

2.4.2 Semantic activation

As with visual tasks, psychedelics impact performance on certain types of cognitive tasks but not others. Barrett et al. (2018) report that psilocybin did not impact performance on measures of episodic memory or executive function. By contrast, psilocybin and LSD both have significant impact on tasks that measure or induce semantic context effects, indicating that the characteristic psychedelic effects on cognition also involve a form of HCM. Using the Forward Flow Task (FFT) (Gray et al. 2019), in which subjects produce word associations from a seed word,[12] Wiessner et al. (2021) found that "LSD increased forward flow, flow distance and flow steps but not semantic spread, indicating that semantic distances of words were *meaningfully increased in relation to their predecessors, successors and neighbors but not overall,*

[12] "For this, the participant receives a seed word and is asked to type the first word that comes to mind from this seed word, followed by the first word that comes to mind from this first written word, and so on until reaching 20 words" (Wiessner et al. 2021).

randomly spread" (Wiessner et al. 2021, emphasis mine). These results are broadly congruent with other studies using cognitive tasks that measure and manipulate semantic context. Spitzer et al. (1996) found that psilocybin enhanced semantic priming for indirectly related (but not directly related or unrelated) word pairs in a lexical decision task, suggesting that psilocybin "leads to an increased availability of remote associations and thereby may bring cognitive contents to mind that under normal circumstances remain nonactivated" (Spitzer et al. 1996, 1057). Broadly consistent with these results, Family et al. (2016) found increased semantic spread under LSD in a picture-naming task (Vigliocco et al. 2002; Snodgrass and Vanderwart 1980) for semantically similar (but not for dissimilar) pictures. Relatedly, in an early study (albeit with some methodological limitations), Barr, Langs, and Holt (1972) asked subjects under LSD or placebo to list the connotations that came to mind as they viewed both fictional words and drawings of faces, presented separately as well as in word-face pairs. Connotations of the words and the faces were largely distinct under placebo, while "in the LSD-altered states, the usual connotations of the word were modified [when presented with the face], presumably by taking on some of the face's qualities" (Barr, Langs, and Holt 1972, 61).

Taken together, these results suggest that psychedelics alter thinking in a specific way, in which thoughts are more readily modulated by remote (but not random) contextual information, producing stronger associations between distantly-related (but not directly-related) concepts as well as between concepts and incoming sensory cues. Existing predictive processing accounts face challenges explaining these effects for reasons similar to the case of OEVs. Reducing the precision-weighting of priors ('relaxed beliefs') would presumably impact *all kinds* of cognitive tasks, including those that use *concrete* prompts and *direct* semantic associations. However, psychedelics did not cause significant differences on these kinds of tasks; their influence was selective to tasks that used abstract, indirectly-related cues and prompts. By contrast, such effects are consistent with HCM because enhanced sensitivity to contextual cues would plausibly lead to a positive correlation between cue ambiguity and the resulting semantic activation. In a state of HCM, trials using concrete, unambiguous prompts

would yield the usual semantic activations, while trials with abstract, ambiguous cues would trigger greater semantic activation that would spread more widely, just as these studies measured under psilocybin and LSD.

Relatedly, consider the "continuous gales of laughter" (Isbell 1959, 32), or "unmotivated laughter" (Preller and Vollenweider 2016) that can occur under psychedelics, an effect captured by the rating scale item "Many things seemed incredibly funny to me" (Dittrich 1998). Humor and laughter have long been linked to contextual shifts in semantic meaning (Beattie 1776; Morreall 2020). It is thus plausible that psychedelics cause excessive laughter by inducing HCM of semantic processing. Since, as we saw above, there is evidence that abstract or ambiguous contextual cues produce greater semantic activation under psychedelics, then, insofar as humor involves unusual semantic shifts, a cognitive form of HCM could increase the likelihood of laughter in response to cues that normally are not funny.

2.4.3 Symbolic thinking

Wiessner et al. (2022) found increased symbolic thinking on the pattern meaning task (PMT),[13] the alternate uses task (AUT),[14] and the figural creativity task[15] under LSD compared with placebo, characterized by "non-concreteness as common denominator ... indicating that abstract, more than concrete, input stimulates the generation of semantically distinct thinking under LSD" (Wiessner et al. 2022). It is worth noting that the PMT and AUT tasks used *visual stimuli* (abstract line patterns, everyday objects) as task prompts. Relatedly, a construct in psychology known as 'primary-process thinking' (Rapaport 1950) defines a mode of cognition marked by increased symbolic thinking linked to mental imagery (Stigler and Pokorny 2001). Under LSD, Kraehenmann, Pokorny, Aicher, et al. (2017) measured increased primary-process thinking using a rating scale consisting of nine categories (Auld,

[13]The pattern meaning task (PMT) involves writing as many creative interpretations as possible for abstract line patterns (8 patterns, 2 min each) (Claridge and McDonald 2009).

[14]The alternate uses task (AUT) involves writing as many uncommon uses as possible for everyday objects (2 objects, 3 min each) (Guilford 1967).

[15]The figural creativity task (FIG) involves producing drawings based on simple line patterns on a sheet of paper and writing creative titles for them (2 patterns, 10 min in total) (Artola et al. 2012).

Goldenberg, and Weiss 1968), which include 'visual representation', 'symbolism', 'fluid transformations', and 'unlikely combinations or events'. Similarly, the Rorschach (inkblot) projective test—another task that uses an abstract visual prompt—measured increased primary-process thinking under LSD (Barr, Langs, and Holt 1972; Holt 2002), "further supporting the notion that abstract and imagined stimuli promote LSD-induced symbolic thinking" (Wiessner et al. 2022). Relatedly, psychedelics increase scores on the rating scale items "Some everyday things acquired special meaning", "Things in my environment had a new strange meaning", and "Objects in my surroundings engaged me emotionally much more than usual" (Studerus, Gamma, and Vollenweider 2010; Schmid et al. 2015; Liechti, Dolder, and Schmid 2017; Holze et al. 2020, 2022; Hasler et al. 2004).

HCM can make sense of increased symbolic thinking under psychedelics. If contextual cues trigger increased modulations at multiple levels of perception and cognition—perhaps underpinned by individual neurons scaling their responses according to activity from a larger-than-usual pool of other neurons (DN)—then we might expect increased attribution of meaning to various external and internal cues.

2.4.4 Set, setting, and HCM

The term 'set and setting' is a slogan coined by Leary, Litwin, and Metzner (1963) to capture a phenomenon (noted as early[16] as Moreau (1845; Hartogsohn 2017)) in which extra-pharmacological factors (non-drug variables) influence the subjective effects of psychedelic drugs to a degree that is disproportionate to other psychoactive drugs (WHO 1958; Abramson 1960; Zinberg 1984; Hartogsohn 2017). The variables in 'set' (mind*set*) include "personality, preparation, expectation, and intention of the person having the experience," while the variables in 'setting' (external environment) include "the physical, social, and cultural environment in which the experience takes place" (Hartogsohn 2017). Importantly, the reasons for this influence remain unclear within

[16] Arguably the ritualistic practices surrounding the use of psychedelics by indigenous cultures reflects a deep and sophisticated understanding of how the variables of set and setting impact subjective drug effects.

certain mechanistic assumptions in pharmacology; namely, "that drugs exert basically conform effects on their users (DeGrandpre 2006). It would seem nonsensical to claim that a drug experience could differ fundamentally depending on the place in which the drug is taken or the people present" (Hartogsohn 2017).

However, set and setting makes more sense if psychedelic effects stem from HCM. HCM *entails* that subjective effects are dependent on set and setting, as the amount of contextual modulations in any given moment depends on the nature of the external and internal contextual cues. Thus, the broad hypersensitivity to surroundings elicited by psychedelics in humans (Eisner 1997) and other mammals (Halberstadt and Geyer 2016) is plausibly due to HCM impacting multiple levels of perception and cognition.

2.4.5 Bad HCM

Relatedly, the valence of psychedelic experiences—their 'pleasantness' or 'unpleasantness'—is highly variable. The same individual can have a positively-valenced 'good trip' on one occasion, yet a separate occasion with the same drug at the same dosage can yield a negatively-valenced 'bad trip' (Cohen 1960; Strassman 1984; Barrett et al. 2016; Carbonaro et al. 2016; Gashi, Sandberg, and Pedersen 2021), a fact that early psychopharmacologists found puzzling and contradictory (Osmond 1957; WHO 1958; Abramson 1960; Hartogsohn 2017). The contradiction is resolved, I argue, when we view HCM as the *primary* action of psychedelics: descriptions of bad trips often detail how a particular visual or auditory stimulus led to a cascade of negative thoughts and feelings (Gashi, Sandberg, and Pedersen 2021). To mitigate such hypercontextual cascades, researchers and illicit users alike have developed protocols for controlling set and setting (Leary, Litwin, and Metzner 1963; Eisner 1997; Johnson, Richards, and Griffiths 2008; Carbonaro et al. 2016; Gashi, Sandberg, and Pedersen 2021)—they control the contextual cues. Amidst the cognitive effects described in previous sections—increased semantic activation, semantic spread, and symbolic thinking—it is unsurprising that trains of thought can go 'off the rails' into startling mental territory as one thought hypermodulates subsequent thoughts. Taken together, the phenomenology and etiology of bad trips offer yet more reason to suspect that HCM is central to

psychedelic drug effects. As one illicit user put it, when it comes to understanding what causes bad trips, "Context is everything" (Gashi, Sandberg, and Pedersen 2021).

2.5 Practical implications

In this section, I describe key takeaways whereby HCM might inform current debates and philosophical questions about the therapeutic use of psychedelics.

2.5.1 Hallucination and HCM

Do psychedelic visuals count as hallucinations? Through the lens of HCM, psychedelic visuals are perceptual consequences of hypersensitivity to contextual cues—*normal* contextual modulation processes are augmented to produce *exaggerated* visual responses. Since we generally don't say that you are hallucinating when you view Figure 2.1, hypercontextual modulations of perception might be more appropriately considered as illusions (Todorović 2020), not hallucinations. Importantly, our concepts of illusion and hallucination are not synonymous, as the two concepts differ with regard to the epistemic status or veridicality of the experiences. Macpherson and Batty (2016), for example, argue that common features of everyday perception have mixed veridicality. If I am right that psychedelic visuals stem from HCM, then we might hold their epistemic status akin to how we regard perceptual context effects: illusory, in a sense, but part of the normal way that everyday perception functions (Schwartz, Hsu, and Dayan 2007; Macpherson and Batty 2016; Todorović 2020)—just exaggerated.

The epistemic status of psychedelic visuals is thus improved by disentangling them from the lousy epistemic reputation of hallucinations, seeing their status instead as roughly on par with garden variety illusions, which brings them much closer to the epistemic status of everyday perception, which, of course, is infused with 'illusory' elements at every turn (Klüver 1966; Purves, Morgenstern, and Wojtach 2015; Macpherson and Batty 2016). Thus, psychedelic visuals are nothing to fear, epistemically speaking.

2.5.2 New context for old cues

Letheby (2021) provides an argument for what he sees as a chief epistemic virtue of psychedelics:

> 1. Psychedelics often facilitate the apprehension of already known facts under new and distinctive modes of presentation.
> 2. If one apprehends an already known fact under a new and distinctive mode of presentation, then one thereby acquires new knowledge of an old fact.
> 3. Therefore, psychedelics often facilitate the acquisition of new knowledge of old facts (Letheby 2021).

In terms of HCM, we might say that psychedelics allow old cues to trigger new contextual modulations. Furthermore, HCM offers a new way to describe and understand the old fact that psychedelics can cause people to see things anew, adding greater specificity to the claim that "psychedelics facilitate the representation of old facts in new modes by disrupting the brain's functional architecture" (Letheby 2021). Many classes of drugs (among other things) can disrupt the brain's functional architecture. Psychedelics are uniquely valuable, I argue, because they cause hypersensitivity to contextual cues, allowing the brain to modulate itself in new ways.

Another epistemic benefit highlighted by Letheby (2021) is that psychedelics might engender *knowledge by acquaintance* (Russell 1910); namely, acquaintance with the fact that our minds have "vast, normally unrealized potential" (Letheby 2021, 184). Here, I argue that the potential we are acquainted with is the mind's capacity for nearly limitless *contextual modulation*—to combine cues in infinite different ways producing infinite varieties of percepts and thoughts—and that psychedelics grant direct acquaintance with this at multiple levels of mental function. HCM also offers a framework for understanding how psychedelics facilitate epistemic gains that take the form of *knowledge how* and *knowledge that* (Letheby 2021). Within a new "*context of discovery*" (Letheby 2021), new insights are made available (*knowledge that*). Insofar as learning new (psychological and emotional) skills arises from enhanced contextual modulation, *knowledge how* might also be gained via HCM.

2.5.3 HCM and psychedelic therapy

HCM can be cashed out in pursuit of a naturalistic, neurocognitive understanding (Shanon 2002; Letheby 2021) of why psychedelics can have therapeutic benefits. Consider that patients with major depressive disorder (MDD) show reduced (*hypo*sensitive) contextual modulation in the processing of visual (Salmela et al. 2021; X. M. Song et al. 2021; Golomb et al. 2009), and emotional (Rottenberg, Gross, and Gotlib 2005) stimuli. Relatedly, a common symptom of MDD is physical anhedonia (Chapman, Chapman, and Raulin 1976), the reduction of interest and enjoyment in sensory stimuli (Shankman et al. 2010; Sagud et al. 2020). Furthermore, MDD patients show blunted responses to everyday stimuli that convey contextual emotional cues, including body movements (Kaletsch et al. 2014), speech (Pang et al. 2014), music (Naseri et al. 2019), and faces (Krause et al. 2021; Bourke, Douglas, and Porter 2010). Conversely, psychedelics appear to do exactly the opposite. Responses to music, as described above, are enhanced (Bonny and Pahnke 1972; Preller et al. 2017; Kaelen et al. 2015). There is substantial evidence that psilocybin "revives emotional responsiveness [to faces] on a neural and psychological level" (Mertens et al. 2020) in MDD patients (Stroud et al. 2017; Roseman et al. 2018; Mertens et al. 2020; Gill et al. 2022) as well as healthy volunteers (Grimm et al. 2018). Altered visual perception of faces under mescaline was reported early on by Klüver (1928): "Human faces seem to undergo certain changes ... the features become more sharply defined." HCM might thus provide a key insight into the general trajectory by which psychedelics move patients out of depression; namely, that MDD involves *hypo*sensitive contextual modulation, while psychedelics perhaps counteract this by inducing *hyper*sensitive contextual modulation.

As argued above, this neurocognitive understanding has the potential to free psychedelic therapy from the lousy epistemic reputation of hallucinations. It might also defuse what Letheby (2021) calls the "Comforting Delusion Objection," which holds that therapeutic benefits derive from false beliefs. HCM offers a naturalistic account of therapeutic benefits that does not rest on the induction of non-naturalistic

beliefs.

2.5.4 Vision(s), symbols, and insight

As Letheby (2021) points out, testimonies from patients suggest that psychological insights and emotional shifts often occur concomitantly with unusual visual experiences, sometimes taking the form of symbolic imagery or 'visual parables': "Visual parables and metaphors constitute an alteration to perceptual experience, but also an experience of apparent *insight* ... they engender novel understanding or comprehension, or at least feelings thereof" (Letheby 2021, 43). Recall that the most significant increases in symbolic thought measured by Wiessner et al. (2022) under LSD came in response to tasks that used *abstract prompts with visual stimuli*, which the authors explicitly link to the therapeutic role of symbolic visions reported by early psychedelic therapists.

There is wide agreement that music listening is critical to psychedelic therapy (Bonny and Pahnke 1972; Kaelen et al. 2018; Barrett et al. 2018). Moreover, indigenous cultures continue to use sound and music—often simple, repetitive motifs and rhythms—to drive and optimize visual effects and concomitant revelations (Schultes 1969; Schultes, Hofmann, and Rätsch 2006; Carod-Artal 2015; George et al. 2021). Less discussed in the literature, but relevant to our concerns here, is the role of external *visual* stimuli.[17] Furnishings and decorations in the treatment room are standard 'setting' protocol in virtually all recent clinical trials (Johnson, Richards, and Griffiths 2008).[18] In many protocols, "the environment in which the treatment is conducted commonly includes mystical themes, use of psychedelic imagery such as mandalas" (Hosanagar, Cusimano, and Radhakrishnan 2021). Interestingly, mandalas were prescribed by Metzner and Leary (1967) to visually drive psychological insight under psychedelics. "The various symbolic figures on the mandala, with letters, colors etc., serve as additional *anchoring points of associations*. The idea is to get as much of

[17] I thank Dr Kathyrn Swanson for pointing out the importance of physical objects in shaping psychedelic experience.

[18] Note that these protocols also encourage the use of eyeshades. This confounds analyses such as Roseman, Nutt, and Carhart-Harris (2017) which examine the degree to which visual alterations correlate with positive clinical outcomes.

the mental contents on to the two-dimensional surface . . . " (Metzner and Leary 1967, emphasis mine). Moreover, indigenous psychedelic rituals place 'sacred objects' within the ritual space, often arranged as shrines; peyote rituals, for example, use an altar "over which thoughts and visions understood travel to and from God" (Stewart 1961), while ayahuasca rituals are often held in spaces with intentional geometric layouts and filled with "visually pleasing objects such as flowers, colorful icons, crystals, and glowing candles, but also by the calculated use of symbology" (Hartogsohn 2021).

Letheby (2021) characterizes perceptual effects as "vehicles," the importance of which, he argues, is "derivative" from the insights they can deliver. However, if the insights are important, then understanding the vehicles that deliver them would be *even more important*. This calls into question the recent tendency to downplay the importance of psychedelic visuals. It also casts doubt on what Letheby (2021) terms "Pure Neuroplasticity Theory," which hopes that *all* acute subjective psychedelic effects are epiphenomenal to what are putatively purely neurobiological therapeutic mechanisms (Hesselgrave et al. 2021; McClure-Begley and Roth 2022; Berg et al. 2022). If therapeutically beneficial experiences come from HCM, perhaps by impacting the serotonergic substrates of DN, then the visuals might come with the territory. At the very least, visuals are a *perceptual marker* that the mind has entered the therapeutically beneficial mode of functioning.

Metzner and Leary (1967) stated that "A psychedelic experience is a period of intensely heightened reactivity to sensory stimuli from within and without." This perspective appears to have faded, as the role of visual stimuli, external objects, and visual imagery in psychedelic therapy continues to be downplayed. HCM offers an antidote to the professional blind eye[19] that has been turned to psychedelic visuals, because it is a naturalistic, neurocognitive explanation capable of linking visuals to therapeutic benefits.

[19]Pun intended (wink).

2.6 Conclusion

Visual perception is a central element of human mental function. We routinely speak about our mental operations using visual metaphors.[20] Psychedelic OEVs thus offer an important clue to how psychedelics impact the mind. I have argued that the phenomenology of OEVs suggests that psychedelic drugs impact contextual modulation such that percepts are hypermodulated in response to the usual contextual cues.

The implications of the HCM understanding of psychedelics are threefold. First, HCM suggests that psychedelic effects on visual perception are congruent with effects on cognition. Second, understanding psychedelics in terms of HCM can serve as a basis for a neurocognitive account of psychedelic therapy, whereby psychological insights are more likely to arise from a sea of exaggerated responses to external and internal cues. Third, HCM might relieve the epistemic stigma associated with visual effects, as both visual and non-visual psychedelic effects can be understood within a unified, naturalistic, neurocognitive framework.

HCM also sketches an empirical research programme, with OEVs as the phenomena of interest, in which the fundamentals of psychedelic effects on low-level perceptual processes could be studied using classic paradigms and modeled using canonical neural computations like divisive normalization to understand how psychedelics alter vision and other mental functions.

There is much to be gained by seeing psychedelic visuals in context.

[20] We *focus* on a topic and *illustrate* our ideas to *show* how they make *sense*; when we have insight, we *see things* in a new *light* and are en*lightened*; ideas can be *illuminated* making their relevance *apparent*; we *view* facts through the *lens* of a conceptual construct; a shift in understanding activates a new *perspective*, out*look*, or world*view* that *reveals* things previously over*looked*. I trust that you *see* my point, or at least the general *picture*, because *seeing* is believing!

Image credits

Figures 1 & 2 panel **A** are adapted from Todorović (2020).

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Figures 1 & 2 panel **F** adapted from Schwartz, Hsu, and Dayan (2007).

Chapter 3

Enhanced visual contrast suppression during peak psilocybin effects: A psychophysical study

> "Most investigators have been more interested in the vision-producing effects ... than in the sensory changes caused by the drug. But an analysis of only the visions would leave our account of the optical effects incomplete ... we should not arrive at a proper understanding of the way the visual world appears to the subjects. ... An enhancement of contrast phenomena seems to be the rule. Very pronounced simultaneous contrast is found; the contours of the objects become sharp and well-defined."
>
> –Heinrich Klüver (1928, 33–35)

ABSTRACT

In visual psychophysics, an effect known as surround suppression occurs when the apparent contrast of a center stimulus is reduced when presented within a surrounding higher-contrast stimulus. Many key aspects of visual perception invoke surround suppression—texture segregation, perceptual constancies, figure-ground segmentation, contour integration, motion detection, and depth perception—yet the neuromodulatory processes involved remain unclear. Psilocybin, a drug garnering renewed interest for its clinical potential, is a serotonergic psychedelic compound known for its robust effects on visual perception, particularly texture, color, object, and motion perception. We asked whether surround suppression is altered under peak effects of psilocybin. Using a contrast-matching task with different center-surround stimulus configurations, we measured surround suppression after a high dose of psilocybin compared with placebo. Our results, while preliminary, suggest that psilocybin enhanced surround suppression. Psilocybin produced no change in contrast discrimination when stimuli were presented without a surround, suggesting that psilocybin selectively impacted center-surround modulation of perceived contrast, which is thought to reflect cortical rather than retinal aspects of visual perception. Furthermore, we found that the intensity of subjective 'psychedelic visuals' induced by psilocybin correlated positively with the magnitude of surround suppression. We note the potential impact of our findings for psychiatry, given that recent studies have demonstrated weakened visual surround suppression in patients with major depressive disorder, for which psilocybin has recently been identified as a breakthrough therapy. Our finding is thus immediately relevant to understanding the linkages between serotonin, surround suppression, the visual effects of psilocybin, mental health disorders, and the mechanisms of psychedelic therapies.[1]

3.1 Introduction

In visual perception, the appearance of a given object is influenced by neighboring objects (Schwartz, Hsu, and Dayan 2007). These interactions, known as spatial context effects, produce many well-known visual illusions (Ebbinghaus 1902; Gibson and Radner 1937; Fraser 1908). Surround suppression of apparent contrast—when the perceived contrast of a target stimulus is reduced (suppressed) by the presence

[1]Link Swanson and Michael-Paul Schallmo designed the experiment. Jessica Nielson, Sophia Jungers, and Link Swanson carried out the experiment. Kathryn Cullen and Ranji Varghese helped with participant safety monitoring. Link Swanson analyzed the data and wrote the manuscript.

of higher-contrast surrounding stimuli—has been robustly demonstrated using psychophysics (Ejima and Takahashi 1985; Chubb, Sperling, and Solomon 1989; Cannon and Fullenkamp 1991; Snowden and Hammett 1998; Olzak and Laurinen 1999; Petrov and McKee 2006; Xing and Heeger 2000, 2001; C. Yu, Klein, and Levi 2001; Schallmo and Murray 2016). However, it remains unclear which neuromodulator systems are critically involved in surround suppression. One approach to investigate the role of neuromodulators in visual perception is to use drugs as pharmacological probes paired with visual tasks. Previous inquiries into surround suppression have probed GABAergic pathways with the drugs ethanol (Read et al. 2015) and lorazepam (Schallmo et al. 2018); cholinergic pathways with donepezil (Gratton et al. 2017; Kosovicheva et al. 2012) and caffeine (Nguyen et al. 2018); dopaminergic pathways with bromocriptine (Gratton et al. 2017); and noradrenergic pathways with guanfacine (Gratton et al. 2017). The GABA system has been the target of many studies of surround suppression in humans (Cook, Hammett, and Larsson 2016; Read et al. 2015; C. Song et al. 2017; Loon et al. 2012; Yoon et al. 2010; Schallmo et al. 2018, 2020) and animal models (Adesnik et al. 2012; Haider et al. 2010; Ma et al. 2010; Nienborg et al. 2013; Ozeki et al. 2004, 2009b; Sato et al. 2016). However, recent work has cast doubt on the hypothesis that surround suppression is directly mediated by GABA (Read et al. 2015; Schallmo et al. 2018; Schach, Surges, and Helmstaedter 2021). To our knowledge, no studies have paired psychophysics with serotonin (5-HT) agonist drugs to probe serotonergic pathways for their possible role in surround suppression in humans. The present study aims to address this gap in knowledge.

The psychedelic drug *psilocybin* (4-phosphoryloxy-N,N-dimethyltryptamine) is a naturally-occurring tryptamine compound (Figure 3.1 **A**) found in at least 144 different species of mushrooms worldwide (Gastón Guzmán 2005; Gaston Guzmán, Allen, and Gartz 1998) (see Figure 3.1 **C**). Psilocybin, which is rapidly metabolized into psilocin (Figure 3.1 **B**) in the body, is a serotonin 2A (5-HT_{2A}) receptor agonist that can alter perception, emotion, cognition, and sense of self (Studerus, Gamma, and Vollenweider 2010; Hirschfeld and Schmidt 2021; Holze et al. 2022). Visual effects ('psychedelic visuals') are the most common and prominent dose-dependent subjective effects of

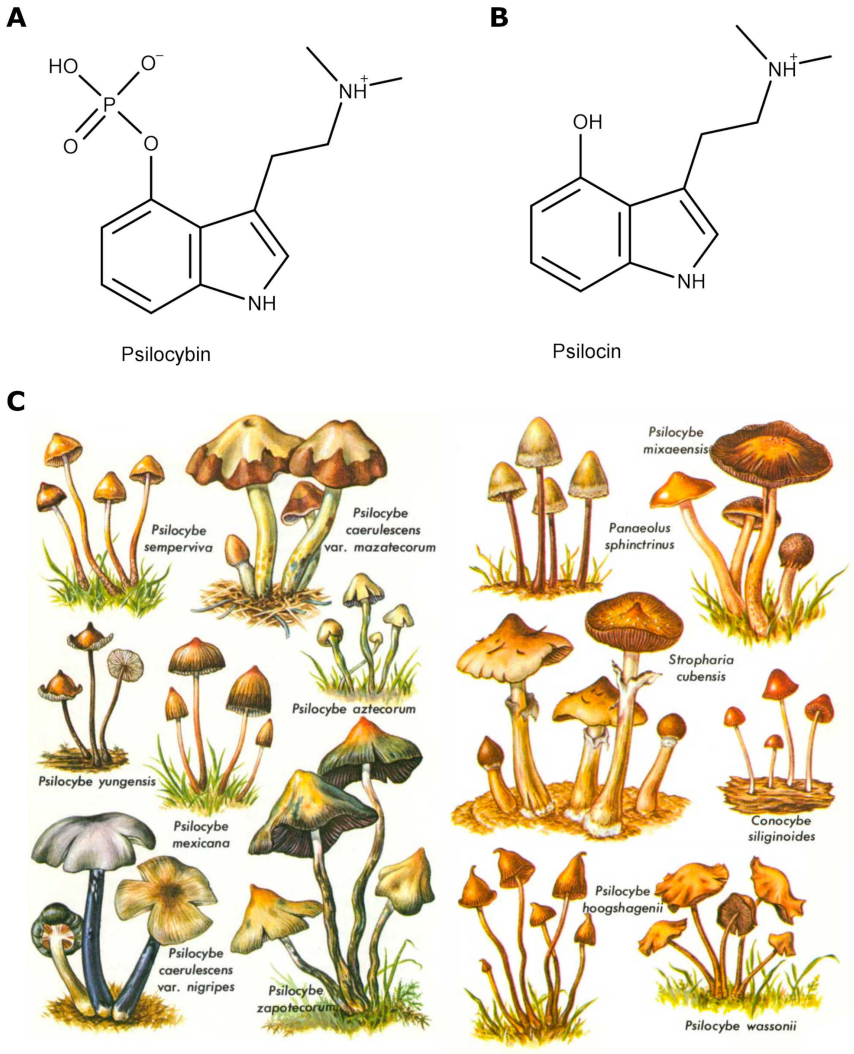

Figure 3.1: Psilocybin (**A**) and psilocin (**B**) are found in more than one-hundred species of mushrooms (examples shown in **C**). Psilocybin is rapidly metabolized into psilocin during metabolism. Mushroom illustrations by Elmer W. Smith (Schultes and Smith 1976)

psilocybin (Studerus, Gamma, and Vollenweider 2010; Carbonaro et al. 2018; Bayne and Carter 2018; Vollenweider and Preller 2020; Hirschfeld and Schmidt 2021; Aday et al. 2021; Holze et al. 2022). Relatively few studies have investigated psilocybin using visual psychophysics (Aday et al. 2021). Psilocybin appears to impact only select visual processes, while others are left intact (Carter et al. 2004; Kometer et al. 2011; Carbonaro et al. 2018; Aday et al. 2021). The phenomenology of psilocybin's visual effects can include alterations in the appearance of textures, the shapes/sizes of objects, motion, and colors—the visual field can take on a kind of 'fluidity', exhibiting animated dynamics described as 'pulsing', 'glowing', 'breathing', 'shifting', 'dancing', etc (see Chapters 1 and 2). Given this visual phenomenology, it is plausible that center-surround interactions are in some way impacted by psilocybin, as surround suppression plays a critical role in certain visual processes (Nurminen and Angelucci 2014; Angelucci et al. 2017), including visual saliency and pop-out (Knierim and Essen 1992), perception of object boundaries (Nothdurft, Gallant, and Van Essen 2000), perceptual constancies (Allman, Miezin, and McGuinness 1985), figure-ground segmentation (Lamme 1995; Supèr, Romeo, and Keil 2010), contour integration (Field, Hayes, and Hess 1993; Kapadia et al. 1995; Polat et al. 1998; Hess and Field 1999), and motion detection (Jones et al. 2001). To our knowledge, no previous study has measured visual contrast suppression under psilocybin in humans.[2] Thus, a closer examination of the links between surround suppression and the subjective effects of psilocybin is warranted.

Psilocybin-assisted therapy has rapid and enduring antidepressant effects in patents with major depressive disorder (MDD) (Davis et al. 2021; Ross et al. 2016; Griffiths et al. 2016; Carhart-Harris, Bolstridge, et al. 2018; Gukasyan et al. 2022). Visual surround suppression is known to be weaker in patients with MDD (Golomb et al. 2009; Salmela et al. 2021), a difference that normalizes somewhat with remission (Salmela et al. 2021). The neuromodulatory causes of weakened surround suppression in MDD are unknown. The links between serotonin and MDD are widely assumed but not well

[2]Michaiel, Parker, and Niell (2019) found reduced surround suppression in mice after administration of the psychedelic drug DOI. Relatedly, Azimi et al. (2020) provide evidence for the role of 5-HT_{2A} in mouse visual gain control.

understood (Cowen and Browning 2015; Carhart-Harris and Nutt 2017). Knowing the impact of psilocybin on surround suppression could thus address multiple knowledge gaps in our understanding of the links between MDD, serotonin, visual surround suppression, and the antidepressant mechanisms of psilocybin-assisted therapy.

In spite of its therapeutic promise, psilocybin's subjective effects have paradoxically (Osmond and Smythies 1952) been characterized as "a schizophrenia-like psychosis" (Vollenweider et al. 1998, 3897). This claim has remained controversial for nearly a century (see Chapter 1) and has been called into question by recent comparisons (Leptourgos et al. 2020). Multiple investigations have found weakened visual surround suppression in schizophrenic patients compared with healthy controls (Dakin, Carlin, and Hemsley 2005; Tadin et al. 2006; Yoon et al. 2009; Yang et al. 2012; Tibber et al. 2013; Serrano-Pedraza et al. 2014; Schallmo, Sponheim, and Olman 2015; V. J. Pokorny et al. 2019; Linares et al. 2020). Understanding the impact of psilocybin on surround suppression could thus illuminate the debates over the exact relationship between psychedelics and psychosis, as well as the possible role of serotonergic neuromodulation in schizophrenia.

Taken together, the above gaps in knowledge indicate a pressing need to study the impact of psilocybin on visual surround suppression. Here, we addressed this need using a psychophysical contrast-matching task to examine suppression of perceived contrast using different center-surround stimulus configurations under peak effects of a high dose of psilocybin in healthy human participants. These results were compared with placebo in a double-blind crossover (i.e., within-subjects) experimental design. Our results indicated that psilocybin selectively enhanced visual surround suppression without impacting generalized contrast discrimination. Furthermore, we found that the magnitude of surround suppression correlated significantly with the intensity of the subjective psychedelic visual effects.

3.2 Methods

This study was conducted as part of a double-blind, randomized, placebo-controlled clinical trial at The University of Minnesota Health Clinical Research Unit (M Health CRU) in Minneapolis, Minnesota.[3]

3.2.1 Participants

Adults aged 25 to 38 years with no current or previous mental health diagnosis, not currently using any prescription medications, with at least one reported previous experience taking a moderate to high dose of psilocybin, and without histories of psychotic disorder were eligible to participate. Six healthy observers with normal or corrected-to-normal vision (3 male and 3 female, mean age 33 years) were included in this study. All participants gave written informed consent and were compensated at a rate of $20 per hour. Experimental protocols were approved by the Institutional Review Board of the University of Minnesota. All experiments were performed in accordance with approved guidelines and regulations, including approval from the United States Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA).

3.2.2 Crossover design

Participants completed two drug dosing sessions—one day with active drug (25mg psilocybin); one day with placebo (100mg niacin)—two weeks apart. Doses of psilocybin and placebo were administered in identical opaque gelatin capsules in the context of a comfortable, decorated hospital room (approximately 9 hours). Participants were randomized into groups where group A received psilocybin on dosing day 1 and placebo on dosing day 2, while group B received the drugs in the reverse order. Participants, experimenters, and all study staff were blind to which drug was administered on any given experimental session. See Table 3.1 for an overview of the study design.

[3]ClinicalTrials.gov Identifier: NCT04424225

Table 3.1: The within-subjects crossover design. Each dosing session was separated by two weeks. For the Dosing 1 and Dosing 2 sessions, participants received either the active drug (psilocybin, 25mg, oral) or the placebo (niacin, 100mg, oral). A within-subjects crossover design, all participants completed all sessions. Participants in Group A were administered psilocybin on their Dosing 1 session. Participants in Group B were administered psilocybin on their Dosing 2 session. Participants were assigned to the groups using an adaptive minimization randomization method to balance age and gender between the groups. Participants, experimenters, and all study staff were blind to the group assignments.

Session	**Group A**	**Group B**
Dosing 1	psilocybin	plaebo
Dosing 2	placebo	psilocybin

3.2.3 Apparatus

Visual stimuli were presented on a Dell P2319H 23-in LED-backlit monitor (1920 $\times$ 1080 pixels, 60 Hz refresh rate) at a viewing distance of 60cm. The monitor was calibrated using a spectrophotometer. Mean luminance was 111.2 cd/m^2. Stimuli were generated and presented using PsychoPy (Peirce et al. 2019) version `2021.2.3`.

3.2.4 Stimuli

Stimuli consisted of annulus sinusoidal luminance modulation gratings presented on a mean gray background at 3° eccentricity to the left and right of fixation. The central fixation mark was constructed according to Thaler et al. (2013) (shown in Figure 3.2). The contrast of one grating (target) was fixed at 50%, while the contrast of the other grating (reference) varied across trials using an adaptive staircase (detailed in Section 3.2.5). Both gratings had an outer diameter of 2°, a spatial frequency of 1.1 cycles/°, and always shared the same orientation, which varied from trial-to-trial in counterbalanced randomized instances of 0°, 45°, 90°, or 135° orientation. In a subset of stimulus conditions (see Table 3.2 and Figure 3.2), the target grating was presented within a larger (4° outer diameter) annular grating, referred to as the surround. The contrast of the surround was fixed at 100% and its spatial frequency and orientation were identical to the target grating. A 0.5° mean luminance 'gap' was placed between

the target grating and the surround grating to prevent brightness induction effects (see C. Yu, Klein, and Levi 2001; Schallmo, Sponheim, and Olman 2015) as well as to help the observers attend only to the central grating in making their judgments (Xing and Heeger 2001). The reference grating was always presented with no surround.

There were 3 experimental conditions: No Surround (NS), Orthogonal Surround (OS), and Parallel Surround (PS). See Figure 3.2 and Table 3.2 for details.

3.2.5 Paradigm

Participants completed the following visual tasks after a 3-hour wash-in period post drug administration. We chose the 3-hour timepoint because it roughly corresponds to the latter half of peak plasma concentration (Brown et al. 2017; Holze et al. 2022) and subjective effects (Carbonaro et al. 2018; Holze et al. 2022) of psilocybin, allowing participants to acclimate to peak subjective effects before starting the task.

We used a two-alternative forced-choice (2AFC) visual psychophysics task designed to measure the point of subjective equality (PSE) at which the difference in contrast between the target and reference gratings was imperceptible to the observer. Participants were asked to choose which circular grating appeared higher in contrast (target or reference, ignoring the surround). Each trial began with a fixation mark presented alone for 500 ms, after which the grating stimuli appeared on either side of fixation. Each trial ended when the participant made a key press to indicate which stimulus was higher contrast. Response time was not limited.

Two staircases per condition (target left and target right; 40 trials each) were presented in a randomized, intermixed order. The adaptive staircase (implemented using PsychoPy's (Peirce et al. 2019) default `StairHandler()` class configured with a one-up, one-down rule) adjusted the contrast of the reference grating on every trial in order to converge on the contrast level at which the observer produced 50% correct responses. See Figure 3.2.

To ensure task comprehension, subjects verbally confirmed their understanding of the task and completed 7 practice trials (one sample trial from each staircase plus one catch trial) before beginning the main experiment. In addition, 40 catch trials

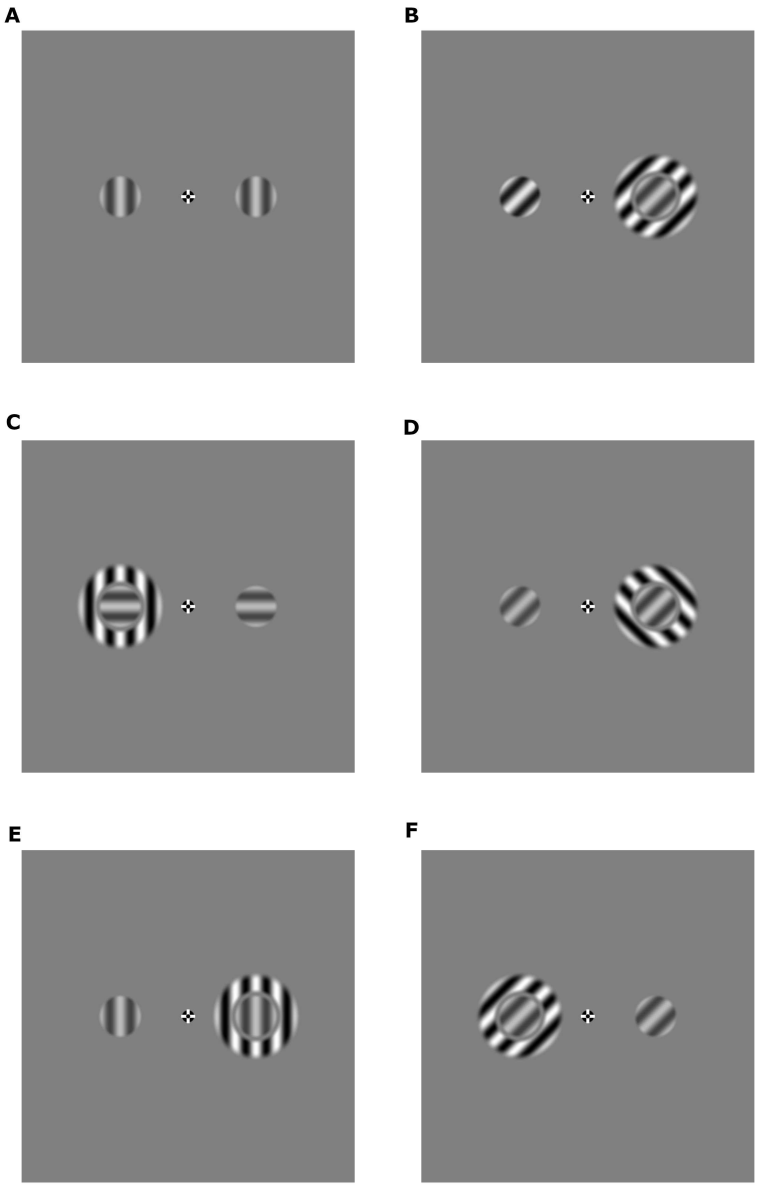

Figure 3.2: Samples of stimuli used in the experiment. **A** is an example of a trial from the no-surround staircases. **B** is an example of a catch trial, in which the reference stimulus appeared with 80% Michelson contrast. (**C-D**) are example trials from the orthogonal surround staircases. (**E-F**) are example trials from the parallel surround staircases.

Table 3.2: The six staircases comprising the three stimulus conditions. Forty trials of each type were presented during one full experimental run. An adaptive staircase dynamically adjusted the contrast of the reference stimulus on every trial. All trials from all staircases were presented intermixed and counterbalanced in random order. The target and surround stimuli were presented in four different orientations (0°, 45°, 90°, or 135°; ten trials of each orientation in each staircase) in random order.

Condition	**Target position**	**Surround**	**Example**	**N trials**
NS-L	left	absent	Figure 3.2 **A**	40
NS-R	right	absent	Figure 3.2 **A**	40
OS-L	left	orthogonal	Figure 3.2 **C**	40
OS-R	right	orthogonal	Figure 3.2 **D**	40
PS-L	left	parallel	Figure 3.2 **F**	40
PS-R	right	parallel	Figure 3.2 **E**	40

(large contrast difference, low difficulty) were included to assess off-task performance. Reference contrast in the catch trials was fixed at 80% (i.e., no staircase was used). Catch trial response accuracy was analyzed to ensure that the participant understood and performed the task correctly. See Section 3.3.2 for detailed catch trial results. Total task duration was approximately 30 minutes.

3.2.6 Subjective drug effects

The Altered States of Consciousness questionnaire (5D-ASC) scale (Dittrich 1998; Studerus, Gamma, and Vollenweider 2010) was used to assess the overall effects of drug on various elements of subjective experience. 5D-ASC is a well-validated 94-item self-rating visual analog scale (VAS) that assesses five "dimensions" of altered states of consciousness: (1) Oceanic Boundlessness, (2) Anxious Ego Dissolution, (3) Visionary Restructuralization, (4) Auditory Alterations and (5) Vigilance Reduction (Dittrich 1998). Studerus, Gamma, and Vollenweider (2010) used confirmatory factor analysis to identify 11 subscales of 5D-ASC (11D-ASC): (1) Experience of Unity, (2) Spiritual Experience, (3) Blissful State, (4) Insightfulness, (5) Disembodiment, (6) Impaired Control and Cognition, (7) Anxiety, (8) Complex Imagery, (9) Elementary Imagery, (10) Audio-Visual Synesthesia, and (11) Changed Meaning of Percepts. Both the

5D-ASC and its 11D-ASC subset are routinely used to assess subjective effects in studies that use psychedelic drugs (Studerus, Gamma, and Vollenweider 2010, 2010; Preller et al. 2017; Liechti, Dolder, and Schmid 2017; Carbonaro et al. 2018; Holze et al. 2019, 2020, 2022; Hirschfeld and Schmidt 2021). Importantly, the 5D-ASC detects the unique mind- and perception-altering effects of serotonergic psychedelic drug effects in particular, as it is sensitive enough to distinguish these from other psychoactive effects such as those produced by D-amphetamine or MDMA (Holze et al. 2020). Of particular interest to the present study is the 5D-ASC Visionary Restructuralization dimension and its 11D-ASC subscales (8) Complex Imagery, (9) Elementary Imagery, (10) Audio-Visual Synesthesia, and (11) Changed Meaning of Percepts, which are comprised of questions that assess alterations to visual experience.

All participants in this study completed all 94 items of the 5D-ASC questionnaire to retrospectively rate drug effects 24h after their psilocybin and placebo dosing sessions.

3.2.7 First-person written narratives

Participants submitted written 'digital journal' entries via webform in response to the following prompt 24 hours after each dosing session.

> Please fill out this digital journal to help us understand what your experience during the dosing session was like, from your perspective. In your own words, please spend 30-60 minutes writing about your experience during the testing session you participated in this week. This is similar to a "trip report" detailing the content of your experience, and any thoughts or feelings this experience brought up for you.

3.2.8 Statistical analyses

The point of subjective equality (PSE) for each observer was calculated independently for each of the six staircases by fitting a Logistic function to the response data.[4] Surround suppression illusion strength was quantified by subtracting the veridical

[4]We obtained the PSE threshold using the `data.FitLogistic()` and `data.functionFromStaircase()` functions provided by PsychoPy (Peirce and MacAskill 2018). Guess rate and lapse rate were set at 4%.

contrast of the target stimulus grating (50.0%) from the PSE value. Data from placebo and psilocybin sessions were analyzed separately, and then compared within participants. Differences in PSE values between psilocybin and placebo were compared in a repeated measures analysis of variance (ANOVA) using drug and stimulus condition as within-subjects factors. 5D-ASC ratings between psilocybin and placebo were compared in a repeated measures ANOVA using drug and ASC subscale/dimension as within-subjects factors. Both ANOVAs were followed-up with *post hoc* pairwise t test comparisons.

Correlation between PSE and 5D-ASC ratings were calculated using the rmcorr technique (Bakdash and Marusich 2017; Bland and Altman 1995a, 1995b) and followed up with pairwise biweight midcorrelation tests (Langfelder and Horvath 2012) using the difference (psilocybin minus placebo) for threshold and rating score pairs for each participant. We chose these methods because they do not require first averaging the data and avoid violating independence assumptions, making them ideal (and more sensitive) for paired repeated-measures data (Bakdash and Marusich 2017).

All statistical analyses were performed using the Pingouin package for Python (Vallat 2018). The criterion for significance was $p < 0.05$.

3.3 Results

To examine the impact of psilocybin on surround suppression of perceived contrast, we measured PSEs in observers under psilocybin and placebo in three stimulus conditions (NS, OS, PS; see Section 3.2 Figure 3.2, Table 3.2, and Table 3.1). In addition, we measured the subjective effects of psilocybin and placebo using the 5D-ASC psychometric instrument (see Section 3.2.6). The following subsections provide results from the different comparisons and correlations across these data points.

3.3.1 Effect of drug on PSE

Repeated measures ANOVA performed on the PSE values revealed a main effect of drug that reached significance ($F_{1,5} = 7.294$, $p = 0.043$, ${n_G}^2 = 0.128$). The main

Table 3.3: Results from a two-way repeated measures ANOVA comparing the effect of drug, stimulus condition, and their interaction on measured PSE values.

Source	Sum Sq.	df1	df2	Mean Sq.	F	p	ng2
drug	180.66	1	5	180.66	7.29	0.043	0.128
condition	759.56	2	10	379.78	8.82	0.006	0.381
drug * condition	73.67	2	10	36.84	3.00	0.095	0.056

effect of stimulus condition reached significance, consistent with surround suppression ($F_{2,10} = 8.822$, $p = 0.006$, $n_G{}^2 = 0.381$). The interaction effect of drug $\times$ condition did not reach significance; however, a notable trend effect was observed ($F_{2,10} = 3.0$, $p = 0.095$, $n_G{}^2 = 0.056$).

A Shapiro-Wilk test did not show evidence of non-normality in the placebo ($W = 0.983$, $p = 0.848$) or the psilocybin ($W = 0.971$, $p = 0.459$) PSE data.

Subsequent *post hoc* pairwise t test (two-sided) comparisons, in which the PSEs from all stimulus conditions were compared between psilocybin and placebo confirmed the significant ANOVA main effect of drug on PSE ($t_5 = 2.701$, $p = 0.043$, Bayes factor = 2.342). Further t test comparisons were performed using PSEs from each stimulus condition. For the No Surround (NS) condition, drug did not have a significant effect on PSE, indicating that psilocybin did not significantly impact general contrast perception when stimuli were presented without a surround ($t_5 = 0.665$, $p = 0.535$, Bayes factor = 0.446). *Post hoc* comparisons revealed a trend effect in the Orthogonal Surround (OS) condition ($t_5 = 2.467$, $p = 0.057$, Bayes factor = 1.905) and a trend effect in the Parallel Surround (PS) condition ($t_5 = 2.268$, $p = 0.073$, Bayes factor = 1.594).

Mean PSE data from psilocybin compared with placebo sessions indicate that psilocybin enhanced surround suppression. Mean PSE values were more negative under psilocybin (i.e., the strength of the illusion was greater, observers perceived contrast less veridically, compared with placebo) for the OS and PS, but not for the NS, stimulus conditions. Figure 3.3 **A** displays the magnitude of illusory suppression of PSE (defined as the PSE minus the target contrast of 50.0% Michelson contrast).

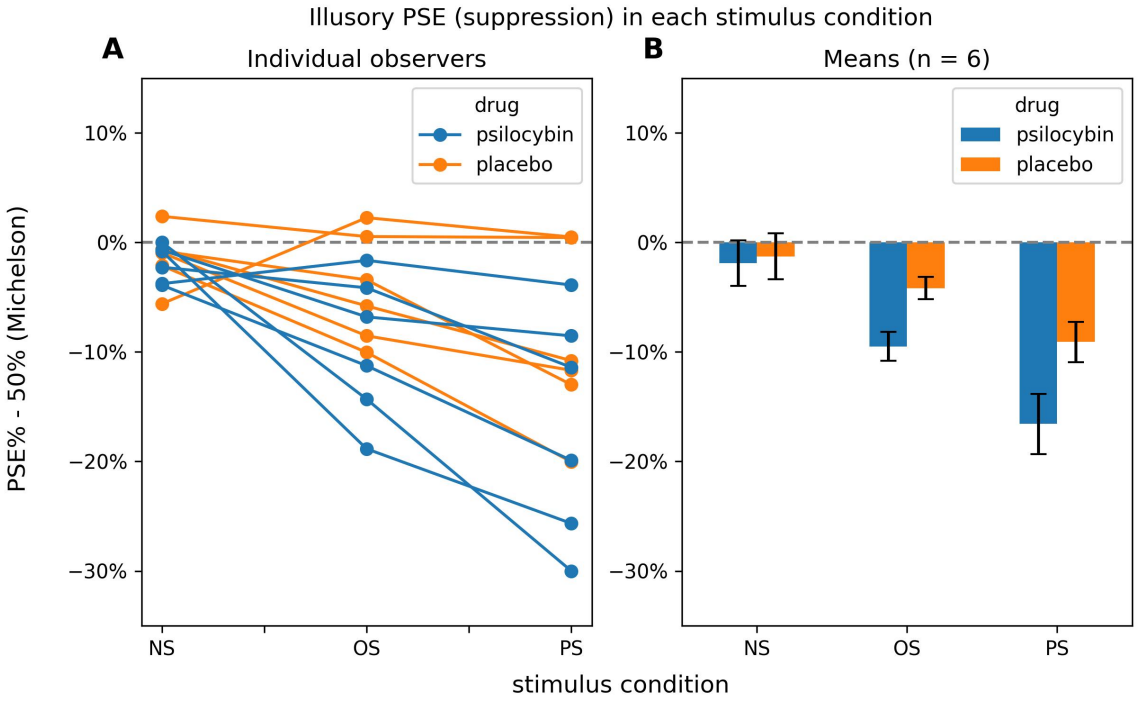

Figure 3.3: Surround suppression under psilocybin (blue) and placebo (orange), shown as the difference between observers' PSEs and the veridical contrast of the target stimulus (PSE minus 50.0%) for the No Surround (NS), Orthogonal Surround (OS), and Parallel Surround (PS) stimulus conditions. Panel **A** shows suppression for individual observers in each stimulus condition. Panel **B** shows means that have been normalized according to the technique in Morey (2008) for within-subjects data. Error bars represent standard error of the mean (SEM).

Table 3.4: Mean PSEs in each stimulus condition measured under psilocybin and placebo.

	mean ± SEM	
	placebo	**psilocybin**
condition		
NS	48.732 ± 2.102	48.105 ± 2.086
OS	45.844 ± 1.033	40.507 ± 1.322
PS	40.914 ± 1.854	33.437 ± 2.748

The PSE thresholds measured in the no-surround (NS) condition fell close to the target stimulus veridical value of 50.0% Michelson contrast. Importantly, this was true for placebo (NS = 48.73% contrast) as well as for psilocybin (NS = 48.1% contrast), suggesting that psilocybin did not significantly impact perceived contrast when no surrounding stimuli were present. We further confirmed this using a two-sided paired t-test, which found no significant differences between psilocybin and placebo in the no-surround (NS) condition (t_5 = -0.6655, p = 0.5352, d = 0.2876). This supports the notion that the trends we observed in the OS and PS surround conditions are the result of psilocybin's selective impact on center-surround interactions and not due to other perturbations in contrast discrimination, motor function, or cognitive functions.

For the orthogonal surround (OS) condition under placebo, the presence of the surround stimulus reduced the mean PSE by approximately 4.16% contrast (suppressing the perceived contrast from veridical 50.0% contrast to a mean PSE of 45.84% contrast). Under psilocybin, the magnitude of OS suppression was larger than placebo—the orthogonal surround reduced the mean PSE by approximately 9.5% contrast (suppressing the perceived contrast from veridical 50.0% contrast to a mean PSE of 40.5% contrast).

For the parallel surround (PS) condition under placebo, the presence of the surround stimuli reduced the mean PSE by approximately 9.09% contrast (suppressing the perceived contrast from veridical 50.0% contrast to a PSE of 40.91% contrast). Under psilocybin, the magnitude of PS suppression was larger than placebo—the parallel surround reduced the mean PSE by approximately 16.57% contrast (suppressing the perceived contrast from veridical 50.0% contrast to a mean PSE of 33.43% contrast).

The effect of psilocybin on PSE for each stimulus condition was quantified as the psilocybin PSE minus the placebo PSE. The mean effect of psilocybin was a shift in the PSE of -7.48% contrast in the parallel surround (PS) condition and -5.34% contrast in the orthogonal surround (OS) condition. By comparison, when stimuli were presented with no surrounds (NS), the difference in the PSE from placebo to psilocybin was -0.63%. Figure 3.4 summarizes our results in terms of the effect of psilocybin on PSE (drug minus placebo) for each stimulus condition. These results

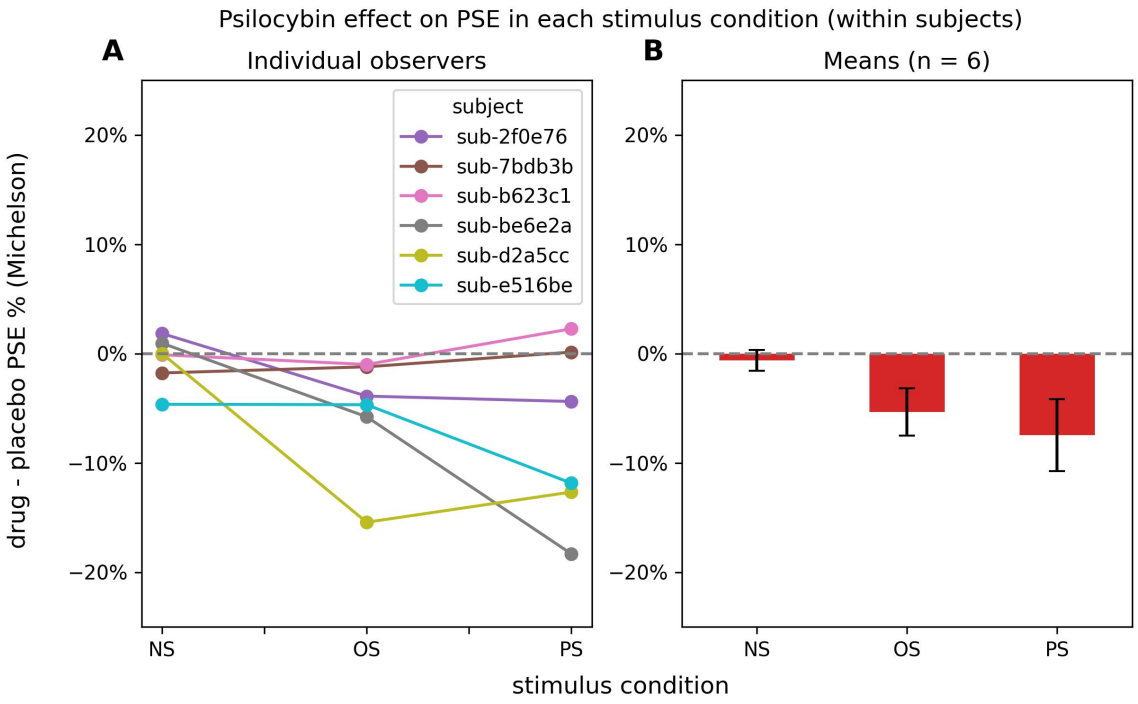

Figure 3.4: Within-subjects effects of the drug were calculated by subtracting the PSE measured under placebo from the PSE measured under psilocybin for each stimulus condition. Panel **A** shows the effect of psilocybin on PSE for each individual observer. Panel **B** shows the mean effect for each stimulus condition. Error bars represent standard error of the mean (SEM).

suggest that psilocybin enhanced the magnitude of visual surround suppression while general contrast discrimination remained unaffected by the drug.

3.3.2 Catch trials

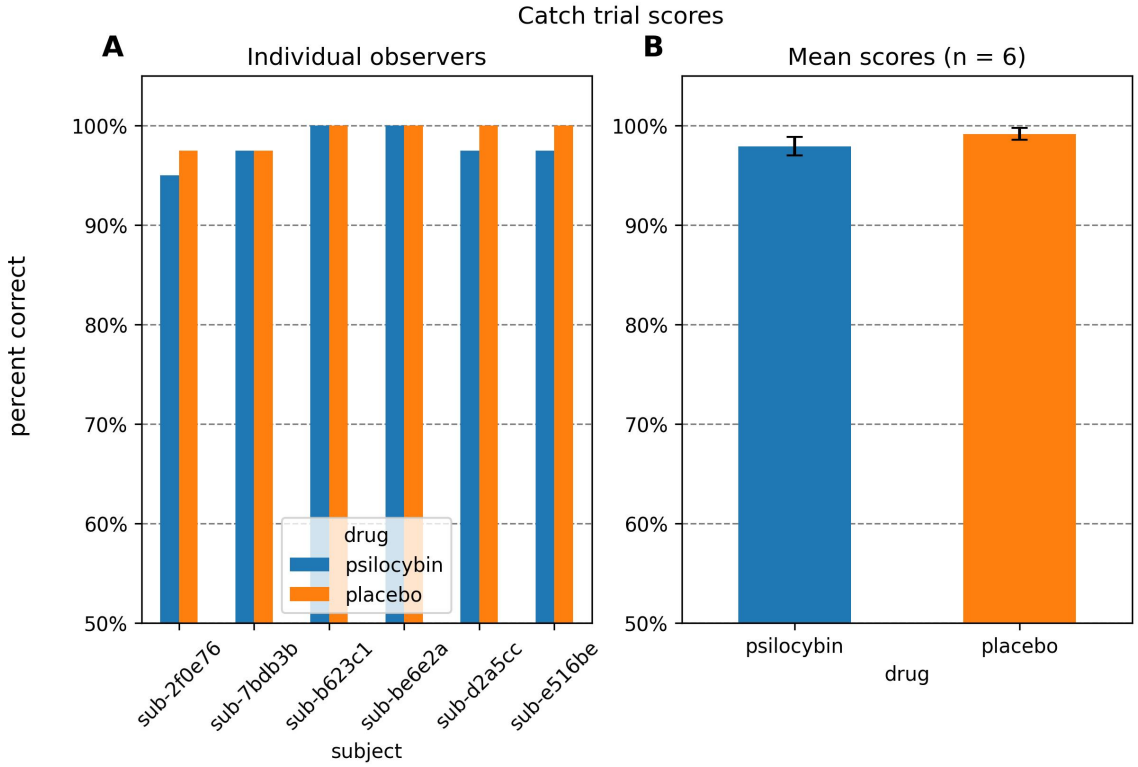

Figure 3.5: Catch trial scores. Values represent the percentage of correct responses to 40 catch trials. **A**: Catch trial scores for each individual observer. **B**: Mean catch trial scores. Error bars represent standard error of the mean (SEM).

Each observer completed 40 'catch' trials intermixed with all of the other trails under both placebo and psilocybin (see Section 3.2 and Figure 3.2 **F**). Catch trials—contrast discrimination tasks with very low difficulty—were used to measure whether the observer was completing trials with sufficient attention, understanding of the task, and ability to judge visual contrast at a basic level.

Catch trial accuracy was high in both placebo (mean = 99.17%, SD = 1.29%) and drug sessions (mean = 97.92%, SD = 1.88%); paired t-test (two-sided), $t_5 = 2.24$, $p = 0.08$—indicating that psilocybin did not significantly interfere with the participants' ability to perform the task correctly. Figure 3.5 summarizes the results of catch trials.

3.3.3 Subjective effects of drug

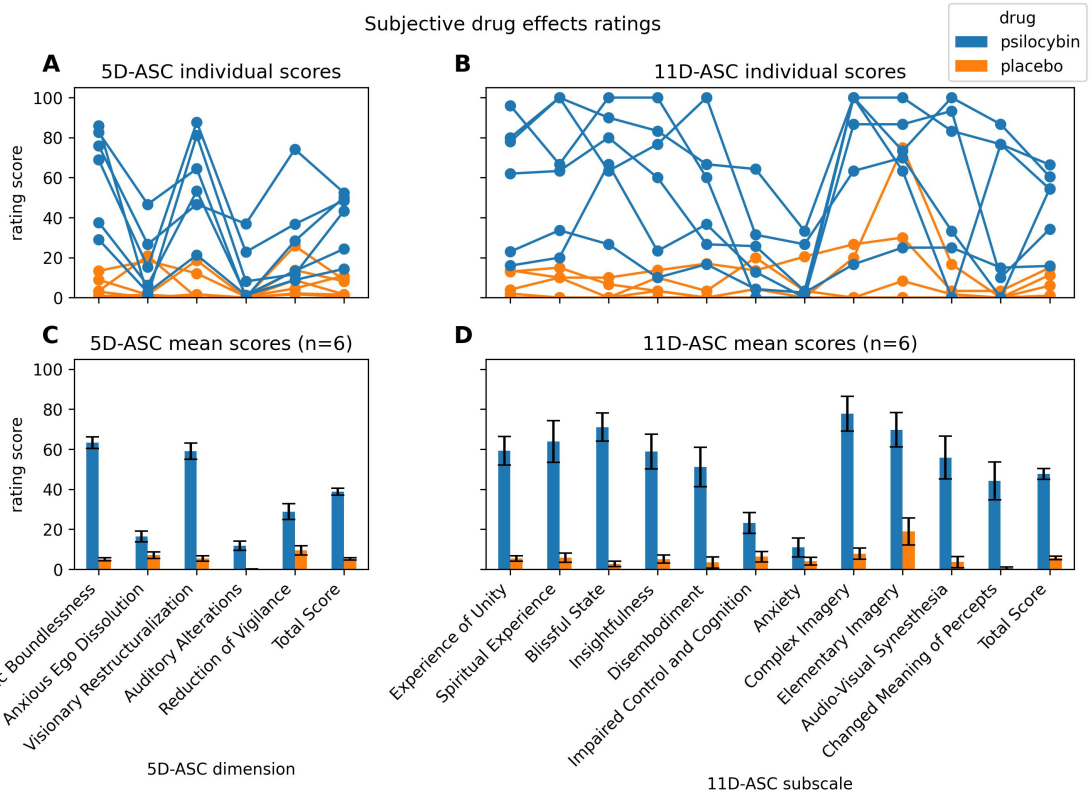

Figure 3.6: Subjective effects of drug as measured by the 5-Dimensional Altered States of Consciousness (5D-ASC) scale and its lower-level 11D-ASC subscales. Panels **A** and **B** show individual participant rating scores for 5D-ASC dimensions and 11D-ASC subscales, respectively, in reference to their psilocybin (blue lines) and placebo (orange lines) dosing sessions. Panels **C** and **D** show mean scores. Error bars represent standard error of the mean (SEM). *Post hoc* pairwise comparisons of scores under each drug revealed significant ($p < 0.05$) differences for the 5D-ASC dimensions Oceanic Boundlessness and Visionary Restructuralization; and the 11D-ASC subscales Blissful State, Spiritual Experience, Complex Imagery, Experience of Unity, Insightfulness, Disembodiment, Audio-Visual Synesthesia, Changed Meaning of Percepts, and Elementary Imagery.

Psilocybin produced robust effects on subjective experience, as indicated by a significant main effect of drug ($F_{1,5} = 20.109$, $p = 0.006$, $\mathrm{n_G}^2 = 0.518$) in a repeated measures (drug × subscale) ANOVA on 5D-ASC score. There was also a significant main effect of subscale ($F_{4,20} = 14.051$, $p < 0.001$, $\mathrm{n_G}^2 = 0.364$) and a significant drug × subscale interaction ($F_{4,20} = 8.484$, $p < 0.001$, $\mathrm{n_G}^2 = 0.342$). Subsequent *post hoc* pairwise comparisons revealed significantly ($p < 0.05$) higher ratings under psilocy-

bin compared with placebo for the 5D-ASC dimensions Oceanic Boundlessness and Visionary Restructuralization. When comparing along the lower-level 11D subscales (see Section 3.2.6), significant ($p < 0.05$) differences were found for scores in Blissful State, Spiritual Experience, Complex Imagery, Experience of Unity, Insightfulness, Disembodiment, Audio-Visual Synesthesia, Changed Meaning of Percepts, and Elementary Imagery, affirming that psilocybin produced marked alterations of mind and perception. See Figure 3.6 for data visualization.

3.3.4 Subjective drug effects and PSE

Next, we asked whether the magnitude of surround suppression correlated in with the intensity of the psychedelic effects reported by the participants. To assess correlation between rating scale scores and PSEs, we used repeated measures correlation (rmcorr), "a statistical technique for determining the common within-individual association for paired measures assessed on two or more occasions for multiple individuals" (Bakdash and Marusich 2017; Bland and Altman 1995a, 1995b).[5] We performed rmcorr analyses by pairing each participant's PSE thresholds with their 5D-ASC ratings of subjective effects from each dosing session. Rmcorr allowed us to assess the links between surround suppression and particular subjective drug effects in a drug-agnostic fashion, regardless of which drug (psilocybin or placebo) induced the effects. We reasoned that such an analysis would be informative, given that the subjective effects of psilocybin span perceptual, emotional, and cognitive domains (Studerus, Gamma, and Vollenweider 2010; Carbonaro et al. 2018; Holze et al. 2022) and can be dependent on many extra-pharmacological factors (Studerus et al. 2012).

On the 5D-ASC scale, rmcorr revealed statistically significant inverse correlations between PSEs and 5D-ASC scores for the data points (OS, Visionary Restructuralization) (r = -0.856, p = 0.014) and (PS, Visionary Restructuralization) (r = -0.836, p = 0.019); higher rating scores (more intense subjective drug effect) were associated

[5] "Rmcorr accounts for non-independence among observations using analysis of covariance (ANCOVA) to statistically adjust for inter-individual variability. By removing measured variance between-participants, rmcorr provides the best linear fit for each participant using parallel regression lines (the same slope) with varying intercepts" (Bakdash and Marusich 2017).

Table 3.5: Results from rmcorr repeated measures within-participants correlation of PSE threshold and ASC subscale scores under psilocybin and placebo.

condition	subscale	dof	r	pval
OS	**Visionary Restructuralization**	5	-0.856	0.014
	Elementary Imagery	5	-0.824	0.023
	Audio-Visual Synesthesia	5	-0.822	0.023
	Complex Imagery	5	-0.770	0.043
	Changed Meaning of Percepts	5	-0.759	0.048
PS	**Audio-Visual Synesthesia**	5	-0.942	0.001
	Visionary Restructuralization	5	-0.836	0.019
	Elementary Imagery	5	-0.802	0.030
	Complex Imagery	5	-0.784	0.037
	Blissful State	5	-0.772	0.042
	Changed Meaning of Percepts	5	-0.757	0.049

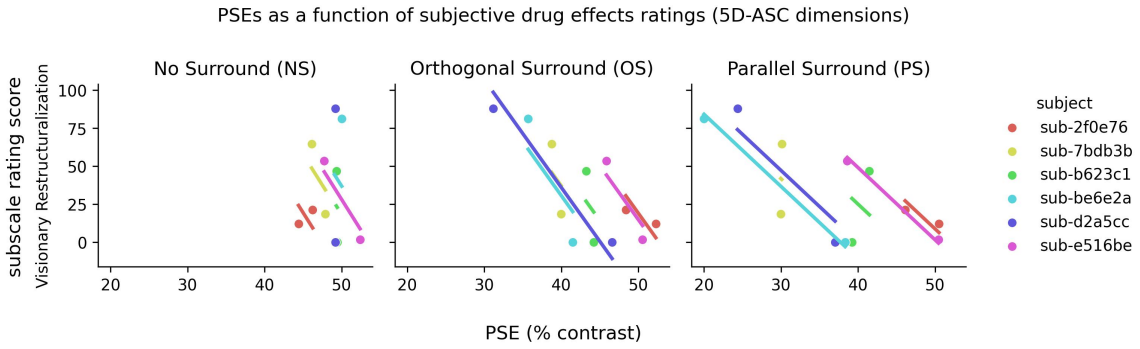

Figure 3.7: Rmcorr plot showing each individual's 5D-ASC dimension scores from placebo and psilocybin as a function of their PSE thresholds in each stimulus condition. The lines show the rmcorr slope fit in relation to each participant's data points.

with greater surround suppression (lower PSEs). At the level of 5D-ASC dimensions, PSE did not significantly correlate with any other type of subjective effects, nor with the overall Total Score.

We performed an additional rmcorr analysis using the 11D-ASC scoring method (Studerus, Gamma, and Vollenweider 2010), which includes eleven lower-level subscales comprised of items from three of the five dimensions of the 5D-ASC scale (see Methods section 3.2.6). This analysis revealed significant inverse correlations at the data points (PS, Audio-Visual Synesthesia) (r = -0.942, p = 0.001), (OS, Elementary Imagery) (r = -0.824, p = 0.023), (OS, Audio-Visual Synesthesia) (r = -0.822, p = 0.023), (PS, Elementary Imagery) (r = -0.802, p = 0.03), (PS, Complex Imagery) (r = -0.784, p = 0.037), (PS, Blissful State) (r = -0.772, p = 0.042), (OS, Complex Imagery) (r = -0.77, p = 0.043), (OS, Changed Meaning of Percepts) (r = -0.759, p = 0.048), and (PS, Changed Meaning of Percepts) (r = -0.757, p = 0.049). Taken together, these results indicate that, only for these specific 11D-ASC subscales, higher rating scores (more intense subjective drug effect) were associated with greater surround suppression (lower PSEs in the OS or PS, but not the NS, stimulus conditions).

For each correlation that reached significance in the rmcorr analysis, subsequent *post hoc* pairwise correlations were performed using robust biweight midcorrelation (Langfelder and Horvath 2012) on the (psilocybin minus placebo) difference values for each data point, which reached significance for the data points (PS, Audio-Visual Synesthesia) (r = -0.898, p = 0.008) and (PS, Complex Imagery) (r = -0.732, p = 0.049). The data points for (OS, Visionary Restructuralization) (r = -0.645, p = 0.084), (PS, Visionary Restructuralization) (r = -0.633, p = 0.089), (OS, Elementary Imagery) (r = -0.618, p = 0.095), (OS, Audio-Visual Synesthesia) (r = -0.704, p = 0.059), (PS, Elementary Imagery) (r = -0.584, p = 0.112), (PS, Blissful State) (r = -0.524, p = 0.143), (OS, Complex Imagery) (r = -0.598, p = 0.105), (OS, Changed Meaning of Percepts) (r = -0.439, p = 0.192), and (PS, Changed Meaning of Percepts) (r = -0.458, p = 0.18) did not reach significance in the post-hoc biweight midcorrelation tests. This discrepency is not unexpected, as rmcorr is considered more sensitive than other available correlations when using within-participants repeated-measures data

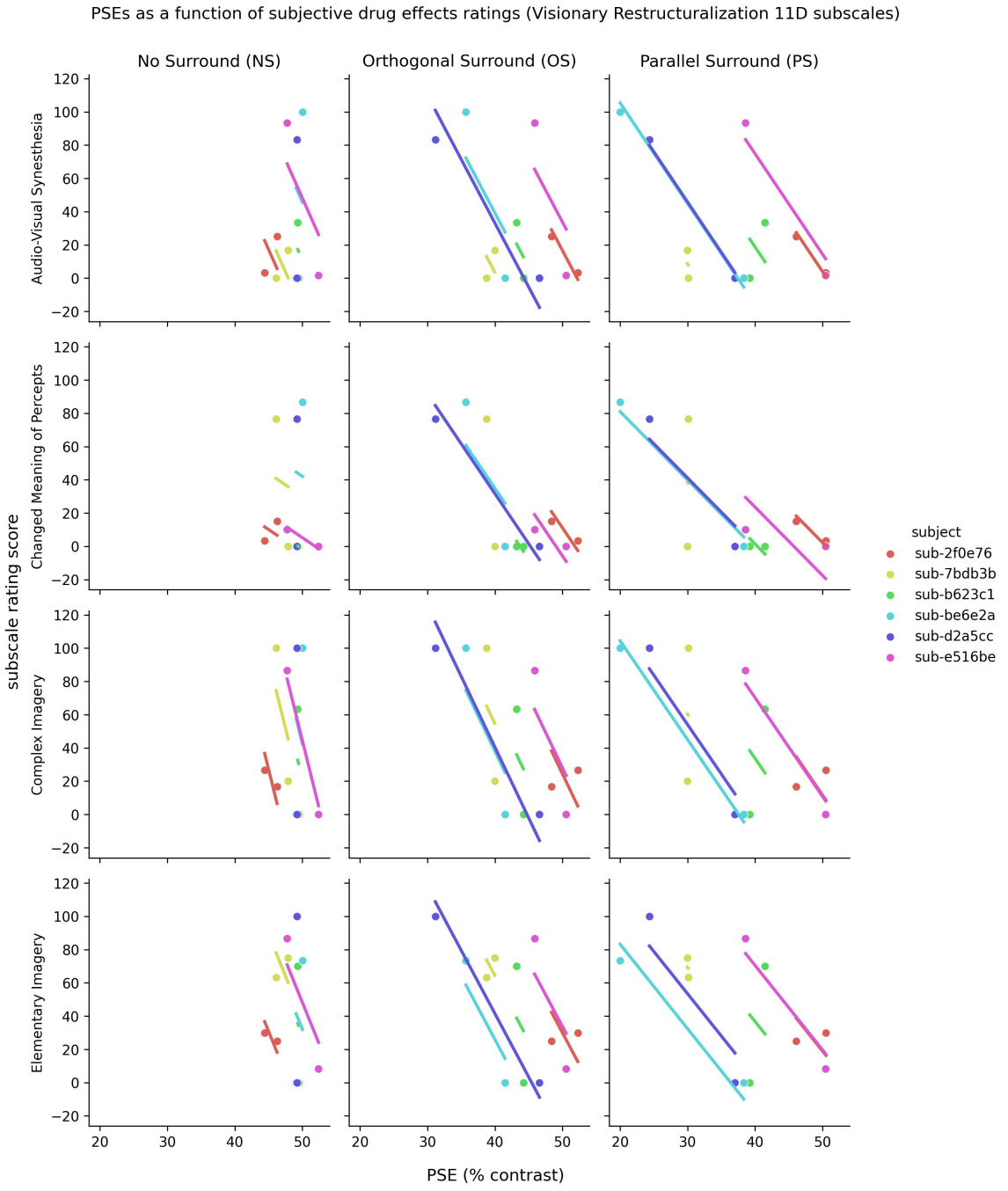

Figure 3.8: Rmcorr plot showing PSE as a function of subjective drug effects rating scores on subscales from the Visionary Restructuralization dimension for each subject in each stimulus condition. The lines show the rmcorr slope fit in relation to each participant's two data points (placebo and psilocybin).

Table 3.6: Questionnaire items from subscales in the Visionary Restructuralization dimension that reached significant correlation with at least one stimulus condition in the rmcorr analysis. Mean scores for placebo (Pla) and psilocybin (Psil) are shown in the right-hand columns.

subscale	item	**text**	**Pla**	**Psil**
Visionary Restructuralization	7	I saw things I knew were not real.	0	83
	58	Things came to my mind that I thought long forgotten.	2	47
	70	Many things seemed incredibly funny to me.	0	73
	77	I had very original thoughts.	2	50
	83	Things in my surroundings appeared smaller or larger.	0	33
	90	I was able to remember certain events with exceeding clarity.	1	35
Audio-Visual Synesthesia	20	Sounds seemed to influence what I saw.	9	72
	23	Shapes seemed to be changed by sounds or noises.	2	52
	75	The colors of things seemed to be altered by sounds or noises.	0	44
Changed Meaning of Percepts	28	Some everyday things acquired special meaning.	2	44
	31	Things in my environment had a new strange meaning.	0	35
	54	Objects in my surroundings engaged me emotionally much more than usual.	0	53
Complex Imagery	39	I saw whole scenes roll by with closed eyes or in complete darkness.	5	85
	72	I could see images from my memory or imagination with extreme clarity.	9	63
	82	My imagination was extremely vivid.	9	85
Elementary Imagery	14	I saw regular patterns with closed eyes or in complete darkness.	20	82
	22	I saw colors with closed eyes or in complete darkness.	22	83
	33	I saw brightness or flashes of light with closed eyes or in complete darkness.	14	44

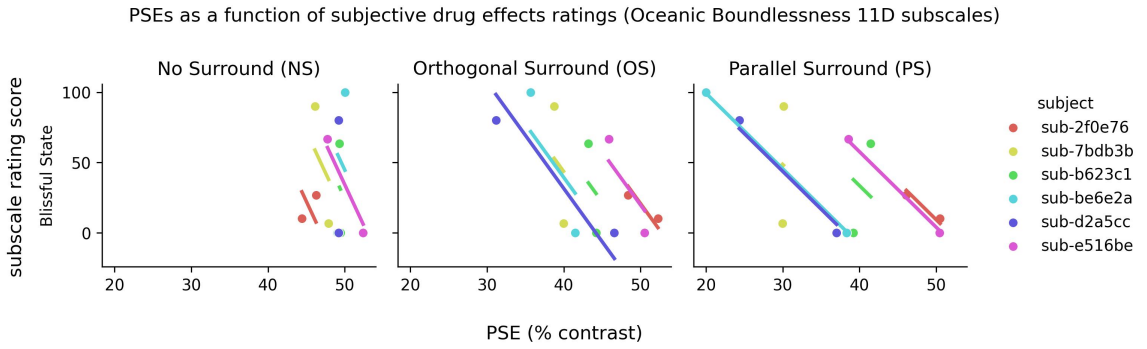

Figure 3.9: Rmcorr plot showing PSE as a function of subjective drug effects rating scores on subscales from the Oceanic Boundlessness dimension for each subject in each stimulus condition. The lines show the rmcorr slope fit in relation to each participant's two data points (placebo and psilocybin).

Table 3.7: Questionnaire items from subscales in the Oceanic Boundlessness dimension that reached significant correlation with at least one stimulus condition in the rmcorr analysis. Mean scores for placebo (Pla) and psilocybin (Psil) are shown in the right-hand columns.

subscale	item	**text**	**Pla**	**Psil**
Blissful State	12	I experienced boundless pleasure.	2	58
	86	I experienced profound inner peace.	3	75
	91	I experienced an all-embracing love.	3	80

(Bakdash and Marusich 2017).

3.3.5 Qualitative first-person narratives

The following sections are excerpts from the digital journal entries of participants (see Methods Section 3.2.7), provided for supplementary insight into the subjective effects of the drug.

3.3.5.1 Performing the visual task under peak psilocybin effects

Many participants shared descriptions of what it was like to complete the visual psychophysics task at the computer screen under peak effects of the drug. A few participants reported that the computer monitor appeared to them overlaid with psychedelic visuals or that the stimuli appeared more "visually interesting" or with "much more humor" or even that the computer screen appeared "beautiful" under psilocybin.

Interestingly, a few participants shared that in spite of these perceptual changes, they were nonetheless able to perform the task without much additional difficulty.

> I recall seeing shapes moving in a circular pattern in the grayscale background of the monitor. Recording answers of which circle had a higher contrast than the other had much more humor to the process than when performed previously, but I did not feel a definitive level of increased ease or difficulty with the task itself.
>
> —Participant `sub-2f0e76`

> When I took the tests on the computer [during the placebo session] they were not nearly as visually interesting [as the psilocybin session].
>
> —Participant `sub-be6e2a`

> I never look at screens while tripping so this was a fun experience. ... [the stimuli were] moving and breathing slightly ... This was enjoyable and common for me.
>
> —Participant `sub-d2a5cc`

> I remember seeing an intricate web of geometric patterns and shapes very lightly woven into the background of the computer screen when I was looking at it ... geometric mandala type grid ... made the testing more interesting. I recall

> feeling like there was more contrast between the testing circles/rings and the background of the screen. I felt like there was more depth between the images and the background and I noticed more separation between the rings and the inner circles when they came up together. I also had instances where the black lines would suddenly pop more on certain circles and could see some of the color bleeding between the lines or outside the circle.
>
> —Participant `sub-d2a5cc`

Some participants shared that, while they were able to perform the contrast-matching task, the psychedelic visuals and other subjective effects tended to distract their attention away from the task at hand.

> The testing was strangely tolerable and the screen was beautiful. The shaded circles were completely fixed but everything around them swirled—they looked like portals. Staying focused on the task was challenging and I was continuously sucked into the world around the circles and losing my sense of self to a point where I became worried that it was getting so deeply immersive that I wouldn't be able to come back ... I would frequently become absorbed in the swirly goo—losing myself and forgetting about the task at hand.
>
> —Participant `sub-7bdb3b`
>
> I started worrying that I wouldn't be able to perform the test. I couldn't picture myself moving or sitting down, and holding on to consciousness seemed really difficult ... I had to read and think about the instructions, to remind myself which finger was which. ... I could see a honey comb pattern in the blank screen, and I saw wiggly neon lines on the outer striped circles. Fun to look at, but made the test difficult.
>
> —Participant `sub-b623c1`

It was common for participants to see psychedelic visuals within the mean gray background of the stimulus presentation, consistent with previous visual psychophysics studies conducted under peak psilocybin effects, as Carter, Pettigrew, et al. (2005) report: "Subjects reported that the computer keyboard and monitor generally remained stable while dynamic textures and patterns would sometimes be seen both within the background grey component of the display and the target stimulus" (Carter, Pettigrew, et al. 2005). Nearly a century earlier, Klüver (1926), under mescaline, noted this phenomena when viewing paper stimuli: "During the experiment the gray background was covered most of the time with ever-changing designs in various forms and color."

Notwithstanding the ongoing open-eyed psychedelic visuals that pervaded their perceptual field during the contrast-matching task, all participants completed the task in a reasonable timeframe and with accuracy comparable to that of their placebo session. Importantly, our psychophysics data suggest that psilocybin did not adversely impair task performance becase: (1) scores on catch trials were highly accurate under psilocybin (mean = 97.92%, SD = 1.88; see Section 3.3.2), (2) contrast judgments in the NS condition under psilocybin were near-veridical and not significantly different from placebo (Figure 3.3), and (3) surround suppression in the OS and PS conditions under psilocybin is proportionate to, albeit stronger than, the placebo data (Figure 3.3).

3.3.5.2 Audio-visual synesthesia, elementary, and complex imagery

Three of the six participants noted that their visual experiences responded dynamically to music[6]—i.e., the subjective effect measured by the 11D-ASC subscale Audio-Visual Synesthesia. Moreover, the below phenomenological descriptions also include attributes of 11D-ASC subscales Elementary Imagery, Complex Imagery, and Changed Meaning of Percepts (see Table 3.6).

> ... sometimes I think the [music] tracks created or guided the scenes that I was seeing.
>
> —Participant `sub-b623c1`

> ... the psychedelic tapestry was alive, mushroom gills taking breaths, paisleys swirling in and out, fronds growing and then shrinking back down. When I covered my eyes again, I could see colors swirling and pulsating in rhythm with the music. Always a type of abstract landscape, different with every song. So many emotions overtook me—this was a very cathartic experience.
>
> —Participant `sub-be6e2a`

> The music was a big driver of my experience as I felt emotionally connected to each song and had strong visuals in my mind that were directed by the music. It felt very cinematic and I thought of things like Fantasia, where the art is tied to each song and there is a mix of specific images and almost narrative structure as well as purely abstract colors and shapes ... it felt very beautiful and magical to me.

[6]Participants did not listen to music during the psychophysics task.

—Participant `sub-d2a5cc`

> . . . the music that I was hearing was spectacularly radiant, captivating and I was completely riveted to every song that came next. I'm not sure which came first, the visions or the tears, but both were plentiful.
>
> —Participant `sub-be6e2a`

Interestingly, we found that surround suppression PSE values correlated with 11D-ASC scores that measure several of the elements in the above phenomenological accounts; namely, Audio-Visual Synesthesia, Elementary Imagery, Complex Imagery, and Changed Meaning of Percepts (see Section 3.3.4 for quantitative statistical analysis).

3.4 Discussion

We examined the extent to which the psychedelic 5-HT_{2A} agonist psilocybin impacted surround suppression using a contrast discrimination task in healthy observers. Our results, while preliminary and limited by the small sample size of our pilot study, indicate that psilocybin enhanced visual surround suppression. Furthermore, we found that the magnitude of visual surround suppression correlated with intensity of subjective psychedelic visuals significantly more than other subjective drug effects.

3.4.1 Psilocybin, surround suppression, and visual context processing

We found that surrounding stimuli had a greater influence on the perceived contrast of a center stimulus under psilocybin compared with placebo. During peak effects of psilocybin, the strength of the illusion was greater (observers perceived the apparent contrast of the center stimulus less veridically). We did not find strong evidence to suggest that this effect depends on stimulus orientation—when the surround had a parallel (collinear) orientation to the center, the effect of psilocybin on suppression was only slightly greater than when the surround orientation was orthogonal (see Figure 3.4).

Importantly, psilocybin reduced PSEs only on the trials that presented a surround——contrast discrimination remained largely unaffected by psilocybin in the No Surround (NS) condition. This suggests that psilocybin's impact on vision may be restricted to modulations in mechanisms that underpin processing of *visual context*, specifically. Moreover, on catch trials—where the reference grating was presented within a surround, but the target grating was fixed at 80% contrast—psilocybin did not significantly impair task performance (see Section 3.3.2 and Figure 3.2).

Taken together, our findings suggest that psilocybin may specifically impact processing of contextual stimuli in the visual system. This interpretation is consistent with previous findings from Carter et al. (2004), who used a psychophysical motion processing experiment conducted under peak effects of psilocybin and concluded that psilocybin "impairs high-level but not low-level motion perception". However, an alternative interpretation of the 'impaired' high-level motion processing in Carter et al. (2004) is that psilocybin *amplified the processing of contextual information* in the visual motion stimuli, which is supported by the observation that "a number of subjects commented that subjectively the global motion task became harder due to an increased salience of the randomly moving dots" leading the authors to note that this raises "the question of whether the coherent motion deficit induced by the psilocybin reflects a reduction in sensitivity to motion signals or reduced inhibition of the non-coherent motion signals" (Carter et al. 2004). In other words, increased influence of visual context, consistent with our results as well as with observations of how psilocybin impacts other domains of mental function (Carhart-Harris, Roseman, et al. 2018).

3.4.2 Serotonin, divisive normalization, and surround suppression

Our findings indicate that serotonergic neuromodulation may be a critical mechanism enabling visual surround suppression in everyday vision. Furthermore, consistent with recent findings (Azimi et al. 2020), our results suggest that serotonin systems play a

role in divisive normalization (Heeger 1992), a canonical neural computation linked to a wide range of contextual functions in perception and cognition, including suround suppression (Schallmo et al. 2018). Azimi et al. (2020) combined optogenetics, wide-field optical imaging, electrophysiology, and pharmacological manipulations to demonstrate that "5-HT_{1A} receptors promote divisive suppression of spontaneous activity, while 5-HT_{2A} receptors act divisively on visual response gain and largely account for normalization of population responses over a range of visual contrasts" (Azimi et al. 2020). Linking psychedelic drug effects to altered neural divisive normalization processes via perturbations in serotonergic signaling offers a novel unified explanation for why psychedelics impact both perception and cognition in the way that they do: divisive normalization is at play in many brain functions, including visual context processing (Schallmo et al. 2018), auditory spectrotemporal contrast (Rabinowitz et al. 2011), multisensory integration (Ohshiro, Angelaki, and DeAngelis 2011), perceptual attention (Reynolds and Heeger 2009), and context-dependent decision making (Louie, Khaw, and Glimcher 2013). We note that the subjective effects of psychedelic drugs involve qualitative shifts in nearly all mental functions currently modeled by divisive normalization.

3.4.3 Surround suppression and psychedelic visual phenomenology

Scores in the Visionary Restructuralization dimension correlated significantly with magnitude of surround suppression in the OS condition (when the orientation of the surround grating was orthogonal to the center grating; see Figure 3.2). We note that this correlation was found exclusively for the Visionary Restructuralization dimension. Interestingly, the Oceanic Boundlessness dimension had the highest mean scores for psilocybin, as well as the largest difference in score between psilocybin and placebo, yet surround suppression did not significantly correlate with this dimension. Similarly, the 5D-ASC Total Score was not predictive of the magnitude of surround suppression. Taken together, these findings indicate that the subjective effects measured by the

Visionary Restructuralization dimension (see Table 3.6) arise concomitantly with visual surround suppression (Figure 3.7). This finding suggests that there is a link between surround suppression, serotonergic signaling, and the phenomenology of classic 'psychedelic visuals' induced by psilocybin.

The 11D-ASC scoring defines four lower-level subscales from items in the Visionary Restructuralization dimension, namely: Audio-Visual Synesthesia, Changed Meaning of Percepts, Elementary Imagery, and Complex Imagery (refer to Table 3.6 for a complete list of items in the Visionary Restructuralization dimension). These subscales are of interest to the present study. The Audio-Visual Synesthesia subscale includes the items "Sounds seemed to influence what I saw", "Shapes seemed to be changed by sounds or noises", and "The colors of things seemed to be altered by sounds or noises". Intriguingly, Audio-Visual Synesthesia scores correlated strongly with magnitude of surround suppression in both the OS and PS conditions; furthermore, correlation in the PS condition was far stronger than that of the other significant correlations and was confirmed in robust biweight midcorrelation tests. How should we interpret this finding? Speculatively, this finding indicates that psilocybin might induce a hypersensitivity to contextual cues from the visual context in the stimulus (the surround) as well as from contexts outside of vision (sounds, noises). It also provides some evidence that perceptual context processing, including visual surround suppression, is influenced by serotonergic neuromodulation.

The Elementary Imagery subscale includes "I saw [regular patterns/colors/brightness or flashes of light] with closed eyes or in complete darkness". Rmcorr revealed significant correlations between the Elementary Imagery rating scores and surround suppression in both the OS and PS conditions. Weaker correlations were found with items in the Complex Imagery subscale, which includes the items "I saw whole scenes roll by with closed eyes or in complete darkness," "I could see images from my memory or imagination with extreme clarity," and "My imagination was extremely vivid". Taken together, the correlations we found suggests that the neural processes leading to enhanced surround suppression under peak effects of psilocybin are linked with the characteristic psychedelic visual effects of the drug.

The Changed Meaning of Percepts subscale includes the items "Some everyday things acquired special meaning", "Things in my environment had a new strange meaning", and "Objects in my surroundings engaged me emotionally much more than usual". Higher ratings in this scale were significantly correlated with greater magnitude of surround suppression in the PS condition. This finding suggests that psilocybin-induced changes in visual context processing span from the cognitive-perceptual ("Things in my environment had a new strange meaning") to the emotional ("Objects in my surroundings engaged me emotionally") to the most basic visual functions—i.e., surround suppression of visual contrast, as measured by our psychophysical task. Considered alongside the Audio-Visual Synesthesia correlations, this finding lends further support to the idea that psilocybin selectively modulates contextual processing concomitantly with subjective effects. Our finding that surround suppression correlated with the Changed Meaning of Percepts subscale in particular may have implications for understanding how psilocybin works to treat major depressive disorder.

3.4.4 Depression, surround suppression, and psilocybin

Psilocybin-assisted psychotherapy has recently shown promise in the treatment of major depressive disorder (MDD) (Davis et al. 2021; Ross et al. 2016; Griffiths et al. 2016; Carhart-Harris, Bolstridge, et al. 2018; Gukasyan et al. 2022). Davis et al. (2021) found "substantial rapid and enduring antidepressant effects of psilocybin-assisted therapy among patients with MDD." However, the exact mechanisms are unclear, and current debate is centered around the question of which subjective psychedelic effects (if any) are critically involved in positive clinical outcomes—some teams strongly emphasize the critical role of mystical-type experiences (Griffiths et al. 2016; Ross et al. 2016) while others question the importance of mystical experiences (Letheby 2021). Meanwhile, some researchers (and corporations) hope to discover novel drugs that could deliver psilocybin's antidepressant effect without producing hallucinogenic effects (McClure-Begley and Roth 2022; Berg et al. 2022). The role of psychedelic visuals receives little attention or is downplayed (Letheby 2021). Roseman, Nutt, and Carhart-Harris (2017) found that positive MDD treatment outcomes did

correlated with intensity visual effects measured with the 5D-ASC or 11D-ASC, but not as strongly as the effects measured by the Blissful State dimension. However, the use of eyeshades in Roseman, Nutt, and Carhart-Harris (2017) placed limits on measuring the subjective effects on *open-eyed* visual perception. Our findings warrant further investigation into the links between psilocybin's visual effects and its antidepressant properties.

During major depressive episodes (MDEs), MDD patients in previous studies show *weakened* surround suppression (Golomb et al. 2009; Salmela et al. 2021). Using stimuli similar to those in the current study, Salmela et al. (2021) measured surround suppression of perceived contrast in patients with unipolar MDD, bipolar disorder, and borderline personality disorder who were actively undergoing MDEs—"[w]hen comparing the patient group with [healthy] controls, we observed a strong and highly significant *reduction* in contrast suppression . . . patients perceived the contrast suppression illusion more veridically ... Furthermore, contrast suppression was similarly *reduced* in patients with unipolar MDD, bipolar disorder and borderline personality disorder" [Salmela et al. (2021); emphasis added]. Importantly, Salmela et al. (2021) found that as some of these patients went into remission (no MDE criterion symptoms), follow-up measurements revealed their weakened surround suppression had *normalized* (moved closer to levels measured in controls)—"a decrease in depression symptoms was associated with an increase in contrast suppression" (Salmela et al. 2021), which suggests that weakened visual surround suppression tracks depressive symptoms. Speculatively, our results hint by corollary that *enhanced* visual surround suppression measured under psilocybin might similarly track the neural shifts that underpin the antidepressant effects of the drug. Future studies could explore this by measuring visual surround suppression along with MDE symptoms before, during, and after psilocybin administration in MDD patients.

Further exploring this line of thought from a phenomenological viewpoint, we note that physical anhedonia (Chapman, Chapman, and Raulin 1976)—a reduction of interest and enjoyment in sensory stimuli—is widespread among MDD patients (Shankman et al. 2010; Sagud et al. 2020). Interestingly, psilocybin consistently produces high

scores on the 11D-ASC Changed Meaning of Percepts subscale (Studerus, Gamma, and Vollenweider 2010; Holze et al. 2022), which includes the items: "Objects in my surroundings engaged me emotionally much more than usual", "Some everyday things acquired special meaning", and "Things in my environment had a new strange meaning". The phenemenology of perception under acute psilocybin is thus antithetical to the phenomenology of sensory anhedonia in MDD. This phenomenological observation has substantial neurophysiological support. The active phase of MDD is associated with deficits (blunted responses) in processing emotional stimuli, including faces (Krause et al. 2021; Bourke, Douglas, and Porter 2010), body movements (Kaletsch et al. 2014), speech (Pang et al. 2014), and music (Naseri et al. 2019). Psilocybin has been found to *enhance* processing of emotional face stimuli in healthy volunteers (Grimm et al. 2018) and can have a restorative effect on deficient responses to emotional stimuli in patients with MDD (Stroud et al. 2017; Roseman et al. 2018; Mertens et al. 2020; Gill et al. 2022)—evidence which suggests that psilocybin "revives emotional responsiveness on a neural and psychological level" (Mertens et al. 2020). In 1928, Klüver noted this about the subjective visual effects of the psychedelic drug mescaline: "Human faces seem to undergo certain changes; they become more 'expressive', the features become more sharply defined ... Some subjects feel that their ability to infer certain traits of personality from facial expressions becomes increased" (Klüver 1928, 37–38). We speculate that the neural mechanisms underpinning the enhanced processing of emotional stimuli are also those that underpin subjective experiences captured by the Changed Meaning of Percepts subscale (specifically item 54, "Objects in my surroundings engaged me emotionally much more than usual"). Notably, we found that surround suppression correlated significantly with Changed Meaning of Percepts scores.[7]

In summary, our results highlight surround suppression as a potential trans-diagnostic neuropsychological mechanism which could be leveraged toward better

[7]Magaraggia, Kuiperes, and Schreiber (2021) argue that the antidepressant effects of psychedelics can be understood in light of their ability to enhance pattern separation. It is currently unclear how pattern separation relates to surround suppression, other than that both involve spatial context processing. The connection is intriguing nonetheless.

understanding the use of serotonergic psychedelic drugs in treating MDD.

3.4.5 Set and setting, suggestibility, flexibility, and surround suppression

Psilocybin and other classic psychedelic drugs' effects are uniquely sensitive to non-drug factors, such as pre-dose mood, drug session environment, and external stimuli (see Chapter 1 Figure 1.1) (Leary, Litwin, and Metzner 1963; Zinberg 1984; Studerus et al. 2012; Hartogsohn 2016, 2017). Known as *set and setting*, the internal mental *context* or 'mindset' (set) and external *context* or environment (setting) of the drug taker can drastically influence the magnitude, character, and content of the effects that psychedelic drugs produce. Speculatively, our results can be thought of as the set and setting phenomenon playing out on a basic perceptual level: the surround (setting) has greater influence on the percept under psilocybin.

Relatedly, psychedelic drugs can increase suggestibility (Leary 1961; Sjoberg and Hollister 1965; Grob and Rios 1992; Carhart-Harris et al. 2015; Timmermann et al. 2021), where suggestibility is defined in the minimal sense of "a person's propensity to respond positively to suggested communications, i.e., thinking and acting following the suggestions of others" (Dupuis 2021; Sidis 1898). Speculatively, it is interesting to view surround suppression itself as a kind of 'perceptual suggestibility' and to see our results as consistent with psilocybin-induced enhancements in suggestibility.

Cognitive flexibility (Scott 1962) "is broadly defined as the mental ability to switch between thinking about two different concepts *according to the context of a situation*" (Uddin 2021; emphasis added). Increases in cognitive flexibility have been measured at the 1-week and 4-week timepoints after a single dose of psilocybin in patients with MDD (Doss et al. 2021)—however, LSD reduced cognitive flexibility scores during acute peak effects (T. Pokorny et al. 2019) and 24 hours after administration (Wießner et al. 2022). While the links between surround suppression and cognitive flexibility are unknown, we note that both involve contextual processing. Speculatively, psilocybin-induced enhancement of surround suppression and alterations to cognitive

flexibility may share an underlying neuromodulatory mechanism.

3.4.6 Schizophrenic psychosis vs psilocybin effects

In line with conclusions from recent comparisons (Leptourgos et al. 2020), our findings warrant caution when comparing psilocybin's visual phenomenology with the perceptual abnormalities found in schizophrenic psychosis. As suggested in Chapter 1 the word 'psychotomimetic' may be apt for psilocybin only in the sense that it suggests *mimicry* and mimicry implies merely superficial *prima facie* likeness rather than meaningful shared properties. Numerous studies have found *weakened* surround suppression in schizophrenic patients compared to healthy controls (Dakin, Carlin, and Hemsley 2005; Tadin et al. 2006; Yoon et al. 2009; Yang et al. 2012; Tibber et al. 2013; Serrano-Pedraza et al. 2014; Schallmo, Sponheim, and Olman 2015; V. J. Pokorny et al. 2019; Linares et al. 2020). Importantly, we found that psilocybin shifted surround suppression in the *opposite direction* (enhancement). This finding is at odds with long-held assumptions that psychedelic drug effects 'resemble' or 'model' schizophrenic psychosis; assumptions that have been used to justify the 'model psychoses' theories that began in the late 1800s and to classify the drugs as *psychotomimetic* (see Chapter 1). In a study titled "Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action" psilocybin is described as a drug that "produces a psychosis-like syndrome in humans that resembles first episodes of schizophrenia . . . perceptual alterations are especially common features of psilocybin-induced and early acute schizophrenic stages" (Vollenweider et al. 1998, 3897). However, our results suggest the opposite, at least for visual surround suppression. Importantly, we found that the subjective visual effects of psilocybin correlated significantly with the magnitude of surround suppression, indicating that the neural mechanisms from which psychedelic visuals emerge may not be the same as those that give rise to the perceptual anomalies found in schizophrenic patients.

Furthermore, our findings are at odds with the theoretical claims of Carhart-Harris and Friston (2019), who argue that in both schizophrenic and psychedelic states "the brain's highest-level priors are ineffective, meaning bottom-up prediction errors travel

more freely up the hierarchy". While the schizophrenia side of their claim is indeed supported by findings of *weakened* surround suppression in schizophrenic patients (Dakin, Carlin, and Hemsley 2005; Tadin et al. 2006; Yoon et al. 2009; Yang et al. 2012; Tibber et al. 2013; Serrano-Pedraza et al. 2014; Schallmo, Sponheim, and Olman 2015; V. J. Pokorny et al. 2019; Linares et al. 2020), our findings do not support the hypothesis that psychedelic drugs induce a similar breakdown of top-down feedback in perceptual processing.

3.4.7 Neural information processing and psychedelic effects

Our results highlight a central ambiguity lurking in recent attempts that use 'predictive processing' (PP; see Chapters 1 and Swanson (2016)) to explain psychedelic effects (Corlett, Frith, and Fletcher 2009; Pink-Hashkes, Rooij, and Kwisthout 2017; Letheby and Gerrans 2017; Carhart-Harris and Friston 2019; Stoliker, Egan, and Razi 2022). The critical question raised in Chapter 1 is: "Do psychedelic molecules perturb top-down (feedback) signaling, or bottom-up (feedforward) signaling, or both?" (Chapter 1 Section 1.5.3). The leading proposals argue that psychedelic effects stem from a 'decomposition' (Pink-Hashkes, Rooij, and Kwisthout 2017) or 'relaxing' (Carhart-Harris and Nutt 2010; Carhart-Harris and Friston 2019) of top-down feedback signaling, "which concomitantly liberates bottom-up signaling" (Carhart-Harris and Friston 2019). However, we found that the surround suppression illusion, which we can reasonably assume is underpinned by top-down feedback signaling from cortex, was *strengthened* under peak effects of psilocybin. Our finding is therefore in tension with the central hypothesis of Carhart-Harris and Friston (2019) who argue that psychedelic effects stem from a "weakening the precision weighting of high-level priors".[8] Furthermore, Carhart-Harris and Friston (2019) state that "the relaxation of high-level priors [under psychedelics] necessarily implies a liberation of bottom-up information flow". Yet if this scenario were true, we would expect to see a weakening, not an enhancement, of surround suppression under psilocybin—greater bottom-up information flow would translate to a weaker visual illusion; i.e., a more veridical percept that matches the

[8]For a primer on the concept of precision in Bayesian theories, see (Yon and Frith 2021).

external stimuli with greater accuracy. However, we found the opposite result in our experiment. One way to address this tension would be to attempt a more nuanced interpretation of our findings, in which psilocybin-induced enhancements of surround suppression are understood as the result of increased weighting of bottom-up cues that *trigger* top-down feedback, whereby the 'liberated' bottom-up signals (i.e., the surround stimulus) are more likely to trigger *stronger* top-down effects (i.e., the suppression illusion) under psychedelics. However, this interpretation would still be in conflict with the core hypotheses of Carhart-Harris and Friston (2019) and Pink-Hashkes, Rooij, and Kwisthout (2017) who clearly argue that psychedelics *weaken* top-down processes.

In summary, our results warrant further inquiry into the behavior of perceptual systems under psychedelics, as well as a closer theoretical examination of how psychedelics might impact the brain's balance of bottom-up (feedforward) signals against top-down (feedback) modulation.

3.5 Limitations

The results presented here are preliminary findings from the first six (n = 6) participants in our pilot study. We plan to expand our sample size to include a total of 40 participants, which will necessarily yield greater statistical power than in our current sample. Furthermore, we did not correct for multiple comparisons (i.e., across the correlations) which limits the conclusions that can be drawn from the results presented here.

Maintaining an effective blind in psychedelic drug investigations is notoriously complicated (Muthukumaraswamy, Forsyth, and Lumley 2021; Burke and Blumberger 2021; Olson et al. 2020) and our study was no exception. We attempted to minimize placebo effects using Niacin as an 'active' placebo; nonetheless, it is likely that unblinding occurred for some experimenters and participants alike. We take seriously the possibility that placebo/nocebo and expectancy could influence PSEs. This possibility is somewhat mitigated by our within-subjects crossover design, in which

half of our participants received psilocybin first, and the other half placebo first (see Table 3.1).

Our inclusion criteria excluded drug-naive subjects (we required at least one prior personal experience with psilocybin), which may have increased the likelihood of expectancy effects in both the psilocybin and placebo conditions.

The dose of psilocybin was a fixed 25mg (oral) for every participant regardless of body mass. Thus, it is possible that dose-response differences occurred between participants, as the intensity of psilocybin's visual effects can be dose-dependent (Hasler et al. 2004; Carter, Pettigrew, et al. 2005; Holze et al. 2022). To mitigate this, future studies could dose psilocybin using a body-mass-relative (mg/kg) ratio.

The role of specific g-protein coupled receptors (GPCRs; e.g., the 5-HT_{2A} receptor) in causing our findings is unknown, as psilocybin has affinity for a variety of serotonergic and dopaminergic receptors (Ray 2010) and we did not employ techniques to isolate pharmacological action. However, previous studies that paired the selective 5-HT_{2A} antagonist ketanserin with psilocybin indicate that 5-HT_{2A} activation is required for psilocybin's subjective visual effects (Vollenweider et al. 1998; Kometer et al. 2013). However, although the ketanserin can block these effects (Vollenweider et al. 1998; Kometer et al. 2013), it does not always block psilocybin's impact on visual functions measured via psychophysics (e.g., Carter et al. 2007). Future studies could use selective 5-HT_{2A} antagonist ketanserin to probe the specific role of 5-HT_{2A} in psilocybin-induced alterations of surround suppression, as well as to test the correlations we found between enhanced surround suppression and subjective effects.

3.6 Conclusion

We found that psilocybin enhanced visual surround suppression in a contrast-matching psychophysics task. Furthermore, the magnitude of surround suppression correlated significantly with self-rated intensity of subjective *visual* effects, but not with overall psychedelic alterations in consciousness. Interestingly, subjective effects measured by the Audio-Visual Synesthesia subscale had the strongest correlation with mag-

nitude of surround suppression. Our results suggest that (1) surround suppression is not weakened and may instead be enhanced under peak effects of psilocybin, (2) serotonergic neuromodulation may be critically involved in surround suppression, (3) enhancements in surround suppression appear to correlate with the intensity of subjective visual effects, (4) psilocybin may shift visual context processing in the opposite direction of that found in patients experiencing major depressive episodes, (5) the visual effects of psychedelics appear to emerge from processes distinct from those underlying abnormal visual perception in schizophrenia, and (6) we may have reason to question the theoretical notion that psychedelic drugs weaken top-down feedback.

Chapter 4

Stronger surround suppression of ERP responses under psilocybin: A pharmaco-EEG study

"Pharmaco-EEG, a neuroscience that was discarded well before its full potential was achieved ... is a quantitative science that yields direct images of ongoing biochemical and neurophysiologic brain events that are intimately connected to human behavior."

–Max Fink (2010, 161–71) "Remembering the Lost Neuroscience of Pharmaco-EEG"

"Drugs with effects comparable to those of LSD-25, for example, have been known for generations, but it is only recently that we have been in a position to study them meaningfully. The long awaited millennium in which biochemical, physiological, and psychological processes can be freely correlated still seems a great distance off. This should not discourage us from responding to the occasional opportunities for observing parallels between these different orders of phenomena as are afforded us in experimental studies."

–Gerald Klee (1963, 473), "Lysergic Acid Diethylamide (LSD-25) and Ego Functions"

ABSTRACT

The perceived contrast and neural responses to a target stimulus can be reduced by surrounding it with higher-contrast stimuli. In this experiment we examined center-surround modulation of visual event-related potential (ERP) amplitude in EEG recordings from humans under the psychedelic drug psilocybin. We found that: (1) under psilocybin, the surround stimulus had a greater suppression effect on the magnitude of the N1 ERP response compared with placebo; (2) this effect was feature-selective, being strongest when the surround stimulus had an orientation parallel to the orientation of the target; and (3) the ERP amplitude in response to center stimuli presented alone (no surround stimulus) was not significantly impacted by psilocybin. The finding suggests that serotonin plays a functional role in suppressing neural responses to visual stimuli, and that psychedelic drugs enhance contextual modulation of neural responses to center-surround stimulus configurations.[1]

4.1 Introduction

Surround suppression in contrast perception is a visual illusion wherein the perceived contrast of a stimulus is reduced (suppressed) by neighboring stimuli in its (surrounding) visual context (see Chapter 3 Section 3.1). In addition to psychophysical measurements, changes in neural activity that occur when a target stimulus is surrounded by contextual stimuli can be measured with neuroimaging techniques. In electroencephalography (EEG) and magnetoencephalography (MEG) recordings, this surround suppression is measured by analyzing the event-related potential (ERP) produced by various center-surround stimulus configurations (Ohtani et al. 2002; Haynes et al. 2003; Appelbaum et al. 2006; Joo, Boynton, and Murray 2012; Joo and Murray 2014; Chen et al. 2016; Vanegas, Blangero, and Kelly 2015; Schallmo, Kale, and Murray 2019). These studies indicate that neural responses in human occipital lobe differ when viewing a center stimulus within the context of a surrounding stimulus versus viewing the center stimulus alone, and that these differences depend on the configuration (e.g., orientation) of the center stimulus in relation to its surround.

[1]Link Swanson and Michael-Paul Schallmo designed the experiment. Jessica Nielson, Sophia Jungers, and Link Swanson carried out the experiment. Kathryn Cullen and Ranji Varghese helped with participant safety monitoring. Link Swanson analyzed the data and wrote the manuscript.

Surrounding stimuli have been shown to alter neural responses in both early (~80 ms) and later (~130 ms) response components in the ERP time course. Generally, the strength of the neural response mirrors the strength of the perceptual illusion for different center-surround configurations, i.e., a surround with parallel orientation will have greater influence on ERP response components (especially the later ~130 ms component) than a surround that is oriented orthogonally in relation to the target stimulus (Ohtani et al. 2002; Haynes et al. 2003; Schallmo, Kale, and Murray 2019). While this phenomenon is empirically well-established, its neural origin within the visual processing hierarchy remains unclear, and the underlying biochemical neuromodulatory mechanisms have not been identified (Schwartz, Hsu, and Dayan 2007; Schallmo et al. 2018; Schallmo, Kale, and Murray 2019).

Pharmacological interventions incorporated into ERP paradigms provide a means for investigating and isolating specific neuromodulator mechanisms (Fink 1969, 2010). The benzodiazepine drug lorazepam, a positive allosteric modulator at the $GABA_A$ receptor, has been found to weaken surround suppression (Schallmo et al. 2018), suggesting that the mechanisms of suppression are not directly mediated by GABAergic inhibition. Rather than direct GABAergic inhibition, an alternative hypothesis is that surround suppression occurs via withdrawal of excitation (Ozeki et al. 2009a; Sato et al. 2016; Schallmo et al. 2018). Serotonergic (5-HT) neurotransmission is known to regulate neuronal excitability in cortical networks, primarily via 5-HT_{1A} and 5-HT_{2A} receptor subtypes (Andrade 2011). In mouse V1, Azimi et al. (2020) found evidence that 5-HT_{2A} receptors serve to (divisively) modulate visual evoked response gain. Visual perception is significantly altered by psychedelic drugs, and these effects critically depend on the agonist activation at 5-HT_{2A} receptors (Vollenweider et al. 1998; Kometer et al. 2011, 2013; Halberstadt and Nichols 2020). The distinct phenomenology of psychedelic visual alterations—which includes "very pronounced simultaneous contrast" (Klüver 1928) as well as other illusory object properties such as "breathing" (Huxley 1954), "wavering" (Hofmann 1980), "undulating movements" (Klüver 1926)—indicates that serotonergic psychedelics may impact mechanisms that regulate gain control of visual evoked responses (Vollenweider and Smallridge 2022).

However, the impact of classic psychedelic drugs on surround suppression in humans has not been investigated.

Our findings reported in Chapter 3 suggest that perceptual surround suppression is enhanced (i.e., stronger, as measured by our psychophysical paradigm) under psilocybin, a classic psychedelic drug that agonizes 5-HT_{2A} and 5-HT_{1A} receptors (Nichols 2004; Ray 2010). We found that when a target stimulus was presented alone, perceptual judgements did not differ under psilocybin vs placebo. By comparison, when the target stimulus was presented within a higher-contrast surround, the perceived contrast of the target stimulus was more greatly suppressed (i.e., the illusion was stronger) under psilocybin, and the magnitude of psilocybin's impact was dependent on surround orientation (stronger for parallel vs orthogonal orientation). Psilocybin thus appears to induce greater contextual modulation, as it had no effect on perceptual judgments in the No Surround condition, and had the strongest effect in the Parallel Surround condition, when the target stimulus was most similar to its surround. This finding is broadly consistent with previous findings that used visual stimuli, where psilocybin was found to impact performance on visual tasks that evoke contextual modulation (Carter et al. 2004; Carter, Burr, et al. 2005; Gouzoulis-Mayfrank et al. 2002; Kometer et al. 2011, 2013), while performance on other tasks was no different from placebo (Carter et al. 2004; Carter, Burr, et al. 2005; Barrett et al. 2018) (see Chapter 2 for more discussion of this point).

The impact of psilocybin (and other psychedelic drugs) on neural responses reflected in visual-evoked event-related potentials (vERPs; as measured by EEG) is largely unknown—only two previous investigations have paired vERP paradigms with psychedelic drugs in humans. The N1/N170 component (Bentin et al. 1996) is a common vERP associated with object recognition and with the perception of illusory object boundaries (Murray 2004), such as Kanizsa's (1979) illusory triangle shape induced by 'pacman' stimulus configurations. Kometer et al. (2011) recorded EEG responses to Kanizsa figures under psilocybin and found that the magnitude of the N1 component was attenuated, and that this attenuation correlated with the intensity of the visual experiences produced by the drug (Kometer et al. 2011). A later study

found that pharmacologically blocking psilocybin's 5-HT_{2A} receptor agonism blocked the effect on the N1 and eliminated all subjective visual effects of the drug (Kometer et al. 2013), indicating that the 5-HT_{2A} receptor was involved in psilocybin's effect on the N1 vERP component.

Phenomenologically, as noted above and in Chapter 2, psilocybin produces illusory shifts in the appearance object forms, often with illusory motion in real objects, and these subjective effects were found to correlate with surround suppression of perceived contrast (Chapter 3) and with decreased N1 amplitude evoked by Kanizsa stimuli (Kometer et al. 2011), which was dependent on psilocybin's 5-HT_{2A} activation (Kometer et al. 2013). Thus, we reasoned that the visual phenomenology characteristic of psilocybin might involve increases in surround suppression, as surround suppression plays a role in the everyday perception of object boundaries, figure-ground segregation, and visual saliency (Angelucci et al. 2017; H. Yu et al. 2022). Furthermore, variations in contrast perception are crucial for perceiving object form, size, and motion features (H. Yu et al. 2022), all of which are altered under psilocybin. Moreover, surround suppression involves shifts in excitation-inhibition balance, which is modulated by serotonergic signaling (Andrade 2011; Azimi et al. 2020). Taken together, we reason that 5-HT_{2A}/5-HT_{1A} signaling may be critically involved in surround suppression ERP responses to center-surround stimulus configurations, and that the visual effects of psilocybin are in part due to its ability to impact this mechanism. This highlights the critical need for investigations that measure context-modulated ERP responses under psilocybin and other serotonergic psychedelic drugs.

Here, we paired psilocybin with a vERP surround suppression paradigm using nearly identical stimuli as in our psychophysical paradigm reported in Chapter 3. The current study was designed to measure psilocybin's impact on ERP responses to differing center-surround stimulus configurations as measured by EEG. Using a double-blind, placebo-controlled within-subjects crossover design, we found that psilocybin increased the surround suppression ERP response in the N1 component time window (~120-250 ms) relative to placebo. Furthermore, the strength of psilocybin's impact on ERP responses depended on stimulus orientation, with the strongest effect being

in the parallel center-surround orientation, and the orthogonal orientation impacted to a lesser degree.

4.2 Methods

4.2.1 Participants

Adults aged 30 to 38 years with no current or previous mental health diagnosis, not currently using any prescription medications, with at least one reported previous experience taking a moderate to high dose of psilocybin, and without histories of psychotic disorder were eligible to participate. Five healthy observers with normal or corrected-to-normal vision (3 male and 2 female, mean age 35 years) were included in this study. A total of 6 completed the experiments; however, data from one participant was excluded due to excessive signal artifacts in the EEG recording. The participants in this experiment were the same individuals who completed the psychophysical task reported in Chapter 3. All participants gave written informed consent and were compensated at a rate of $20 per hour. Experimental protocols were approved by the Institutional Review Board of the University of Minnesota. All experiments were performed in accordance with approved guidelines and regulations, including approval from the United States Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA).

4.2.2 Drug administration and timing

For this experiment, participants completed the EEG task 5 hours after psilocybin was administered, which means the measurements were taken *after* drug-plasma concentrations had likely peaked, as the strongest 'peak' subjective drug effects had begun to gradually diminish. This timing differs substantially from our psychophysical measurements (Chapter 3), which were performed three hours post-drug administration, during typical peak subjective drug effects (Carbonaro et al. 2018; Holze et al. 2022) and typical peak plasma concentrations (Brown et al. 2017; Holze et al. 2022). Thus,

the present experiment reflects psilocybin's effect on ERP responses *post-peak*, during the transition out of the psilocybin state returning to the baseline waking state. This should be kept in mind when considering all findings presented here.

4.2.3 Crossover design

Every participant completed two drug dosing sessions—one day with active drug (25mg psilocybin); one day with placebo (100mg niacin)—two weeks apart. EEG recordings were also obtained at separate non-drug baseline and follow-up sessions, but these data are not reported here as they will be analyzed for a future report, along with fMRI and psychophysical measurements from baseline and follow-up sessions. Participants were randomized into groups where group A received psilocybin on dosing day 1 and placebo on dosing day 2, while group B received the drugs in the reverse order. Participants, experimenters, and all study staff were blind to which drug was administered on any given experimental session. See Chapter 3 for more detail on the study design.[2]

4.2.4 Apparatus

EEG data were recorded using a Wearable Sensing DSI-24 dry electrode EEG headset at a sampling rate of 600 Hz, except for three sessions, which were inadvertently recorded at 300 Hz. All recordings were downsampled to 300 Hz to achieve a uniform sampling rate across all recordings included in the analysis. The DSI-24 has 21 channels in a fixed position compliant with the 10-20 International System.[3] The CZ sensor was positioned halfway between the nasion and inion points, which positions the remaining fixed-position sensors of the DSI-24 headset as shown in Figure 4.1. The DSI-24 was used in *wired mode* for all data acquisition sessions. Data were captured using WearableSensing's DSI-Streamer software running on Windows 10.

Visual stimuli were presented on a Dell P2319H 23-in LED-backlit monitor (1920

[2]ClinicalTrials.gov Identifier: NCT04424225

[3]21 sensors at 10-20 locations: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T7/T3, T8/T4, Pz, P3, P4, P7/T5, P8/T6, O1, O2, A1, A2.

× 1080 pixels, 60 Hz refresh rate) at a viewing distance of 60cm. The monitor was calibrated using a spectrophotometer. Mean luminance was 111.2 cd/m^2. Stimuli were generated and presented using PsychoPy (Peirce et al. 2019) version `2021.2.3`. Event codes (triggers) were transmitted from PsychoPy over LTP (parallel) port into a WearableSensing Trigger Hub device, and from there sent to the DSI-24 headset where they were recorded into the final data stream as a dedicated channel alongside the electrode channels. Latency differences between software triggers sent by PsychoPy and actual on-screen stimulus presentation time were quantified using a photodiode, resulting in a latency offset of `48.387` ms. A correction for this offset was applied to the EEG data as described in Section 4.2.8 below.

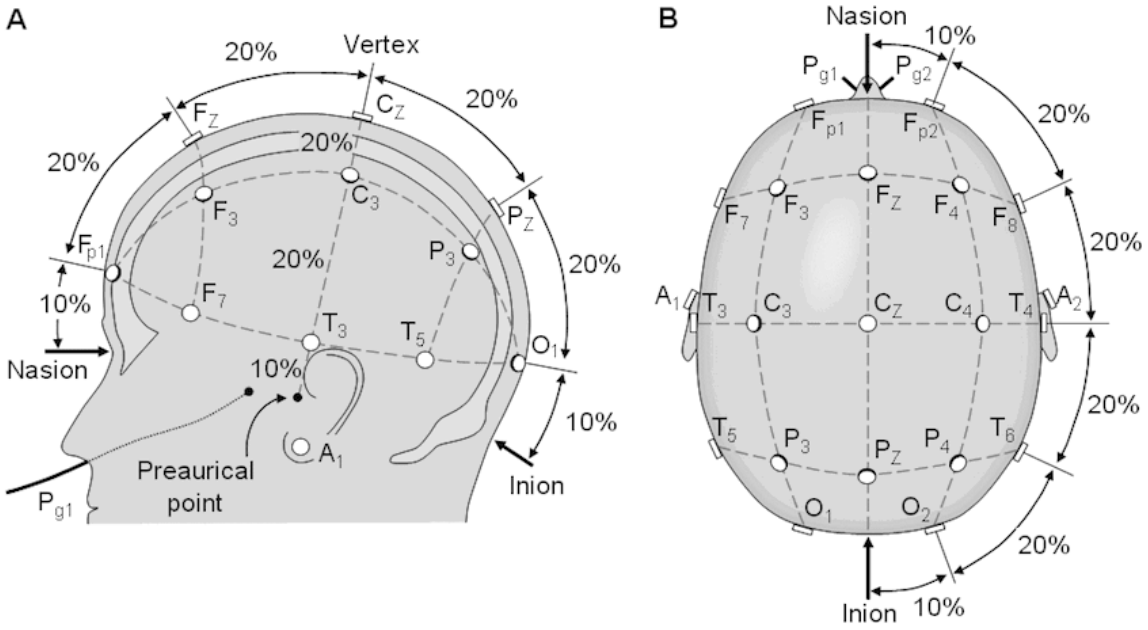

Figure 4.1: DSI-24 EEG headset sensor positions.

4.2.5 Stimuli

Visual stimuli were the same as in the psychophysics experiment in Chapter 3 Section 3.2.4, except for the following differences. *Two* circular gratings ("centers") were presented simultaneously at 2.8° to the left and right, and 1.1° above fixation, with fixed 50% contrast. The central fixation marker was constructed according to Thaler

Table 4.1: The three different stimulus conditions. One set of 105 trials was presented for each stimulus condition intermixed with the other sets in counterbalanced random order. Four different orientation variations were used (0°, 45°, 90°, or 135°; 105 trials of each) presented in random order.

Condition	**Surround stimulus**	**Example**	**N trials**
NS	None	Figure 3.2 **A**	105
OS	Orthogonal	Figure 3.2 **C–D**	105
PS	Parallel	Figure 3.2 **E–F**	105

et al. (2013) (shown in Figure 4.2). On a subset of the trials, the centers appeared within larger gratings–referred to as "surrounds"—that were 4° in diameter, were spatially in-phase with the center gratings, with 100% contrast. Surround orientation was either parallel or orthogonal to the center (see below).

4.2.6 Paradigm

The experiment was designed to measure the effect of psilocybin versus placebo on the ERP evoked by the center stimuli as measured by the EEG recording. Three stimulus conditions (No Surround, Orthogonal Surround, Parallel Surround) mirrored the psychophysics experiment in Chapter 3. A fourth condition ("catch") was included in which the center gratings were replaced with plaid (checkered) gratings. The participants' task was to report (via key press) whether centers were stripes or plaids on each trial. When present, surrounds were presented 1.5-2.5 s (randomized) before, during, and 500 ms after presentation of centers (200 ms; see Figure 4.3), so that the ERP response to the centers could be distinguished in time from the response to the surrounds (see Ohtani et al. 2002; Haynes et al. 2003; Joo, Boynton, and Murray 2012; Joo and Murray 2014; Schallmo, Kale, and Murray 2019). The No Surround condition provided an isolated centers-only reference ERP response. 105 trials per condition were collected (a total of 420 trials), with breaks about every 5 minutes for a total duration of about 50 minutes.

At the beginning of each trial, the fixation mark changed from blue to red, and participants were instructed avoid blinking and responding until fixation marker turned

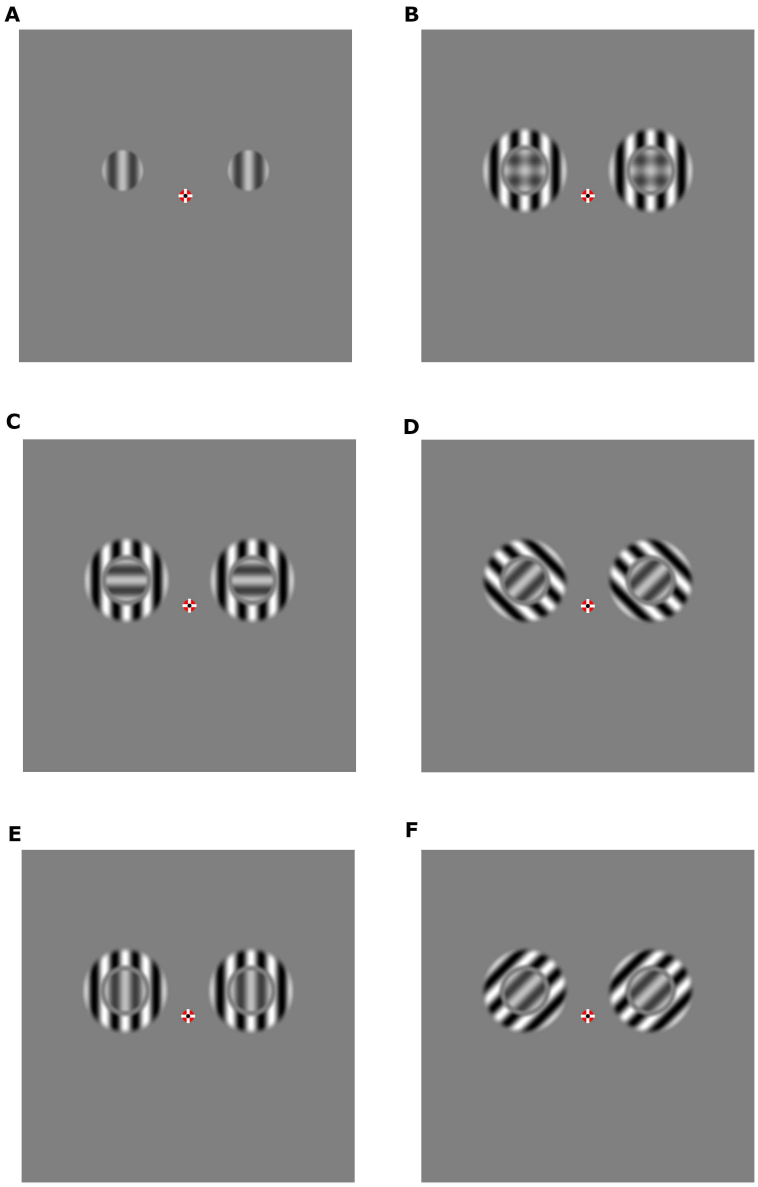

Figure 4.2: Samples of stimuli used in the experiment. **A** is an example of the no-surround (NS) condition. **B** is an example of the plaid grating ('catch' trial) to which participants were instructed to respond with a specific key press. (**C**–**D**) are examples of the orthogonal surround (OS) condition. (**E**–**F**) are examples of the parallel surround (PS) condition. All conditions appeared in four orientation variants (0°, 45°, 90°, or 135°) in counterbalanced randomized order.

back to blue (see Figure 4.3).

4.2.7 Subjective drug effects

The Altered States of Consciousness questionnaire (5D-ASC) scale (Dittrich 1998; Studerus, Gamma, and Vollenweider 2010) was used to assess the overall effects of drug on various elements of subjective experience. See Chapter 3 Section 3.2.6 for a full description of the measure.

4.2.8 Data processing

EEG recordings were processed using the open-source EEGLAB toolbox software package (Delorme and Makeig 2004) version 2022.1 integrated with MATLAB (The Mathworks, Inc., Natick, MA, USA) version 2021b. A high-pass filter (0.05 Hz) and notch filter (58–62 Hz) were applied sequentially using the `pop_eegfiltnew()` filter function in EEGLAB toolbox. Each continuous recording was inspected visually and any non-trial (i.e., beginning, end, breaks) sections were removed. Next, an independent components analysis (using EEGLAB) was used to identify signal artifacts produced by eye blinks, eye movements, muscle movements, and channel noise, which were reviewed manually, flagged for removal, and removed using EEGLAB's `pop_subcomp()` function. Signals from each electrode were re-referenced from the hardware vendor's Pz reference electrode to a more common Cz reference using EERLAB's `pop_reref()` function.

ERP analyses were performed with the open-source ERPLAB toolbox (Lopez-Calderon and Luck 2014) version 9.0 in MATLAB. Trials were examined within time-locked epochs from -200 to +500 ms relative to target stimulus onset. Baseline correction was performed by subtracting the average voltage from the -200 to 0 ms period from all time points within each trial. Epochs were then screened for artifacts using a peak-to-peak algorithm via ERPLAB's `pop_artmwppth()` function, and excluded from analysis if activity exceeded a 100µV threshold.[4] Included trial

[4]The mean number of excluded trials per condition per participant is reported in Table 4.2.

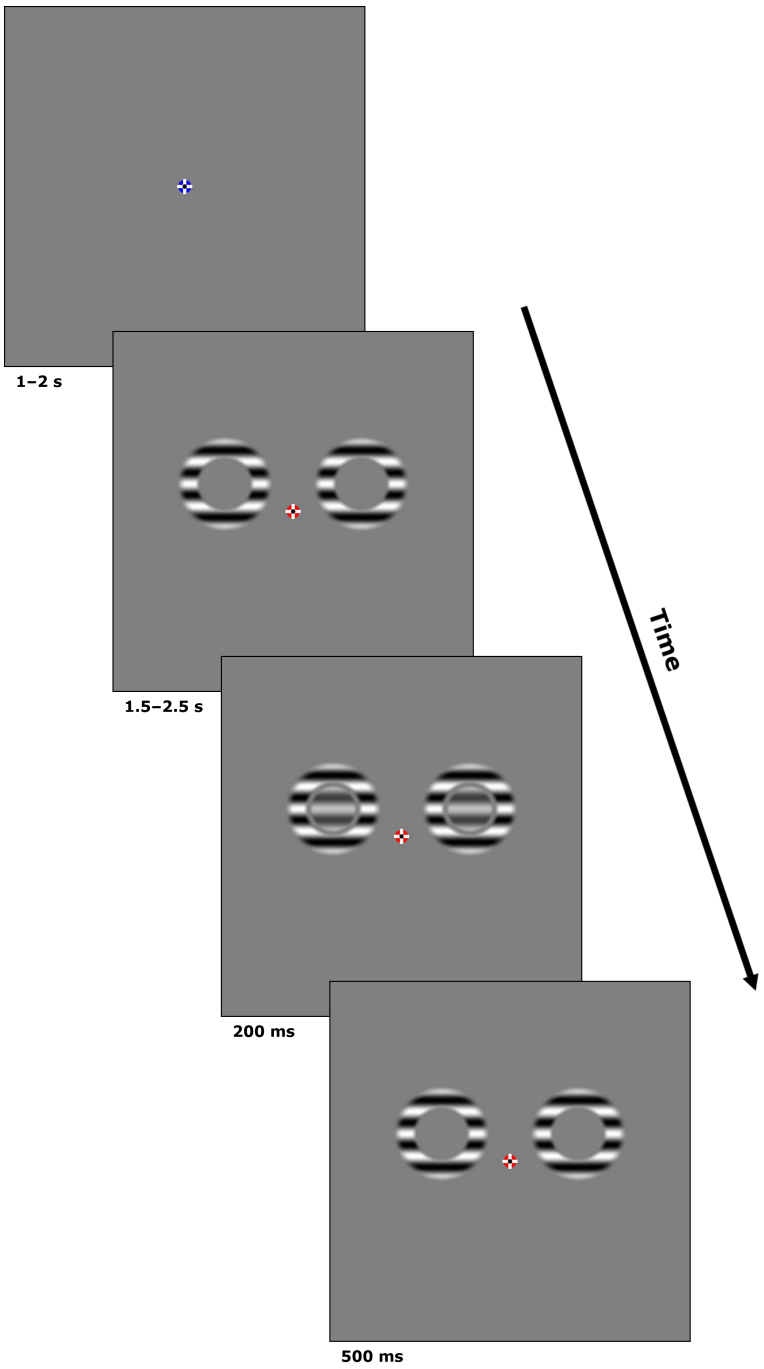

Figure 4.3: Presentation timing for a single trial. Each trial begins after a 1–2 s (duration randomized) inter-trial interval. The trial begins with the onset of the surrounds, which are presented continuously until the trial ends. Centers appear after a randomized duration of 1.5–2.5s, are presented for 200ms. Surrounds remain for an additional 500ms after center offset, at which point the trial ends.

Table 4.2: Descriptive statistics on trials excluded from analysis due to artifacts. Values represent number of trials removed for each subject in each stimulus condition under each drug.

	drug	mean	max	std
NS	**placebo**	3.20	5	1.30
	psilocybin	5.20	10	4.60
OS	**placebo**	3.80	6	1.48
	psilocybin	5.20	11	5.40
PS	**placebo**	3.40	4	0.89
	psilocybin	5.60	11	4.39

epochs were then separated into bins grouped by stimulus condition (NS, OS, PS). Catch trials were not examined in the current study, as the ERP responses to the oddball plaid stimuli would introduce complications in interpreting these results. ERP amplitudes from all trials in each condition were then averaged for each participant using ERPLAB's `pop_averager()` function.

We identified locations O1 and O2 (occipital) as a priori electrodes of interest for the analysis, based on previous studies (V. P. Clark, Fan, and Hillyard 1994; Joo, Boynton, and Murray 2012; Joo and Murray 2014; Schallmo, Kale, and Murray 2019). Scalp maps of grand average mean amplitude for each electrode at successive 20ms latencies over the entire trial epoch (-200 ms pre- to +500 ms post-stimulus onset; Figure 4.4) support our a priori choice of electrodes.

Four ERP components were selected a priori for analyses: P1, N1, and P2. To identify the separate ERP component time windows, we grand-averaged O1 & O2 amplitudes from all from all 5 subjects in all three surround stimulus conditions (NS, OS, PS) combined, plotted the grand average ERP waveform, and visually demarcated the start and end points for the P1, N1, and P2 components (Figure 4.5).

We then computed average response magnitudes within each ERP time window, using the average time course across trials within each condition for each participant, for psilocybin and placebo separately.

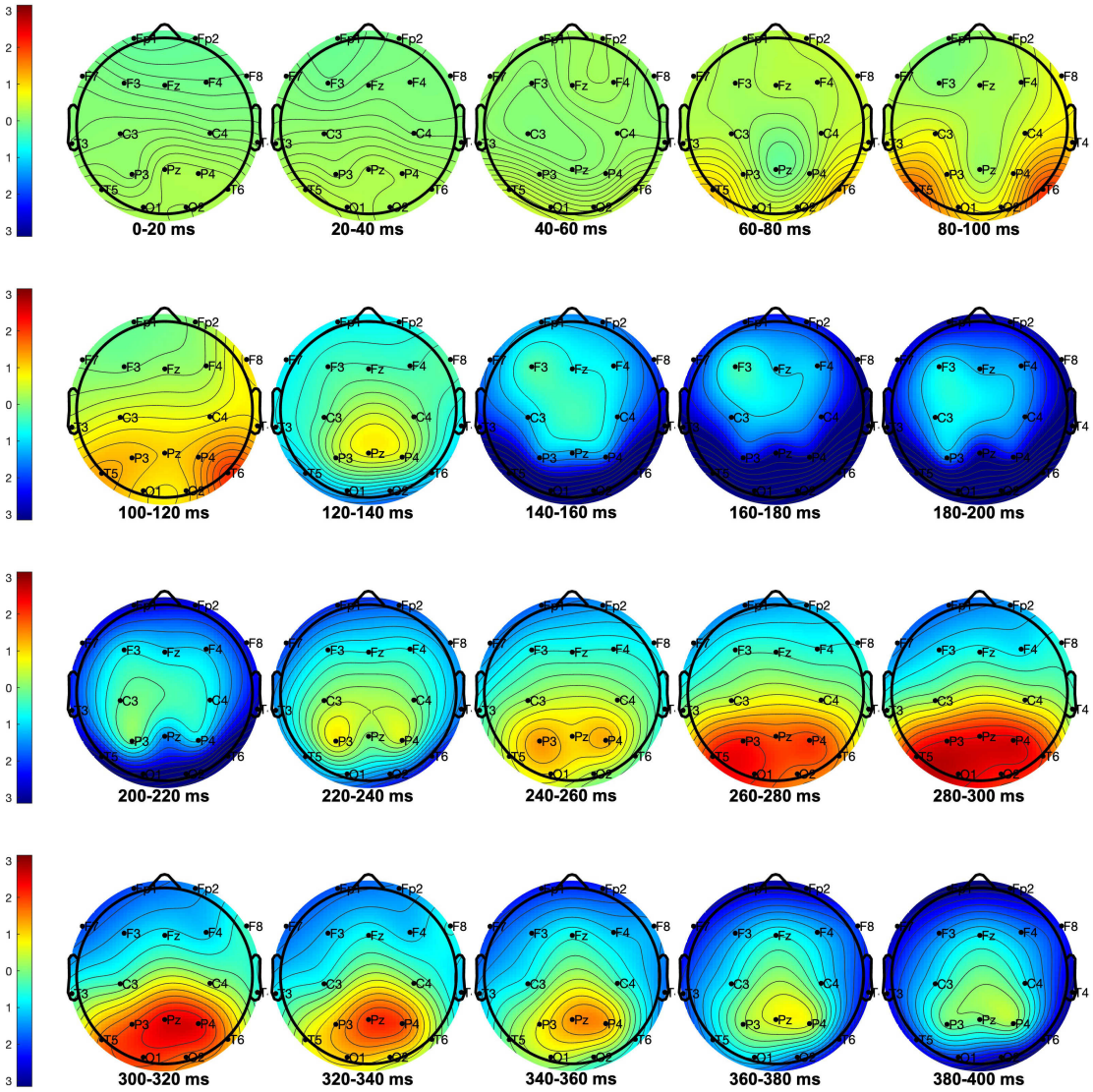

Figure 4.4: Grand average amplitudes from all 20 electrodes placed across the scalp are shown in 20 ms segments across the epoch time window from 0 to 400 ms post-stimulus onset.

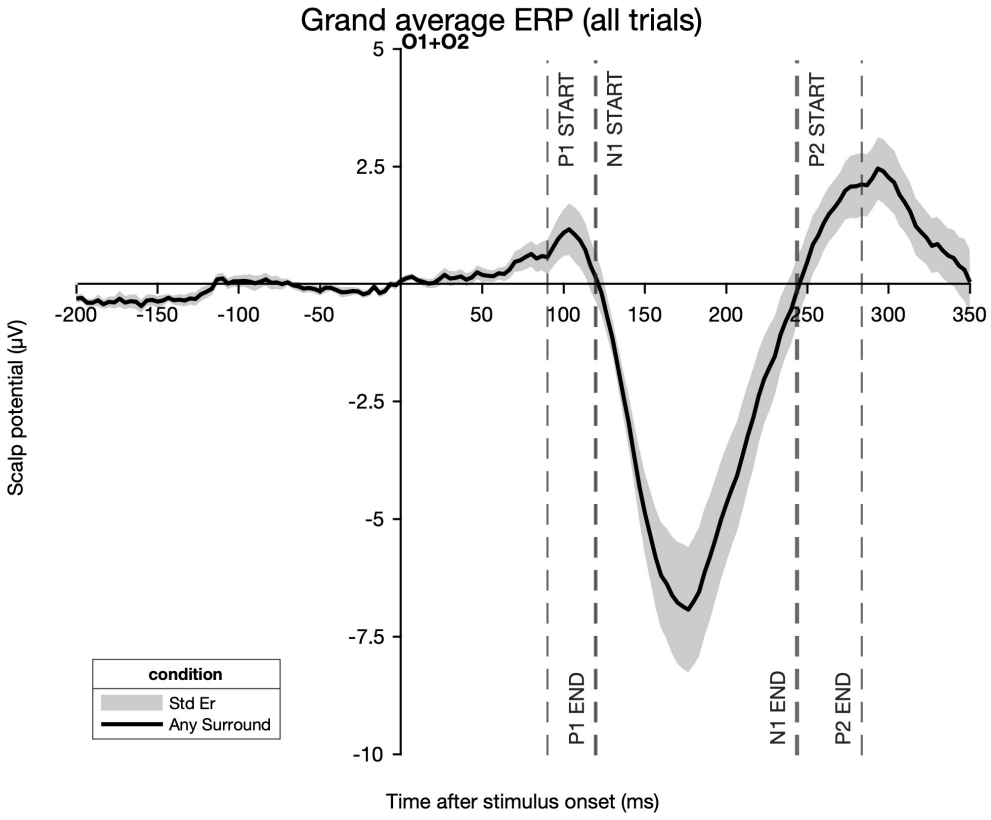

Figure 4.5: The grand average ERP waveform (all included trials in all conditions form all participants). Mean amplitudes from the O1 and O2 electrodes are plotted in time, with zero being the stimulus onset. Dashed lines indicate the time windows we chose to demarcate each component in our analyses. Shaded area shows SEM.

Table 4.3: Time windows for ERP components (ms). These time windows were defined qualitatively from the grand average ERP waveform.

	N1	**P1**	**P2**
Start	120.0	90.0	244.3
End	243.0	119.3	283.3

4.2.9 Statistical analyses

Data from placebo and psilocybin sessions were analyzed separately, then compared within participants. ERP responses for each component (mean voltage across the time window) were compared in separate repeated-measures analyses of variance (ANOVAs) using drug and stimulus condition as within-subjects factors. ANOVAs that reached significance were followed-up with *post hoc* pairwise *t*-test comparisons.

5D-ASC subjective drug effects ratings were compared in a repeated measures ANOVA using drug and ASC subscale/dimension as within-subjects factors (results reported in Chapter 3 Section 3.3.3).

Correlation between ERP component amplitudes and 5D-ASC ratings were calculated using RMcorr, "a statistical technique for determining the common within-individual association for paired measures assessed on two or more occasions for multiple individuals" (Bakdash and Marusich 2017; Bland and Altman 1995a, 1995b).[5] and followed up with pairwise biweight midcorrelation tests (Langfelder and Horvath 2012) using the difference (psilocybin minus placebo) for ERP amplitude and rating score pairs for each participant. We chose these correlation methods because they do not require first averaging the data and avoid violating independence assumptions, making them ideal (and more sensitive) for paired repeated-measures data (Bakdash and Marusich 2017).

All statistical analyses were performed using the Pingouin package for Python (Vallat 2018). The criterion for significance was $p < 0.05$.

[5] "Rmcorr accounts for non-independence among observations using analysis of covariance (ANCOVA) to statistically adjust for inter-individual variability. By removing measured variance between-participants, rmcorr provides the best linear fit for each participant using parallel regression lines (the same slope) with varying intercepts" (Bakdash and Marusich 2017).

4.3 Results

Each of five participants completed the EEG task under psilocybin and placebo on separate days. To examine the impact of psilocybin on visual-evoked ERP amplitudes, we analyzed four distinct ERP waveform components—P1, N1, and P2—from EEG recordings under psilocybin and placebo in three stimulus conditions (NS, OS, PS; see Section 4.2 Figures 4.2). Repeated measures ANOVA analyses were performed separately for each ERP component latency time window. The full ERP waveform showing mean amplitude time course over the epoch time window for all three stimulus conditions is shown in Figure 4.6 for psilocybin (**A**) and placebo (**B**).

To assess correlation between subjective rating scale item scores and ERP component responses, we performed rmcorr analyses by pairing each participant's (psilocybin minus placebo) ERP component amplitudes with their 5D-ASC ratings of subjective effects from each dosing session.

We chose the N1 component as our ERP time window of interest based on previous findings that the N1 component is sensitive to center-surround stimulus configurations in normal healthy adults (Schallmo, Kale, and Murray 2019), together with evidence that psilocybin impacts ERP at the N1 time window (Kometer et al. 2013). Although the N1 component was our time window of interest, we nonetheless performed separate statistical analyses on each of the P1, N1, and P2 components, which are provided in the sections below, in chronological order (relative to stimulus onset time).

4.3.1 P1 component (90.0 - 119.3 ms)

Our ANOVA analysis of P1 amplitudes found no significant main effect of drug ($p = 0.592$) or stimulus condition ($p = 0.236$). The drug $\times$ condition interaction effect likewise did not reach significance ($p = 0.851$).

A Shapiro-Wilk test did not show evidence of non-normality in the placebo ($W = 0.942$, $p = 0.41$) or the psilocybin ($W = 0.952$, $p = 0.549$) amplitudes data.

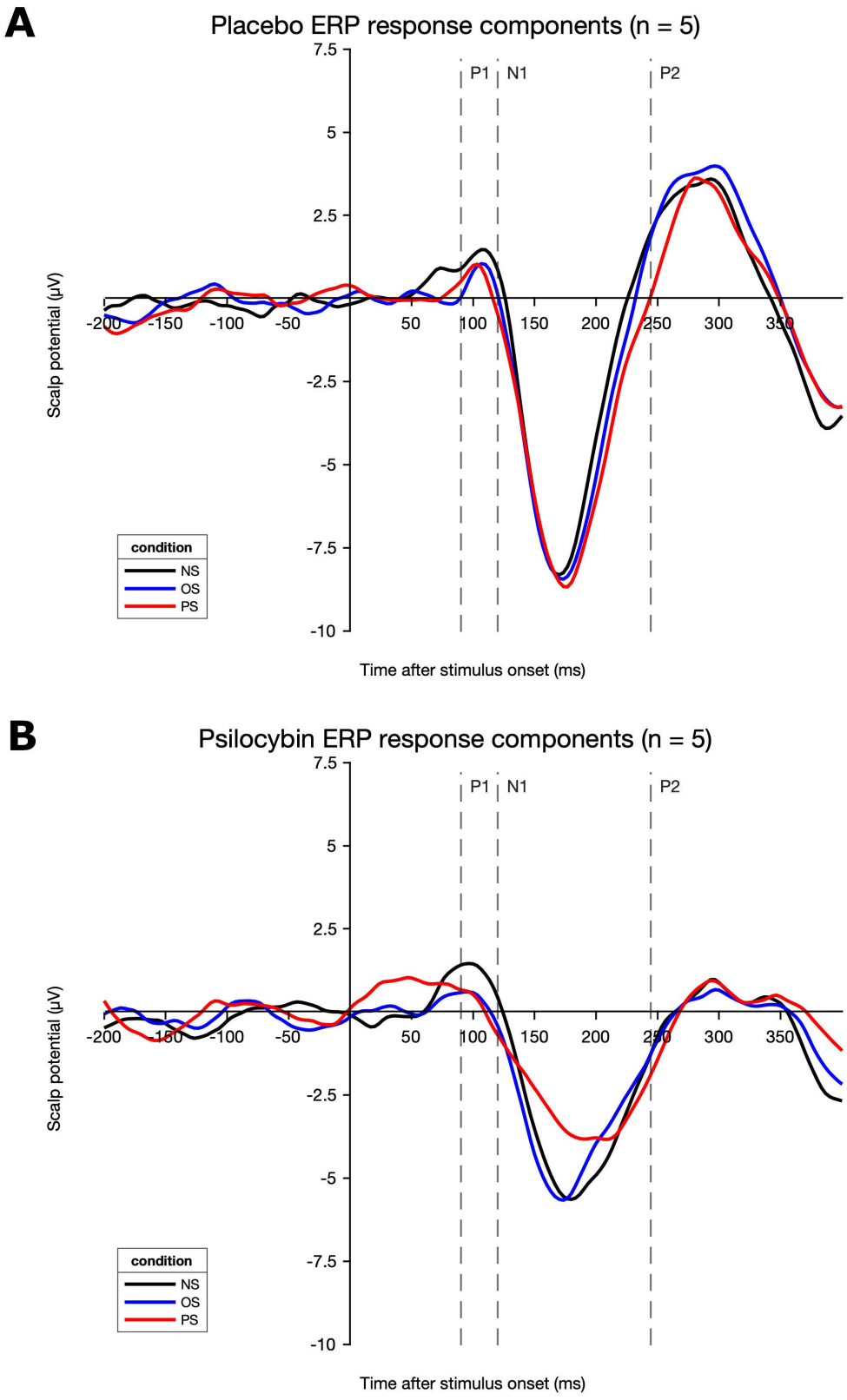

Figure 4.6: Full ERP waveform showing mean amplitude time course over the epoch time window for all three stimulus conditions under placebo (**A**) and psilocybin (**B**).

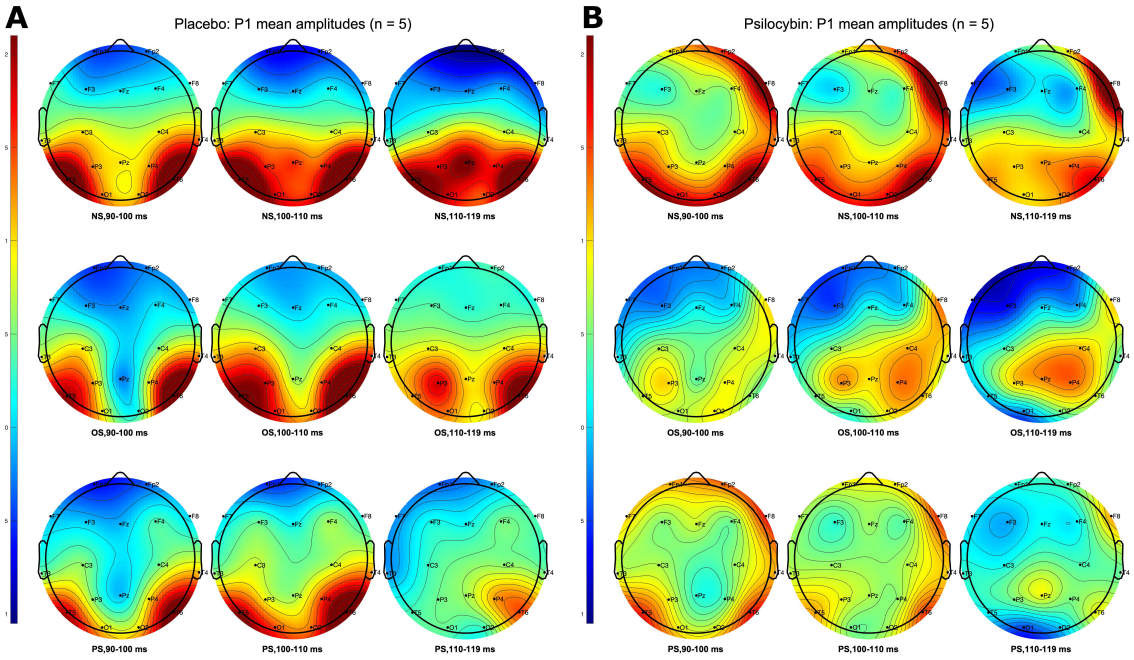

Figure 4.7: Mean amplitude of all electrodes during three temporal segments within the P1 time course in each stimulus condition under placebo (**A**) and psilocybin (**B**).

Table 4.4: Mean ERP amplitude for the P1 component in each stimulus condition measured under psilocybin and placebo.

	mean ± SEM	
condition	**placebo**	**psilocybin**
NS	1.506 ± 0.642	1.451 ± 0.426
OS	0.977 ± 0.347	0.553 ± 0.455
PS	0.853 ± 0.382	0.381 ± 0.427

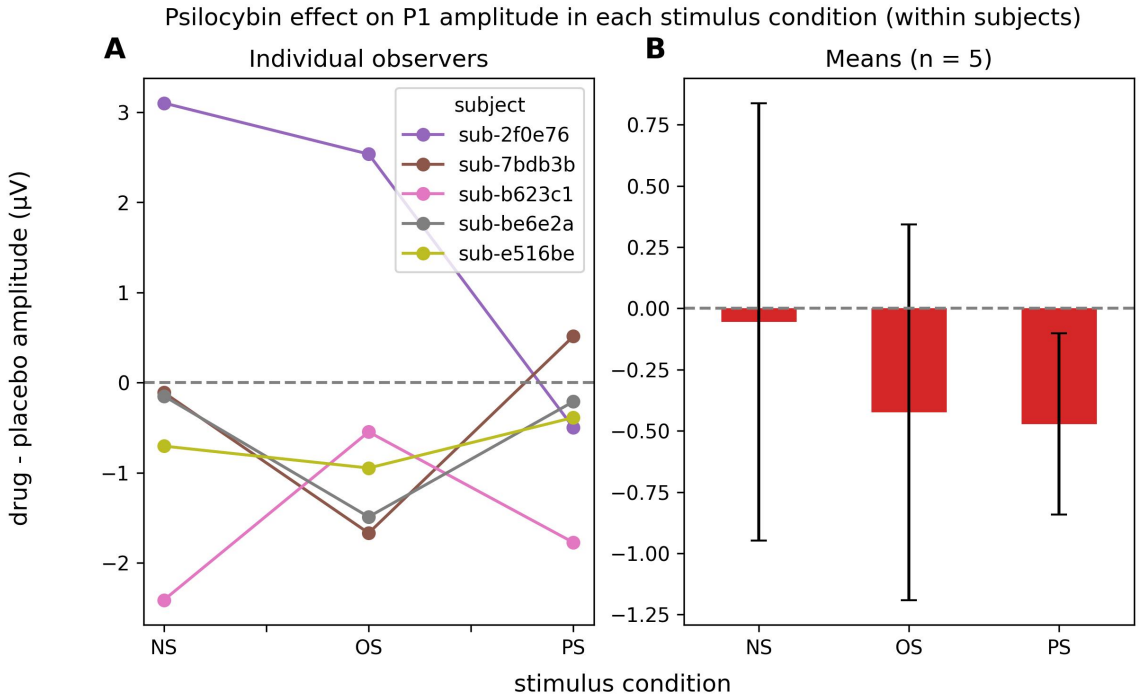

Figure 4.8: Within-subjects effects of the drug were calculated by subtracting the P1 amplitude measured under placebo from that measured under psilocybin for each stimulus condition. Panel **A** shows the effect of psilocybin on P1 amplitude for each individual participant. Panel **B** shows the mean effect for each stimulus condition. Error bars represent standard error of the mean (SEM).

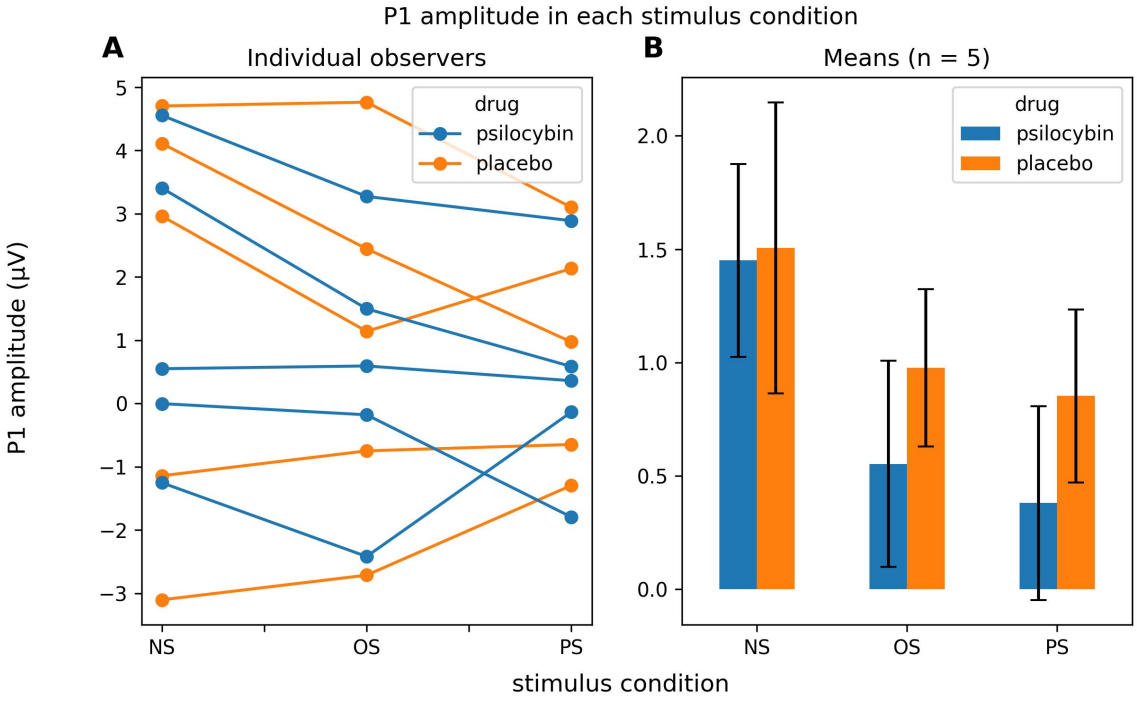

Figure 4.9: P1 amplitudes under psilocybin (blue) and placebo (orange) for the No Surround (NS), Orthogonal Surround (OS), and Parallel Surround (PS) stimulus conditions. Panel **A** shows amplitudes for individual participants in each stimulus condition. Panel **B** shows means that have been normalized according to the technique in Morey (2008) for within-subjects data. Error bars represent standard error of the mean (SEM).

4.3.2 N1 component (120.0 - 243.0 ms)

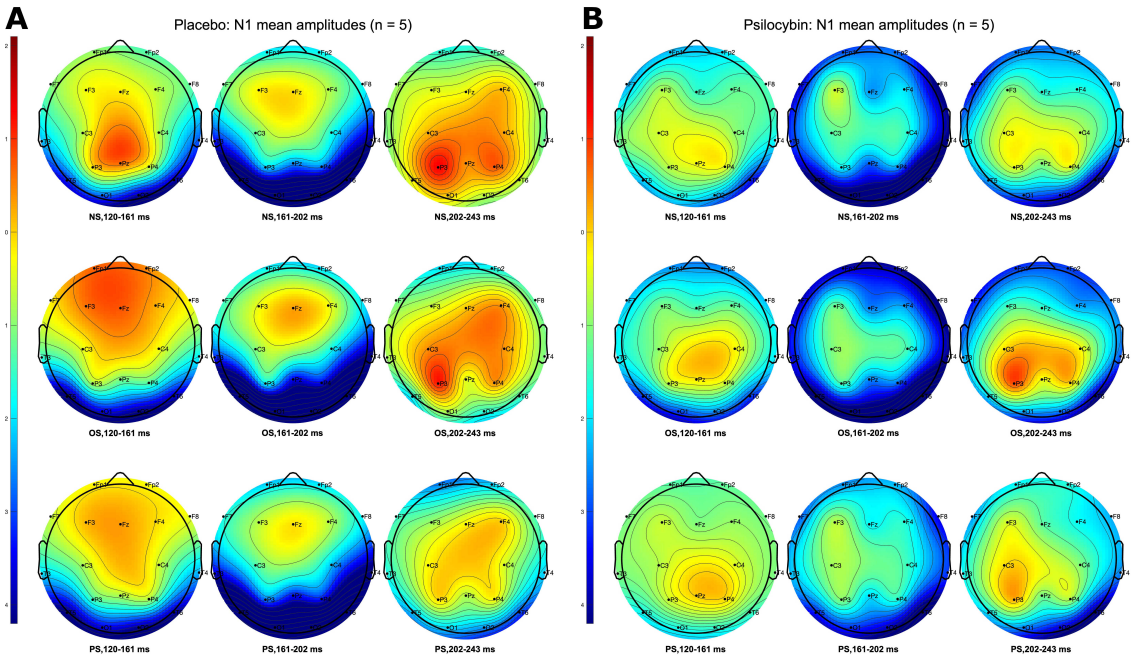

Figure 4.10: Mean amplitude of all electrodes during three temporal segments within the N1 time course in each stimulus condition under placebo (**A**) and psilocybin (**B**).

Main effect of drug on N1 amplitudes did not reach significance ($F_{1,4} = 0.477$, $p = 0.528$, $n_G{}^2 = 0.016$). The main effect of stimulus condition did not reach significance, likely due to insufficient statistical power ($F_{2,8} = 0.192$, $p = 0.829$, $n_G{}^2 = 0.001$). The drug × condition interaction effect reached significance ($F_{2,8} = 4.611$, $p = 0.047$, $n_G{}^2 = 0.011$).

A Shapiro-Wilk test did not show evidence of non-normality in the placebo ($W = 0.9$, $p = 0.096$) or the psilocybin ($W = 0.925$, $p = 0.229$) amplitudes data.

Subsequent *post hoc* pairwise t test (two-sided) comparisons in which the N1 amplitudes from each stimulus condition were compared between psilocybin and placebo did not reveal a main effect of drug on N1 amplitude ($t_4 = -0.69$, $p = 0.528$, Bayes factor = 0.48). Further t test comparisons were performed using N1 mean amplitudes from each stimulus condition. For the No Surround (NS) condition, drug did not have a significant effect on N1 amplitude ($t_4 = -0.055$, $p = 0.959$, Bayes factor = 0.398). *Post hoc* comparisons did not reveal an effect in the Orthogonal Surround

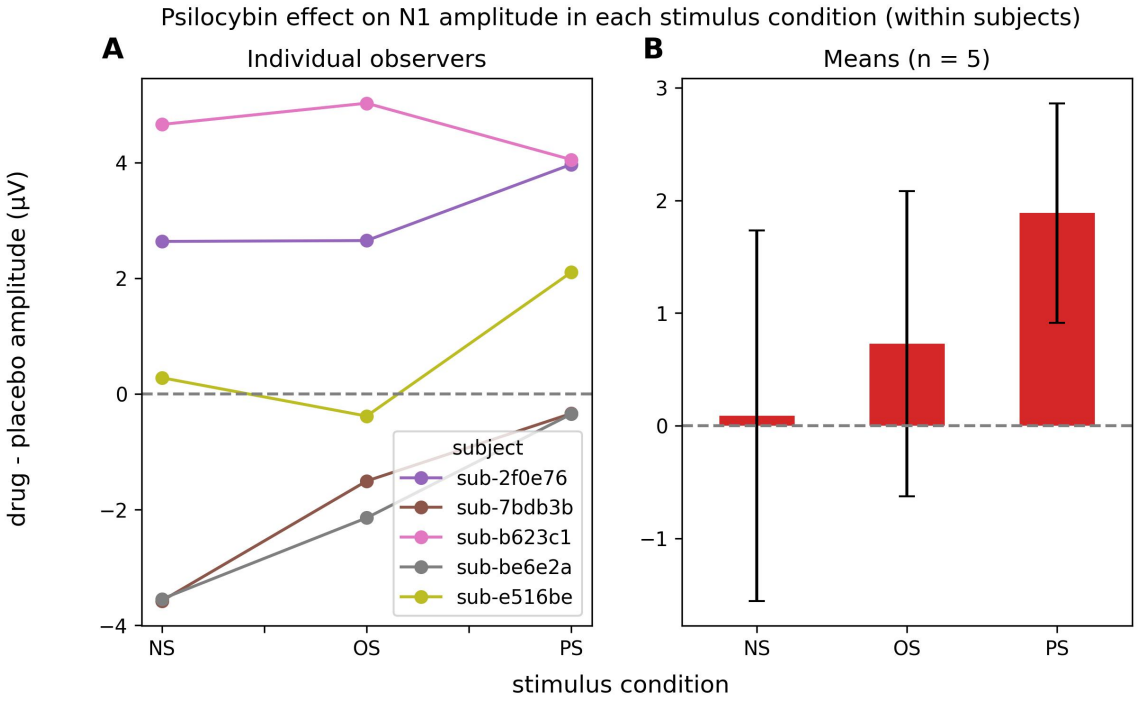

Figure 4.11: Within-subjects effects of the drug were calculated by subtracting the N1 amplitude measured under placebo from that measured under psilocybin for each stimulus condition. Panel **A** shows the effect of psilocybin on N1 amplitude for each individual participant. Panel **B** shows the mean effect for each stimulus condition. Error bars represent standard error of the mean (SEM).

Table 4.5: Results from a two-way repeated measures ANOVA comparing the effect of drug, stimulus condition, and their interaction on mean amplitudes in theN1 component time window.

Source	Sum Sq.	df1	df2	Mean Sq.	F	p	ng2
drug	6.11	1	4	6.11	0.48	0.528	0.016
condition	0.47	2	8	0.24	0.19	0.829	0.001
drug * condition	4.15	2	8	2.07	4.61	0.047	0.011

(OS) condition (t_4 = -0.539, p = 0.619, Bayes factor = 0.447). No significant effect was found in the Parallel Surround (PS) condition (t_4 = -1.936, p = 0.125, Bayes factor = 1.167).

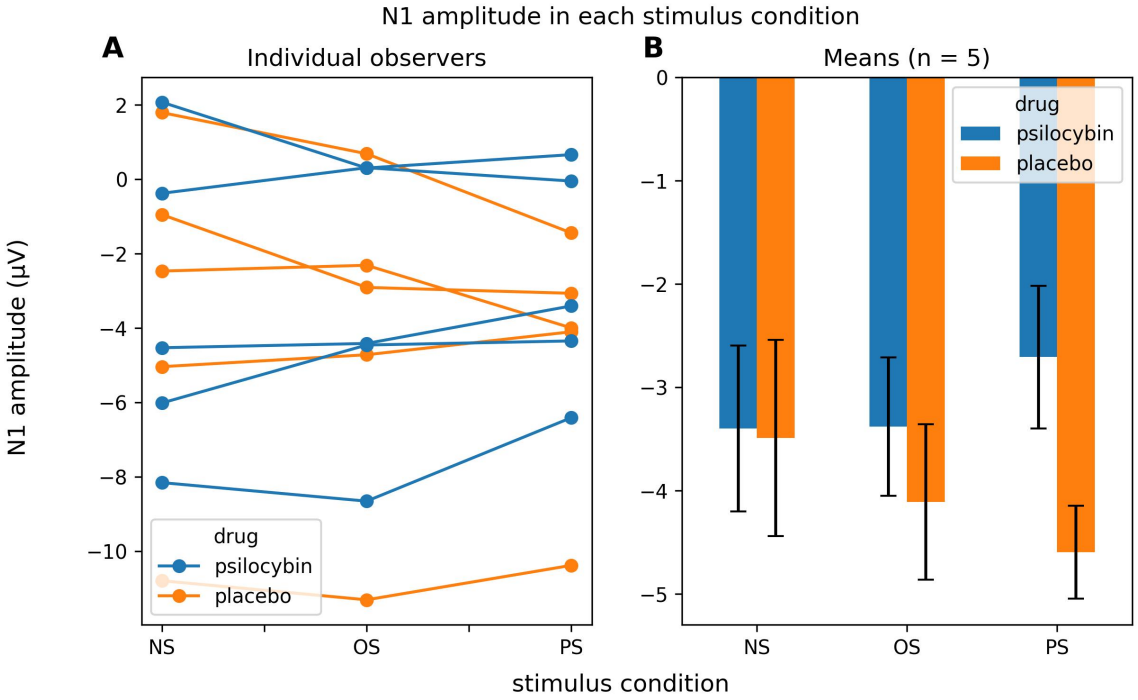

Figure 4.12: N1 amplitudes under psilocybin (blue) and placebo (orange) for the No Surround (NS), Orthogonal Surround (OS), and Parallel Surround (PS) stimulus conditions. Panel **A** shows amplitudes for individual participants in each stimulus condition. Panel **B** shows means that have been normalized according to the technique in Morey (2008) for within-subjects data. Error bars represent standard error of the mean (SEM).

The mean N1 amplitude measured in the No Surround condition under placebo was -3.49μV and under psilocybin was -3.4μV, suggesting that the N1 component was not impacted by psilocybin when no surrounding stimuli were present.

We further confirmed this using a two-sided paired t-test, which found no significant differences between psilocybin and placebo in the no-surround (NS) condition (t_4 = 0.0552, p = 0.9587, d = 0.0202). This supports the notion that the mean trends we observed in the OS and PS surround conditions for the N1 component are specific to stimulus-driven center-surround interactions.

The effect of psilocybin on N1 amplitude for each stimulus condition was quantified

Table 4.6: Mean ERP amplitude for the N1 component in each stimulus condition measured under psilocybin and placebo.

	mean ± SEM	
	placebo	**psilocybin**
condition		
NS	-3.489 ± 0.95	-3.398 ± 0.801
OS	-4.109 ± 0.751	-3.38 ± 0.669
PS	-4.594 ± 0.45	-2.707 ± 0.691

as the psilocybin N1 amplitude minus the placebo N1 amplitude. The mean effect of psilocybin was a shift in the N1 amplitude of 1.887µV in the parallel surround (PS) condition and 0.729µV in the orthogonal surround (OS) condition. By comparison, when stimuli were presented with no surrounds (NS), the difference in the N1 amplitude from placebo to psilocybin was 0.091µV. Figure 4.11 summarizes our results in terms of the effect of psilocybin on N1 amplitude (drug minus placebo) for each stimulus condition.

4.3.2.1 Subjective drug effects and the N1 component

Since ANOVA found some significant effects of drug on N1 amplitudes, we performed rmcorr analyses to assess whether these differences correlated with ratings of subjective drug effects on the 5D-ASC questionnaire. Our analyses found no significant correlations between N1 amplitudes and 5D-ASC subjective rating scores.

4.3.3 P2 component (244.3 - 283.3 ms)

Main effect of drug on P2 amplitudes showed trend effects ($F_{1,4} = 5.831$, $p = 0.073$, ${n_G}^2 = 0.378$). The main effect of stimulus condition did not reach significance, likely due to insufficient statistical power ($F_{2,8} = 2.28$, $p = 0.165$, ${n_G}^2 = 0.019$). The drug × condition interaction effect did not reach significance ($F_{2,8} = 0.647$, $p = 0.549$, ${n_G}^2 = 0.007$).

A Shapiro-Wilk test did not show evidence of non-normality in the placebo ($W = 0.926$, $p = 0.241$) or the psilocybin ($W = 0.925$, $p = 0.231$) amplitudes data.

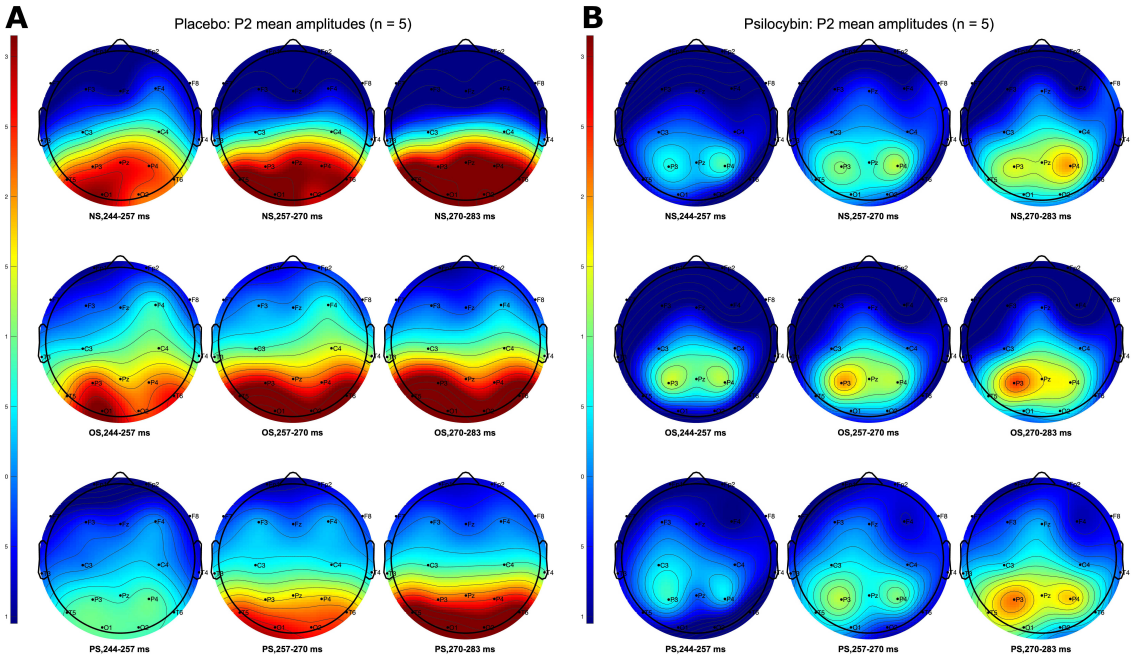

Figure 4.13: Mean amplitude of all electrodes during three temporal segments within the P2 time course in each stimulus condition under placebo (**A**) and psilocybin (**B**).

Table 4.7: Results from a two-way repeated measures ANOVA comparing the effect of drug, stimulus condition, and their interaction on mean amplitudes in theP2 component time window.

Source	Sum Sq.	df1	df2	Mean Sq.	F	p	ng2
drug	71.66	1	4	71.66	5.83	0.073	0.378
condition	2.29	2	8	1.15	2.28	0.165	0.019
drug * condition	0.87	2	8	0.44	0.65	0.549	0.007

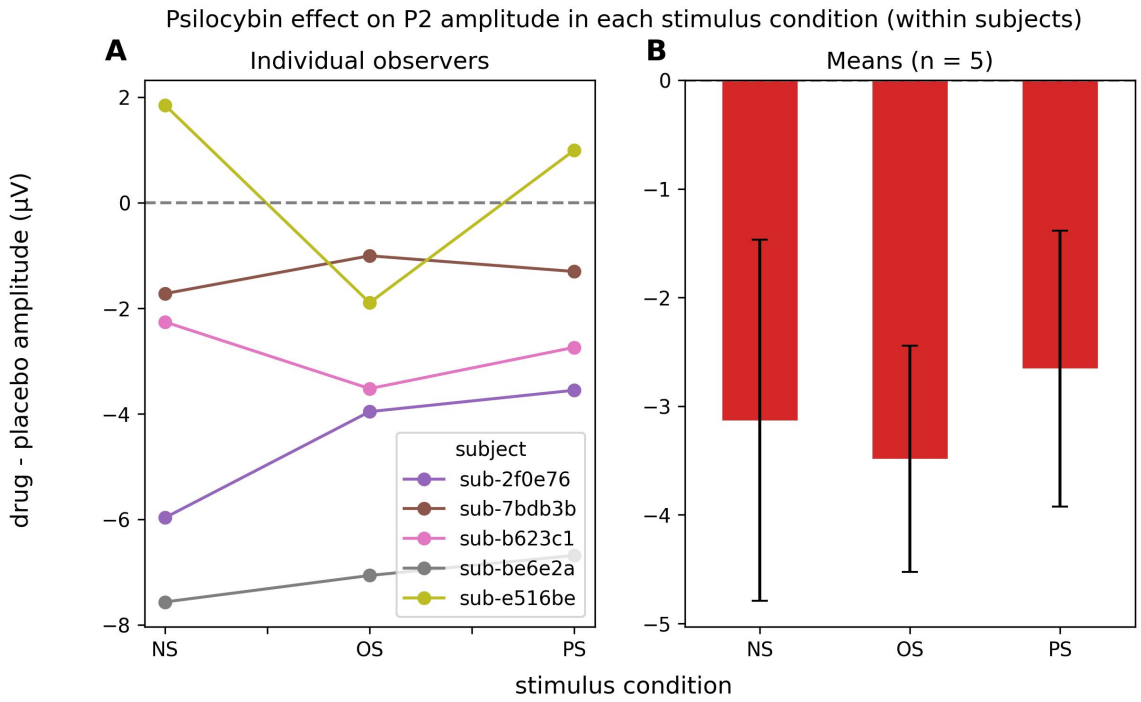

Figure 4.14: Within-subjects effects of the drug were calculated by subtracting the P2 amplitude measured under placebo from that measured under psilocybin for each stimulus condition. Panel **A** shows the effect of psilocybin on P2 amplitude for each individual participant. Panel **B** shows the mean effect for each stimulus condition. Error bars represent standard error of the mean (SEM).

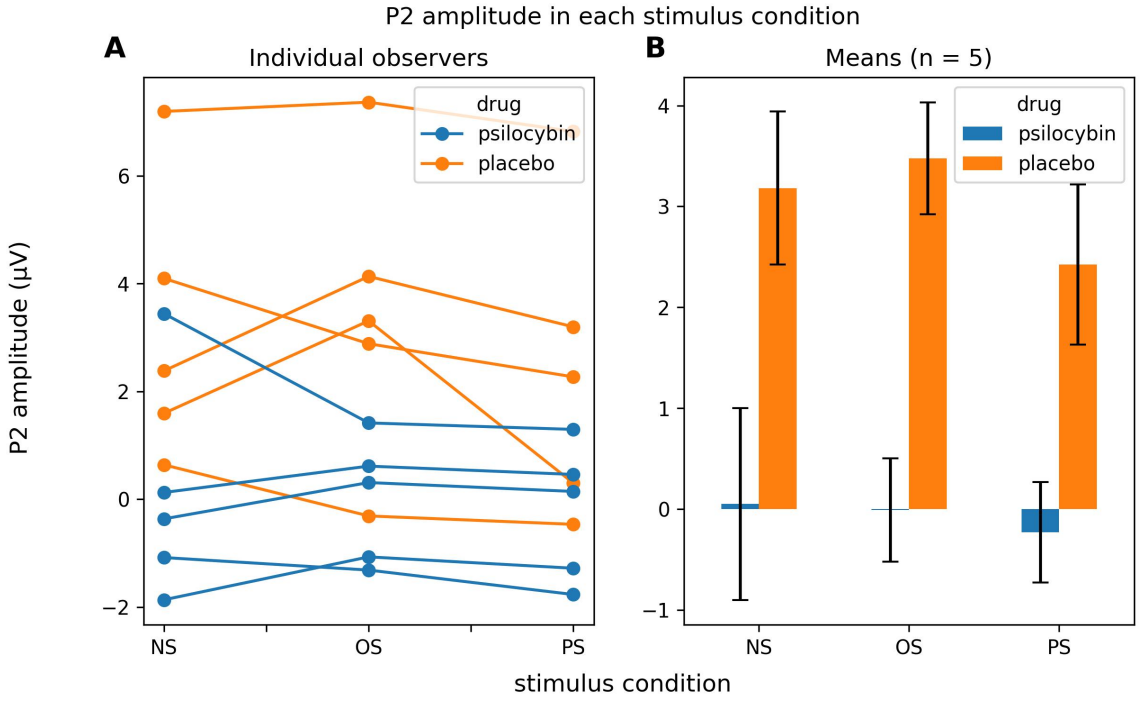

Figure 4.15: P2 amplitudes under psilocybin (blue) and placebo (orange) for the No Surround (NS), Orthogonal Surround (OS), and Parallel Surround (PS) stimulus conditions. Panel **A** shows amplitudes for individual participants in each stimulus condition. Panel **B** shows means that have been normalized according to the technique in Morey (2008) for within-subjects data. Error bars represent standard error of the mean (SEM).

Table 4.8: Mean ERP amplitude for the P2 component in each stimulus condition measured under psilocybin and placebo.

	mean ± SEM	
	placebo	**psilocybin**
condition		
NS	3.182 ± 0.759	0.051 ± 0.95
OS	3.478 ± 0.556	-0.009 ± 0.512
PS	2.425 ± 0.795	-0.23 ± 0.497

The mean P2 amplitude measured in the No Surround condition under placebo was 3.18µV and under psilocybin was 0.05µV, suggesting that the P2 component was impacted by psilocybin even when no surrounding stimuli were present.

The effect of psilocybin on P2 amplitude for each stimulus condition was quantified as the psilocybin P2 amplitude minus the placebo P2 amplitude. The mean effect of psilocybin was a shift in the P2 amplitude of -2.655µV in the parallel surround (PS) condition and -3.487µV in the orthogonal surround (OS) condition. By comparison, when stimuli were presented with no surrounds (NS), the difference in the P2 amplitude from placebo to psilocybin was -3.131µV. Figure 4.14 summarizes our results in terms of the effect of psilocybin on P2 amplitude (drug minus placebo) for each stimulus condition.

4.3.3.1 Subjective drug effects and the P2 component

Since ANOVA found some trend effects of drug on P2 amplitudes, we performed rmcorr analyses to assess whether these differences correlated with ratings of subjective drug effects on the 5D-ASC questionnaire.

On the 5D-ASC scoring scale, rmcorr revealed statistically significant correlations between P2 amplitudes and 5D-ASC scores for the data points (OS, Visionary Restructuralization) (r = -0.866, p = 0.026) and (OS, Oceanic Boundlessness) (r = -0.836, p = 0.038); higher rating scores (more intense subjective drug effect) for the psychedelic effects in these subscales were associated with P2 amplitudes.

Subsequent *post hoc* pairwise biweight midcorrelation tests did not reach significance

Table 4.9: Results from rmcorr repeated measures within-participants correlation of P2 amplitude and ASC subscale scores under psilocybin and placebo.

condition	subscale	dof	r	pval
OS	**Visionary Restructuralization**	4	-0.866	0.026
	Experience of Unity	4	-0.842	0.036
	Oceanic Boundlessness	4	-0.836	0.038
	Blissful State	4	-0.828	0.042
	Audio-Visual Synesthesia	4	-0.825	0.043
PS	**Experience of Unity**	4	-0.827	0.043

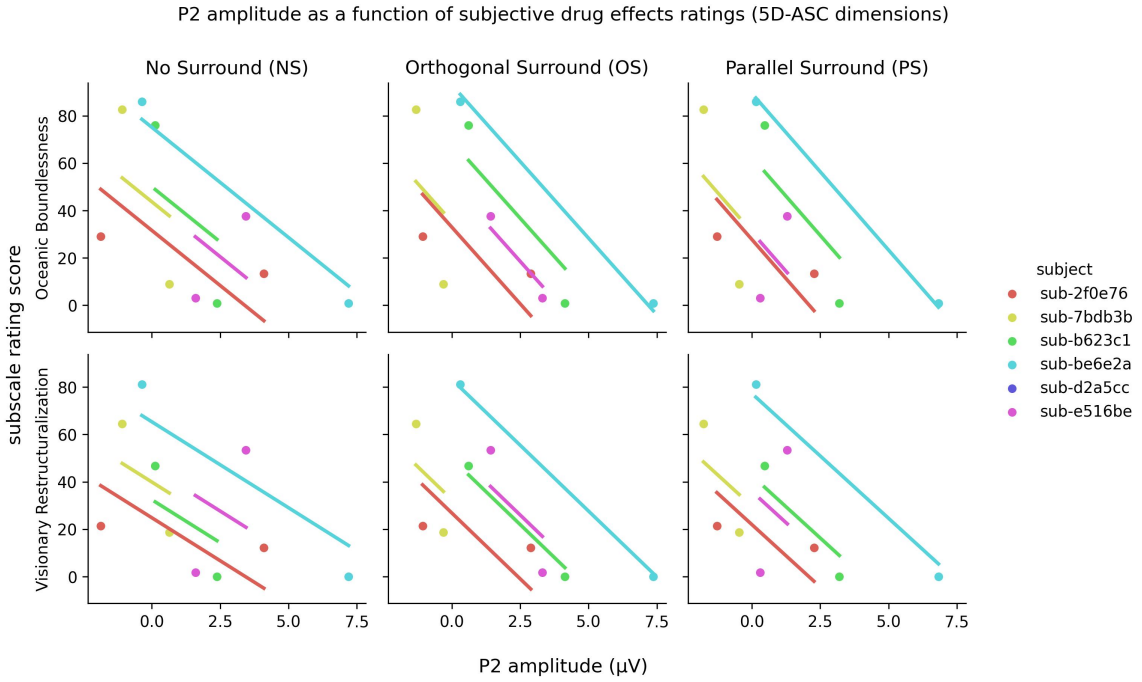

Figure 4.16: Rmcorr plot showing each individual's 5D-ASC dimension scores from placebo and psilocybin as a function of their P2 amplitude in each stimulus condition. The lines show the rmcorr slope fit in relation to each participant's data points.

for any of the significant rmcorr ERP/ASC results for ERP responses in the P2 component.

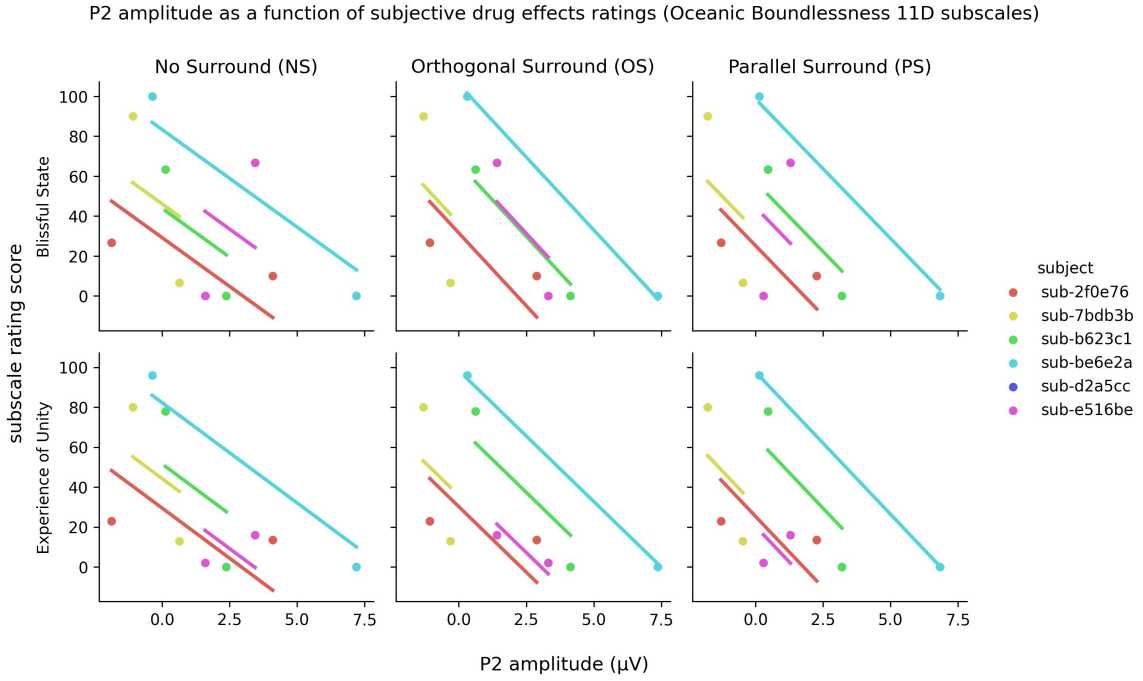

Figure 4.17: Rmcorr plot showing P2 amplitudes as a function of subjective drug effects rating scores on subscales from the Oceanic Boundlessness dimension for each subject in each stimulus condition. The lines show the rmcorr slope fit in relation to each participant's two data points (placebo and psilocybin).

Rmcorr analysis revealed significant correlations between P2 amplitudes and 11D-ASC subscale items at the data points (OS, Experience of Unity) (r = -0.842, p = 0.036), (OS, Blissful State) (r = -0.828, p = 0.042), (PS, Experience of Unity) (r = -0.827, p = 0.043), and (OS, Audio-Visual Synesthesia) (r = -0.825, p = 0.043). For these data points, higher rating scores (more intense subjective drug effect) were associated with P2 amplitudes.

Subsequent *post hoc* pairwise biweight midcorrelation tests reached significance for the data points (OS, Blissful State) (r = -0.85, p = 0.034). The data points for (OS, Experience of Unity) (r = -0.53, p = 0.179), (PS, Experience of Unity) (r = -0.712, p = 0.089), and (OS, Audio-Visual Synesthesia) (r = -0.49, p = 0.201) did not reach significance in the post-hoc tests.

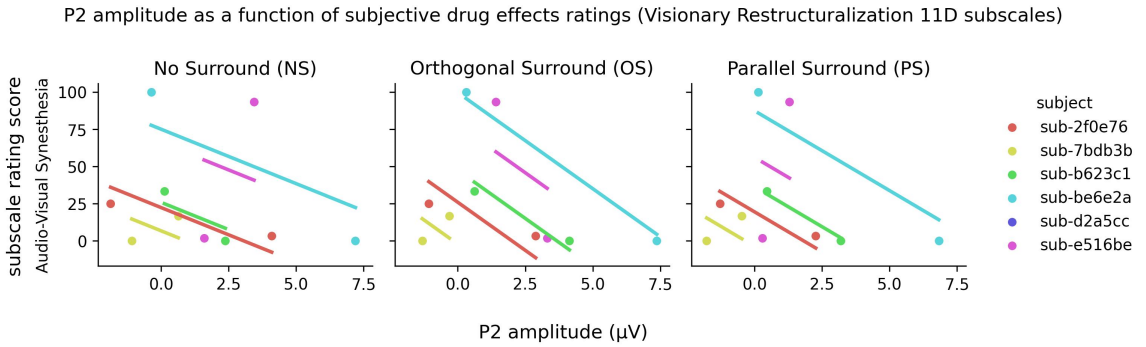

Figure 4.18: Rmcorr plot showing P2 amplitudes as a function of subjective drug effects rating scores on subscales from the Visionary Restructuralization dimension for each subject in each stimulus condition. The lines show the rmcorr slope fit in relation to each participant's two data points (placebo and psilocybin).

Table 4.10: Questionnaire items from 11D-ASC subscale **Audio-Visual Synesthesia** that reached significant correlation with P2 amplitudes in at least one stimulus condition in the rmcorr analysis. Mean scores for placebo (Pla) and psilocybin (Psil) are shown in the right-hand columns.

item	text	Pla	Psil
20	Sounds seemed to influence what I saw.	9	72
23	Shapes seemed to be changed by sounds or noises.	2	52
75	The colors of things seemed to be altered by sounds or noises.	0	44

Table 4.11: Questionnaire items from 11D-ASC subscale **Blissful State** that reached significant correlation with P2 amplitudes in at least one stimulus condition in the rmcorr analysis. Mean scores for placebo (Pla) and psilocybin (Psil) are shown in the right-hand columns.

item	text	Pla	Psil
12	I experienced boundless pleasure.	2	58
86	I experienced profound inner peace.	3	75
91	I experienced an all-embracing love.	3	80

Table 4.12: Questionnaire items from 11D-ASC subscale **Experience of Unity** that reached significant correlation with P2 amplitudes in at least one stimulus condition in the rmcorr analysis. Mean scores for placebo (Pla) and psilocybin (Psil) are shown in the right-hand columns.

item	**text**	**Pla**	**Psil**
18	Everything seemed to unify into a oneness.	3	50
34	I felt one with my surroundings.	7	80
41	I experienced a touch of eternity.	6	59
42	Conflicts and contradictions seemed to dissolve.	5	60
52	I experienced past, present, and future as a oneness.	7	47

4.4 Limitations

This was a pilot study with a small sample size (n = 5). A total of six participants completed the study; however we excluded data from one participant in this analysis due to excessive artifacts in all of their EEG recordings. This skewed the counterbalancing of sex (M = 3; F = 2) and the order in which the participants received the drug (placebo first = 3; psilocybin first = 2).

Our analysis does not include signal source localization analyses to identify the anatomical regions of origin for the ERP responses, other than our choice of including only occipital electrode locations O1 and O2. While we feel that this is appropriate for the early P1 and N1 components (Schallmo, Kale, and Murray 2019), excluding data from the other electrodes likely limits the conclusions that can be drawn from our analyses regarding the P2 component, as the neural responses in this component are usually stronger in higher brain regions. Furthermore, our vendor EEG hardware had 21 channels, which is relatively fewer channels than other ERP studies.

While the visual effects of psilocybin are linked to its 5-HT_{2A} receptor agonism, we did not implement any method for determining whether our findings result from psilocybin's 5-HT_{2A} agonism versus its affinity at other receptor sites. While there are pharmacological methods for investigating this (e.g., by administering ketanserin to block psilocybin's 5-HT_{2A} agonism in a separate experimental condition), we did not employ this method. It will be important to do so in future studies, as Carter,

Burr, et al. (2005) found that at least some cognitive-perceptual effects of psilocybin are not blocked when ketanserin is used to block its 5-HT_{2A} agonism, suggesting that its 5-HT_{1A} agonist properties might also play a role in some of its effects. Taken together, these points illustrate that our findings are inclonclusive about whether 5-HT_{2A} agonism, 5-HT_{1A} agonism, or other pharmacological properties of psilocybin caused the effects on ERP that we observed.

As noted in Section 4.2.2, the EEG task began exactly 5 hours post-drug administration, meaning that the strongest 'peak' drug effects (and plasma levels) had diminished by the time the EEG task started. As a result, all EEG findings should be considered 'post-peak' psilocybin effects. The differences between psilocybin and placebo reported here would likely be stronger if the task had occurred during peak drug effects, but we cannot be sure until future experiments are done at the peak effects (~2.5 hours) timepoint. Furthermore, due to individual differences in drug metabolism rates, there is greater individual variability in the intensity of drug effects at this later time-point. We reason that measurements obtained at the peak-effects time point would show less individual variability.

4.5 Discussion

We obtained EEG recordings while participants viewed visual stimuli with differing center-surround configurations under psilocybin and placebo, and compared ERP responses under each drug. Our analyses of ERP responses were segmented into four time windows (known as ERP components)—P1, N1, and P2 (Table 4.3). We asked whether psilocybin impacted surround suppression, a form of contextual modulation where neural responses differ depending on the center-surround configurations of the stimuli. Previous studies have found that the strength of the N1 response is reduced (amplitude is less negative) when the target stimulus appears within a surround versus when it appears alone, and that this effect is strongest in parallel vs orthogonal surrounds (Schallmo, Kale, and Murray 2019). Our main finding was that psilocybin increased surround suppression in the N1 ERP component time window; i.e., the

magnitude of stimulus-evoked N1 responses was lower for the Parallel Surround stimulus under psilocybin compared with placebo, indicating that psilocybin increased surround suppression (as measured by ERP) in an orientation-selective manner.

4.5.1 Enhanced ERP surround suppression in the N1 component

We observed a marked effect of psilocybin on the average N1 response in the Parallel Surround condition (Figures 4.6, 4.12, and 4.11). ANOVA results revealed a significant interaction effect of drug × condition ($F_{2,8} = 4.611$, $p = 0.047$, $n_G{}^2 = 0.011$). While subsequent *post hoc* pairwise t test (two-sided) comparisons did not confirm the effect of psilocybin on N1 ERP response in the Parallel Surround condition, the statistical effect in the t test for the PS condition (t_4 = -1.936, $p = 0.125$, Bayes factor = 1.167) was much stronger than in the OS condition (t_4 = -0.539, $p = 0.619$, Bayes factor = 0.447) or the NS condition (t_4 = -0.055, $p = 0.959$, Bayes factor = 0.398), indicating that the effect we observed in the PS condition is specific to the parallel orientation of the surround and could possibly reach significance in future research with larger sample sizes.

Due to our small sample size and limited statistical power, the effect we observed on the ERP response in the N1 component should be considered a preliminary trend effect. Nonetheless, it suggests that psilocybin led to an *increase* in contextual modulation: when the target stimulus appeared within a parallel-oriented surround, the mean N1 response (-2.71µV) was less strong (less negative) than it was in the No Surround (-3.4µV) and Orthogonal Surround (-3.38µV) conditions (see Figures 4.6, 4.12, and 4.11). Taken together, this trend suggests that psilocybin may *increase* neural surround suppression in the N1 ERP response, possibly reflecting a *strengthening of contextual modulation* during neural processing after about 120 ms post-stimulus—the Parallel Surround condition having stronger contextual cues than the OS and NS stimuli.

This trend mirrors the behavioral results from the psychophysics experiment in Chapter 3. Using a perceived contrast matching task, we found that surround stimuli

produced a stronger illusion under psilocybin than they did under placebo, leading subjects to perceive the contrast of the target stimulus less veridically compared with placebo. Furthermore, the impact of psilocybin was strongest in the Parallel Surround condition, less strong in the Orthogonal Surround condition, and psilocybin had no impact on contrast perception in the No Surround condition. Thus, the present ERP findings (in N1 responses) are generally consistent with our psychophysical measurements of contrast suppression in perception reported in Chapter 3.

Chapter 2 argues that the visual effects of psychedelic drugs occur because the brain becomes hypersensitive to contextual cues. Section 2.3.3 reviewed multiple studies (Barrett et al. 2018; Carter et al. 2004; Gouzoulis-Mayfrank et al. 2002) which suggest that psilocybin impacts performance on visual tasks if and only if the task induces contextual modulation.

Taken together with our behavioral findings reported in Chapter 3, the present ERP findings lend further support to this theory. The trends we found in the present ERP study provide some evidence that, like task performance, neural responses display greater spatial context-sensitivity under psilocybin. We found that ERP responses evoked by our stimuli under psilocybin were most different from placebo when the stimulus induced strong contextual modulation (i.e., the Parallel Surround). As Figures 4.6, 4.12, and 4.11 show, psilocybin's impact on ERP responses increased as a function of the level of contextual information in the stimuli, suggesting that participants became hypersensitive to visual contextual cues under psilocybin.

4.5.2 The general effect of psilocybin on ERP responses

We found reduced mean amplitudes across all components in the ERP time course under psilocybin. This finding was expected, as MEG and EEG studies have found consistent reductions in amplitudes and oscillatory power across a broad frequency range under psilocybin (Muthukumaraswamy et al. 2013; Kometer et al. 2015; Schartner et al. 2017), as well as ayahuasca (Riba et al. 2002, 2004; Schenberg et al. 2015; Valle et al. 2016) and LSD (Carhart-Harris, Muthukumaraswamy, et al. 2016; Schartner et al. 2017).

As shown in Figure 4.6, all ERP components were less pronounced (the peaks of the waveform are 'flattened') under psilocybin compared with placebo. The significant correlations we found between P2 amplitudes and intensity of subjective effects is likely due to the general reduced amplitude in all ERP components under psilocybin, which would trigger significant correlations with higher scores on the 5D-ASC in response to the psilocybin experience. Furthermore, our analyses are not ideal for probing the effect of psilocybin on the later ERP components (e.g., the P2), as we confined our analyses to data in the occipital electrodes of interest (O1 & O2); the later-latency components should be investigated using a different (and broader) selection of electrode sites. We are therefore reluctant to draw conclusions from the correlations we reported between subjective effects and reduced ERP responses in the P2 component time window. Nonetheless, the results have been included here to inform future hypotheses and study designs.

4.5.3 Contextual modulation, top-down feedback, and 5-HT_{2A}

Schallmo, Kale, and Murray (2019) argue that feature-selective N1 surround suppression reflects top-down feedback modulation from higher to lower visual areas, consistent with findings from electrophysiology in primates Webb et al. (2005). When our result is considered within this line of reasoning, the (preliminary) conclusion is that psilocybin *enhanced* top-down modulation, because the magnitude of the N1 response was suppressed in a feature-selective manner, consistent with stronger top-down feedback on V1 responses.

Our finding is thus inconsistent with the theoretical tenets of Carhart-Harris and Friston (2019), who argue:

> that psychedelics act preferentially via stimulating 5-HT_{2A}Rs on deep pyramidal cells within the visual cortex as well as at higher levels of the cortical hierarchy ... Computationally, this process corresponds to reducing the precision of higher-level prior beliefs ... It is our view that psychedelics affect not just high-level priors but intermediate-level priors also (e.g., those instantiated within the visual cortex) (Carhart-Harris and Friston 2019).

The "REBUS" model thus proposes a fundamental tenet of "*reduced* top-down processing under psychedelics" (Carhart-Harris and Friston 2019, emphasis added) including feedback from higher to lower visual areas. However, our findings suggest the opposite. The enhanced feature-selective N1 surround suppression under psilocybin we observed here suggests that psilocybin *increased* top-down feedback from higher to lower visual areas. The differences between our stimulus conditions (no surround vs. parallel vs. orthogonal surround) are reasonably assumed to depend on top-down priors recruited during stimulus processing. As the enhanced N1 surround suppression we observed was feature-selective, basic visual priors appear to be preserved—and their influence strengthened—under psilocybin. Taken together, these considerations illustrate how our result might contribute to the ongoing debates, (Corlett, Frith, and Fletcher 2009; Pink-Hashkes, Rooij, and Kwisthout 2017; Letheby and Gerrans 2017; Swanson 2018; Carhart-Harris and Friston 2019), which currently present conflicting heterogenous interpretations (see Chapter 1, Section 1.5.3 and also Chapter 2 Section 2.3.4) about how to characterize serotonergic psychedelic effects within a theoretical framework of predictive processing.

4.5.4 Future research

Future ERP studies with psychedelics are needed to more precisely characterize the impact of psychedelics on visual stimulus-evoked ERPs. The present study demonstrates that differences in responses across the ERP time course can be measured under psychedelics using carefully designed stimulus conditions. Moreover, theoretically impactful predictions can be tested—regarding visual processing, serotonin, and psychedelic effects—using such pharmaco-EEG paradigms.

Conclusion

In this dissertation, I examined the effects that psychedelic drugs have on visual perception. In this final chapter I summarize the key findings, discuss their implications, and suggest ways in which this work might contribute to our knowledge of visual perception, psychedelic drugs, and mental health. I also note important limitations and suggest areas of future research.

Main findings

The research question of my historical literature review in Chapter 1 was: What is the best explanation of psychedelic drug effects to date? After examining and comparing early and more recent theories of psychedelic effects, I concluded that a truly unifying understanding has yet to emerge. I identified some important universal themes—in particular, the notion that psychedelics 'loosen constraints' on neural activity, widening the 'filter' or opening up the 'reducing valve' of the mind. I noted that this general idea, which inspired Osmond and Huxley to coin the word 'psychedelic', has roots in the ideas of James (1890), Bergson (1911), Broad (1923), and Freud (1895). This idea is often leveraged to explain why psychedelic effects overlap with symptoms of early psychosis, which *prima facie* appear to share presentation of hallucinatory and mystical themes. The reasoning is that psychedelics can 'model psychoses' because they 'loosen constraints' on the mind (Osmond and Smythies 1952). I pointed out that contemporary theoretical neuroscience continues to think along these lines. Entropic Brain Theory characterizes the "system-level mechanics of the psychedelic state as an exemplar of a regressive style of cognition that can also be observed in REM sleep and

early psychosis" (Carhart-Harris et al. 2014, 5). These system-level mechanics have been characterized in terms of hierarchical predictive coding as a *reduced influence* of higher over lower cortical areas (Carhart-Harris and Friston 2019), an idea linked to Freud's neural theory of ego function (Carhart-Harris and Friston 2010; Savage 1955; Klee 1963). A central idea in predictive coding theories of brain function is that "high-level areas tell lower levels to 'shut up' " (Kersten, Mamassian, and Yuille 2004, 297). Carhart-Harris and Friston (2010) argue that under psychedelics higher-level cortical structures are less likely to suppress activity in lower areas, and in a later paper Carhart-Harris and Friston (2019) see this as a property that psychedelic states share with schizophrenia, stating that "our view of the etiology of schizophrenia is that ... the brain's highest-level priors are ineffective, meaning bottom-up prediction errors travel more freely up the hierarchy ... This much is consistent with the psychedelic experience". Taken together, the idea is that top-down feedback modulation is reduced under psychedelics, and that this process is also at play in the processing characteristic of schizophrenic patients.

Thus, on the above model, surround suppression should be *weaker* in schizophrenic patients. Indeed, weakened surround suppression has been found in schizophrenic patients (Dakin, Carlin, and Hemsley 2005; Tadin et al. 2006; Yoon et al. 2009; Yang et al. 2012; Tibber et al. 2013; Serrano-Pedraza et al. 2014; Schallmo, Sponheim, and Olman 2015; V. J. Pokorny et al. 2019; Linares et al. 2020). Based on these findings, taken together with the idea that psychedelic states follow a comparable pattern of 'weakened priors' and reduced top-down feedback modulation of higher over lower cortical areas, our initial hypothesis was that we would find weaker surround suppression under psilocybin. However, this hypothesis was not confirmed, as both the behavioral results from our psychophysics experiment and the ERP results from our EEG experiment found *stronger* surround suppression under psilocybin.

Our psychophysical experiment in Chapter 3 found that surround suppression was *stronger* under peak effects of a high dose of psilocybin in healthy human participants. In this experiment, some trials involved context-modulating (surround) stimuli, while other trials did not. For the trials using stimuli not designed to modulate spatial

context, psilocybin had no impact on task performance compared with placebo. By comparison, psilocybin significantly impacted task performance on trials that presented the target stimulus within a context-modulating surround stimulus. The direction of impact was that psilocybin *increased* the influence that the surround had over the percept of the target stimulus. In other words, under peak effects of psilocybin, surround suppression was enhanced; the strength of the illusion was greater; the percept of the target stimuli was less veridical. These results suggest that some of the visual effects of psilocybin and other classic serotonergic psychedelic drugs may reflect increased contextual modulation in perception. The findings presented in Chapter 3 addressed my third research objective—To measure the impact of a psychedelic drug on visual contrast perception and surround suppression in humans—as well as my third research question: Does psilocybin impact contrast perception and surround suppression in humans? The results indicate that contrast perception is preserved under psilocybin when the target stimuli appear in isolation, but the influence of higher-contrast surrounding stimuli is stronger, suggesting that the drug selectively targets contextual modulation in visual contrast perception.

In Chapter 4 we used similar stimuli to measure evoked neural responses with EEG equipment, and analyzed the event-related potentials (ERPs) that occurred under psilocybin and placebo. We found a preliminary result indicating that psilocybin increased the effect that the surround stimulus had on the magnitude of the N1 component of the ERP wave form. In other words, psilocybin enhanced surround suppression in the ERP, mirroring the psychophysical results we reported in Chapter 3. Furthermore, the effect of psilocybin on N1 ERP surround suppression was stimulus feature-selective, in that it occurred only in the condition when the surround had the same orientation as the target stimulus. In other words, when the contextual cues were stronger, the visual-evoked ERP response showed the greatest difference under psilocybin compared with placebo.

Returning to theoretical considerations, our finding calls into question the posit (e.g., Carhart-Harris and Friston 2019) that psychedelics weaken the kind of top-down feedback that surround suppression is thought to stem from. Our findings, while

preliminary, are thus anomalous to the idea that psychedelics work by weakening top-down feedback in perceptual processing. They also challenge the century-old 'model psychoses' assumption that psychedelics produce modes of brain function comparable to psychosis, as our surround suppression finding (enhanced under psilocybin) is the opposite of what is found in schizophrenia (weakened surround suppression).

I thus began to question the theoretical notion that psychedelic effects result from weakened influence of priors, asking: What alternative mechanism would cause psilocybin to enhance surround suppression? One way to address the tension between our findings and Carhart-Harris and Friston (2019), who state that "the relaxation of high-level priors [under psychedelics] necessarily implies a liberation of bottom-up information flow" would be to consider the possibility that psilocybin-induced enhancements of surround suppression might be the result of increased weighting of bottom-up cues that *trigger* top-down feedback, whereby the 'liberated' bottom-up signals (i.e., the surround stimulus) are more likely to trigger *stronger* top-down effects (i.e., the suppression illusion) under psychedelics. However, this interpretation would still be in conflict with the core hypotheses of Carhart-Harris and Friston (2019) and Pink-Hashkes, Rooij, and Kwisthout (2017) who clearly argue that psychedelics *weaken* top-down processes. The alternative I propose is that the brain becomes more sensitive to bottom-up cues, and in response recruits *stronger* top-down feedback from higher-level priors.

In Chapter 2 I argued in support of the notion that many hallmark psychedelic effects might be understood as resulting from psychedelic molecules inducing a hypersensitivity to contextual cues. The same mechanisms of contextual modulation that produce classic visual illusions in everyday perception—which are thought to involve top-down feedback from higher-level priors, triggered by specific stimulus properties—may be selectively impacted by psychedelic drugs, exaggerating everyday visual context effects to produce characteristic psychedelic visuals. I then argued that, if the mechanisms of contextual modulation that produce classic everyday illusions were exaggerated pharmacologically, the resulting phenomenology would potentially match that of classic open-eyed psychedelic visuals. Importantly, this theoretical

principle has advantages over existing theories reviewed in Chapter 1 because it can be operationalized both empirically (using well-known psychophysical paradigms that induce and measure contextual modulation) as well as neurocomputationally (using divisive normalization and/or predictive coding models of visual illusions). I named this idea hypercontextual modulation (HCM) and applied it to explain not only psychedelic visuals, but also classic psychedelic effects in non-visual modalities, including music listening, cognitive semantic activation, and symbolic thinking. Taken together, the analysis presented in Chapter 2 addressed my second research objective—To taxonomize and analyze the phenomenology of psychedelic visuals—as well as my second research question: Do psychedelic drugs affect contextual modulation in visual processes?

In summary, the main takeaways from this dissertation are as follows. First, existing theories of psychedelic effects present conflicting and heterogenous posits (Chapter 1). Second, our (preliminary) results found that psilocybin enhanced surround suppression in perception and in neural responses (Chapters 3 & 4). Third, our findings are in tension with the idea that psychedelic effects result from weakened influence of top-down priors, and challenge the assumption that psychedelic states share patterns of neural processing with psychosis. Fourth, an alternative view of psychedelics was proposed to resolve these tensions; namely the idea of hypercontextual modulation, which understands psychedelic effects as resulting from over-active contextual modulation in response to bottom-up contextual cues (Chapter 2). Fifth and more generally, I hope that this dissertation demonstrates the promise of focused thinking about the *visual* effects of psychedelics. I argue that treating psychedelic visuals as specimens to be examined toward understanding psychedelic action in the brain is a pragmatic approach. Visual perception is relatively well-understood (in comparison with other mental functions) and thus experiments can be designed to characterize the ways in which psychedelics alter neural and perceptual responses to visual stimuli, providing scoped characterizations of high scientific value.

Contributions and significance

The most straightforward contribution of this dissertation is to the field of visual neuroscience. The experimental findings in Chapters 3 and 4, which suggest that psilocybin selectively enhances surround suppression in human contrast perception, indicate that serotonergic (5-HT_{2A}/5-HT_{1A}) signaling is used by the visual system to shape neural responses according to contextual cues. Because the visual effects of psilocybin are critically linked to activation of 5-HT_{2A}/5-HT_{1A} receptors, our findings hint that serotonergic mechanisms may underlie the suppression (and possibly also facilitation) of neural responses to visual stimuli. Moreover, the analysis in Chapter 2 provides rationale to suspect that serotonin might be a canonical sensory neuromodulator that shapes experience in response to contextual cues in vision, possibly other perceptual modalities, and even cognition. The general logic is this: (1) psychedelics alter perception and cognition in characteristic ways, (2) these alterations depend on 5-HT_{2A}/5-HT_{1A} agonism, (3) therefore, 5-HT_{2A}/5-HT_{1A} signaling may be critically involved in certain everyday perceptual functions. The present work demonstrates how probing the serotonin-perception relationship using targeted analytical and empirical methods can have significant scientific payoff toward understanding how visual perception is implemented in the brain.

The second contribution is to the field of psychedelic research. Psychedelic experiences are unique mental phenomena that the cognitive sciences and philosophy have largely missed out on—and have almost completely ignored—since 1970. As a result, works that apply modern methods to psychedelic phenomena are currently in high demand. Chapter 1 was published in *Frontiers in Pharmacology* in 2018. The essence of this contribution is in its synthesis—it has served as a conceptual anchor-point within which researchers have framed their questions and interpreted their results. Citing publications often reference Chapter 1 for its synthesis of theoretical concepts and its analysis of open research questions. It is also commonly referenced as an overview of the phenomenology of acute psychedelic drug effects. As Chapter 2 provides analyses, literature review, and descriptions of visual phenomenology, it has the potential to

have a similar impact on psychedelic research.

As mentioned in the Introduction chapter, the visual effects of psychedelics have been largely understudied for the past 100 years, since the early work of Klüver (1928), and remain in the sidelines as recent work has focused instead on task-free (resting-state) neuroimaging and subjective ego-dissolution and mystical experiences. Thus, the visual-focused analysis in Chapter 2, the psychophysical experiment in Chapter 3, and the visual task-oriented EEG experiment in Chapter 4 all address important gaps in contemporary knowledge of how psychedelics impact visual perception. The empirical chapters are likely to spur more studies into how psychedelics alter contextual modulation in perception. The theory that I propose in Chapter 2 will hopefully contribute new ways of understanding psychedelic drug mechanisms; namely, that many effects might be due to selective exaggeration of contextual modulation processes in neural responses.

The third contribution is to the field of psychiatry. Currently, the arguably impressive therapeutic efficacy of psilocybin remains scientifically mysterious and actively debated (Yaden and Griffiths 2020; Letheby 2021; Hesselgrave et al. 2021; McClure-Begley and Roth 2022; Berg et al. 2022). A central contribution to psychiatry that I make with the present work is the suggestion that psilocybin (and other classic serotonergic psychedelics) shift sensory processing in the *opposite direction* of the sensory deficits found in the disorders that psilocybin is effective at treating. For instance, a recent study found that patients actively experiencing major depressive episodes show *weakened* surround suppression in visual contrast perception relative to healthy controls (Salmela et al. 2021), while our results in Chapter 3 found that psilocybin *strengthened* surround suppression relative to placebo in healthy participants, and the same stimuli evoked *greater* surround suppression in EEG/ERP responses as reported in 4. Meanwhile, other studies have shown that depressed patients show blunted reactions to emotional face stimuli, while psilocybin has been shown to *enhance* reactions to faces. In Chapter 2 I argue that the hypersensitivity induced by psychedelics might serve to counteract the *hypo*sensitivity to sensory cues found in patients with active depressive episodes (i.e., anhedonia, reduced appreciation

for music, reduced sense of richness in sensory phenomenology). Thus, the contribution to psychiatry and psychedelic therapy that I make in the present work is the notion that hypercontextual modulation is a candidate mechanism by which these drugs confer therapeutic benefits for certain patients. Importantly, this notion offers greater scientific tractability than alternative theories that currently emphasize ego-dissolution and mystical experiences as causal therapeutic mechanisms, as these concepts are by comparison more challenging to operationalize clinically. Furthermore, the empirical and analytical contributions I make in this dissertation, while preliminary, have the potential to spur innovations in clinical practices that use psychedelic drugs to improve mental health, perhaps by inspiring methodologies that better harness the context-modulating properties of these drugs.

Limitations

The main empirical limitation of the experiments in Chapters 3 and 4 is the small number of participants (n = 6). Psychedelic research is resource-intensive, requiring significant amounts of funding for administrative staff, facilities, and large amounts of time for navigating complex regulatory requirements of the research institution and the federal government. While I feel lucky to have been able to collect data from this many participants for the present dissertation, the results of the empirical chapters should be considered preliminary findings from a pilot study. I am hopeful that the future will bring further opportunities to confirm the findings, refine the methodologies, and test alternative hypotheses.

The empirical chapters excluded drug-naive participants. This decision was made due to the demanding nature of completing the visual tasks under a high dose of psilocybin, and we felt that some prior experience with the effects of psilocybin would reduce the likelihood of participants becoming overwhelmed by the stimuli and the task. This limits the generalizability of our findings; the measurements may have turned out differently if we had included drug-naive participants. A second limitation with the EEG experiment, as noted in Chapter 4, is that the task was performed 'post-peak', 5

hours after psilocybin administration, while the most intense subjective effects had diminished (the psychophysics experiment, by contrast, was completed during peak effects). Thus, the neural responses we measured with EEG are not reflective of brain activity during peak drug effect. A third limitation that applies to both experiments is that we did not attempt to isolate 5-HT_{2A} from other receptor agonism produced by psilocybin, so we cannot determine which pharmacological properties of psilocybin were responsible for the effect we measured.

Chapter 2 is my own theoretical contribution. It is based on first-principles analysis, taking subjective phenomenology as a starting point, then applying analytical reasoning to interpret previous empirical findings to arrive at a theory of how psychedelics alter perception and other mental processes. Although philosophy has preceded scientific progress throughout history, this type of approach has its limitations. The arguments I offer demand empirical vetting. Though the findings from the experiments in Chapters 3 and 4 are highly consistent with the theoretical conclusions I draw in Chapter 2, further inquiry is needed.

While the insights and findings presented here have bearing on understanding how psychedelics facilitate therapy and mental health—and I hope they will do so—they are not intended to serve as prescriptive therapeutic practices, and it is important to emphasize that the mechanisms and efficacy of psychedelics in treating mental health disorders remain largely unknown. The passages in which I discuss therapeutic mechanisms should be considered entirely speculative. They are offered solely as conceptual navigation tools for future research.

Finally, I wish to point out that analytical reasoning and scientific methods have upper limits in what they can offer toward improving our understanding of psychedelic experiences. Experiments, models, theories, and verbal descriptions of subjective experience do not capture the complete nature of the rich subjective phenomena that psychedelics produce in human consciousness. The experiences that these molecules engender remain *qualitatively* mysterious and elusive.

Future research

The central finding of the present work is that psychedelics impact visual processes in a feature-selective and context-sensitive manner. We found that both perceptual and neural responses to visual stimuli differed most from placebo when the stimulus was designed to elicit contextual modulation. This finding is consistent with the theoretical framework of hypercontextual modulation proposed in Chapter 2 to explain psychedelic visuals and other hallmark psychedelic effects in perception and cognition. While the findings are tentative and preliminary, and the theory is highly speculative, I believe that together they offer a highly promising line of research.

The first task will be to carry out a full-scale study on visual surround suppression under psilocybin. As the present study demonstrates, this paradigm is an effective means of measuring differences in contextual modulation in response to visual stimuli under psychedelic drugs. I envision such a study as involving four key components. First, it should collect at least two separate baseline measurements before any drug is taken. Second, it should be multimodal, collecting three data points under peak drug effects: (1) psychophysical measurements of perception, (2) EEG/MEG measurements for temporal resolution, and (3) fMRI measurements for spatial/anatomical resolution. Third, it should implement dose-response techniques, comparing low-medium with higher drug doses. Fourth, it should implement a separate experimental condition in which a 5-HT_{2A} antagonist drug (such as ketanserin) is administered simultaneously with psilocybin, in order to enable scientific inferences about the neuromodulator mechanisms that are causally involved in surround suppression. Finally, follow-up measurements should be conducted on at least two separate time-points post-drug.

A further expansion of the surround suppression under psychedelics research programme will be to investigate a variety of psychedelic drugs. LSD, DMT, and mescaline each have unique phenomenological profiles and pharmacological properties distinct from psilocybin. It would thus be informative to characterize their impact on visual contextual modulation using the same multimodal paradigm described above.

The next task will be to measure surround suppression in a clinical population of

MDD patients who undergo psilocybin therapy. I envision such a study as measuring surround suppression pre- and post-psilocybin therapy (not during acute drug effects), with a control group of patients who receive non-psilocybin therapy, and another control group of healthy participants. Such a study would provide insight into the relationship between MDD, contextual modulation in visual processing, and the therapeutic mechanisms of psilocybin. Previous work that used stimuli almost identical to ours (Salmela et al. 2021) found *reduced* surround suppression in MDD patients while they were experiencing a major depressive episode (MDE), and that their levels of visual surround suppression returned closer to healthy controls once they were in remission and no longer experiencing an MDE. A future study measuring visual surround suppression in MDD patients at timepoints before and after psilocybin therapy would thus be of great scientific value. It could directly test the hypothesis that blunted contextual modulation in MDD is restored by the hypercontextual modulation induced by psilocybin.

Beyond surround suppression, contextual modulation paradigms in auditory perception, verbal processing, and cognitive tasks should be carried out in healthy participants under acute psychedelic effects. Such experiments would expand the characterization of how psychedelics impact contextual processing across the brain and in different dimensions of mental function.

Once the above data is collected, computational modeling for observed neural and behavioral responses to contextual stimuli will aid the development of theoretical understanding. As mentioned in Chapter 2, divisive normalization is a promising computational model that captures contextual modulation as a canonical computation carried out in multiple neural processes. Future modeling work using data collected from neural responses to context-modulating stimuli under psychedelic drugs could contribute significantly to understanding how the brain modulates its responses using contextual cues, and the neuromodulatory substrates that underpin normalization computations.

Final thoughts

Our minds are fluid manifolds of contextual interactions. Sensory stimuli are continuously bound together into patterns that become subjectively meaningful via processes that have long been elusive. The visual effects of psychedelics magnify this process in a spectacular manner. In the present work, I have used these phenomena as a handle to get a grip on what psychedelics do to human minds. As Metzner and Leary (1967) put it, "A psychedelic experience is a period of intensely heightened reactivity to sensory stimuli from within and without." It is my hope that readers will see the value in taking psychedelic visuals seriously as important phenomena with the potential to enhance our understanding of psychedelics, visual perception, and the way in which our minds transform contextual cues into the subjective stream of meaningful contents that we experience in perception and cognition.

Bibliography

Abbott, L F. 2008. "Theoretical Neuroscience Rising." *Neuron* 60 (3): 489–95. https://doi.org/10.1016/j.neuron.2008.10.019.

Abraham, H. 1996. "The Psychopharmacology of Hallucinogens." *Neuropsychopharmacology* 14 (4): 285–98. https://doi.org/10.1016/0893-133x(95)00136-2.

Abramson, Harold A. 1956. *Neuropharmacology: Transactions of the Second Conference, May 25, 26, and 27, 1955, Princeton, NJ.* Josiah Macy, Jr. Foundation.

———. 1960. *The Use of LSD in Psychotherapy : Transactions of a Conference on d-Lysergic Acid Diethylamide (LSD-25), April 22, 23, and 24, 1959, Princeton, n.j.* New York, N.Y.

Aday, Jacob S., Julia R. Wood, Emily K. Bloesch, and Christopher C. Davoli. 2021. "Psychedelic Drugs and Perception: A Narrative Review of the First Era of Research." *Reviews in the Neurosciences* 32 (5): 559–71. https://doi.org/10.1515/revneuro-2020-0094.

Adelson, Edward H. 2000. "Lightness Perception and Lightness Illusions. The New Cognitive Neurosciences." Cambridge, MA: MIT Press.

Adesnik, Hillel, William Bruns, Hiroki Taniguchi, Z Josh Huang, and Massimo Scanziani. 2012. "A Neural Circuit for Spatial Summation in Visual Cortex." *Nature* 490 (7419): 226–31. https://doi.org/10.1038/nature11526.

Allen, Emily J., and Andrew J. Oxenham. 2014. "Symmetric Interactions and Interference Between Pitch and Timbre." *The Journal of the Acoustical Society of America* 135 (3): 1371–79. https://doi.org/10.1121/1.4863269.

Allen, Micah, and Karl J Friston. 2016. "From Cognitivism to Autopoiesis: Towards a Computational Framework for the Embodied Mind." *Synthese*, December, 1–24. https://doi.org/10.1007/s11229-016-1288-5.

Allman, J, F Miezin, and E McGuinness. 1985. "Stimulus Specific Responses from Beyond the Classical Receptive Field: Neurophysiological Mechanisms for Local-Global Comparisons in Visual Neurons." *Annual Review of Neuroscience* 8 (1): 407–30. https://doi.org/10.1146/annurev.ne.08.030185.002203.

Alonso, Joan Francesc, Sergio Romero, Miquel Àngel Mañanas, and Jordi Riba. 2015. "Serotonergic Psychedelics Temporarily Modify Information Transfer in Humans." *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum* 18 (8). https://doi.org/10.1093/ijnp/pyv039.

Anderson, Barton L., and Jonathan Winawer. 2005. "Image Segmentation and

Lightness Perception." *Nature* 434 (7029): 79–83. https://doi.org/10.1038/nature03271.

Anderson, Michael L, and Tony Chemero. 2013. "The Problem with Brain GUTs: Conflation of Different Senses of 'Prediction' Threatens Metaphysical Disaster." *The Behavioral and Brain Sciences* 36 (03): 204–5. https://doi.org/10.1017/s0140525x1200221x.

Andrade, R. 2011. "Serotonergic Regulation of Neuronal Excitability in the Prefrontal Cortex." *Neuropharmacology* 61 (3): 382–86. https://doi.org/10.1016/j.neuropharm.2011.01.015.

Angelucci, Alessandra, Maryam Bijanzadeh, Lauri Nurminen, Frederick Federer, Sam Merlin, and Paul C. Bressloff. 2017. "Circuits and Mechanisms for Surround Modulation in Visual Cortex." *Annual Review of Neuroscience* 40 (1): 425–51. https://doi.org/10.1146/annurev-neuro-072116-031418.

Angelucci, Alessandra, Jonathan B. Levitt, Emma J. S. Walton, Jean-Michel Hupé, Jean Bullier, and Jennifer S. Lund. 2002. "Circuits for Local and Global Signal Integration in Primary Visual Cortex." *Journal of Neuroscience* 22 (19): 8633–46. https://doi.org/10.1523/JNEUROSCI.22-19-08633.2002.

Appelbaum, L. G., A. R. Wade, V. Y. Vildavski, M. W. Pettet, and A. M. Norcia. 2006. "Cue-Invariant Networks for Figure and Background Processing in Human Visual Cortex." *Journal of Neuroscience* 26 (45): 11695–708. https://doi.org/10.1523/jneurosci.2741-06.2006.

Aqil, Marco, Tomas Knapen, and Serge O. Dumoulin. 2021. "Divisive Normalization Unifies Disparate Response Signatures Throughout the Human Visual Hierarchy." *Proceedings of the National Academy of Sciences* 118 (46). https://doi.org/10.1073/pnas.2108713118.

Araujo, Draulio B de, Sidarta Ribeiro, Guillermo A Cecchi, Fabiana M Carvalho, Tiago A Sanchez, Joel P Pinto, Bruno S de Martinis, Jose A Crippa, Jaime E C Hallak, and Antonio C Santos. 2012. "Seeing with the Eyes Shut: Neural Basis of Enhanced Imagery Following Ayahuasca Ingestion." *Human Brain Mapping* 33 (11): 2550–60.

Argento, Elena, Steffanie A Strathdee, Kenneth Tupper, Melissa Braschel, Evan Wood, and Kate Shannon. 2017. "Does Psychedelic Drug Use Reduce Risk of Suicidality? Evidence from a Longitudinal Community-Based Cohort of Marginalised Women in a Canadian Setting." *BMJ Open* 7 (9): e016025. https://doi.org/10.1136/bmjopen-2017-016025.

Arminjon, Mathieu. 2011. "The Four Postulates of Freudian Unconscious Neurocognitive Convergences." *Frontiers in Psychology* 2 (June): 125. https://doi.org/10.3389/fpsyg.2011.00125.

Artola, T., P. Mosteiro, B. Poveda, J. Barraca, I. Ancillo, and N. Sánchez. 2012. "Prueba de Imaginación Creativa Para Adultos." *Madrid: TEA Ediciones*.

Atasoy, Selen, Gustavo Deco, Morten L Kringelbach, and Joel Pearson. 2017. "Harmonic Brain Modes: A Unifying Framework for Linking Space and Time in Brain Dynamics." *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, September, 1073858417728032. https://doi.org/10.1177/1073858417728032.

Atasoy, Selen, Leor Roseman, Mendel Kaelen, Morten L Kringelbach, Gustavo Deco, and Robin L Carhart-Harris. 2017. "Connectome-Harmonic Decomposition of Human Brain Activity Reveals Dynamical Repertoire Re-Organisation Under LSD." https://doi.org/10.1038/s41598-017-17546-0.

Auerbach, Benjamin D., and Howard J. Gritton. 2022. "Hearing in Complex Environments: Auditory Gain Control, Attention, and Hearing Loss." *Frontiers in Neuroscience* 16 (February). https://doi.org/10.3389/fnins.2022.799787.

Auld, Frank, Gary M. Goldenberg, and Jutta V. Weiss. 1968. "Measurement of Primary-Process Thinking in Dream Reports." *Journal of Personality and Social Psychology* 8 (4, Pt.1): 418–26. https://doi.org/10.1037/h0025488.

Azimi, Zohre, Ruxandra Barzan, Katharina Spoida, Tatjana Surdin, Patric Wollenweber, Melanie D Mark, Stefan Herlitze, and Dirk Jancke. 2020. "Separable Gain Control of Ongoing and Evoked Activity in the Visual Cortex by Serotonergic Input." Edited by Eran Lottem, Joshua I Gold, and Magor Lorincz. *eLife* 9 (April): e53552. https://doi.org/10.7554/eLife.53552.

Baggott, Matthew J. 2015. "Psychedelics and Creativity: A Review of the Quantitative Literature." e1468. PeerJ PrePrints; PeerJ Inc. https://doi.org/10.7287/peerj.preprints.1202.

Bakdash, Jonathan Z., and Laura R. Marusich. 2017. "Repeated Measures Correlation." *Frontiers in Psychology* 8 (April). https://doi.org/10.3389/fpsyg.2017.00456.

Barr, Harriet L., Robert. Langs, and Robert R. Holt. 1972. *LSD: Personality and Experience*. New York: Wiley-Interscience.

Barrett, Frederick S, Matthew P Bradstreet, Jeannie-Marie S Leoutsakos, Matthew W Johnson, and Roland R Griffiths. 2016. "The Challenging Experience Questionnaire: Characterization of Challenging Experiences with Psilocybin Mushrooms." *Journal of Psychopharmacology* 30 (12): 1279–95. https://doi.org/10.1177/0269881116678781.

Barrett, Frederick S, Theresa M Carbonaro, Ethan Hurwitz, Matthew W Johnson, and Roland R Griffiths. 2018. "Double-Blind Comparison of the Two Hallucinogens Psilocybin and Dextromethorphan: Effects on Cognition." *Psychopharmacology* 235 (10): 2915–27. https://doi.org/10.1007/s00213-018-4981-x.

Barrett, Frederick S, and Roland R Griffiths. 2017. "Classic Hallucinogens and Mystical Experiences: Phenomenology and Neural Correlates." *Current Topics in Behavioral Neurosciences*, March. https://doi.org/10.1007/7854_2017_474.

Barrett, Frederick S, Matthew W Johnson, and Roland R Griffiths. 2015. "Validation of the Revised Mystical Experience Questionnaire in Experimental Sessions with Psilocybin." *Journal of Psychopharmacology* 29 (11): 1182–90. https://doi.org/10.1177/0269881115609019.

———. 2017. "Neuroticism Is Associated with Challenging Experiences with Psilocybin Mushrooms." *Personality and Individual Differences* 117 (October): 155–60. https://doi.org/10.1016/j.paid.2017.06.004.

Barrett, Frederick S, Katrin H Preller, Marcus Herdener, Petr Janata, and Franz X Vollenweider. 2017. "Serotonin 2a Receptor Signaling Underlies LSD-induced Alteration of the Neural Response to Dynamic Changes in Music." *Cerebral Cortex*, September, 1–12. https://doi.org/10.1093/cercor/bhx257.

Barrett, Frederick S, Hollis Robbins, David Smooke, Jenine L. Brown, and Roland R. Griffiths. 2017. "Qualitative and Quantitative Features of Music Reported to Support Peak Mystical Experiences During Psychedelic Therapy Sessions." *Frontiers in Psychology* 8 (July). https://doi.org/10.3389/fpsyg.2017.01238.

Baumeister, Roy F, and Julie J Exline. 2002. "Mystical Self Loss: A Challenge for Psychological Theory." *The International Journal for the Psychology of Religion* 12 (1): 15–20. https://doi.org/10.1207/s15327582ijpr1201_02.

Bayne, Tim, and Olivia Carter. 2018. "Dimensions of Consciousness and the Psychedelic State." *Neuroscience of Consciousness* 2018 (1). https://doi.org/10.1093/nc/niy008.

Beattie, James. 1776. *An Essay on Laughter and Ludicrous Composition, Written in the Year 1764.* [Edinburgh]: [Printed for W. Creech; E.; C. Dilly].

Beggs, John M, and Dietmar Plenz. 2003. "Neuronal Avalanches in Neocortical Circuits." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 23 (35): 11167–77. https://doi.org/10.1523/jneurosci.23-35-11167.2003.

Belser, Alexander B, Gabrielle Agin-Liebes, T Cody Swift, Sara Terrana, Neşe Devenot, Harris L Friedman, Jeffrey Guss, Anthony Bossis, and Stephen Ross. 2017. "Patient Experiences of Psilocybin-Assisted Psychotherapy: An Interpretative Phenomenological Analysis." *Journal of Humanistic Psychology* 57 (4): 354–88. https://doi.org/10.1177/0022167817706884.

Bentin, Shlomo, Truett Allison, Aina Puce, Erik Perez, and Gregory McCarthy. 1996. "Electrophysiological Studies of Face Perception in Humans." *Journal of Cognitive Neuroscience* 8 (6): 551–65. https://doi.org/10.1162/jocn.1996.8.6.551.

Benton, Arthur L. 2016. "Bergson and Freud on Aphasia: A Comparison." In *Bergson and Modern Thought*, edited by Pete A Y Gunter.

Berg, Manon van den, Igor Magaraggia, Rudy Schreiber, Todd M. Hillhouse, and Joseph H. Porter. 2022. "How to Account for Hallucinations in the Interpretation of the Antidepressant Effects of Psychedelics: A Translational Framework." *Psychopharmacology* 239 (6): 1853–79. https://doi.org/10.1007/s00213-022-06106-8.

Bergson, Henri. 1911. *Matter and Memory.* New York: Macm. https://doi.org/10.1037/13803-000.

———. 1931. *The Two Sources of Morality and Religion.* Garden City: Doubleday. https://doi.org/10.1097/00005053-193608000-00042.

Beringer, Kurt. 1927. *Der Meskalinrausch (Mescaline Intoxication).* Monographien Aus Dem Gesamtgebiete Der Neurologie Und Psychiatrie. Springer Berlin Heidelberg.

Berkeley, George. 1709. *An Essay Towards a New Theory of Vision.* Aaron Rhames.

Bland, J M., and D. G Altman. 1995a. "Statistics Notes: Calculating Correlation Coefficients with Repeated Observations: Part 1–Correlation Within Subjects." *BMJ* 310 (6977): 446–46. https://doi.org/10.1136/bmj.310.6977.446.

———. 1995b. "Statistics Notes: Calculating Correlation Coefficients with Repeated Observations: Part 2–Correlation Between Subjects." *BMJ* 310 (6980): 633–33. https://doi.org/10.1136/bmj.310.6980.633.

Blokpoel, Mark, Johan Kwisthout, and Iris van Rooij. 2012. "When Can Predictive

Brains Be Truly Bayesian?" *Frontiers in Psychology* 3 (November): 406. https://doi.org/10.3389/fpsyg.2012.00406.

Bogenschutz, Michael P., Alyssa A. Forcehimes, Jessica A. Pommy, Claire E. Wilcox, P. C. R. Barbosa, and Rick J. Strassman. 2015. "Psilocybin-Assisted Treatment for Alcohol Dependence: A Proof-of-Concept Study." *Journal of Psychopharmacology* 29 (3): 289–99. https://doi.org/10.1177/0269881114565144.

Bogenschutz, Michael P, and Matthew W Johnson. 2016. "Classic Hallucinogens in the Treatment of Addictions." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 64 (January): 250–58. https://doi.org/10.1016/j.pnpbp.2015.03.002.

Bonny, Helen L, and Walter N Pahnke. 1972. "The Use of Music in Psychedelic (LSD) Psychotherapy." *Journal of Music Therapy* 9 (2): 64–87. https://doi.org/10.1093/jmt/9.2.64.

Borchert, Elizabeth M. O., Christophe Micheyl, and Andrew J. Oxenham. 2011. "Perceptual Grouping Affects Pitch Judgments Across Time and Frequency." *Journal of Experimental Psychology: Human Perception and Performance* 37 (1): 257–69. https://doi.org/10.1037/a0020670.

Bourke, Cecilia, Katie Douglas, and Richard Porter. 2010. "Processing of Facial Emotion Expression in Major Depression: A Review." *Australian and New Zealand Journal of Psychiatry* 44 (8): 681–96. https://doi.org/10.3109/00048674.2010.496359.

Bouso, José Carlos, Josep Maria Fábregas, Rosa Maria Antonijoan, Antoni Rodríguez-Fornells, and Jordi Riba. 2013. "Acute Effects of Ayahuasca on Neuropsychological Performance: Differences in Executive Function Between Experienced and Occasional Users." *Psychopharmacology* 230 (3): 415–24. https://doi.org/10.1007/s00213-013-3167-9.

Bouso, José Carlos, Fernanda Palhano-Fontes, Antoni Rodríguez-Fornells, Sidarta Ribeiro, Rafael Sanches, José Alexandre S Crippa, Jaime E C Hallak, Draulio B de Araujo, and Jordi Riba. 2015. "Long-Term Use of Psychedelic Drugs Is Associated with Differences in Brain Structure and Personality in Humans." *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 25 (4): 483–92. https://doi.org/10.1016/j.euroneuro.2015.01.008.

Bouso, José Carlos, Eduardo José Pedrero-Pérez, Sam Gandy, and Miguel Ángel Alcázar-Córcoles. 2016. "Measuring the Subjective: Revisiting the Psychometric Properties of Three Rating Scales That Assess the Acute Effects of Hallucinogens." *Human Psychopharmacology* 31 (5): 356–72. https://doi.org/10.1002/hup.2545.

Bressloff, Paul C., Jack D. Cowan, Martin Golubitsky, Peter J. Thomas, and Matthew C. Wiener. 2002. "What Geometric Visual Hallucinations Tell Us about the Visual Cortex." *Neural Computation* 14 (3): 473–91. https://doi.org/10.1162/089976602317250861.

Broad, C D. 1923. *The Mind and Its Place in Nature*. London: Routledge & K. Paul. https://doi.org/10.4324/9781315824147.

Brogaard, Berit. 2013. "Serotonergic Hyperactivity as a Potential Factor in Developmental, Acquired and Drug-Induced Synesthesia." *Frontiers in Human Neuroscience* 7 (October): 657. https://doi.org/10.3389/fnhum.2013.00657.

Brook, Andrew. 2007. *The Prehistory of Cognitive Science*. Palgrave Macmillan.

Brown, Randall T, Christopher R Nicholas, Nicholas V Cozzi, Michele C Gassman, Karen M Cooper, Daniel Muller, Chantelle D Thomas, et al. 2017. "Pharmacokinetics of Escalating Doses of Oral Psilocybin in Healthy Adults." *Clinical Pharmacokinetics*, March. https://doi.org/10.1007/s40262-017-0540-6.

Buckner, Randy L, Jessica R Andrews-Hanna, and Daniel L Schacter. 2008. "The Brain's Default Network: Anatomy, Function, and Relevance to Disease." *Annals of the New York Academy of Sciences* 1124 (March): 1–38. https://doi.org/10.1196/annals.1440.011.

Burke, Matthew J., and Daniel M. Blumberger. 2021. "Caution at Psychiatry's Psychedelic Frontier." *Nature Medicine* 27 (10): 1687–88. https://doi.org/10.1038/s41591-021-01524-1.

Buzsáki, György, and Andreas Draguhn. 2004. "Neuronal Oscillations in Cortical Networks." *Science* 304 (5679): 1926–29.

Caclin, Anne, Patrick Bouchet, Farida Djoulah, Elodie Pirat, Jacques Pernier, and Marie-Hélène Giard. 2011. "Auditory Enhancement of Visual Perception at Threshold Depends on Visual Abilities." *Brain Research* 1396 (June): 35–44. https://doi.org/10.1016/j.brainres.2011.04.016.

Cannon, Mark W., and Steven C. Fullenkamp. 1991. "Spatial Interactions in Apparent Contrast: Inhibitory Effects Among Grating Patterns of Different Spatial Frequencies, Spatial Positions and Orientations." *Vision Research* 31 (11): 1985–98. https://doi.org/10.1016/0042-6989(91)90193-9.

Cao, Dongmei, Jing Yu, Huan Wang, Zhipu Luo, Xinyu Liu, Licong He, Jianzhong Qi, et al. 2022. "Structure-Based Discovery of Nonhallucinogenic Psychedelic Analogs." *Science* 375 (6579): 403–11. https://doi.org/10.1126/science.abl8615.

Carandini, Matteo, and David J Heeger. 2011. "Normalization as a Canonical Neural Computation." *Nature Reviews. Neuroscience* 13 (1): 51–62. https://doi.org/10.1038/nrn3136.

Carandini, Matteo, David J. Heeger, and Walter Senn. 2002. "A Synaptic Explanation of Suppression in Visual Cortex." *Journal of Neuroscience* 22 (22): 10053–65. https://doi.org/10.1523/JNEUROSCI.22-22-10053.2002.

Carbonaro, Theresa M, Matthew P Bradstreet, Frederick S Barrett, Katherine A MacLean, Robert Jesse, Matthew W Johnson, and Roland R Griffiths. 2016. "Survey Study of Challenging Experiences After Ingesting Psilocybin Mushrooms: Acute and Enduring Positive and Negative Consequences." *Journal of Psychopharmacology* 30 (12): 1268–78. https://doi.org/10.1177/0269881116662634.

Carbonaro, Theresa M, Matthew W. Johnson, and Roland R. Griffiths. 2020. "Subjective Features of the Psilocybin Experience That May Account for Its Self-Administration by Humans: A Double-Blind Comparison of Psilocybin and Dextromethorphan." *Psychopharmacology* 237 (8): 2293–2304. https://doi.org/10.1007/s00213-020-05533-9.

Carbonaro, Theresa M, Matthew W Johnson, Ethan Hurwitz, and Roland R Griffiths. 2018. "Double-Blind Comparison of the Two Hallucinogens Psilocybin and Dextromethorphan: Similarities and Differences in Subjective Experiences." *Psychopharmacology* 235 (2): 521–34.

Carhart-Harris, Robin L, Mark Bolstridge, James Rucker, Camilla M J Day, David Erritzoe, Mendel Kaelen, Michael Bloomfield, et al. 2016. "Psilocybin with Psychological Support for Treatment-Resistant Depression: An Open-Label Feasibility Study." *The Lancet. Psychiatry*, May. https://doi.org/10.1016/s2215-0366(16)30065-7.

Carhart-Harris, Robin L, M Bolstridge, C M J Day, J Rucker, R Watts, D E Erritzoe, M Kaelen, et al. 2018. "Psilocybin with Psychological Support for Treatment-Resistant Depression: Six-month Follow-up." *Psychopharmacology* 235 (2): 399–408. https://doi.org/10.1007/s00213-017-4771-x.

Carhart-Harris, Robin L, David Erritzoe, Tim Williams, James M Stone, Laurence J Reed, Alessandro Colasanti, Robin J Tyacke, et al. 2012. "Neural Correlates of the Psychedelic State as Determined by fMRI Studies with Psilocybin." *Proceedings of the National Academy of Sciences of the United States of America* 109 (6): 2138–43. https://doi.org/10.1073/pnas.1119598109.

Carhart-Harris, Robin L, D Erritzoe, E Haijen, Mendel Kaelen, and R Watts. 2017. "Psychedelics and Connectedness." *Psychopharmacology*, August. https://doi.org/10.1007/s00213-017-4701-y.

Carhart-Harris, Robin L, and Karl Friston. 2010. "The Default-Mode, Ego-Functions and Free-Energy: A Neurobiological Account of Freudian Ideas." *Brain: A Journal of Neurology* 133 (Pt 4): 1265–83. https://doi.org/10.1093/brain/awq010.

Carhart-Harris, Robin L, and Karl J Friston. 2019. "REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics." *Pharmacological Reviews* 71 (3): 316–44. https://doi.org/10.1124/pr.118.017160.

Carhart-Harris, Robin L, and Guy M Goodwin. 2017. "The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, April. https://doi.org/10.1038/npp.2017.84.

Carhart-Harris, Robin L, Mendel Kaelen, M Bolstridge, T M Williams, L T Williams, R Underwood, A Feilding, and D J Nutt. 2016. "The Paradoxical Psychological Effects of Lysergic Acid Diethylamide (LSD)." *Psychological Medicine*, February, 1–12. https://doi.org/10.1017/s0033291715002901.

Carhart-Harris, Robin L, Mendel Kaelen, M G Whalley, M Bolstridge, A Feilding, and D J Nutt. 2015. "LSD Enhances Suggestibility in Healthy Volunteers." *Psychopharmacology* 232 (4): 785–94.

Carhart-Harris, Robin L, Robert Leech, David Erritzoe, Tim M Williams, James M Stone, John Evans, David J Sharp, Amanda Feilding, Richard G Wise, and David J Nutt. 2013. "Functional Connectivity Measures After Psilocybin Inform a Novel Hypothesis of Early Psychosis." *Schizophrenia Bulletin* 39 (6): 1343–51.

Carhart-Harris, Robin L, Robert Leech, Peter J Hellyer, Murray Shanahan, Amanda Feilding, Enzo Tagliazucchi, Dante R Chialvo, and David Nutt. 2014. "The Entropic Brain: A Theory of Conscious States Informed by Neuroimaging Research with Psychedelic Drugs." *Frontiers in Human Neuroscience* 8 (February): 20. https://doi.org/10.3389/fnhum.2014.00020.

Carhart-Harris, Robin L, R Leech, T M Williams, D Erritzoe, N Abbasi, T Bargiotas, P Hobden, et al. 2012. "Implications for Psychedelic-Assisted Psychotherapy:

Functional Magnetic Resonance Imaging Study with Psilocybin." *The British Journal of Psychiatry: The Journal of Mental Science* 200 (3): 238–44. https://doi.org/10.1192/bjp.bp.111.103309.

Carhart-Harris, Robin L, Suresh Muthukumaraswamy, Leor Roseman, Mendel Kaelen, Wouter Droog, Kevin Murphy, Enzo Tagliazucchi, et al. 2016. "Neural Correlates of the LSD Experience Revealed by Multimodal Neuroimaging." *Proceedings of the National Academy of Sciences* 113 (17): 4853–58. https://doi.org/10.1073/pnas.1518377113.

Carhart-Harris, Robin L, and D J Nutt. 2010. "User Perceptions of the Benefits and Harms of Hallucinogenic Drug Use: A Web-Based Questionnaire Study." *Journal of Substance Use* 15 (4): 283–300. https://doi.org/10.3109/14659890903271624.

———. 2017. "Serotonin and Brain Function: A Tale of Two Receptors." *Journal of Psychopharmacology* 31 (9): 1091–1120. https://doi.org/10.1177/0269881117725915.

Carhart-Harris, Robin L, Leor Roseman, Eline Haijen, David Erritzoe, Rosalind Watts, Igor Branchi, and Mendel Kaelen. 2018. "Psychedelics and the Essential Importance of Context." *Journal of Psychopharmacology*, February, 269881118754710. https://doi.org/10.1177/0269881118754710.

Carod-Artal, F. J. 2015. "Hallucinogenic Drugs in Pre-Columbian Mesoamerican Cultures." *Neurología (English Edition)* 30 (1): 42–49. https://doi.org/10.1016/j.nrleng.2011.07.010.

Carter, Olivia L, David C Burr, John D Pettigrew, Guy M Wallis, Felix Hasler, and Franz X Vollenweider. 2005. "Using Psilocybin to Investigate the Relationship Between Attention, Working Memory, and the Serotonin 1a and 2a Receptors." *Journal of Cognitive Neuroscience* 17 (10): 1497–1508. https://doi.org/10.1162/089892905774597191.

Carter, Olivia L, Felix Hasler, John D Pettigrew, Guy M Wallis, Guang B Liu, and Franz X Vollenweider. 2007. "Psilocybin Links Binocular Rivalry Switch Rate to Attention and Subjective Arousal Levels in Humans." *Psychopharmacology* 195 (3): 415–24. https://doi.org/10.1007/s00213-007-0930-9.

Carter, Olivia L, John D Pettigrew, David C Burr, David Alais, Felix Hasler, and Franz X Vollenweider. 2004. "Psilocybin Impairs High-Level but Not Low-Level Motion Perception." *Neuroreport* 15 (12): 1947–51. https://doi.org/10.1097/00001756-200408260-00023.

Carter, Olivia L, John D Pettigrew, Felix Hasler, Guy M Wallis, Guang B Liu, Daniel Hell, and Franz X Vollenweider. 2005. "Modulating the Rate and Rhythmicity of Perceptual Rivalry Alternations with the Mixed 5-Ht2a and 5-Ht1a Agonist Psilocybin." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 30 (6): 1154–62. https://doi.org/10.1038/sj.npp.1300621.

Chapman, Loren J., Jean P. Chapman, and Michael L. Raulin. 1976. "Scales for Physical and Social Anhedonia." *Journal of Abnormal Psychology* 85 (4): 374–82. https://doi.org/10.1037/0021-843x.85.4.374.

Chen, Juan, Qing Yu, Ziyun Zhu, Yujia Peng, and Fang Fang. 2016. "Spatial Summation Revealed in the Earliest Visual Evoked Component C1 and the Effect

of Attention on Its Linearity." *Journal of Neurophysiology* 115 (1): 500–509. https://doi.org/10.1152/jn.00044.2015.

Chevreul, M. A. 1860. *The Laws of Contrast of Colour.* Routledge.

Chubb, Charles, George Sperling, and Joshua A Solomon. 1989. "Texture Interactions Determine Perceived Contrast." *Proceedings of the National Academy of Sciences* 86 (23): 9631–35. https://doi.org/10.1073/pnas.86.23.9631.

Claridge, Gordon, and Anna McDonald. 2009. "An Investigation into the Relationships Between Convergent and Divergent Thinking, Schizotypy, and Autistic Traits." *Personality and Individual Differences* 46 (8): 794–99. https://doi.org/10.1016/j.paid.2009.01.018.

Clark, Andy. 2013. "Whatever Next? Predictive Brains, Situated Agents, and the Future of Cognitive Science." *The Behavioral and Brain Sciences* 36 (3): 181–204. https://doi.org/10.1017/s0140525x12000477.

———. 2015. *Surfing Uncertainty: Prediction, Action, and the Embodied Mind*. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780190217013.001.0001.

Clark, Vincent P., Silu Fan, and Steven A. Hillyard. 1994. "Identification of Early Visual Evoked Potential Generators by Retinotopic and Topographic Analyses." *Human Brain Mapping* 2 (3): 170–87. https://doi.org/10.1002/hbm.460020306.

Clifford, Colin W G. 2014. "The Tilt Illusion: Phenomenology and Functional Implications." *Vision Research* 104 (November): 3–11. https://doi.org/10.1016/j.visres.2014.06.009.

Coen-Cagli, Ruben, Peter Dayan, and Odelia Schwartz. 2012. "Cortical Surround Interactions and Perceptual Salience via Natural Scene Statistics." Edited by Olaf Sporns. *PLoS Computational Biology* 8 (3): e1002405. https://doi.org/10.1371/journal.pcbi.1002405.

Coen-Cagli, Ruben, Adam Kohn, and Odelia Schwartz. 2015. "Flexible Gating of Contextual Influences in Natural Vision." *Nature Neuroscience* 18 (11): 1648–55. https://doi.org/10.1038/nn.4128.

Cohen, Sidney. 1960. "LYSERGIC ACID DIETHYLAMIDE." *The Journal of Nervous and Mental Disease* 130 (1): 30–40. https://doi.org/10.1097/00005053-196001000-00005.

———. 1965. *The Beyond Within : The LSD Story*. New York: Atheneum.

Cohen, Sidney, and Betty Eisner. 1959. "Use of Lysergic Acid Diethylamide in a Psychotherapeutic Setting." *A.M.A. Archives of Neurology and Psychiatry* 81 (5): 615–19. https://doi.org/10.1001/archneurpsyc.1959.02340170081008.

Collins, David J. 2018. "The Cambridge History of Magic and Witchcraft in the West from Antiquity to the Present." https://www.vlebooks.com/vleweb/product/openreader?id=none&isbn=9781139043021.

Cook, Emily, Stephen T Hammett, and Jonas Larsson. 2016. "GABA Predicts Visual Intelligence." *Neuroscience Letters* 632 (October): 50–54.

Corlett, P R, C D Frith, and P C Fletcher. 2009. "From Drugs to Deprivation: A Bayesian Framework for Understanding Models of Psychosis." *Psychopharmacology* 206 (4): 515–30. https://doi.org/10.1007/s00213-009-1561-0.

Cowen, Philip J., and Michael Browning. 2015. "What Has Serotonin to Do with Depression?" *World Psychiatry* 14 (2): 158–60. https://doi.org/10.1002/wps.20229.

Crick, Francis. 1998. "Consciousness and Neuroscience." *Cerebral Cortex* 8 (2): 97–107. https://doi.org/10.1093/cercor/8.2.97.

Crick, Francis, and Christof Koch. 1998. "Feature Article Consciousness and Neuroscience." *Cerebral Cortex Mar* 8: 97–107.

Curtis, Lindsay R., and Inc. Texas Alcohol Narcotics Education. 1968. *LSD: Trip or Trap?* Dallas: Texas Alcohol Narcotics Education.

Dakin, Steven, Patricia Carlin, and David Hemsley. 2005. "Weak Suppression of Visual Context in Chronic Schizophrenia." *Current Biology* 15 (20): R822–24. https://doi.org/10.1016/j.cub.2005.10.015.

Davis, Alan K., Frederick S. Barrett, Darrick G. May, Mary P. Cosimano, Nathan D. Sepeda, Matthew W. Johnson, Patrick H. Finan, and Roland R. Griffiths. 2021. "Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder." *JAMA Psychiatry* 78 (5): 481. https://doi.org/10.1001/jamapsychiatry.2020.3285.

Dayan, P, G E Hinton, R M Neal, and R S Zemel. 1995. "The Helmholtz Machine." *Neural Computation* 7 (5): 889–904. https://doi.org/10.1162/neco.1995.7.5.889.

Deco, Gustavo, Viktor K Jirsa, and Anthony R McIntosh. 2011. "Emerging Concepts for the Dynamical Organization of Resting-State Activity in the Brain." *Nature Reviews. Neuroscience* 12 (1): 43–56.

DeGrandpre, Richard. 2006. *The Cult of Pharmacology.* Duke University Press. https://doi.org/10.1215/9780822388197.

Delorme, Arnaud, and Scott Makeig. 2004. "EEGLAB: An Open Source Toolbox for Analysis of Single-Trial EEG Dynamics Including Independent Component Analysis." *Journal of Neuroscience Methods* 134 (1): 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009.

Díaz, José Luis. 2010. "Sacred Plants and Visionary Consciousness." *Phenomenology and the Cognitive Sciences* 9 (2): 159–70. https://doi.org/10.1007/s11097-010-9157-z.

Dittrich, A. 1998. "The Standardized Psychometric Assessment of Altered States of Consciousness (ASCs) in Humans." *Pharmacopsychiatry* 31 Suppl 2 (July): 80–84. https://doi.org/10.1055/s-2007-979351.

Dittrich, A, D Lamparter, and M Maurer. 2010. "5d-ASC: Questionnaire for the Assessment of Altered States of Consciousness." *A Short Introduction. Zurich, Switzerland: PSIN.*

Dolder, Patrick C, Yasmin Schmid, Felix Müller, Stefan Borgwardt, and Matthias E Liechti. 2016. "LSD Acutely Impairs Fear Recognition and Enhances Emotional Empathy and Sociality." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 41 (11): 2638–46. https://doi.org/10.1038/npp.2016.82.

Dos Santos, Rafael G, Flávia L Osório, José Alexandre S Crippa, Jordi Riba, Antônio W Zuardi, and Jaime E C Hallak. 2016. "Antidepressive, Anxiolytic, and Antiaddictive Effects of Ayahuasca, Psilocybin and Lysergic Acid Diethylamide (LSD): A Systematic Review of Clinical Trials Published in the Last 25 Years." *Therapeutic Advances in Psychopharmacology* 6 (3): 193–213. https://doi.org/10.1177/2045125316638008.

Doss, Manoj K., Michal Považan, Monica D. Rosenberg, Nathan D. Sepeda, Alan

K. Davis, Patrick H. Finan, Gwenn S. Smith, et al. 2021. "Psilocybin Therapy Increases Cognitive and Neural Flexibility in Patients with Major Depressive Disorder." *Translational Psychiatry* 11 (1). https://doi.org/10.1038/s41398-021-01706-y.

Dupuis, David. 2021. "Psychedelics as Tools for Belief Transmission. Set, Setting, Suggestibility, and Persuasion in the Ritual Use of Hallucinogens." *Frontiers in Psychology* 12 (November). https://doi.org/10.3389/fpsyg.2021.730031.

Ebbinghaus, H. 1902. "Grundzu «Ge Der Psychologie Volumes i and II (Leipzig: Verlag von Viet & Co.)."

Edelman, Shimon. 2012. "Six Challenges to Theoretical and Philosophical Psychology." *Frontiers in Psychology* 3 (July): 219. https://doi.org/10.3389/fpsyg.2012.00219.

Eisner, Betty. 1997. "Set, Setting, and Matrix." *Journal of Psychoactive Drugs* 29 (2): 213–16. https://doi.org/10.1080/02791072.1997.10400190.

Eisner, Betty, and Sidney Cohen. 1958. "Psychotherapy with Lysergic Acid Diethylamide." *The Journal of Nervous and Mental Disease* 127 (6): 528–39. https://doi.org/10.1097/00005053-195812000-00006.

Ejima, Y, and S Takahashi. 1985. "Apparent Contrast of a Sinusoidal Grating in the Simultaneous Presence of Peripheral Gratings." *Vision Research* 25 (9): 1223–32. https://doi.org/10.1016/0042-6989(85)90036-7.

Ellis, Havelock. 1898. *Mescal: A New Artificial Paradise*. US Government Printing Office.

Erowid. 1995. 1995. https://www.erowid.org/.

Evarts, Edward V. 1957. "A REVIEW OF THE NEUROPHYSIOLOGICAL EFFECTS OF LYSERGIC ACID DIETHYLAMIDE (LSD) AND OTHER PSYCHOTOMIMETIC AGENTS." *Annals of the New York Academy of Sciences* 66 (3): 479–95. https://doi.org/10.1111/j.1749-6632.1957.tb40744.x.

Family, Neiloufar, David Vinson, Gabriella Vigliocco, Mendel Kaelen, Mark Bolstridge, David J Nutt, and Robin L Carhart-Harris. 2016. "Semantic Activation in LSD: Evidence from Picture Naming." *Language, Cognition and Neuroscience* 0 (0): 1–8. https://doi.org/10.1080/23273798.2016.1217030.

Field, David J., Anthony Hayes, and Robert F. Hess. 1993. "Contour Integration by the Human Visual System: Evidence for a Local "Association Field"." *Vision Research* 33 (2): 173–93. https://doi.org/10.1016/0042-6989(93)90156-q.

Fink, Max. 1969. "EEG and Human Psychopharmacology." *Annual Review of Pharmacology* 9 (1): 241–58. https://doi.org/10.1146/annurev.pa.09.040169.001325.

———. 2010. "Remembering the Lost Neuroscience of Pharmaco-EEG." *Acta Psychiatrica Scandinavica* 121 (3): 161–73. https://doi.org/10.1111/j.1600-0447.2009.01467.x.

Fleming, Stephen M, Raymond J Dolan, and Christopher D Frith. 2012. "Metacognition: Computation, Biology and Function." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 367 (1594): 1280–86. https://doi.org/10.1098/rstb.2012.0021.

Forman, Robert K C (ed). 1998. *The Innate Capacity: Mysticism, Psychology, and Philosophy*. Oxford University Press. https://doi.org/10.2307/1387614.

Forstmann, Birte U, Eric-Jan Wagenmakers, Tom Eichele, Scott Brown, and John T Serences. 2011. "Reciprocal Relations Between Cognitive Neuroscience and Formal Cognitive Models: Opposites Attract?" *Trends in Cognitive Sciences* 15 (6): 272–79. https://doi.org/10.1016/j.tics.2011.04.002.

Fox, Michael D, and Marcus E Raichle. 2007. "Spontaneous Fluctuations in Brain Activity Observed with Functional Magnetic Resonance Imaging." *Nature Reviews. Neuroscience* 8 (9): 700–711. https://doi.org/10.1038/nrn2201.

Fraser, James. 1908. "A New Visual Illusion of Direction." *British Journal of Psychology* 2 (3): 307. https://doi.org/10.1111/j.2044-8295.1908.tb00182.x.

Frecska, E, K D White, and L E Luna. 2004. "Effects of Ayahuasca on Binocular Rivalry with Dichoptic Stimulus Alternation." *Psychopharmacology* 173 (1-2): 79–87. https://doi.org/10.1007/s00213-003-1701-x.

Freeman, Jeremy, Corey M Ziemba, David J Heeger, Eero P Simoncelli, and J Anthony Movshon. 2013. "A Functional and Perceptual Signature of the Second Visual Area in Primates." *Nature Neuroscience* 16 (7): 974–81. https://doi.org/10.1038/nn.3402.

Freud, Sigmund. 1895. "Project for a Scientific Psychology." In *Standard Edition Vol. 1*. London: Vintage.

———. 1900. *The Interpretation of Dreams*. London: Penguin. https://doi.org/10.1037/10561-000.

———. 1915. "The Unconscious." In *Standard Edition Vol. 14*. Vol. 14. London: Vintage. https://doi.org/10.4324/9781351226387-21.

———. 1940. *An Outline of Psycho-Analysis*. London: Hogarth.

Friedman, Michael. 1983. *Foundations of Space-Time Theories : Relativistic Physics and Philosophy of Science*. https://doi.org/10.1515/9781400855124.

Frigg, Roman, and Stephan Hartmann. 2017. "Models in Science." In *The Stanford Encyclopedia of Philosophy*, edited by Edward N Zalta, Spring 2017. Metaphysics Research Lab, Stanford University.

Friston, Karl. 2005. "A Theory of Cortical Responses." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 360 (1456): 815–36. https://doi.org/10.1098/rstb.2005.1622.

———. 2010. "The Free-Energy Principle: A Unified Brain Theory?" *Nature Reviews. Neuroscience* 11 (2): 127–38. https://doi.org/10.1038/nrn2787.

Friston, Karl, Rebecca Lawson, and Chris Frith. 2013. "On Hyperpriors and Hypopriors: Comment on Pellicano and Burr." *Trends in Cognitive Sciences* 17 (1): 1. https://doi.org/10.1016/j.tics.2012.11.003.

Friston, Karl, Jérémie Mattout, Nelson Trujillo-Barreto, John Ashburner, and Will Penny. 2007. "Variational Free Energy and the Laplace Approximation." *NeuroImage* 34 (1): 220–34. https://doi.org/10.1016/j.neuroimage.2006.08.035.

Friston, Karl, Francesco Rigoli, Dimitri Ognibene, Christoph Mathys, Thomas Fitzgerald, and Giovanni Pezzulo. 2015. "Active Inference and Epistemic Value." *Cognitive Neuroscience* 6 (4): 187–214. https://doi.org/10.1080/17588928.2015.1020053.

Gaddum, J H. 1953. "Antagonism Between Lysergic Acid Diethylamide and 5-Hydroxytryptamine." *The Journal of Physiology* 121 (1): 15P.

Gaddum, J H, and K A Hameed. 1954. "Drugs Which Antagonize 5-

Hydroxytryptamine." *British Journal of Pharmacology and Chemotherapy* 9 (2): 240–48. https://doi.org/10.1111/j.1476-5381.1954.tb00848.x.

Gallimore, Andrew R. 2015. "Restructuring Consciousness -the Psychedelic State in Light of Integrated Information Theory." *Frontiers in Human Neuroscience* 9 (June): 346. https://doi.org/10.3389/fnhum.2015.00346.

Gashi, Liridona, Sveinung Sandberg, and Willy Pedersen. 2021. "Making "Bad Trips" Good: How Users of Psychedelics Narratively Transform Challenging Trips into Valuable Experiences." *International Journal of Drug Policy* 87 (January): 102997. https://doi.org/10.1016/j.drugpo.2020.102997.

Gasser, Peter, Dominique Holstein, Yvonne Michel, Rick Doblin, Berra Yazar-Klosinski, Torsten Passie, and Rudolf Brenneisen. 2014. "Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated with Life-Threatening Diseases." *The Journal of Nervous and Mental Disease* 202 (7): 513–20. https://doi.org/10.1097/nmd.0000000000000113.

GebhartSayer, Angelika. 1985. "The Geometric Designs of the Shipibo-Conibo in Ritual Context (Peruvian Indian Art)." *Journal of Latin American Lore* 11 (2): 143–75.

George, Daniel R., Ryan Hanson, Darryl Wilkinson, and Albert Garcia-Romeu. 2021. "Ancient Roots of Today's Emerging Renaissance in Psychedelic Medicine." *Culture, Medicine, and Psychiatry*, September. https://doi.org/10.1007/s11013-021-09749-y.

Gibson, J J, and M Radner. 1937. "Adaptation, After-Effect and Contrast in the Perception of Tilted Lines. I. Quantitative Studies." *Journal of Experimental Psychology* 20 (5): 453–67. https://doi.org/10.1037/h0059826.

Gill, Hartej, Parnian Puramat, Pankti Patel, Barjot Gill, CéAnn A. Marks, Nelson B. Rodrigues, David Castle, et al. 2022. "The Effects of Psilocybin in Adults with Major Depressive Disorder and the General Population: Findings from Neuroimaging Studies." *Psychiatry Research* 313 (July): 114577. https://doi.org/10.1016/j.psychres.2022.114577.

Glennon, Richard A, Milt Titeler, and J D McKenney. 1984. "Evidence for 5-Ht2 Involvement in the Mechanism of Action of Hallucinogenic Agents." *Life Sciences* 35 (25): 2505–11. https://doi.org/10.1016/0024-3205(84)90436-3.

Goddard, Erin, Colin W. G. Clifford, and Samuel G. Solomon. 2008. "Centre-Surround Effects on Perceived Orientation in Complex Images." *Vision Research* 48 (12): 1374–82. https://doi.org/10.1016/j.visres.2008.02.023.

Golomb, Julie D, Jenika R B McDavitt, Barbara M Ruf, Jason I Chen, Aybala Saricicek, Kathleen H Maloney, Jian Hu, Marvin M Chun, and Zubin Bhagwagar. 2009. "Enhanced Visual Motion Perception in Major Depressive Disorder." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 29 (28): 9072–77. https://doi.org/10.1523/jneurosci.1003-09.2009.

Goodman, N. 1983. *Fact, Fiction, and Forecast*. Harvard University Press.

Gouzoulis-Mayfrank, E, B Thelen, S Maier, K Heekeren, K-A Kovar, H Sass, and M Spitzer. 2002. "Effects of the Hallucinogen Psilocybin on Covert Orienting of Visual Attention in Humans." *Neuropsychobiology* 45 (4): 205–12. https://doi.org/10.1159/000063672.

Gratton, Caterina, Sahar Yousef, Esther Aarts, Deanna L Wallace, Mark D'Esposito, and Michael A Silver. 2017. "Cholinergic, but Not Dopaminergic or Noradrenergic, Enhancement Sharpens Visual Spatial Perception in Humans." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 37 (16): 4405–15. https://doi.org/10.1523/jneurosci.2405-16.2017.

Gray, Kurt, Stephen Anderson, Eric Evan Chen, John Michael Kelly, Michael S. Christian, John Patrick, Laura Huang, Yoed N. Kenett, and Kevin Lewis. 2019. "Forward Flow: A New Measure to Quantify Free Thought and Predict Creativity." *American Psychologist* 74 (5): 539–54. https://doi.org/10.1037/amp0000391.

Green, A R. 2008. "Gaddum and LSD: The Birth and Growth of Experimental and Clinical Neuropharmacology Research on 5-HT in the UK." *British Journal of Pharmacology* 154 (8): 1583–99. https://doi.org/10.1038/bjp.2008.207.

Gregory, Richard L. 1968. "Perceptual Illusions and Brain Models." *Proceedings of the Royal Society of London. Series B. Biological Sciences* 171 (1024): 279–96. https://doi.org/10.1098/rspb.1968.0071.

Griffiths, Roland R, Matthew W Johnson, Michael A Carducci, Annie Umbricht, William A Richards, Brian D Richards, Mary P Cosimano, and Margaret A Klinedinst. 2016. "Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial." *Journal of Psychopharmacology* 30 (12): 1181–97. https://doi.org/10.1177/0269881116675513.

Griffiths, Roland R, Matthew W Johnson, William A Richards, Brian D Richards, Una McCann, and Robert Jesse. 2011. "Psilocybin Occasioned Mystical-Type Experiences: Immediate and Persisting Dose-Related Effects." *Psychopharmacology* 218 (4): 649–65. https://doi.org/10.1007/s00213-011-2358-5.

Griffiths, Roland R, Wa Richards, Matthew W Johnson, Ud McCann, and R Jesse. 2008. "Mystical-Type Experiences Occasioned by Psilocybin Mediate the Attribution of Personal Meaning and Spiritual Significance 14 Months Later." *Journal of Psychopharmacology* 22 (6): 621–32. https://doi.org/10.1177/0269881108094300.

Grimm, O, R Kraehenmann, Katrin H Preller, E Seifritz, and Franz X Vollenweider. 2018. "Psilocybin Modulates Functional Connectivity of the Amygdala During Emotional Face Discrimination." *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 28 (6): 691–700. https://doi.org/10.1016/j.euroneuro.2018.03.016.

Grinspoon, Lester, and James B Bakalar. 1979. *Psychedelic Drugs Reconsidered*. New York: Basic Books. https://doi.org/10.2307/1387601.

Grob, Charles, Alicia L Danforth, Gurpreet S Chopra, Marycie Hagerty, Charles R McKay, Adam L Halberstadt, and George R Greer. 2011. "Pilot Study of Psilocybin Treatment for Anxiety in Patients with Advanced-Stage Cancer." *Archives of General Psychiatry* 68 (1): 71–78. https://doi.org/10.1001/archgenpsychiatry.2010.116.

Grob, Charles, and Marlene Dobkin de Rios. 1992. "Adolescent Drug Use in Cross-Cultural Perspective." *Journal of Drug Issues* 22 (1): 121–38. https://doi.org/10.1177/002204269202200108.

Grof, Stanislav. 1976. *Realms of the Human Unconscious : Observations from LSD*

Research. New York: E.P. Dutton. https://doi.org/10.2307/1385643.

———. 1980. *LSD Psychotherapy*. Pomona, Calif: Hunter House.

Guilford, Joy Paul. 1967. "The Nature of Human Intelligence."

Gukasyan, Natalie, Alan K Davis, Frederick S Barrett, Mary P Cosimano, Nathan D Sepeda, Matthew W Johnson, and Roland R Griffiths. 2022. "Efficacy and Safety of Psilocybin-Assisted Treatment for Major Depressive Disorder: Prospective 12-Month Follow-up." *Journal of Psychopharmacology* 36 (2): 151–58. https://doi.org/10.1177/02698811211073759.

Guttmann, Erich. 1936. "Artificial Psychoses Produced by Mescaline." *The British Journal of Psychiatry: The Journal of Mental Science* 82 (338): 203–21. https://doi.org/10.1192/bjp.82.338.203.

Guzmán, Gastón. 2005. "Species Diversity in the Genus Psilocybe (Basidiomycotina, Agaricales, Strophariaceae) of World Mycobiota, with Special Attention to Hallucinogenic Properties." *International Journal of Medicinal Mushrooms* 7 (1/2): 305.

Guzmán, Gaston, John W Allen, and Jochen Gartz. 1998. "A Worldwide Geographical Distribution of the Neurotropic Fungi, an Analysis and Discussion." *Ann. Mus. Civ. Rovereto* 14: 189–280.

Haider, Bilal, Matthew R Krause, Alvaro Duque, Yuguo Yu, Jonathan Touryan, James A Mazer, and David A McCormick. 2010. "Synaptic and Network Mechanisms of Sparse and Reliable Visual Cortical Activity During Nonclassical Receptive Field Stimulation." *Neuron* 65 (1): 107–21. https://doi.org/10.1016/j.neuron.2009.12.005.

Halberstadt, Adam L. 2015. "Recent Advances in the Neuropsychopharmacology of Serotonergic Hallucinogens." *Behavioural Brain Research* 277 (Supplement C): 99–120. https://doi.org/10.1016/j.bbr.2014.07.016.

Halberstadt, Adam L, and Mark A. Geyer. 2016. "Effect of Hallucinogens on Unconditioned Behavior." In *Behavioral Neurobiology of Psychedelic Drugs*, 159–99. Springer Berlin Heidelberg. https://doi.org/10.1007/7854_2016_466.

Halberstadt, Adam L, and David E. Nichols. 2020. "Serotonin and Serotonin Receptors in Hallucinogen Action." In *Handbook of Behavioral Neuroscience*, edited by Christian P. Müller and Kathryn A. Cunningham, 843–63. Elsevier. https://doi.org/10.1016/b978-0-444-64125-0.00043-8.

Hartogsohn, Ido. 2016. "Set and Setting, Psychedelics and the Placebo Response: An Extra-Pharmacological Perspective on Psychopharmacology." *Journal of Psychopharmacology* 30 (12): 1259–67. https://doi.org/10.1177/0269881116677852.

———. 2017. "Constructing Drug Effects: A History of Set and Setting." *Drug Science, Policy and Law* 3 (January): 205032451668332. https://doi.org/10.1177/2050324516683325.

———. 2021. "Set and Setting in the Santo Daime." *Frontiers in Pharmacology* 12 (May). https://doi.org/10.3389/fphar.2021.651037.

Hasler, Felix, Ulrike Grimberg, Marco A Benz, Theo Huber, and Franz X Vollenweider. 2004. "Acute Psychological and Physiological Effects of Psilocybin in Healthy Humans: A Double-Blind, Placebo-Controlled Dose–Effect Study." *Psychopharmacology* 172 (2): 145–56. https://doi.org/10.1007/s00213-003-1640-6.

Haynes, J. D., G. Roth, M. Stadler, and H. J. Heinze. 2003. "Neuromagnetic Correlates of Perceived Contrast in Primary Visual Cortex." *Journal of Neurophysiology* 89 (5): 2655–66. https://doi.org/10.1152/jn.00820.2002.

Heeger, David J. 1992. "Normalization of Cell Responses in Cat Striate Cortex." *Visual Neuroscience* 9 (2): 181–97. https://doi.org/10.1017/s0952523800009640.

Heffter, A. 1898. "Ueber Pellote." *Archiv für Experimentelle Pathologie Und Pharmakologie* 40 (5-6): 385–429. https://doi.org/10.1007/bf01825267.

Heimann, H. 1963. "OBSERVATIONS ON DISTURBED TIME PERCEPTION IN MODEL PSYCHOSIS." *Europepmc.org*.

Helmholtz, Heinrich von. 1867. *Treatise on Physiological Optics Vol. III*. Dover Publications.

Hendricks, Peter S, Christopher B Thorne, C Brendan Clark, David W Coombs, and Matthew W Johnson. 2015. "Classic Psychedelic Use Is Associated with Reduced Psychological Distress and Suicidality in the United States Adult Population." *Journal of Psychopharmacology* 29 (3): 280–88. https://doi.org/10.1177/0269881114565653.

Hering, Ewald. 1861. *Beitrage Zur Physiologie*. W. Engelmann.

Hershenson, Maurice, ed. 2013. *The Moon Illusion*. Psychology Press. https://doi.org/10.4324/9780203771303.

Hess, Robert, and David Field. 1999. "Integration of Contours: New Insights." *Trends in Cognitive Sciences* 3 (12): 480–86. https://doi.org/10.1016/s1364-6613(99)01410-2.

Hesselgrave, Natalie, Timothy A. Troppoli, Andreas B. Wulff, Anthony B. Cole, and Scott M. Thompson. 2021. "Harnessing Psilocybin: Antidepressant-like Behavioral and Synaptic Actions of Psilocybin Are Independent of 5-HT2R Activation in Mice." *Proceedings of the National Academy of Sciences* 118 (17). https://doi.org/10.1073/pnas.2022489118.

Himwich, H E. 1959. "Neuropharmacology : Transactions of the Second Conference." *American Journal of Psychiatry* 116 (1): 88–88. https://doi.org/10.1176/ajp.116.1.88.

Hintzen, Annelie, and Torsten Passie. 2010. *The Pharmacology of LSD : A Critical Review*. Oxford: Oxford University Press : Beckley Foundation Press.

Hirschfeld, Tim, and Timo T Schmidt. 2021. "Dose–response Relationships of Psilocybin-Induced Subjective Experiences in Humans." *Journal of Psychopharmacology* 35 (4): 384–97. https://doi.org/10.1177/0269881121992676.

Hoffer, A, H Osmond, and J Smythies. 1954. "Schizophrenia; a New Approach. II. Result of a Year's Research." *The Journal of Mental Science* 100 (418): 29–45. https://doi.org/10.1192/bjp.100.418.29.

Hofmann, Albert. 1980. *LSD, My Problem Child*. New York: McGraw-Hill. https://doi.org/10.2307/4638477.

Hohwy, Jakob. 2013. *The Predictive Mind*. OUP Oxford. https://doi.org/10.1093/acprof:oso/9780199682737.001.0001.

Holt, Robert R. 2002. "Quantitative Research on the Primary Process: Method and Findings." *Journal of the American Psychoanalytic Association* 50 (2): 457–82. https://doi.org/10.1177/00030651020500021501.

Holze, Friederike, Laura Ley, Felix Müller, Anna M. Becker, Isabelle Straumann, Patrick Vizeli, Sebastian Silva Kuehne, et al. 2022. "Direct Comparison of the Acute Effects of Lysergic Acid Diethylamide and Psilocybin in a Double-Blind Placebo-Controlled Study in Healthy Subjects." *Neuropsychopharmacology* 47 (6): 1180–87. https://doi.org/10.1038/s41386-022-01297-2.

Holze, Friederike, Patrick Vizeli, Laura Ley, Felix Müller, Patrick Dolder, Melanie Stocker, Urs Duthaler, et al. 2020. "Acute Dose-Dependent Effects of Lysergic Acid Diethylamide in a Double-Blind Placebo-Controlled Study in Healthy Subjects." *Neuropsychopharmacology* 46 (3): 537–44. https://doi.org/10.1038/s41386-020-00883-6.

Holze, Friederike, Patrick Vizeli, Felix Müller, Laura Ley, Raoul Duerig, Nimmy Varghese, Anne Eckert, Stefan Borgwardt, and Matthias E. Liechti. 2019. "Distinct Acute Effects of LSD, MDMA, and d-Amphetamine in Healthy Subjects." *Neuropsychopharmacology* 45 (3): 462–71. https://doi.org/10.1038/s41386-019-0569-3.

Hood, Ralph W. 2001. "Review: Cleansing the Doors of Perception: The Religious Significance of Entheogenic Plants and Chemicals." *The International Journal for the Psychology of Religion* 11 (4): 285–86. https://doi.org/10.1207/s15327582ijpr1104_08.

Hosanagar, Avinash, Joseph Cusimano, and Rajiv Radhakrishnan. 2021. "Therapeutic Potential of Psychedelics in Treatment of Psychiatric Disorders, Part 2." *The Journal of Clinical Psychiatry* 82 (3). https://doi.org/10.4088/jcp.20ac13787.

Huang, Gregory. 2008. "Is This a Unified Theory of the Brain." *New Scientist* 2658: 30–33.

Huxley, Aldous. 1945. *The Perennial Philosophy*. New York; London: Harper & Bros. https://doi.org/10.2307/3706996.

———. 1953. "Letters to Dr. Humphrey Osmond." In *Moksha : Aldous Huxley's Classic Writings on Psychedelics and the Visionary Experience*, edited by Michael Horowitz and Cynthia Palmer.

———. 1954. *The Doors of Perception*. New York: Harper.

———. 1956. "History of Tension." In *Moksha : Aldous Huxley's Classic Writings on Psychedelics and the Visionary Experience*, edited by Michael Horowitz and Cynthia Palmer, 117–28.

———. 1961. "Visionary Experience." In *Moksha : Aldous Huxley's Classic Writings on Psychedelics and the Visionary Experience*, edited by Michael Horowitz and Cynthia Palmer.

Isbell, H. 1959. "Comparison of the Reactions Induced by Psilocybin and LSD-25 in Man." *Psychopharmacologia* 1: 29–38. https://doi.org/10.1007/bf00408109.

Itti, Laurent, and Christof Koch. 2000. "A Saliency-Based Search Mechanism for Overt and Covert Shifts of Visual Attention." *Vision Research* 40 (10-12): 1489–1506. https://doi.org/10.1016/s0042-6989(99)00163-7.

James, William. 1882. "Subjective Effects of Nitrous Oxide."

———. 1890. "The Principles of Psychology." In. Henry Holt; Company. https://doi.org/10.1037/11059-000.

———. 1902. *The Varieties of Religious Experience : A Study in Human Nature*. New York: Longmans, Green. https://doi.org/10.1037/10004-000.

Johnson, Matthew W, Albert Garcia-Romeu, Mary P Cosimano, and Roland R Griffiths. 2014. "Pilot Study of the 5-Ht2ar Agonist Psilocybin in the Treatment of Tobacco Addiction." *Journal of Psychopharmacology* 28 (11): 983–92. https://doi.org/10.1177/0269881114548296.

Johnson, Matthew W, Wa Richards, and Roland R Griffiths. 2008. "Human Hallucinogen Research: Guidelines for Safety." *Journal of Psychopharmacology* 22 (6): 603–20. https://doi.org/10.1177/0269881108093587.

Jones, H. E., K. L. Grieve, W. Wang, and A. M. Sillito. 2001. "Surround Suppression in Primate V1." *Journal of Neurophysiology* 86 (4): 2011–28. https://doi.org/10.1152/jn.2001.86.4.2011.

Joo, Sung Jun, Geoffrey M. Boynton, and Scott O. Murray. 2012. "Long-Range, Pattern-Dependent Contextual Effects in Early Human Visual Cortex." *Current Biology* 22 (9): 781–86. https://doi.org/10.1016/j.cub.2012.02.067.

Joo, Sung Jun, and Scott O. Murray. 2014. "Contextual Effects in Human Visual Cortex Depend on Surface Structure." *Journal of Neurophysiology* 111 (9): 1783–91. https://doi.org/10.1152/jn.00671.2013.

Kaelen, Mendel, F S Barrett, Leor Roseman, R Lorenz, N Family, M Bolstridge, H V Curran, A Feilding, D J Nutt, and Robin L Carhart-Harris. 2015. "LSD Enhances the Emotional Response to Music." *Psychopharmacology* 232 (19): 3607–14. https://doi.org/10.1007/s00213-015-4014-y.

Kaelen, Mendel, Bruna Giribaldi, Jordan Raine, Lisa Evans, Christopher Timmerman, Natalie Rodriguez, Leor Roseman, Amanda Feilding, David Nutt, and Robin L Carhart-Harris. 2018. "The Hidden Therapist: Evidence for a Central Role of Music in Psychedelic Therapy." *Psychopharmacology* 235 (2): 505–19.

Kaelen, Mendel, Leor Roseman, Joshua Kahan, Andre Santos-Ribeiro, Csaba Orban, Romy Lorenz, Frederick S Barrett, et al. 2016. "LSD Modulates Music-Induced Imagery via Changes in Parahippocampal Connectivity." *European Neuropsychopharmacology*. https://doi.org/10.1016/j.euroneuro.2016.03.018.

Kaletsch, Morten, Sebastian Pilgramm, Matthias Bischoff, Stefan Kindermann, Isabell Sauerbier, Rudolf Stark, Stefanie Lis, et al. 2014. "Major Depressive Disorder Alters Perception of Emotional Body Movements." *Frontiers in Psychiatry* 5. https://doi.org/10.3389/fpsyt.2014.00004.

Kanizsa, Gaetano. 1979. *Organization in Vision: Essays on Gestalt Perception*. Praeger Publishers.

Kant, Immanuel. 1787. *Critique of Pure Reason, Second Edition*. Edited by W S Pluhar. Hackett Classics. Hackett Publishing Company.

Kapadia, Mitesh K., Minami Ito, Charles D. Gilbert, and Gerald Westheimer. 1995. "Improvement in Visual Sensitivity by Changes in Local Context: Parallel Studies in Human Observers and in V1 of Alert Monkeys." *Neuron* 15 (4): 843–56. https://doi.org/10.1016/0896-6273(95)90175-2.

Kay, Kendrick N. 2017. "Principles for Models of Neural Information Processing." *NeuroImage*, August. https://doi.org/10.1016/j.neuroimage.2017.08.016.

Kemp, Charles, Amy Perfors, and Joshua B Tenenbaum. 2007. "Learning Overhypotheses with Hierarchical Bayesian Models." *Developmental Science* 10 (3): 307–21. https://doi.org/10.1111/j.1467-7687.2007.00585.x.

Kersten, Daniel, Pascal Mamassian, and Alan Yuille. 2004. "Object Perception as Bayesian Inference." *Annual Review of Psychology* 55: 271–304. https://doi.org/10.1146/annurev.psych.55.090902.142005.

Kersten, Daniel, and Alan Yuille. 2003. "Bayesian Models of Object Perception." *Current Opinion in Neurobiology* 13 (2): 150–58. https://doi.org/10.1016/s0959-4388(03)00042-4.

Kitcher, Philip. 1981. "Explanatory Unification." *Philosophy of Science* 48 (4): 507–31. https://doi.org/10.1086/289019.

———. 1989. "Explanatory Unification and the Causal Structure of the World." In *Scientific Explanation*, edited by Philip Kitcher and Wesley Salmon, 410–505. Minneapolis: University of Minnesota Press.

Klee, G D. 1963. "Lysergic Acid Diethylamide (LSD-25) and Ego Functions." *Archives of General Psychiatry* 8 (May): 461–74. https://doi.org/10.1001/archpsyc.1963.01720110037005.

Klüver, Heinrich. 1926. "Mescal Visions and Eidetic Vision." *The American Journal of Psychology* 37 (4): 502–15. https://doi.org/10.2307/1414910.

———. 1928. *Mescal: The 'Divine' Plant and Its Psychological Effects*. London: Kegan Paul, Trench, Trubner & Co.

———. 1942. "Mechanisms of Hallucinations." In *Studies in Personality.*, edited by M. A. Q. McNemar & Merrill, 175–207. New York, NY, US: McGraw-Hill. https://doi.org/10.1037/13305-015.

———. 1966. *Mescal and Mechanisms of Hallucinations*. Chicago: Univ. of Chicago Press.

Knauer, Alwyn, and William J M A Maloney. 1913. "A Preliminary Note on the Psychic Action of Mescalin, with Special Reference to the Mechanism of Visual Hallucinations." *The Journal of Nervous and Mental Disease* 40 (7): 425. https://doi.org/10.1097/00005053-191307000-00001.

Knierim, J. J., and D. C. van Essen. 1992. "Neuronal Responses to Static Texture Patterns in Area V1 of the Alert Macaque Monkey." *Journal of Neurophysiology* 67 (4): 961–80. https://doi.org/10.1152/jn.1992.67.4.961.

Knill, David C, and Alexandre Pouget. 2004. "The Bayesian Brain: The Role of Uncertainty in Neural Coding and Computation." *Trends in Neurosciences* 27 (12): 712–19. https://doi.org/10.1016/j.tins.2004.10.007.

Kometer, Michael, B Rael Cahn, David Andel, Olivia L Carter, and Franz X Vollenweider. 2011. "The 5-Ht2a/1a Agonist Psilocybin Disrupts Modal Object Completion Associated with Visual Hallucinations." *Biological Psychiatry* 69 (5): 399–406. https://doi.org/10.1016/j.biopsych.2010.10.002.

Kometer, Michael, Thomas Pokorny, Erich Seifritz, and Franz X Volleinweider. 2015. "Psilocybin-Induced Spiritual Experiences and Insightfulness Are Associated with Synchronization of Neuronal Oscillations." *Psychopharmacology* 232 (19): 3663–76. https://doi.org/10.1007/s00213-015-4026-7.

Kometer, Michael, André Schmidt, Rosilla Bachmann, Erich Studerus, Erich Seifritz, and Franz X Vollenweider. 2012. "Psilocybin Biases Facial Recognition, Goal-Directed Behavior, and Mood State Toward Positive Relative to Negative Emotions Through Different Serotonergic Subreceptors." *Biological Psychiatry* 72 (11):

898–906. https://doi.org/10.1016/j.biopsych.2012.04.005.

Kometer, Michael, André Schmidt, Lutz Jäncke, and Franz X Vollenweider. 2013. "Activation of Serotonin 2a Receptors Underlies the Psilocybin-Induced Effects on α Oscillations, N170 Visual-Evoked Potentials, and Visual Hallucinations." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 33 (25): 10544–51. https://doi.org/10.1523/jneurosci.3007-12.2013.

Kometer, Michael, and Franz X Vollenweider. 2016. "Serotonergic Hallucinogen-Induced Visual Perceptual Alterations." In, 257–82. Springer Berlin Heidelberg. https://doi.org/10.1007/7854_2016_461.

Kosovicheva, Anna A., Summer L. Sheremata, Ariel Rokem, Ayelet N. Landau, and Michael A. Silver. 2012. "Cholinergic Enhancement Reduces Orientation-Specific Surround Suppression but Not Visual Crowding." *Frontiers in Behavioral Neuroscience* 6. https://doi.org/10.3389/fnbeh.2012.00061.

Kraehenmann, Rainer, Dan Pokorny, Helena Aicher, Katrin H Preller, Thomas Pokorny, Oliver G Bosch, Erich Seifritz, and Franz X Vollenweider. 2017. "LSD Increases Primary Process Thinking via Serotonin 2a Receptor Activation." *Frontiers in Pharmacology* 8: 814. https://doi.org/10.3389/fphar.2017.00814.

Kraehenmann, Rainer, Dan Pokorny, Leonie Vollenweider, Katrin H Preller, Thomas Pokorny, Erich Seifritz, and Franz X Vollenweider. 2017. "Dreamlike Effects of LSD on Waking Imagery in Humans Depend on Serotonin 2a Receptor Activation." *Psychopharmacology* 234 (13): 2031–46. https://doi.org/10.1007/s00213-017-4610-0.

Kraepelin, Emil. 1892. *Ueber Die Beeinflussung Einfacher Psychischer Vorgänge Durch Einige Arzneimittel: Experimentelle Untersuchungen.* G. Fischer.

Krause, Fernando C., Eftihia Linardatos, David M. Fresco, and Michael T. Moore. 2021. "Facial Emotion Recognition in Major Depressive Disorder: A Meta-Analytic Review." *Journal of Affective Disorders* 293 (October): 320–28. https://doi.org/10.1016/j.jad.2021.06.053.

Krebs, Teri S, and Pål-Ørjan Johansen. 2013. "Psychedelics and Mental Health: A Population Study." *PloS One* 8 (8): e63972. https://doi.org/10.1371/journal.pone.0063972.

Kuypers, K P C, Jordi Riba, M de la Fuente Revenga, S Barker, E L Theunissen, and J G Ramaekers. 2016. "Ayahuasca Enhances Creative Divergent Thinking While Decreasing Conventional Convergent Thinking." *Psychopharmacology* 233 (18): 3395–3403. https://doi.org/10.1007/s00213-016-4377-8.

Kwisthout, Johan, Harold Bekkering, and Iris van Rooij. 2017. "To Be Precise, the Details Don't Matter: On Predictive Processing, Precision, and Level of Detail of Predictions." *Brain and Cognition* 112 (March): 84–91. https://doi.org/10.1016/j.bandc.2016.02.008.

Kwisthout, Johan, and Iris van Rooij. 2015. "Free Energy Minimization and Information Gain: The Devil Is in the Details." *Cognitive Neuroscience* 6 (4): 216–18. https://doi.org/10.1080/17588928.2015.1051014.

Lamme, VA. 1995. "The Neurophysiology of Figure-Ground Segregation in Primary Visual Cortex." *The Journal of Neuroscience* 15 (2): 1605–15. https://doi.org/10.1523/jneurosci.15-02-01605.1995.

Langfelder, Peter, and Steve Horvath. 2012. "Fast r Functions for Robust Correlations and Hierarchical Clustering." *Journal of Statistical Software* 46 (23050260): i11.

Lawn, Timothy, Ottavia Dipasquale, Alexandros Vamvakas, Ioannis Tsougos, Mitul A. Mehta, and Matthew A. Howard. 2022. "Differential Contributions of Serotonergic and Dopaminergic Functional Connectivity to the Phenomenology of LSD." *Psychopharmacology* 239 (6): 1797–1808. https://doi.org/10.1007/s00213-022-06117-5.

Lawrence, David Wyndham, Robin Carhart-Harris, Roland Griffiths, and Christopher Timmermann. 2022. "Phenomenology and Content of the Inhaled n, n-Dimethyltryptamine (n, n-DMT) Experience." *Scientific Reports* 12 (1). https://doi.org/10.1038/s41598-022-11999-8.

Leary, Timothy. 1961. "Drugs, Set & Suggestibility." In *Annual Meeting of the American Psychological Association*. Vol. 6.

Leary, Timothy, George H Litwin, and Ralph Metzner. 1963. "REACTIONS TO PSILOCYBJN ADMINISTERED IN a SUPPORTIVE ENVIRONMENT." *The Journal of Nervous and Mental Disease* 137 (6): 561. https://doi.org/10.1097/00005053-196312000-00007.

Leary, Timothy, Ralph Metzner, and Richard Alpert. 1964. *The Psychedelic Experience : A Manual Based on the Tibetan Book of the Dead*. New York: University Books.

Lebedev, A V, Mendel Kaelen, M Lövdén, J Nilsson, A Feilding, D J Nutt, and Robin L Carhart-Harris. 2016. "LSD-induced Entropic Brain Activity Predicts Subsequent Personality Change." *Human Brain Mapping*, May. https://doi.org/10.1002/hbm.23234.

Lee, Tai Sing, and David Mumford. 2003. "Hierarchical Bayesian Inference in the Visual Cortex." *Journal of the Optical Society of America. A, Optics, Image Science, and Vision* 20 (7): 1434–48. https://doi.org/10.1364/JOSAA.20.001434.

Leptourgos, Pantelis, Martin Fortier-Davy, Robin L Carhart-Harris, Philip R. Corlett, David Dupuis, Adam L Halberstadt, Michael Kometer, et al. 2020. "Hallucinations Under Psychedelics and in the Schizophrenia Spectrum: An Interdisciplinary and Multiscale Comparison." *Schizophrenia Bulletin* 46 (6): 1396–1408. https://doi.org/10.1093/schbul/sbaa117.

Letheby, Chris. 2021. *Philosophy of Psychedelics*. Oxford University Press. https://doi.org/10.1093/med/9780198843122.001.0001.

Letheby, Chris, and Philip Gerrans. 2017. "Self Unbound: Ego Dissolution in Psychedelic Experience." *Neuroscience of Consciousness* 3 (1). https://doi.org/10.1093/nc/nix016.

———. n.d. *Philosophical Perspectives on the Psychedelic Renaissance*. Oxford University Press.

Lewicki, Michael S, Bruno A Olshausen, Annemarie Surlykke, and Cynthia F Moss. 2014. "Scene Analysis in the Natural Environment." *Frontiers in Psychology* 5 (February). https://doi.org/10.3389/fpsyg.2014.00199.

Lewin, Louis. 1894. "On Anhalonium Lewinii and Other Cacti." *Archiv für Experimentelle Pathologie Und Pharmakologie*.

———. 1927. *Phantastica, Narcotic and Stimulating Drugs*. Stilke Berlin. https://doi.org/10.1097/00000441-193209000-00032.

Lieberman, Jeffrey A, and Daniel Shalev. 2016. "Back to the Future: Research Re-

newed on the Clinical Utility of Psychedelic Drugs." *Journal of Psychopharmacology* 30 (12): 1198–1200. https://doi.org/10.1177/0269881116675755.

Liechti, Matthias E, Patrick C Dolder, and Yasmin Schmid. 2017. "Alterations of Consciousness and Mystical-Type Experiences After Acute LSD in Humans." *Psychopharmacology* 234 (9-10): 1499–1510.

Limanowski, Jakub, and Felix Blankenburg. 2013. "Minimal Self-Models and the Free Energy Principle." *Frontiers in Human Neuroscience* 7 (September): 547. https://doi.org/10.3389/fnhum.2013.00547.

Linares, Daniel, Silvia Amoretti, Rafael Marin-Campos, André Sousa, Laia Prades, Josep Dalmau, Miquel Bernardo, and Albert Compte. 2020. "Spatial Suppression and Sensitivity for Motion in Schizophrenia." *Schizophrenia Bulletin Open* 1 (1). https://doi.org/10.1093/schizbullopen/sgaa045.

Loon, Anouk M van, H Steven Scholte, Simon van Gaal, Björn J J van der Hoort, and Victor A F Lamme. 2012. "GABAA Agonist Reduces Visual Awareness: A masking-EEG Experiment." *Journal of Cognitive Neuroscience* 24 (4): 965–74. https://doi.org/10.1162/jocn_a_00197.

Lopez-Calderon, Javier, and Steven J. Luck. 2014. "ERPLAB: An Open-Source Toolbox for the Analysis of Event-Related Potentials." *Frontiers in Human Neuroscience* 8 (April). https://doi.org/10.3389/fnhum.2014.00213.

Louie, Kenway, and Paul W. Glimcher. 2019. "Normalization Principles in Computational Neuroscience." Oxford University Press. https://doi.org/10.1093/acrefore/9780190264086.013.43.

Louie, Kenway, Mel W. Khaw, and Paul W. Glimcher. 2013. "Normalization Is a General Neural Mechanism for Context-Dependent Decision Making." *Proceedings of the National Academy of Sciences* 110 (15): 6139–44. https://doi.org/10.1073/pnas.1217854110.

Louie, Kenway, T. LoFaro, R. Webb, and P. W. Glimcher. 2014. "Dynamic Divisive Normalization Predicts Time-Varying Value Coding in Decision-Related Circuits." *Journal of Neuroscience* 34 (48): 16046–57. https://doi.org/10.1523/jneurosci.2851-14.2014.

Luke, David P, and Devin B Terhune. 2013. "The Induction of Synaesthesia with Chemical Agents: A Systematic Review." *Frontiers in Psychology* 4 (October): 753. https://doi.org/10.3389/fpsyg.2013.00753.

Ma, Wen-Pei, Bao-Hua Liu, Ya-Tang Li, Z Josh Huang, Li I Zhang, and Huizhong W Tao. 2010. "Visual Representations by Cortical Somatostatin Inhibitory Neurons–Selective but with Weak and Delayed Responses." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 30 (43): 14371–79. https://doi.org/10.1523/jneurosci.3248-10.2010.

MacKay, D Mo. 1956. "The Epistemological Problem for Automata." In *Automata Studies: Annals of Mathematics Studies. Number 34*, edited by W R Ashby, C E Shannon, and J McCarthy. Automata Studies, Princeton, NJ: Princeton University Press. https://doi.org/10.1515/9781400882618-012.

MacLean, Katherine A, Matthew W Johnson, and Roland R Griffiths. 2011. "Mystical Experiences Occasioned by the Hallucinogen Psilocybin Lead to Increases in the Personality Domain of Openness." *Journal of Psychopharmacology* 25 (11): 1453–61.

https://doi.org/10.1177/0269881111420188.
Maclean, Katherine A, Jeannie-Marie S Leoutsakos, Matthew W Johnson, and Roland R Griffiths. 2012. "Factor Analysis of the Mystical Experience Questionnaire: A Study of Experiences Occasioned by the Hallucinogen Psilocybin." *Journal for the Scientific Study of Religion* 51 (4): 721–37. https://doi.org/10.1111/j.1468-5906.2012.01685.x.
Macpherson, Fiona, and Clare Batty. 2016. "REDEFINING ILLUSION AND HALLUCINATION IN LIGHT OF NEW CASES." *Philosophical Issues* 26: 263–96. https://www.jstor.org/stable/26611239.
Magaraggia, Igor, Zilla Kuiperes, and Rudy Schreiber. 2021. "Improving Cognitive Functioning in Major Depressive Disorder with Psychedelics: A Dimensional Approach." *Neurobiology of Learning and Memory* 183 (September): 107467. https://doi.org/10.1016/j.nlm.2021.107467.
Majić, Tomislav, Timo T Schmidt, and Jürgen Gallinat. 2015. "Peak Experiences and the Afterglow Phenomenon: When and How Do Therapeutic Effects of Hallucinogens Depend on Psychedelic Experiences?" *Journal of Psychopharmacology* 29 (3): 241–53. https://doi.org/10.1177/0269881114568040.
Marino, Joseph. 2022. "Predictive Coding, Variational Autoencoders, and Biological Connections." *Neural Computation* 34 (1): 1–44. https://doi.org/10.1162/neco_a_01458.
Marozeau, Jeremy, and Alain de Cheveigné. 2007. "The Effect of Fundamental Frequency on the Brightness Dimension of Timbre." *The Journal of the Acoustical Society of America* 121 (1): 383–87. https://doi.org/10.1121/1.2384910.
Marshall, Paul. 2005. "Mind Beyond the Brain: Reducing Valves and Metaphysics." In *Mystical Encounters with the Natural World*. Oxford: Oxford University Press.
Martindale, C, and R Fischer. 1977. "The Effects of Psilocybin on Primary Process Content in Language." *Confinia Psychiatrica. Borderland of Psychiatry. Grenzgebiete Der Psychiatrie. Les Confins de La Psychiatrie* 20 (4): 195–202.
Masters, Robert E L, and Jean Houston. 1966. *The Varieties of Psychedelic Experience,*. New York: Holt, Rinehart; Winston. https://doi.org/10.2307/1141632.
McClure-Begley, Tristan D., and Bryan L. Roth. 2022. "The Promises and Perils of Psychedelic Pharmacology for Psychiatry." *Nature Reviews Drug Discovery* 21 (6): 463–73. https://doi.org/10.1038/s41573-022-00421-7.
McGurk, Harry, and John MacDonald. 1976. "Hearing Lips and Seeing Voices." *Nature* 264 (5588): 746–48. https://doi.org/10.1038/264746a0.
McKenna, Dennis J, D B Repke, L Lo, and S J Peroutka. 1990. "Differential Interactions of Indolealkylamines with 5-Hydroxytryptamine Receptor Subtypes." *Neuropharmacology* 29 (3): 193–98. https://doi.org/10.1016/0028-3908(90)90001-8.
McKenna, Dennis J, and Jordi Riba. 2015. "New World Tryptamine Hallucinogens and the Neuroscience of Ayahuasca." *Current Topics in Behavioral Neurosciences*, February. https://doi.org/10.1007/7854_2015_368.
McKenna, Dennis J, G H Towers, and F Abbott. 1984. "Monoamine Oxidase Inhibitors in South American Hallucinogenic Plants: Tryptamine and Beta-Carboline Constituents of Ayahuasca." *Journal of Ethnopharmacology* 10 (2): 195–223.

https://doi.org/10.1016/0378-8741(84)90003-5.
Melara, Robert D., and Lawrence E. Marks. 1990. "Interaction Among Auditory Dimensions: Timbre, Pitch, and Loudness." *Perception & Psychophysics* 48 (2): 169–78. https://doi.org/10.3758/bf03207084.
Merkur, Daniel. 1998. *The Ecstatic Immagination : Psychedelic Experiences and the Psychoanalysis of Self-Actualization*. Albany: State University of New York Press.
Merriam-Webster. 2017. "Model." In *Merriam-Webster.com.* Merriam-Webster.com.
Mertens, Lea J, Matthew B Wall, Leor Roseman, Lysia Demetriou, David J Nutt, and Robin L Carhart-Harris. 2020. "Therapeutic Mechanisms of Psilocybin: Changes in Amygdala and Prefrontal Functional Connectivity During Emotional Processing After Psilocybin for Treatment-Resistant Depression." *Journal of Psychopharmacology* 34 (2): 167–80. https://doi.org/10.1177/0269881119895520.
Metzinger, Thomas. 2003. *Being No One : The Self-Model Theory of Subjectivity*. Cambridge; London: The MIT Press. https://doi.org/10.7551/mitpress/1551.001.0001.
Metzner, Ralph, and Timothy Leary. 1967. "On Programming Psychedelic Experiences." *Psychedelic Review* 9: 5–19.
Michaiel, Angie M., Philip R. L. Parker, and Cristopher M. Niell. 2019. "A Hallucinogenic serotonin-2A Receptor Agonist Reduces Visual Response Gain and Alters Temporal Dynamics in Mouse V1." *Cell Reports* 26 (13): 3475–3483.e4. https://doi.org/10.1016/j.celrep.2019.02.104.
Miller, George A. 2003. "The Cognitive Revolution: A Historical Perspective." *Trends in Cognitive Sciences* 7 (3): 141–44. https://doi.org/10.1016/s1364-6613(03)00029-9.
Millière, Raphaël. 2017. "Looking for the Self: Phenomenology, Neurophysiology and Philosophical Significance of Drug-Induced Ego Dissolution." *Frontiers in Human Neuroscience* 11: 245. https://doi.org/10.3389/fnhum.2017.00245.
Mitchell, S W. 1896. "Remarks on the Effects of Anhelonium Lewinii (the Mescal Button)." *British Medical Journal* 2 (1875): 1625–29. https://doi.org/10.1136/bmj.2.1875.1625.
Montague, P Read, Raymond J Dolan, Karl J Friston, and Peter Dayan. 2012. "Computational Psychiatry." *Trends in Cognitive Sciences* 16 (1): 72–80. https://doi.org/10.1016/j.tics.2011.11.018.
Moore, Tyler M., Steven P. Reise, Raquel E. Gur, Hakon Hakonarson, and Ruben C. Gur. 2015. "Psychometric Properties of the Penn Computerized Neurocognitive Battery." *Neuropsychology* 29 (2): 235–46. https://doi.org/10.1037/neu0000093.
Moreau, Jacques Joseph. 1845. *Du Hachisch Et de l'aliénation Mentale: études Psychologiques*. Paris: Fortin, Masson.
Moreno, Francisco A, Christopher B Wiegand, E Keolani Taitano, and Pedro L Delgado. 2006. "Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients with Obsessive-Compulsive Disorder." *The Journal of Clinical Psychiatry* 67 (11): 1735–40. https://doi.org/10.4088/jcp.v67n1110.
Morey, Richard D. 2008. "Confidence Intervals from Normalized Data: A Correction to Cousineau (2005)." *Tutorials in Quantitative Methods for Psychology* 4 (2): 61–64.

Morreall, John. 2020. "Philosophy of Humor." In *The Stanford Encyclopedia of Philosophy*, edited by Edward N. Zalta, Fall 2020. https://plato.stanford.edu/archives/fall2020/entries/humor/; Metaphysics Research Lab, Stanford University.

Morrison, Margaret. 2000. *Unifying Scientific Theories : Physical Concepts and Mathematical Structures*. Cambridge: Cambridge University Press. https://doi.org/10.1017/cbo9780511527333.

Müller, Ulrich, Paul C Fletcher, and Holger Steinberg. 2006. "The Origin of Pharmacopsychology: Emil Kraepelin's Experiments in Leipzig, Dorpat and Heidelberg (1882-1892)." *Psychopharmacology* 184 (2): 131–38.

Müller-Lyer, F. C. 1889. "Optical Illusions." In *The Contributions of f c Müller-Lyer*, edited by Ross H Day.

Mumford, D. 1992. "On the Computational Architecture of the Neocortex." *Biological Cybernetics* 66 (3): 241–51. https://doi.org/10.1007/bf00198477.

Murray, M. M. 2004. "Setting Boundaries: Brain Dynamics of Modal and Amodal Illusory Shape Completion in Humans." *Journal of Neuroscience* 24 (31): 6898–6903. https://doi.org/10.1523/jneurosci.1996-04.2004.

Muthukumaraswamy, Suresh, Robin L Carhart-Harris, Rosalyn J Moran, Matthew J Brookes, Tim M Williams, David Errtizoe, Ben Sessa, et al. 2013. "Broadband Cortical Desynchronization Underlies the Human Psychedelic State." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 33 (38): 15171–83. https://doi.org/10.1523/jneurosci.2063-13.2013.

Muthukumaraswamy, Suresh, Anna Forsyth, and Thomas Lumley. 2021. "Blinding and Expectancy Confounds in Psychedelic Randomized Controlled Trials." *Expert Review of Clinical Pharmacology* 14 (9): 1133–52. https://doi.org/10.1080/17512433.2021.1933434.

Myers, F W H. 1903. *Human Personality and Its Survival of Bodily Death*. London: Longmans & Co. https://doi.org/10.1037/13858-000.

Naseri, Parisa, Hamid Alavi Majd, Mohammad Tabatabae, Naghmeh Khadembashi, and Morteza Najibi. 2019. "Functional Brain Response to Emotional Musical Stimuli in Depression, Using INLA Approach for Approximate Bayesian Inference." *Basic and Clinical Neuroscience Journal*, November. https://doi.org/10.32598/bcn.9.10.480.

Natale, M, C C Dahlberg, and J Jaffe. 1978. "Effect of Psychotomimetics (LSD and Dextroamphetamine) on the Use of Primary- and Secondary-Process Language." *Journal of Consulting and Clinical Psychology* 46 (2): 352–53. https://doi.org/10.1037/0022-006x.46.2.352.

Natale, M, M Kowitt, Dahlberg -Journal of consulting, . . . C C, and 1978. 1978. "Effect of Psychototmimetics (LSD and Dextroamphetamine) on the Use of Figurative Language During Psychoanalysis." *Psycnet.apa.org*. https://doi.org/10.1037/0022-006x.46.6.1579.

Neisser, Ulric. 1967. "Cognitive Psychology." https://doi.org/10.4324/9781315736174.

Nguyen, Bao N, Sui-Ann Hew, John Ly, Hee-Young Shin, Jessica C Wong, Emily Yeung, and Allison M McKendrick. 2018. "Acute Caffeine Ingestion Affects Surround Suppression of Perceived Contrast." *Journal of Psychopharmacology* 32 (1): 81–88.

Nichols, David E. 2004. "Hallucinogens." *Pharmacology & Therapeutics* 101 (2): 131–81. https://doi.org/10.1007/978-3-642-27772-6_44-2.

———. 2016. "Psychedelics." *Pharmacological Reviews* 68 (2): 264–355. https://doi.org/10.1124/pr.115.011478.

Nienborg, Hendrikje, Andrea Hasenstaub, Ian Nauhaus, Hiroki Taniguchi, Z Josh Huang, and Edward M Callaway. 2013. "Contrast Dependence and Differential Contributions from Somatostatin- and Parvalbumin-Expressing Neurons to Spatial Integration in Mouse V1." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 33 (27): 11145–54. https://doi.org/10.1523/jneurosci.5320-12.2013.

Nothdurft, H. C., J. L. Gallant, and D. C. Van Essen. 2000. "Response Profiles to Texture Border Patterns in Area V1." *Visual Neuroscience* 17 (3): 421–36. https://doi.org/10.1017/s0952523800173092.

Nour, Matthew M, Lisa Evans, David Nutt, and Robin L Carhart-Harris. 2016. "Ego-Dissolution and Psychedelics: Validation of the Ego-Dissolution Inventory (EDI)." *Frontiers in Human Neuroscience* 10 (May). https://doi.org/10.3389/fnhum.2016.00269.

Nurminen, Lauri, and Alessandra Angelucci. 2014. "Multiple Components of Surround Modulation in Primary Visual Cortex: Multiple Neural Circuits with Multiple Functions?" *Vision Research* 104 (November): 47–56. https://doi.org/10.1016/j.visres.2014.08.018.

Ohshiro, Tomokazu, Dora E. Angelaki, and Gregory C. DeAngelis. 2011. "A Normalization Model of Multisensory Integration." *Nature Neuroscience* 14 (6): 775–82. https://doi.org/10.1038/nn.2815.

Ohtani, Yoshio, Shoichi Okamura, Yoshikazu Yoshida, Keisuke Toyama, and Yoshimichi Ejima. 2002. "Surround Suppression in the Human Visual Cortex: An Analysis Using Magnetoencephalography." *Vision Research* 42 (15): 1825–35. https://doi.org/10.1016/s0042-6989(02)00103-7.

Oizumi, Masafumi, Larissa Albantakis, and Giulio Tononi. 2014. "From the Phenomenology to the Mechanisms of Consciousness: Integrated Information Theory 3.0." *PLoS Computational Biology* 10 (5): e1003588. https://doi.org/10.1371/journal.pcbi.1003588.

Olson, Jay A., Léah Suissa-Rocheleau, Michael Lifshitz, Amir Raz, and Samuel P. L. Veissière. 2020. "Tripping on Nothing: Placebo Psychedelics and Contextual Factors." *Psychopharmacology* 237 (5): 1371–82. https://doi.org/10.1007/s00213-020-05464-5.

Olzak, Lynn A, and Pentti I Laurinen. 1999. "Multiple Gain Control Processes in Contrast–contrast Phenomena." *Vision Research* 39 (24): 3983–87. https://doi.org/10.1016/s0042-6989(99)00131-5.

Osborne, Hannah. 2017. "Scientists Show LSD and Ketamine Make the Brain Enter a 'Higher State of Consciousness'." http://www.newsweek.com/psychedelic-drugs-lsd-ketamine-brain-higher-consciousness-586076.

Osmond, H. 1957. "A Review of the Clinical Effects of Psychotomimetic Agents." *Annals of the New York Academy of Sciences* 66 (3): 418–34. https://doi.org/10.1111/j.1749-6632.1957.tb40738.x.

Osmond, H, and J Smythies. 1952. "Schizophrenia: A New Approach." *The Journal of Mental Science* 98 (411): 309–15. https://doi.org/10.1192/bjp.98.411.309.

Ott, U. 2007. "States of Absorption: In Search of Neurobiological Foundations." *Hypnosis and Conscious States: The Cognitive*.

Ozeki, Hirofumi, Ian M. Finn, Evan S. Schaffer, Kenneth D. Miller, and David Ferster. 2009a. "Inhibitory Stabilization of the Cortical Network Underlies Visual Surround Suppression." *Neuron* 62 (4): 578–92. https://doi.org/10.1016/j.neuron.2009.03.028.

Ozeki, Hirofumi, Ian M Finn, Evan S Schaffer, Kenneth D Miller, and David Ferster. 2009b. "Inhibitory Stabilization of the Cortical Network Underlies Visual Surround Suppression." *Neuron* 62 (4): 578–92. https://doi.org/10.1016/j.neures.2009.09.1125.

Ozeki, Hirofumi, Osamu Sadakane, Takafumi Akasaki, Tomoyuki Naito, Satoshi Shimegi, and Hiromichi Sato. 2004. "Relationship Between Excitation and Inhibition Underlying Size Tuning and Contextual Response Modulation in the Cat Primary Visual Cortex." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 24 (6): 1428–38. https://doi.org/10.1523/jneurosci.3852-03.2004.

Pahnke, Walter N. 1966. "Drugs and Mysticism." *International Journal of Parapsychology* 8 (2): 295–313.

Palhano-Fontes, Fernanda, Katia C Andrade, Luis F Tofoli, Antonio C Santos, Jose Alexandre S Crippa, Jaime E C Hallak, Sidarta Ribeiro, and Draulio B de Araujo. 2015. "The Psychedelic State Induced by Ayahuasca Modulates the Activity and Connectivity of the Default Mode Network." *PloS One* 10 (2): e0118143. https://doi.org/10.1371/journal.pone.0118143.

Pallavicini, Carla, Federico Cavanna, Federico Zamberlan, Laura A de la Fuente, Yayla Ilksoy, Yonatan S Perl, Mauricio Arias, et al. 2021. "Neural and Subjective Effects of Inhaled n,n-Dimethyltryptamine in Natural Settings." *Journal of Psychopharmacology* 35 (4): 406–20. https://doi.org/10.1177/0269881120981384.

Pang, Xiaomei, Jing Xu, Yi Chang, Di Tang, Ya Zheng, Yanhua Liu, and Yiming Sun. 2014. "Mismatch Negativity of Sad Syllables Is Absent in Patients with Major Depressive Disorder." Edited by Piia Susanna Astikainen. *PLoS ONE* 9 (3): e91995. https://doi.org/10.1371/journal.pone.0091995.

Peirce, Jonathan, Jeremy R. Gray, Sol Simpson, Michael MacAskill, Richard Höchenberger, Hiroyuki Sogo, Erik Kastman, and Jonas Kristoffer Lindeløv. 2019. "PsychoPy2: Experiments in Behavior Made Easy." *Behavior Research Methods* 51 (1): 195–203. https://doi.org/10.3758/s13428-018-01193-y.

Peirce, Jonathan, and Michael MacAskill. 2018. *Building Experiments in PsychoPy*.

Petrov, Yury, and Suzanne P. McKee. 2006. "The Effect of Spatial Configuration on Surround Suppression of Contrast Sensitivity." *Journal of Vision* 6 (3): 4. https://doi.org/10.1167/6.3.4.

Pink-Hashkes, Sarit, Iris van Rooij, and Johan Kwisthout. 2017. "Perception Is in the Details: A Predictive Coding Account of the Psychedelic Phenomenon." In *Proceedings of the 39th Annual Meeting of the Cognitive Science Society*, 2907–12. London, UK.

Pokorny, Thomas, Patricia Duerler, Erich Seifritz, Franz X. Vollenweider, and Katrin H. Preller. 2019. "LSD Acutely Impairs Working Memory, Executive Functions, and Cognitive Flexibility, but Not Risk-Based Decision-Making." *Psychological Medicine* 50 (13): 2255–64. https://doi.org/10.1017/s0033291719002393.

Pokorny, Thomas, Katrin H Preller, Michael Kometer, Isabel Dziobek, and Franz X Vollenweider. 2017. "Effect of Psilocybin on Empathy and Moral Decision-Making." *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum* 20 (9): 747–57. https://doi.org/10.1093/ijnp/pyx047.

Pokorny, Thomas, Katrin H Preller, Rainer Kraehenmann, and Franz X Vollenweider. 2016. "Modulatory Effect of the 5-Ht1a Agonist Buspirone and the Mixed Non-Hallucinogenic 5-Ht1a/2a Agonist Ergotamine on Psilocybin-Induced Psychedelic Experience." *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 26 (4): 756–66. https://doi.org/10.1016/j.euroneuro.2016.01.005.

Pokorny, Victor J., Timothy J. Lano, Michael-Paul Schallmo, Cheryl A. Olman, and Scott R. Sponheim. 2019. "Reduced Influence of Perceptual Context in Schizophrenia: Behavioral and Neurophysiological Evidence." *Psychological Medicine* 51 (5): 786–94. https://doi.org/10.1017/s0033291719003751.

Polat, Uri, Keiko Mizobe, Mark W. Pettet, Takuji Kasamatsu, and Anthony M. Norcia. 1998. "Collinear Stimuli Regulate Visual Responses Depending on Cell's Contrast Threshold." *Nature* 391 (6667): 580–84. https://doi.org/10.1038/35372.

Preller, Katrin H, Marcus Herdener, Thomas Pokorny, Amanda Planzer, Rainer Kraehenmann, Philipp Stämpfli, Matthias E Liechti, Erich Seifritz, and Franz X Vollenweider. 2017. "The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2a Receptor Activation." *Current Biology: CB* 27 (3): 451–57. https://doi.org/10.1016/j.cub.2016.12.030.

Preller, Katrin H, and Franz X Vollenweider. 2016. "Phenomenology, Structure, and Dynamic of Psychedelic States." In, 221–56. Springer Berlin Heidelberg. https://doi.org/10.1007/7854_2016_459.

———. 2018. "Phenomenology, Structure, and Dynamic of Psychedelic States." *Current Topics in Behavioral Neurosciences* 36: 221–56.

Prentiss, D W, and T P Morgan. 1895. "Anhalonium Lewinie (Mescal Buttons)." *Therapeutic Gazette* 9: 577–85.

Purpura, D P. 1968. "Neurophysiological Actions of LSD." In *LSD, Man & Society*.

Purves, Dale, Yaniv Morgenstern, and William T Wojtach. 2015. "Perception and Reality: Why a Wholly Empirical Paradigm Is Needed to Understand Vision." *Frontiers in Systems Neuroscience* 9 (November): 156. https://doi.org/10.3389/fnsys.2015.00156.

Qiu, Cheng, Daniel Kersten, and Cheryl A Olman. 2013. "Segmentation Decreases the Magnitude of the Tilt Illusion." *Journal of Vision* 13 (13): 19. https://doi.org/10.1167/13.13.19.

Quaia, Christian, Lance M. Optican, and Bruce G. Cumming. 2017. "Suppression and Contrast Normalization in Motion Processing." *The Journal of Neuroscience* 37 (45): 11051–66. https://doi.org/10.1523/jneurosci.1572-17.2017.

Rabinowitz, Neil C., Ben D. B. Willmore, Jan W. H. Schnupp, and Andrew J. King. 2011. "Contrast Gain Control in Auditory Cortex." *Neuron* 70 (6): 1178–91. https://doi.org/10.1016/j.neuron.2011.04.030.

Rao, R P, and D H Ballard. 1999. "Predictive Coding in the Visual Cortex: A Functional Interpretation of Some Extra-Classical Receptive-Field Effects." *Nature Neuroscience* 2 (1): 79–87. https://doi.org/10.1038/4580.

Rapaport, D. 1950. "On the Psycho-Analytic Theory of Thinking." *The International Journal of Psycho-Analysis*.

Ray, Thomas S. 2010. "Psychedelics and the Human Receptorome." *PloS One* 5 (2): e9019. https://doi.org/10.1371/journal.pone.0009019.

———. 2016. "Constructing the Ecstasy of MDMA from Its Component Mental Organs: Proposing the Primer/Probe Method." *Medical Hypotheses* 87 (February): 48–60. https://doi.org/10.1016/j.mehy.2015.12.018.

Read, Jenny C A, Renos Georgiou, Claire Brash, Partow Yazdani, Roger Whittaker, Andrew J Trevelyan, and Ignacio Serrano-Pedraza. 2015. "Moderate Acute Alcohol Intoxication Has Minimal Effect on Surround Suppression Measured with a Motion Direction Discrimination Task." *Journal of Vision* 15 (1): 1515. https://doi.org/10.1167/15.1.5.

Reynolds, John H, and David J Heeger. 2009. "The Normalization Model of Attention." *Neuron* 61 (2): 168–85. https://doi.org/10.1016/j.neuron.2009.01.002.

Riba, Jordi, Peter Anderer, Francesc Jané, Bernd Saletu, and Manel J Barbanoj. 2004. "Effects of the South American Psychoactive Beverage Ayahuasca on Regional Brain Electrical Activity in Humans: A Functional Neuroimaging Study Using Low-Resolution Electromagnetic Tomography." *Neuropsychobiology* 50 (1): 89–101.

Riba, Jordi, Peter Anderer, Adelaida Morte, Gloria Urbano, Francesc Jané, Bernd Saletu, and Manel J Barbanoj. 2002. "Topographic pharmaco-EEG Mapping of the Effects of the South American Psychoactive Beverage Ayahuasca in Healthy Volunteers." *British Journal of Clinical Pharmacology* 53 (6): 613–28. https://doi.org/10.1046/j.1365-2125.2002.01609.x.

Riba, Jordi, A Rodriguez-Fornells, G Urbano, A Morte, R Antonijoan, M Montero, J C Callaway, and M J Barbanoj. 2001. "Subjective Effects and Tolerability of the South American Psychoactive Beverage Ayahuasca in Healthy Volunteers." *Psychopharmacology* 154 (1): 85–95. https://doi.org/10.1007/s002130000606.

Riba, Jordi, A. Rodríguez-Fornells, Rick J. Strassman, and M. J. Barbanoj. 2001. "Psychometric Assessment of the Hallucinogen Rating Scale." *Drug and Alcohol Dependence* 62 (3): 215–23. https://doi.org/10.1016/s0376-8716(00)00175-7.

Richards, William. 2015. *Sacred Knowledge*. Columbia University Press. https://doi.org/10.7312/columbia/9780231174060.001.0001.

Rickli, Anna, Olivier D Moning, Marius C Hoener, and Matthias E Liechti. 2016. "Receptor Interaction Profiles of Novel Psychoactive Tryptamines Compared with Classic Hallucinogens." *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 26 (8): 1327–37. https://doi.org/10.1016/j.euroneuro.2016.05.001.

Roseman, Leor, Lysia Demetriou, Matthew B Wall, David J Nutt, and Robin L Carhart-Harris. 2018. "Increased Amygdala Responses to Emotional Faces After Psilocybin

for Treatment-Resistant Depression." *Neuropharmacology* 142 (November): 263–69. https://doi.org/10.1016/j.neuropharm.2017.12.041.

Roseman, Leor, David Nutt, and Robin L Carhart-Harris. 2017. "Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression." *Frontiers in Pharmacology* 8: 974. https://doi.org/10.3389/fphar.2017.00974.

Roseman, Leor, M I Sereno, R Leech, and Mendel Kaelen. 2016. "LSD Alters Eyes-Closed Functional Connectivity Within the Early Visual Cortex in a Retinotopic Fashion." *Wiley Online Library*. https://doi.org/10.1002/hbm.23224.

Ross, Stephen, Anthony Bossis, Jeffrey Guss, Gabrielle Agin-Liebes, Tara Malone, Barry Cohen, Sarah E Mennenga, et al. 2016. "Rapid and Sustained Symptom Reduction Following Psilocybin Treatment for Anxiety and Depression in Patients with Life-Threatening Cancer: A Randomized Controlled Trial." *Journal of Psychopharmacology* 30 (12): 1165–80. https://doi.org/10.1177/0269881116675512.

Rottenberg, Jonathan, James J. Gross, and Ian H. Gotlib. 2005. "Emotion Context Insensitivity in Major Depressive Disorder." *Journal of Abnormal Psychology* 114 (4): 627–39. https://doi.org/10.1037/0021-843x.114.4.627.

Rouhier, A. 1927. *Le Peyotl*. G. Doin.

Russ, S L, and M S Elliott. 2017. "Antecedents of Mystical Experience and Dread in Intensive Meditation." *Psychology of Consciousness: Theory*. https://doi.org/10.1037/cns0000119.

Russell, Bertrand. 1910. "Knowledge by Acquaintance and Knowledge by Description." *Proceedings of the Aristotelian Society* 11: 108–28. http://www.jstor.org/stable/4543805.

Sagud, Marina, Lucija Tudor, Lucija Šimunić, Dejana Jezernik, Zoran Madžarac, Nenad Jakšić, Alma Mihaljević Peleš, et al. 2020. "Physical and Social Anhedonia Are Associated with Suicidality in Major Depression, but Not in Schizophrenia." *Suicide and Life-Threatening Behavior* 51 (3): 446–54. https://doi.org/10.1111/sltb.12724.

Salmela, Viljami, Lumikukka Socada, John Söderholm, Roope Heikkilä, Jari Lahti, Jesper Ekelund, and Erkki Isometsä. 2021. "Reduced Visual Contrast Suppression During Major Depressive Episodes." *Journal of Psychiatry and Neuroscience* 46 (2). https://doi.org/10.1503/jpn.200091.

Sandison, R A. 1954. "Psychological Aspects of the LSD Treatment of the Neuroses." *The Journal of Mental Science* 100 (419): 508–15. https://doi.org/10.1192/bjp.100.419.508.

Sandison, R A, and J D Whitelaw. 1957. "Further Studies in the Therapeutic Value of Lysergic Acid Diethylamide in Mental Illness." *The Journal of Mental Science* 103 (431): 332–43. https://doi.org/10.1192/bjp.103.431.332.

Sanz, Camila, and Enzo Tagliazucchi. 2018. "The Experience Elicited by Hallucinogens Presents the Highest Similarity to Dreaming Within a Large Database of Psychoactive Substance Reports." *Frontiers in Neuroscience* 12: 7. https://doi.org/10.3389/fnins.2018.00007.

Sato, Tatsuo K, Bilal Haider, Michael Häusser, and Matteo Carandini. 2016. "An Excitatory Basis for Divisive Normalization in Visual Cortex." *Nature Neuroscience*

19 (4): 568–70. https://doi.org/10.1038/nn.4249.

Savage, C. 1955. "Variations in Ego Feeling Induced by d-Lysergic Acid Diethylamide (LSD-25)." *Psychoanalytic Review* 42 (1): 1–16.

Schach, Sophia, Rainer Surges, and Christoph Helmstaedter. 2021. "Visual Surround Suppression in People with Epilepsy Correlates with Attentional-Executive Functioning, but Not with Epilepsy or Seizure Types." *Epilepsy & Behavior* 121 (August): 108080. https://doi.org/10.1016/j.yebeh.2021.108080.

Schallmo, Michael-Paul, Alex M. Kale, and Scott O. Murray. 2019. "The Time Course of Different Surround Suppression Mechanisms." *Journal of Vision* 19 (4): 12. https://doi.org/10.1167/19.4.12.

Schallmo, Michael-Paul, Alexander M Kale, Rachel Millin, Anastasia V Flevaris, Zoran Brkanac, Richard Ae Edden, Raphael A Bernier, and Scott O Murray. 2018. "Suppression and Facilitation of Human Neural Responses." *eLife* 7 (January). https://doi.org/10.7554/elife.30334.

Schallmo, Michael-Paul, Hannah R. Moser, Caroline Demro, Malgorzata Marjanska, and Scott R. Sponheim. 2020. "The Role of GABA During Visual Contrast Perception in Psychosis." *Journal of Vision* 20 (11): 340. https://doi.org/10.1167/jov.20.11.340.

Schallmo, Michael-Paul, and Scott O. Murray. 2016. "Identifying Separate Components of Surround Suppression." *Journal of Vision* 16 (1): 2–2. https://doi.org/10.1167/16.1.2.

Schallmo, Michael-Paul, Scott R Sponheim, and Cheryl A Olman. 2015. "Reduced Contextual Effects on Visual Contrast Perception in Schizophrenia and Bipolar Affective Disorder." *Psychological Medicine* 45 (16): 3527–37. https://doi.org/10.1017/s0033291715001439.

Schartner, Michael M, Robin L Carhart-Harris, Adam B Barrett, Anil K Seth, and Suresh Muthukumaraswamy. 2017. "Increased Spontaneous MEG Signal Diversity for Psychoactive Doses of Ketamine, LSD and Psilocybin." *Scientific Reports* 7 (April): 46421. https://doi.org/10.1038/srep46421.

Schenberg, Eduardo Ekman, João Felipe Morel Alexandre, Renato Filev, Andre Mascioli Cravo, João Ricardo Sato, Suresh Muthukumaraswamy, Maurício Yonamine, et al. 2015. "Acute Biphasic Effects of Ayahuasca." *PloS One* 10 (9): e0137202. https://doi.org/10.1371/journal.pone.0137202.

Schmid, Yasmin, Florian Enzler, Peter Gasser, Eric Grouzmann, Katrin H. Preller, Franz X. Vollenweider, Rudolf Brenneisen, Felix Müller, Stefan Borgwardt, and Matthias E. Liechti. 2015. "Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects." *Biological Psychiatry* 78 (8): 544–53. https://doi.org/10.1016/j.biopsych.2014.11.015.

Schmied, Lori A, Hannah Steinberg, and Elizabeth A B Sykes. 2006. "Psychopharmacology's Debt to Experimental Psychology." *History of Psychology* 9 (2): 144–57. https://doi.org/10.1037/1093-4510.9.2.144.

Schultes, Richard Evans. 1969. "Hallucinogens of Plant Origin." *Science* 163 (3864): 245–54. https://doi.org/10.1126/science.163.3864.245.

Schultes, Richard Evans, and Albert Hofmann. 1973. *The Botany and Chemistry of Hallucinogens*. Springfield: Charles C. Thomas. https://doi.org/10.2307/2806315.

Schultes, Richard Evans, Albert Hofmann, and Christian Rätsch. 2006. *Plants of the Gods : Their Sacred, Healing and Hallucinogenic Powers*. Rochester, Vt.: Healing Arts Press.

Schultes, Richard Evans, and Elmer W. Smith. 1976. *Hallucinogenic Plants*. New York: Golden Press.

Schwartz, Odelia, Anne Hsu, and Peter Dayan. 2007. "Space and Time in Visual Context." *Nature Reviews. Neuroscience* 8 (7): 522–35. https://doi.org/10.1038/nrn2155.

Scott, William A. 1962. "Cognitive Complexity and Cognitive Flexibility." *Sociometry* 25 (4): 405. https://doi.org/10.2307/2785779.

Serrano-Pedraza, Ignacio, VerÃˆ3nica Romero-Ferreiro, Jenny C. A. Read, Teresa DiÃguez-Risco, Alexandra Bagney, Montserrat Caballero-GonzÃlez, Javier RodrÃguez-Torresano, and Roberto Rodriguez-Jimenez. 2014. "Reduced Visual Surround Suppression in Schizophrenia Shown by Measuring Contrast Detection Thresholds." *Frontiers in Psychology* 5 (December). https://doi.org/10.3389/fpsyg.2014.01431.

Sessa, B. 2008. "Is It Time to Revisit the Role of Psychedelic Drugs in Enhancing Human Creativity?" *Journal of Psychopharmacology* 22 (8): 821–27. https://doi.org/10.1177/0269881108091597.

Seth, Anil. 2009. "Explanatory Correlates of Consciousness: Theoretical and Computational Challenges." *Cognitive Computation* 1 (1): 50–63. https://doi.org/10.1007/s12559-009-9007-x.

Shams, Ladan, Yukiyasu Kamitani, and Shinsuke Shimojo. 2000. "What You See Is What You Hear." *Nature* 408 (6814): 788–88. https://doi.org/10.1038/35048669.

Shankman, Stewart A., Brady D. Nelson, Martin Harrow, and Robert Faull. 2010. "Does Physical Anhedonia Play a Role in Depression? A 20-Year Longitudinal Study." *Journal of Affective Disorders* 120 (1-3): 170–76. https://doi.org/10.1016/j.jad.2009.05.002.

Shanon, Benny. 2002. *The Antipodes of the Mind : Charting the Phenomenology of the Ayahuasca Experience*. New York: Oxford University Press.

Shaw, E, and D W Woolley. 1956. "Some Serotoninlike Activities of Lysergic Acid Diethylamide." *Science* 124 (3212): 121–22. https://doi.org/10.1126/science.124.3212.121.

Shimamura, A P. 2000. "Toward a Cognitive Neuroscience of Metacognition." *Consciousness and Cognition* 9 (2 Pt 1): 313-23; discussion 324-6. https://doi.org/10.1006/ccog.2000.0450.

Shulgin, Alexander T, and Ann Shulgin. 1997. *Tihkal : The Continuation*. Berkeley, Calif.: Transform Press.

Sidis, Boris. 1898. *The Psychology of Suggestion: A Research into the Subconscious Nature of Man and Society.* D Appleton & Company. https://doi.org/10.1037/10578-000.

Siegel, Ronald K, and Louis Jolyon West. 1975. *Hallucinations : Behavior, Experience, and Theory*. Vol. 37. New York: Wiley. https://doi.org/10.1037/031728.

Sinke, Christopher, John H Halpern, Markus Zedler, Janina Neufeld, Hinderk M Emrich, and Torsten Passie. 2012. "Genuine and Drug-Induced Synesthesia: A

Comparison." *Consciousness and Cognition* 21 (3): 1419–34. https://doi.org/10.1016/j.concog.2012.03.009.

Sjoberg, B. M., and L. E. Hollister. 1965. "The Effects of Psychotomimetic Drugs on Primary Suggestibility." *Psychopharmacologia* 8 (4): 251–62. https://doi.org/10.1007/bf00407857.

Smythies, John R. 1956. *Analysis of Perception*. London: Routledge; Paul. https://doi.org/10.4324/9781315009407.

Snodgrass, Joan G., and Mary Vanderwart. 1980. "A Standardized Set of 260 Pictures: Norms for Name Agreement, Image Agreement, Familiarity, and Visual Complexity." *Journal of Experimental Psychology: Human Learning and Memory* 6 (2): 174–215. https://doi.org/10.1037/0278-7393.6.2.174.

Snowden, Robert J, and Stephen T Hammett. 1998. "The Effects of Surround Contrast on Contrast Thresholds, Perceived Contrast and Contrast Discrimination." *Vision Research* 38 (13): 1935–45. https://doi.org/10.1016/s0042-6989(97)00379-9.

Song, Chen, Kristian Sandberg, Lau Møller Andersen, Jakob Udby Blicher, and Geraint Rees. 2017. "Human Occipital and Parietal GABA Selectively Influence Visual Perception of Orientation and Size." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 37 (37): 8929–37. https://doi.org/10.1523/jneurosci.3945-16.2017.

Song, Xue Mei, Xi-Wen Hu, Zhe Li, Yuan Gao, Xuan Ju, Dong-Yu Liu, Qian-Nan Wang, et al. 2021. "Reduction of Higher-Order Occipital GABA and Impaired Visual Perception in Acute Major Depressive Disorder." *Molecular Psychiatry* 26 (11): 6747–55. https://doi.org/10.1038/s41380-021-01090-5.

Späth, Ernst. 1919. "Über dieAnhalonium-Alkaloide." *Monatshefte für Chemie Und Verwandte Teile Anderer Wissenschaften* 40 (2): 129–54. https://doi.org/10.1007/bf01774466.

Speth, Jana, Clemens Speth, Mendel Kaelen, Astrid M Schloerscheidt, Amanda Feilding, David J Nutt, and Robin L Carhart-Harris. 2016. "Decreased Mental Time Travel to the Past Correlates with Default-Mode Network Disintegration Under Lysergic Acid Diethylamide." *Journal of Psychopharmacology* 30 (4): 344–53. https://doi.org/10.1177/0269881116628430.

Spitzer, M, M Thimm, L Hermle, P Holzmann, K A Kovar, H Heimann, E Gouzoulis-Mayfrank, U Kischka, and F Schneider. 1996. "Increased Activation of Indirect Semantic Associations Under Psilocybin." *Biological Psychiatry* 39 (12): 1055–57. https://doi.org/10.1016/0006-3223(95)00418-1.

Srinivasan, Mandyam Veerambudi, Simon Barry Laughlin, and A. Dubs. 1982. "Predictive Coding: A Fresh View of Inhibition in the Retina." *Proceedings of the Royal Society of London. Series B. Biological Sciences* 216 (1205): 427–59. https://doi.org/10.1098/rspb.1982.0085.

Stace, W T. 1960. *Mysticism and Philosophy*. New York: MacMillan. https://doi.org/10.2307/2217211.

Stamets, Paul. 1996. *Psilocybin Mushrooms of the World*. Berkeley Calif: Ten Speed Press.

Stewart, Omer Call. 1961. *The Native American Church and the Law, with Description of Peyote Religious Services*.

Stigler, Michael, and Dan Pokorny. 2001. "Emotions and Primary Process in Guided Imagery Psychotherapy: Computerized Text-Analytic Measures." *Psychotherapy Research* 11 (4): 415–31. https://doi.org/10.1093/ptr/11.4.415.

Stilp, Christian. 2019. "Acoustic Context Effects in Speech Perception." *WIREs Cognitive Science* 11 (1). https://doi.org/10.1002/wcs.1517.

Stockings, G T. 1940. "A Clinical Study of the Mescaline Psychosis, with Special Reference to the Mechanism of the Genesis of Schizophenic and Other Psychotic States." *RCP*. https://doi.org/10.1192/bjp.86.360.29.

Stoliker, Devon, Gary F. Egan, and Adeel Razi. 2022. "Reduced Precision Underwrites Ego Dissolution and Therapeutic Outcomes Under Psychedelics." *Frontiers in Neuroscience* 16 (March). https://doi.org/10.3389/fnins.2022.827400.

Stoll, W. 1947. "Lysergsäure-Diäthylamid, Ein Phantastikum Aus Der Mutterkornгruppe. [Lysergic Acid Diethylamide, a Phantasticant of the Ergot Class.]." *Schweizer Archiv Für Neurologie Und Psychiatrie*, no. 60: 279–323.

Strassman, Rick J. 1984. "Adverse Reactions to Psychedelic Drugs: A Review of the Literature." *The Journal of Nervous and Mental Disease* 172 (10): 577. https://doi.org/10.1097/00005053-198410000-00001.

———. 1995. "Human Psychopharmacology of n,n-Dimethyltryptamine." *Behavioural Brain Research* 73 (1-2): 121–24. https://doi.org/10.1016/0166-4328(96)00081-2.

Strassman, Rick J., C. R. Qualls, E. H. Uhlenhuth, and R. Kellner. 1994. "Dose-Response Study of N,N-dimethyltryptamine in Humans. II. Subjective Effects and Preliminary Results of a New Rating Scale." *Archives of General Psychiatry* 51 (2): 98–108. https://doi.org/10.1001/archpsyc.1994.03950020022002.

Stroud, Jack, T. P. Freeman, R. Leech, C. Hindocha, W. Lawn, D. J. Nutt, H. V Curran, and Robin L. Carhart-Harris. 2017. "Psilocybin with Psychological Support Improves Emotional Face Recognition in Treatment-Resistant Depression." *Psychopharmacology* 235 (2): 459–66. https://doi.org/10.1007/s00213-017-4754-y.

Studerus, Erich, Alex Gamma, Michael Kometer, and Franz X Vollenweider. 2012. "Prediction of Psilocybin Response in Healthy Volunteers." *PloS One* 7 (2): e30800. https://doi.org/10.1371/journal.pone.0030800.

Studerus, Erich, Alex Gamma, and Franz X Vollenweider. 2010. "Psychometric Evaluation of the Altered States of Consciousness Rating Scale (OAV)." *PloS One* 5 (8): e12412. https://doi.org/10.1371/journal.pone.0012412.

Studerus, Erich, Michael Kometer, Felix Hasler, and Franz X Vollenweider. 2010. "Acute, Subacute and Long-Term Subjective Effects of Psilocybin in Healthy Humans: A Pooled Analysis of Experimental Studies." *Journal of Psychopharmacology* 25 (11): 1434–52. https://doi.org/10.1177/0269881110382466.

Suler, J R. 1980. "Primary Process Thinking and Creativity." *Psychological Bulletin*. https://doi.org/10.1037/0033-2909.88.1.144.

Supèr, Hans, August Romeo, and Matthias Keil. 2010. "Feed-Forward Segmentation of Figure-Ground and Assignment of Border-Ownership." Edited by Vladimir Brezina. *PLoS ONE* 5 (5): e10705. https://doi.org/10.1371/journal.pone.0010705.

Swanson, Link Ray. 2016. "The Predictive Processing Paradigm Has Roots in Kant." *Frontiers in Systems Neuroscience* 10 (October). https://doi.org/10.3389/fnsys.2016.00079.

———. 2018. "Unifying Theories of Psychedelic Drug Effects." *Frontiers in Pharmacology* 9 (172). https://doi.org/10.3389/fphar.2018.00172.

Sweat, Noah W, Larry W Bates, and Peter S Hendricks. 2016. "The Associations of Naturalistic Classic Psychedelic Use, Mystical Experience, and Creative Problem Solving." *Journal of Psychoactive Drugs* 48 (5): 344–50. https://doi.org/10.1080/02791072.2016.1234090.

Tadin, Duje, Jejoong Kim, Mikisha L Doop, Crystal Gibson, Joseph S Lappin, Randolph Blake, and Sohee Park. 2006. "Weakened Center-Surround Interactions in Visual Motion Processing in Schizophrenia." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 26 (44): 11403–12. https://doi.org/10.1523/jneurosci.2592-06.2006.

Tagliazucchi, Enzo, Robin L Carhart-Harris, Robert Leech, David Nutt, and Dante R Chialvo. 2014. "Enhanced Repertoire of Brain Dynamical States During the Psychedelic Experience." *Human Brain Mapping* 35 (11): 5442–56. https://doi.org/10.1002/hbm.22562.

Tagliazucchi, Enzo, Leor Roseman, Mendel Kaelen, Csaba Orban, Suresh Muthukumaraswamy, Kevin Murphy, Helmut Laufs, et al. 2016. "Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution." *Current Biology: CB*, April. https://doi.org/10.1016/j.cub.2016.02.010.

Tenenbaum, Joshua B, Charles Kemp, Thomas L Griffiths, and Noah D Goodman. 2011. "How to Grow a Mind: Statistics, Structure, and Abstraction." *Science* 331 (6022): 1279–85. https://doi.org/10.1126/science.1192788.

Terhune, Devin B, David P Luke, Mendel Kaelen, Mark Bolstridge, Amanda Feilding, David Nutt, Robin L Carhart-Harris, and Jamie Ward. 2016. "A Placebo-Controlled Investigation of Synaesthesia-Like Experiences Under LSD." *Neuropsychologia*, April. https://doi.org/10.1016/j.neuropsychologia.2016.04.005.

Thagard, Paul. 2009. "Why Cognitive Science Needs Philosophy and Vice Versa." *Topics in Cognitive Science* 1 (2): 237–54. https://doi.org/10.1111/j.1756-8765.2009.01016.x.

Thaler, L., A. C. Schütz, M. A. Goodale, and K. R. Gegenfurtner. 2013. "What Is the Best Fixation Target? The Effect of Target Shape on Stability of Fixational Eye Movements." *Vision Research* 76 (January): 31–42. https://doi.org/10.1016/j.visres.2012.10.012.

Tibber, Marc S, Elaine J Anderson, Tracy Bobin, Elena Antonova, Alice Seabright, Bernice Wright, Patricia Carlin, Sukhwinder S Shergill, and Steven C Dakin. 2013. "Visual Surround Suppression in Schizophrenia." *Frontiers in Psychology* 4 (February): 88. https://doi.org/10.3389/fpsyg.2013.00088.

Timmermann, Christopher, Hannes Kettner, Chris Letheby, Leor Roseman, Fernando Rosas, and Robin L. Carhart-Harris. 2021. "Psychedelics Alter Metaphysical Beliefs," June. https://doi.org/10.31234/osf.io/f6sjk.

Titchener, Edward Bradford. 1905. *Experimental Psychology: A Manual of Laboratory Practice*. Vol. 2. Macmillan. https://doi.org/10.2307/2177896.

Todorović, Dejan. 2020. "What Are Visual Illusions?" *Perception* 49 (11): 1128–99. https://doi.org/10.1177/0301006620962279.

Tononi, Giulio. 2004. "An Information Integration Theory of Consciousness." *BMC*

Neuroscience 5 (November): 42. https://doi.org/10.1002/9780470751466.ch23.

———. 2008. "Consciousness as Integrated Information: A Provisional Manifesto." *The Biological Bulletin* 215 (3): 216–42. https://doi.org/10.2307/25470707.

Tononi, Giulio, and G M Edelman. 1998. "Consciousness and Complexity." *Science* 282 (5395): 1846–51. https://doi.org/10.1126/science.282.5395.1846.

Tononi, Giulio, and Christof Koch. 2008. "The Neural Correlates of Consciousness: An Update." *Annals of the New York Academy of Sciences* 1124 (March): 239–61. https://doi.org/10.1196/annals.1440.004.

Tupper, Kenneth W, Evan Wood, Richard Yensen, and Matthew W Johnson. 2015. "Psychedelic Medicine: A Re-Emerging Therapeutic Paradigm." *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne* 187 (14): 1054–59. https://doi.org/10.1503/cmaj.141124.

Turton, S, D J Nutt, and Robin L Carhart-Harris. 2014. "A Qualitative Report on the Subjective Experience of Intravenous Psilocybin Administered in an FMRI Environment." *Current Drug Abuse Reviews* 7 (2): 117–27. https://doi.org/10.2174/1874473708666150107120930.

Uddin, Lucina Q. 2021. "Cognitive and Behavioural Flexibility: Neural Mechanisms and Clinical Considerations." *Nature Reviews Neuroscience* 22 (3): 167–79. https://doi.org/10.1038/s41583-021-00428-w.

Vallat, Raphael. 2018. "Pingouin: Statistics in Python." *Journal of Open Source Software* 3 (31): 1026. https://doi.org/10.21105/joss.01026.

Valle, Marta, Ana Elda Maqueda, Mireia Rabella, Aina Rodríguez-Pujadas, Rosa Maria Antonijoan, Sergio Romero, Joan Francesc Alonso, et al. 2016. "Inhibition of Alpha Oscillations Through serotonin-2A Receptor Activation Underlies the Visual Effects of Ayahuasca in Humans." *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology* 26 (7): 1161–75. https://doi.org/10.1016/j.euroneuro.2016.03.012.

Vanegas, M. Isabel, Annabelle Blangero, and Simon P. Kelly. 2015. "Electrophysiological Indices of Surround Suppression in Humans." *Journal of Neurophysiology* 113 (4): 1100–1109. https://doi.org/10.1152/jn.00774.2014.

Verrill, A. E. 1914. "A Recent Case of Mushroom Intoxication." *Science* 40 (1029): 408–10. http://www.jstor.org/stable/1639976.

Vigliocco, Gabriella, David P Vinson, Markus F Damian, and Willem Levelt. 2002. "Semantic Distance Effects on Object and Action Naming." *Cognition* 85 (3): B61–69. https://doi.org/10.1016/s0010-0277(02)00107-5.

Viol, A, Fernanda Palhano-Fontes, Heloisa Onias, Draulio B de Araujo, and G M Viswanathan. 2016. "Shannon Entropy of Brain Functional Complex Networks Under the Influence of the Psychedelic Ayahuasca," November. https://doi.org/10.1038/s41598-017-06854-0.

Vollenweider, Franz X, Philipp A Csomor, Bernhard Knappe, Mark A Geyer, and Boris B Quednow. 2007. "The Effects of the Preferential 5-Ht2a Agonist Psilocybin on Prepulse Inhibition of Startle in Healthy Human Volunteers Depend on Interstimulus Interval." *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 32 (9): 1876–87. https://doi.org/10.1038/sj.npp.1301324.

Vollenweider, Franz X, and Katrin H Preller. 2020. "Psychedelic Drugs: Neurobiology and Potential for Treatment of Psychiatric Disorders" 21 (11): 611–24. https://doi.org/10.1038/s41583-020-0367-2.

Vollenweider, Franz X, and John W. Smallridge. 2022. "Classic Psychedelic Drugs: Update on Biological Mechanisms." *Pharmacopsychiatry* 55 (03): 121–38. https://doi.org/10.1055/a-1721-2914.

Vollenweider, Franz X, M F Vollenweider-Scherpenhuyzen, A Bäbler, H Vogel, and D Hell. 1998. "Psilocybin Induces Schizophrenia-Like Psychosis in Humans via a Serotonin-2 Agonist Action." *Neuroreport* 9 (17): 3897–3902. https://doi.org/10.1097/00001756-199812010-00024.

Wackermann, Jiří, Marc Wittmann, Felix Hasler, and Franz X Vollenweider. 2008. "Effects of Varied Doses of Psilocybin on Time Interval Reproduction in Human Subjects." *Neuroscience Letters* 435 (1): 51–55. https://doi.org/10.1016/j.neulet.2008.02.006.

Waldman, Ayelet. 2017. *A Really Good Day: How Microdosing Made a Mega Difference in My Mood, My Marriage, and My Life*. Knopf Doubleday Publishing Group.

Wallace, Anthony F. C. 1959. "Cultural Determinants of Response to Hallucinatory Experience." *Archives of General Psychiatry* 1 (1): 58. https://doi.org/10.1001/archpsyc.1959.03590010074009.

Walshe, R. Calen, and Wilson S. Geisler. 2020. "Detection of Occluding Targets in Natural Backgrounds." *Journal of Vision* 20 (13): 14. https://doi.org/10.1167/jov.20.13.14.

Walter, W. Grey, R. Cooper, V. J. Aldridge, W. C. Mccallum, and A. L. Winter. 1964. "Contingent Negative Variation : An Electric Sign of Sensori-Motor Association and Expectancy in the Human Brain." *Nature* 203 (4943): 380–84. https://doi.org/10.1038/203380a0.

Wang, Ningyuan, Heather A. Kreft, and Andrew J. Oxenham. 2015. "Loudness Context Effects in Normal-Hearing Listeners and Cochlear-Implant Users." *Journal of the Association for Research in Otolaryngology* 16 (4): 535–45. https://doi.org/10.1007/s10162-015-0523-y.

Ward, Jamie. 2013. "Synesthesia." *Annual Review of Psychology* 64: 49–75. https://doi.org/10.1146/annurev-psych-113011-143840.

Watts, R, C Day, J Krzanowski, D Nutt - Journal of ..., and 2017. 2017. "Patients' Accounts of Increased 'Connectedness' and 'Acceptance' After Psilocybin for Treatment-Resistant Depression." *Journals.sagepub.com*.

Weasel, Pope. 1994. "Trans-High Market Quotations, October 1994." *High Times.*, October, 82–83. https://archive.hightimes.com/article/1994/10/01/trans-high-market-quotations.

Webb, Ben S, Neel T Dhruv, Samuel G Solomon, Chris Tailby, and Peter Lennie. 2005. "Early and Late Mechanisms of Surround Suppression in Striate Cortex of Macaque." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 25 (50): 11666–75. https://doi.org/10.1523/jneurosci.3414-05.2005.

WHO. 1958. "ATARACTIC and Hallucinogenic Drugs in Psychiatry; Report of a Study Group." *World Health Organization Technical Report Series* 58: 1–72.

Wiese, Wanja, and Thomas Metzinger. 2017. "Vanilla PP for Philosophers: A Primer on Predictive Processing." In *Philosophy and Predictive Processing*. MIND Group, Frankfurt am Main.

Wiessner, Isabel, Marcelo Falchi, Lucas Oliveira Maia, Dimitri Daldegan-Bueno, Fernanda Palhano-Fontes, Natasha L Mason, Johannes G Ramaekers, et al. 2022. "LSD and Creativity: Increased Novelty and Symbolic Thinking, Decreased Utility and Convergent Thinking." *Journal of Psychopharmacology* 36 (3): 348–59. https://doi.org/10.1177/02698811211069113.

Wiessner, Isabel, Marcelo Falchi, Fernanda Palhano-Fontes, Lucas Oliveira Maia, Amanda Feilding, Sidarta Ribeiro, Natalia Bezerra Mota, Draulio B. Araujo, and Luis Fernando Tofoli. 2021. "Low-Dose LSD and the Stream of Thought: Increased Discontinuity of Mind, Deep Thoughts and Abstract Flow." *Psychopharmacology* 239 (6): 1721–33. https://doi.org/10.1007/s00213-021-06006-3.

Wießner, Isabel, Rodolfo Olivieri, Marcelo Falchi, Fernanda Palhano-Fontes, Lucas Oliveira Maia, Amanda Feilding, Draulio B. Araujo, Sidarta Ribeiro, and Luís Fernando Tófoli. 2022. "LSD, Afterglow and Hangover: Increased Episodic Memory and Verbal Fluency, Decreased Cognitive Flexibility." *European Neuropsychopharmacology* 58 (May): 7–19. https://doi.org/10.1016/j.euroneuro.2022.01.114.

Winkelman, Michael J. 2017. "The Mechanisms of Psychedelic Visionary Experiences: Hypotheses from Evolutionary Psychology." *Frontiers in Neuroscience* 11: 539. https://doi.org/10.3389/fnins.2017.00539.

Wittmann, Marc, Olivia Carter, Felix Hasler, B Rael Cahn, Ulrike Grimberg, Philipp Spring, Daniel Hell, Hans Flohr, and Franz X Vollenweider. 2007. "Effects of Psilocybin on Time Perception and Temporal Control of Behaviour in Humans." *Journal of Psychopharmacology* 21 (1): 50–64.

Wong, Sam. 2017. "Leading the High Life." *New Scientist* 234 (3130): 22–23. https://doi.org/10.1016/s0262-4079(17)31161-2.

Woolley, D W, and E Shaw. 1954. "A BIOCHEMICAL AND PHARMACOLOGICAL SUGGESTION ABOUT CERTAIN MENTAL DISORDERS." *Proceedings of the National Academy of Sciences of the United States of America* 40 (4): 228–31. https://doi.org/10.1073/pnas.40.4.228.

Xing, J., and D. J. Heeger. 2000. "Center-Surround Interactions in Foveal and Peripheral Vision." *Vision Research* 40 (22): 3065–72. https://doi.org/10.1016/s0042-6989(00)00152-8.

———. 2001. "Measurement and Modeling of Center-Surround Suppression and Enhancement." *Vision Research* 41 (5): 571–83. https://doi.org/10.1016/s0042-6989(00)00270-4.

Yaden, David B., and Roland R. Griffiths. 2020. "The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects." *ACS Pharmacology & Translational Science* 4 (2): 568–72. https://doi.org/10.1021/acsptsci.0c00194.

Yang, Eunice, Duje Tadin, Davis M. Glasser, Sang Wook Hong, Randolph Blake, and Sohee Park. 2012. "Visual Context Processing in Schizophrenia." *Clinical Psychological Science* 1 (1): 5–15. https://doi.org/10.1177/2167702612464618.

Yon, Daniel, and Chris D. Frith. 2021. "Precision and the Bayesian Brain." *Current*

Biology 31 (17): R1026–32. https://doi.org/10.1016/j.cub.2021.07.044.

Yoon, Jong H., Richard J. Maddock, Ariel Rokem, Michael A. Silver, Michael J. Minzenberg, J. Daniel Ragland, and Cameron S. Carter. 2010. "GABA Concentration Is Reduced in Visual Cortex in Schizophrenia and Correlates with Orientation-Specific Surround Suppression." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 30 (10): 3777–81. https://doi.org/10.1523/jneurosci.6158-09.2010.

Yoon, Jong H., A. S. Rokem, M. A. Silver, M. J. Minzenberg, S. Ursu, J. D. Ragland, and C. S. Carter. 2009. "Diminished Orientation-Specific Surround Suppression of Visual Processing in Schizophrenia." *Schizophrenia Bulletin* 35 (6): 1078–84. https://doi.org/10.1093/schbul/sbp064.

Yu, Cong, Stanley A. Klein, and Dennis M. Levi. 2001. "Surround Modulation of Perceived Contrast and the Role of Brightness Induction." *Journal of Vision* 1 (1): 3. https://doi.org/10.1167/1.1.3.

Yu, Hao, Fei Xu, Xiangmei Hu, Yanni Tu, Qiuyu Zhang, Zheng Ye, and Tianmiao Hua. 2022. "Mechanisms of Surround Suppression Effect on the Contrast Sensitivity of V1 Neurons in Cats." Edited by J. Michael Wyss. *Neural Plasticity* 2022 (March): 1–16. https://doi.org/10.1155/2022/5677655.

Zhou, Chunhong, and Bartlett W. Mel. 2008. "Cue Combination and Color Edge Detection in Natural Scenes." *Journal of Vision* 8 (4): 4. https://doi.org/10.1167/8.4.4.

Ziemba, Corey M., Jeremy Freeman, J. Anthony Movshon, and Eero P. Simoncelli. 2016. "Selectivity and Tolerance for Visual Texture in Macaque V2." *Proceedings of the National Academy of Sciences* 113 (22). https://doi.org/10.1073/pnas.1510847113.

Zinberg, Norman Earl. 1984. *Drug, Set, and Setting : The Basis for Controlled Intoxicant Use*. New Haven [Conn.]: Yale University Press.

Zizo. 2013. "How Psilocybin Works: Addition by Subtraction - Psychedelic Frontier." http://psychedelicfrontier.com/how-psilocybin-works-addition-by-subtraction/.

Zöllner, Friedrich. 1860. "Ueber Eine Neue Art von Pseudoskopie Und Ihre Beziehungen Zu Den von Plateau Und Oppel Beschriebenen Bewegungsphänomenen." *Annalen Der Physik* 186 (7): 500–523. https://doi.org/10.1002/andp.18601860712.