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Claremont McKenna College

**Psychedelic-assisted therapy: Support for the REBUS hypothesis and its  
application to specific psychiatric illnesses**

Submitted to  
Wei-Chin Hwang

by  
Wren Cilimburg

for  
Senior Thesis  
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### **Abstract**

For centuries, psychedelic substances have been a part of human culture. Classic psychedelics such as LSD and psilocybin are characterized by their agonism of 5HT-2A receptors, and recent clinical trials have found that these substances hold great promise for treating mental disorders. Neurobiological evidence supports the recent theory that psychedelic-assisted therapy works by increasing neuroplasticity and allowing for the revision of maladaptive predictions. This theory is called the REBUS hypothesis, and it is situated within a predictive processing model of cognition. There is evidence that individuals with mental disorders such as depression, addiction, and eating disorders have a diminished ability to update predictions in response to changing sensory input. Thus, psychedelic-assisted therapy is a promising mode of treatment for these conditions. Mental disorders involving mania or psychosis are not characterized by an overreliance on predictions, and case reports suggest that psychedelics may be dangerous for individuals with a personal or family history of these disorders. These ideas point to the larger conclusion that increasing neuroplasticity is important for the healing of many mental health conditions, and this extends to more traditional psychiatric care. Although psychedelic-assisted therapy has thus far shown promising results, limitations such as bias and small, non-representative samples highlight a need for further research in which diversity and accessibility should be a top priority.

*Keywords:* psychedelics, therapy, mental illness, REBUS hypothesis, predictive processing

## **Part One: Background**

Today, around one in five American adults live with a diagnosable psychiatric disorder (“Mental Illness”, 2022). These conditions are costly on a societal scale and can severely impact an individual's quality of life (Christensen et al., 2020). Although some helpful treatments have been developed, they are often insufficient. One-third of people diagnosed with major depression do not show improvement, even after multiple treatment attempts such as different antidepressants in combination with augmentation strategies such as psychotherapy (Gaynes et al., 2012). Clearly, there is a need to investigate novel treatment options. The resurgent field of psychedelic-assisted therapy demonstrates great promise, with recent clinical trials finding significant improvement following treatment for psychiatric disorders ranging from depression to PTSD to addiction (Argento et al., 2019; Luoma et al., 2020). However, the neurobiological mechanisms of psychedelic-assisted therapy have not been thoroughly mapped. This thesis explores the evidence for a recent theory of these mechanisms: the REBUS hypothesis (Carhart-Harris & Friston, 2019), and how this model relates to specific psychiatric illnesses. A brief discussion of disorders that may be contraindicated with classic psychedelics is included, as is an exploration of ketamine therapy. The review concludes with limitations, ethical considerations, and recommendations for the future.

### **History of psychedelic substances**

Psychedelic drugs have been a part of human life for centuries. Bulbs of the peyote cactus, which are used to brew a psychedelic tea, have been found in caves in Texas and have been radiocarbon dated to 3780–3660 BC (Johnson et al., 2019). There are records of ayahuasca and other hallucinogen use in cultures around the world for

centuries before these drugs became well-known in the United States (Pollan, 2019). In many indigenous cultures, people partook in psychedelics with guidance from a religious or spiritual authority figure (George et al., 2019). It is important to recognize that the new wave of clinical psychedelic research is far from the original uses of these substances.

The accidental discovery of LSD in 1938 by Albert Hoffman sparked a period of interest in psychedelics by the Western medical community (Carhart-Harris & Goodwin, 2017). Psychedelic research blossomed in the 1950s, and the psychiatric community in the United States largely embraced the use of these drugs to treat psychiatric disorders—estimates suggest that tens of thousands of patients were treated with psychedelic-assisted therapy during this period (Grinspoon & Bakalar, 1998). Because these drugs were legal at the time, and because the subjective experiences of those who took the drugs—including many of the early researchers—were powerfully positive, it may have been inevitable that these compounds would “escape the laboratory”. This occurred during the Vietnam War, and American culture was in a period of upheaval. As the counterculture movement arose in the 1960s, these substances became associated with the rebellion and anti-government sentiment shared by many in the anti-war movement (Carhart-Harris & Goodwin, 2017). Many anti-war protesters were also active in the psychedelic movement, and psychedelics were soon vilified by the establishment (Wesson, 2011). Timothy Leary, a strong advocate of psychedelics, gave a speech in 1966 in which he advised young people in the “psychedelic world” to “turn on, tune in, and drop out.” (Wesson, 2011). Leary’s sentiment furthered the message that these compounds were associated with rejecting societal norms, and the government and mainstream media began to spread false information about the risks of psychedelics (Hall, 2022; Pollan, 2019). Caught in the



crossfire of this culture war, LSD was criminalized in 1968, and researchers and psychiatrists were no longer able to access psychedelics (Belouin & Henningfield, 2018). The promising research into the therapeutic benefits of these drugs was lost for many years.

In recent years, there has been a resurgence of interest in researching the potential of psychedelics for treating various mental health conditions (Carhart-Harris, & Goodwin, 2017). Initial studies demonstrate promising results for a variety of disorders, such as depression, addiction, and end-of-life anxiety (Carhart-Harris et al., 2012; Griffiths et al., 2016; Nutt & Carhart-Harris, 2020; Pollan, 2019).

### **Defining features of classic psychedelics**

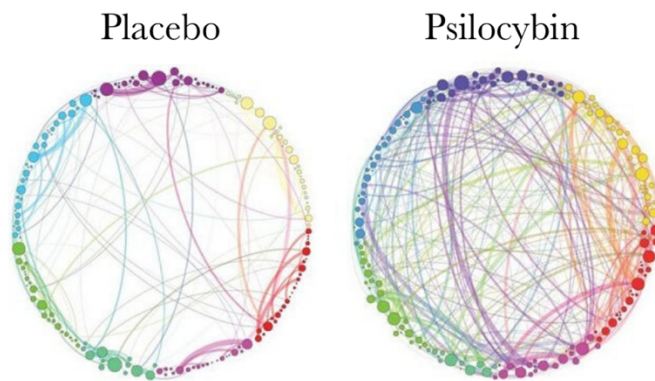
The classification of “psychedelic” can be rather broad and ambiguous. This paper will focus largely on the classic psychedelics, with a brief exploration into ketamine. Classic psychedelics include psilocybin, LSD, and more traditional drugs such as ayahuasca and mescaline (dos Santos et al., 2021). This class of drugs is defined by their neural mechanisms— they act primarily on the serotonergic system (Bosch et al., 2022). Specifically, they are all agonist or partial agonists of a certain type of serotonin receptor: 5HT-2A receptors (Johnson et al., 2019). This agonism is their defining feature, thus the neural mechanisms and implications of the activation of this receptor subtype is discussed at length later in this review. The subjective effects of these compounds include mystical experiences, visual distortions, and feelings of connection and acceptance (Carhart-Harris et al., 2018, Johnson et al., 2019, Watts et al., 2017). Additionally, individuals may see geometric patterns, find that their thoughts wander more freely than usual, or experience a dreamlike quality of being (Carhart-Harris et al., 2018). Many

people who participate in psychedelic-assisted therapy also report increased feelings of connectedness after their experience (Carhart-Harris et al., 2018; Watts et al., 2017)

Psychedelics have been found to lead to increased entropy in the brain, where neural networks that are typically separate are connected (Figure 1) (Carhart-Harris & Friston, 2019). One recent imaging study that looked at the brains of healthy volunteers under the influence of psilocybin found that while on the drug, a much higher proportion of the brain was involved in visual processing than normal. Thus, the authors suggest that “anarchic patterns of excitation” lead to visual hallucinations in the psychedelic state (Carhart-Harris et al., 2016).

### Figure 1

*The brain on psilocybin*



*Note.* This model was created by Petri et al. (2014) based on an imaging study done after participants has consumed either a placebo or psilocybin.

Psychedelics have been found to lead to a deactivation of a brain network called the Default Mode Network (DMN) (Johnson et al., 2019). The DMN is a self-referential network that consists of three major brain areas: the posterior cingulate cortex (PCC), which is related to internally directed cognition; the medial prefrontal cortex (mPFC),

which is involved in rumination and self-judgment; and the lateral parietal cortex (LPC), which is responsible for cognitively situating oneself within space (Carhart-Harris & Nutt, 2017). Psychedelics have been shown to lead to decreased blood flow to the DMN, especially to the PCC and mPFC— one study found that blood flow to the PCC decreased by up to 20% while participants were under the influence of psychedelics (Carhart-Harris et al., 2012). Psychedelic effects on the DMN are not only that of deactivation. In line with the idea that psychedelics lead to increased entropy, a recent study found that participants exhibited increased connectivity within the DMN while in a psychedelic state (Johnson et al., 2019).

Studies that have administered classic psychedelics to healthy participants have found consistent positive effects, including long-lasting increases in well-being, positive behaviors, and altruistic social effects, changes that participants attributed to the psychedelic trip (Griffiths et al., 2006; Schmid & Liechti, 2018). Many participants report the experience being one of the most meaningful of their lives (Griffiths et al., 2006).

## **Part Two: The REBUS Hypothesis**

### **People interpret their environment through predictive processing**

Psychedelics affect the ways people interact with their environment, and thus it is important to understand how behaviors and responses to environmental stimuli occur (Carhart-Harris & Friston, 2019). Historically, the dominant model of cognition was that people obtain sensory inputs from their environment, and this information is then communicated to higher levels of brain circuitry— neural networks that perform more complex cognitive processes (Keller & Masic-Flogel, 2018; Koch, 1993). This “bottom-up” model of cognition began to come under skepticism in the mid twentieth century,

when researchers found certain stimuli responses that the model was unable to explain (Keller & Mrsic-Flogel, 2018).

Bottom-up cognition implies that two situations with identical sensory inputs would lead to the same result, but studies have shown that this is not always the case (Inoshita & Hirano, 2018). For example, when you look at something in the right of the visual field, your eyes remain focused on the object of your attention (Sperry, 1950). In contrast, if your body spins to the right, the eyes engage in an automatic reflex in which they are continuously snapped back to the center of your gaze as you spin (Inoshita & Hirano, 2018). This reflex is called the optokinetic response and it allows for gaze stability (Wang et al., 2021). In these two cases (spinning versus looking), the sensory input that the eyes receive is the same, but the response is different: in one case the optokinetic response occurs and in one case it does not (Sperry, 1950). This demonstrates that the brain differentiates between external sensory input (in the case of spinning) and self-generated sensory input (in the case of looking), something that a “bottom-up” model cannot explain (Inoshita & Hirano, 2018). Because of examples like this, the predictive processing model has largely become the dominant model of cognition.

This model posits that people interact with their environment by integrating environmental information with high-level predictions (Fabry, 2017; Walsh et al., 2020). These predictions about what environmental stimuli will be encountered originate in higher level brain networks, and are being made constantly (Walsh et al., 2020; Villiger, 2022). The brain contains a large number of top-down neural connections: neuronal pathways that connect higher-level brain networks to lower-level ones, which supports the predictive processing model (Walsh et al., 2020). Evidence suggests that the

DMN is one brain network that is involved with prediction. This brain network performs cognitively complex tasks, and is active when participants perform behaviors on “autopilot”-- a context when one is acting solely on the predictions they already have (Bressler & Menon, 2010; Vatansever et al., 2017). The DMN is extraordinarily metabolically active, even when people are not “doing” anything, supporting the idea that this network is constantly forming predictions (Passow et al., 2015).

In a predictive processing model of cognition, there are two major neuronal populations. The first is expectation units, which communicate predictions from higher level brain networks (i.e. the DMN) to lower ones. The other is error units, which communicate back up when sensory information does not match predictions (Walsh et al., 2020). This mismatch is a prediction error, which can be thought of as “free energy” (Friston, 2010). Any kind of system wants to minimize free energy in order to function most efficiently (Friston et al., 2006). Humans are biological systems, and thus want to reduce free energy in order to efficiently maintain homeostasis (Friston, 2010). In the case that sensory information does not match high-level predictions, there are two possible responses. Predictions can be updated, or sensory input can be filtered so that it does match the original prediction (Barrett & Simmons, 2015), the implications of which will be discussed later in this paper.

### **Predictive processing extends to interoceptive perception**

The idea of predictive processing does not only apply to the external environment (Friston, 2010). To the brain, bodily sensations themselves are a part of that external environment, so it has been theorized that predictions about how the body will feel work similarly to the general predictive processing model (Barrett & Simmons, 2015). This

idea is referred to as “interoceptive predictive processing”. A concrete example of this is the effects of placebos (Villiger, 2022). The efficacy of placebos to treat a variety of mental and physical conditions has long been established (Benedetti et al., 2018), but previous models of the brain have not been able to explain the placebo effect. In a predictive processing model, placebos work because the brain predicts a positive outcome and then attunes to sensory input (whether that be bodily or environmental) that leads to that result occurring— sometimes literally producing the chemicals necessary for the predicted outcome (Villiger, 2022). For example, someone could present with excessive fatigue and be given a placebo that they are told will make them more energized. Their brain predicts they will feel more energized, so in order to avoid prediction error, sensory information that communicates energy will be attenuated, while sensory information that communicates fatigue will be ignored. Thus, a prediction error is avoided. When predictions about bodily states are consistently wrong, it is thought that disorders of mood, metabolism, and appetite may occur (Barrett & Simmons, 2015). In fact, many psychiatric disorders can be explained as a failure to update predictions in the face of changing sensory inputs, an idea that will be discussed at length further in this paper (Kube et al., 2020; Smith et al., 2020).

A variety of studies have examined the role of predictions in relation to physical responses and provide support for the idea of interoceptive predictive processing. One study gave a group of 46 participants a milkshake, where half of the participants were told the shake was “indulgent” and had 620 calories, while the other half were told the shake had only 140 calories and was deemed “sensible”. The group who thought the shake they were consuming was indulgent had significantly lower ghrelin (the hunger

hormone) levels post-consumption than the other group— predicting that a shake is going to be satiating literally makes it so (Crum et al., 2011). Another study examined a group of 87 employees that worked cleaning hotel rooms. Half of the sample was told that the work they do is good exercise and sufficient to meet recommendations, while the other half was not. The employees did not change their behavior, but after 4 weeks the group that had learned that their work was healthy had significant improvements in a variety of physical markers of health (lower blood pressure, weight, body fat, etc.) (Crum & Langer, 2007). Predictions we make can directly change physiological responses within our own bodies.

### **The effects of classic psychedelics depend on 5-HT<sub>2A</sub> receptors**

Classic psychedelics are serotonergic substances, meaning that they exert the majority of their effects by acting on the serotonin system, specifically by agonism of 5HT-2A receptors (Johnson et al., 2019). This section will explore how this system works and what role it plays in psychiatric illnesses in order to better understand the neurobiological mechanisms of psychedelic-assisted therapy. Given the prevalence of SSRIs, serotonin seems to play an important role in mood disorders, but this elusive neurotransmitter is not well understood (Carhart-Harris & Nutt, 2017). It appears to play a role in anxiety, as well as in moderating neuroplasticity, which the brain's ability to change (Deakin, 2013; Miyazaki et al., 2011). Serotonin (5HT) has two major receptor types: 5HT-2A and 5HT-1A, both of which are common and widespread throughout the brain (Carhart & Nutt, 2017). Both of these receptor types are important for coping, but in different ways. 5HT-1A receptors are thought to be involved in passive coping: tolerating psychological distress without necessarily needing to change it (Carhart &

Nutt, 2017). Passive coping could look like using deep breathing to cope with anxiety about a test—the stressor, as well as mindset and behavior, remain the same. 5HT-1A receptors are expressed in high density on stress circuitry (Puglisi-Allegra & Andolina, 2015). 5HT-2A receptors are thought to aid in active coping: dealing with psychological distress by changing one's relationship to it (Carhart & Nutt, 2017). This is related to neuroplasticity, and can mean changing one's mindset or behavior. For example, in the case of test anxiety, active coping could mean shifting one's perspective to view tests as something that does not measure self-worth. 5HT-2A receptors are expressed in high density in high level thinking circuitry (Puglisi-Allegra & Andolina, 2015).

Serotonin is important in mental states, but the idea that depression and other psychiatric illnesses are caused by low levels of serotonin has consistently been shown to be a myth (Cowen & Browning, 2015). What we do know is that decreasing serotonin leads to aggression and impulsivity, while raising levels increases the ability to tolerate pain, anxiety, and delay (Carhart & Nutt, 2017). The decrease in aggression and anxiety is related to the activation of the 5-HT<sub>1A</sub> receptors (Carhart-Harris & Nutt, 2017). Rodents whose 5HT-1A receptors have been blocked show increased symptoms of anxiety, and drugs that are direct agonists of 5HT-1A receptors (e.g. buspirone) lead to lessened anxiety (Heisler et al., 1998; Howland, 2015). Thus, this receptor subtype is related to many of serotonin's functions, including stress and aggression.

So, what is the role of the 5-HT<sub>2A</sub> receptors and where are they found? This receptor subtype is found in high concentrations in high level cognitive networks, including the DMN (Beliveau et al., 2016; Singleton et al., 2021). Recently, it has been proposed that activation of 5HT-2A receptors introduces a window of heightened



plasticity (Carhart-Harris et al., 2016c; Carhart-Harris & Nutt, 2017). During important periods of human development, expression of 5HT-2A receptors is higher than other points in life, supporting this hypothesis (Sheline et al., 2002; Volgin et al., 2003). Additionally, a study in mice found that stimulating 5HT-2A receptors led to an increased ability to unlearn fear-related memories when compared to controls (Zhang et al., 2013). This suggests that the plasticity introduced by 5HT-2A agonism facilitates learning and adjustment (Carhart-Harris & Nutt, 2017). To frame these findings in a predictive processing framework, it seems that 5HT-2A receptors are associated with the updating of high-level predictions (Carhart-Harris & Nutt, 2017; Singleton et al., 2021).

Evidence suggests that 5HT-2A agonism is the central mechanism of classic psychedelics. In a study that assessed the effects of ayahuasca, participants consumed the drug either after taking a placebo or after taking ketanserin, a 5HT-2A antagonist. In the ketanserin condition, participants did not experience the typical visual effects of the drug, and the changes in brain activity that are typical of the psychedelic state did not occur (Valle et al., 2016). Additionally, a recent study synthesized a compound that acted solely as an agonist of 5HT-2A receptors (i.e. it did not produce typical “psychedelic” effects such as hallucinations), and found that administration of this compound led to antidepressant effects in mice (Kaplan et al., 2022). Since agonism of 5HT-2A receptors appears to lead to increased prediction updating, it follows that this would be a key piece of the effects of psychedelics (Carhart-Harris & Friston, 2019).

### **Psychedelics effect predictive processing: The REBUS hypothesis**

This idea is highlighted in a recent theory proposed in 2019: the RELaxed Beliefs Under pSYchedelics (REBUS) hypothesis (Carhart-Harris & Friston, 2019). The

hypothesis is based on two major principles: the idea that organisms seek to minimize free energy through reduction of prediction errors, and the entropic brain hypothesis (Carhart-Harris & Friston, 2019; Villiger, 2022). The entropic brain hypothesis is the idea that psychedelics introduce more disorder into the brain in that neural connections are increased and more variable than usual (Villiger, 2022). This is important, as certain mental disorders are characterized by too much disorder in the brain (e.g. psychosis) while others are characterized by too much order (e.g. OCD) (Carhart-Harris & Friston, 2019; Faust & Kenett, 2014; Villiger, 2022).

The REBUS hypothesis proposes that when people are in a psychedelic state, there is less emphasis placed on prior beliefs, and more on incoming sensory inputs (Carhart-Harris & Friston, 2019; Villiger, 2022). In this more flexible state, maladaptive predictions that have long been wired in people's minds are able to be revised with new sensory data (Carhart-Harris & Friston, 2019). This can be seen in the subjective experiences of people who have participated in psychedelic-assisted therapy, such as one participant who reported "My natural state is the opposite of mindfulness—its mindlessness. I'm usually quite far away from the moment. I was very much there, very connected." (Watts & Luoma, 2020). Many people experience an increased intensity in their visual perception, such as another participant in the same study who said "A veil dropped from my eyes, things were suddenly clear, glowing, bright. I looked at plants and felt their beauty. I can still look at my orchids and experience that" (Watts & Luoma, 2020). Qualitative data shows us that many people have a heightened sensory experience while taking psychedelics, and quantitative data supports the idea too. One study found

significant increases in psychological flexibility both two and four weeks after a psychedelic experience (Close et al., 2020).

### **Part Three: Evidence for the REBUS Hypothesis**

The REBUS hypothesis can explain many different aspects of the psychedelic experience, from visual hallucinations to ego death to altered perception of time (Carhart-Harris & Friston, 2019). It is a recent theory, but much data exists to support its underlying concepts. A thoughtful look at the overlap between the neural mechanisms of predictive processing and what we know about the neural effects of psychedelics provides evidence for the REBUS hypothesis.

#### **The claustrum**

Evidence for the REBUS hypothesis emerges when looking at a specific part of the brain, the claustrum. The claustrum is a thin sheet of gray matter, accounting for only a quarter of 1% of the cerebral cortex volume and is the most densely connected neuronal structure of the entire brain (Crick & Koch, 2005). It is challenging to specify a singular function of the claustrum, but in recent years it has been proposed as a gatekeeper for what neural information makes it to conscious awareness (Torgersen et al., 2014). Supporting this idea, a study in rodents found that the claustrum is part of a brain network that filters sensory information and determines what is relevant (Smith et al., 2019).

Importantly, 5HT-2A receptors are expressed more densely in the claustrum than anywhere else in the brain (Nichols et al., 2016). Additionally, there are certain 5HT-2A receptors that are more sensitive to psychedelics than others, and many of these neurons are in the claustrum, suggesting that this region is especially important in the effects of psychedelics (Martin & Nichols, 2016). If the claustrum is indeed a sort of gatekeeper as

to which information makes it to conscious awareness, it provides evidence for the REBUS hypothesis. Psychedelics act on 5HT-2A receptors in the claustrum, and this agonism opens the metaphorical gates so that the claustrum allows a higher amount of sensory information to be brought into conscious awareness (Johnson et al., 2019; Torgersen et al., 2014). Supporting this idea, people with depression have been found to have reduced claustrum volume, suggesting that this gatekeeper is not as active in this population (i.e. not as much sensory input is being brought conscious awareness) (Bernstein et al., 2015).

### **Alpha oscillations**

Another important neural piece of predictive processing is neural oscillations (Euler, 2018). Neural oscillations are patterns of brain activity that look like sine waves—neural activity peaks and then declines, hitting a low point, and then increases and peaks again (Basar, 2013). These patterns of brain activity occur with different frequencies, one of which being a frequency of 10 Hz. Oscillations occurring at around 10 Hz are called “alpha oscillations”, and these are relevant to predictive processing (Arnal & Giraud, 2012). What the brain deems to be cognitively relevant is modulated by alpha band activity, which then determines what sensory information is utilized in forming responses, behaviors, and decisions (Arnal & Giraud, 2012). When an individual encounters a temporally unpredictable stimulus (i.e. they do not know *when* it was going to occur), the way their brain responds to this stimulus depends on the phase of alpha oscillation that was occurring (Scheeringa et al., 2011; Busch, et al., 2009). Alpha oscillations are complex, but they are thought to play a role in specific types of attention: there is an increase in alpha band oscillations when a task requires suppression of

information not relevant to the task (Klimesch, 2012). Similarly, when someone expects a stimulus to occur and then it does not, alpha band activity is desynchronized (Klimesch et al., 1992). There is an increase in alpha band activity when people engage in top-down controlled cognition (Zanto et al., 2011). Activity in the alpha band correlates positively with DMN activity (Carhart-Harris & Friston, 2019). The key takeaway for this paper is that higher levels of alpha band activity appear to be associated with high-level predictions.

Classic psychedelics have been shown to reduce spontaneous oscillations of brain activity, especially in the alpha band (Valle et al., 2016). This is directly related to the agonism of 5HT-2A receptors, as when an antagonist of 5HT-2A receptors is taken before drug ingestion, changes in alpha band activity do not occur (Valle et al., 2016; Kometer et al., 2013). As established above, alpha oscillations are important in predictive processing, and alpha band activity is high when people are engaged in top-down cognition (Benedek et al., 2011). Thus, the reduced alpha band activity seen when individuals are in a psychedelic state seems to be related to less predictive cognition, providing support for the REBUS hypothesis.

### **Neurogenesis**

Further evidence for the REBUS hypothesis relates to neurogenesis, or the growth of new neurons. Classic psychedelics have been linked to increased neurogenesis in specific brain regions, especially the hippocampus (Catlow et al., 2016; Magaraggia et al., 2021). Magaraggia et al. (2021) proposed that neurogenesis in the hippocampus increases the ability of individuals to distinguish between similar inputs. If an individual has an overreliance on predictions and an under reliance on sensory information, the

capability to discriminate between similar inputs may be diminished. Thus, the neurogenesis in the hippocampus that occurs following psychedelic usage supports the idea that these substances lead to prediction updating. Supporting this, data from animal studies suggests that adult hippocampal neurogenesis is linked to increased learning ability in certain cognitive tasks (Ehninger & Kempermann, 2006).

### **Functional connectivity**

Studies of the functional connectivity of the brain when in a psychedelic state support the REBUS hypothesis. A recent study administered LSD to healthy participants and found that after drug ingestion there was a higher level of neural connectivity from the thalamus to the posterior cingulate cortex (PCC), but less connectivity from the PCC to the thalamus (Preller et al., 2019). These changes in functional connectivity depend *specifically* on the 5HT-2A receptors, since when participants received pretreatment with a 5HT-2A antagonist the changes in thalamic-PCC connectivity did not occur (Preller et al., 2019). The thalamus has been shown to play a role in controlling the weight given to predictions versus sensory inputs (Steriade, 2004). The PCC is part of the DMN and has been found to play “a key role in altering behavior in response to unexpected change” (Pearson et al., 2011). The thalamus and the PCC both have complex functions, but based on the data here it can be theorized that higher connectivity from the thalamus to the PCC means more prediction errors are being communicated to the PCC. This then allows for prediction updating (Rikhye et al., 2018; Preller et al., 2019). Supporting this, people with mild cognitive impairment have reduced thalamic to PCC connectivity, and prediction deficits have been shown in these patients (Alderson et al., 2017; León-Cabrera et al., 2021).

## **The Default Mode Network**

People who are under the influence of psychedelics have decreased neural activity in the DMN (Carhart-Harris et al., 2012). For example, an imaging study of participants who had consumed ayahuasca found that the substance led to decreased blood flow to most parts of the DMN, especially major hubs such as the mPFC and PCC (Palhano-Fontes et al., 2015). A similar study that utilized psilocybin found similar results, as well as decreased connectivity between the mPFC and PCC (Carhart-Harris et al., 2012). As established above, there is evidence that in general, DMN activation is associated with making predictions (Carhart-Harris & Friston, 2019). Further evidence comes from a study that had participants perform a card sorting task which consisted of a rule acquisition phase and a rule application phase. Results demonstrated that the DMN was more active during the application phase, which consists of making predictions based on memory (Vatansever et al., 2017). This provides support for the REBUS hypothesis: less DMN activity signifies less prediction utilization, and there is less DMN activity in a psychedelic state.

## **Long term neural changes from psychedelic usage**

Interestingly, long-term psychedelic use is associated with systematic differences in neural connectivity, and the nature of these changes provide support for the REBUS hypothesis. A study of 22 long-term ayahuasca users found that these individuals had an increase in cortical thickness in the anterior cingulate cortex (ACC) and a decrease in cortical thickness in the PCC (Bouso et al., 2015). Increased cortical thickness is typically due to increased cognition of the brain area where the changes occur (Jiang et al., 2016). Thus, it appears that people who have habitually used psychedelics tend to have higher

neural activity in the ACC and lower activity in the PCC. The ACC has been found to play a role in determining how much adaptation occurs in response to prediction errors, so increased cortical thickness of the ACC could result from a higher level of prediction updating (Weber et al., 2016). Thus, long-term psychedelic users may have increased adaptation to prediction errors, supporting the REBUS hypothesis. The thinning of the cortical thickness of the PCC provides support for the idea of a lasting decrease in self-referential thought, as the PCC is a major hub in the DMN (Bouso et al., 2015; Carhart & Nutt, 2017).

Further data on long-term neural changes comes not from psychedelic imaging studies, which are limited, but from imaging studies of long-term meditation practitioners. Meditative and psychedelic states are surprisingly similar: both are characterized by an acute decrease in DMN activity (Garrison et al., 2015; Johnson et al., 2019; Carhart-Harris et al., 2016), and both can elicit similar mystical experiences (Winkelman, 2017). In meditation, this acute DMN quieting has been shown to lead to lasting changes: long term mindfulness meditators have significantly reduced DMN activity compared to controls during a resting state (Berkovich-Ohana et al., 2016). Given the connection of the DMN to predictions, this finding suggests that acute reduction in DMN activity can lead to a long-term reduction in prediction making (Laukkonen & Slagter, 2021). Supporting this, mindfulness meditation interventions have been shown to have positive therapeutic effects for certain psychiatric illnesses (Fjorback & Walach, 2012).



### **Summary of the evidence for the REBUS hypothesis**

The REBUS hypothesis is a recently proposed theory of why psychedelic-assisted therapy has been found to be useful for varying psychiatric conditions. Given its recency, it is important to review supporting evidence in order to discern the plausibility of the theory. Here, I have presented evidence relating to claustrum function, alpha oscillations, the DMN, functional brain connectivity, and long-term neural changes. This review of relevant literature supports the idea that people in a psychedelic state rely more heavily on sensory inputs and less heavily on predictions than they do at baseline, and that this change can create long-term benefits.

### **Part Three: Application to Mental Illnesses**

The recent resurgence of clinical trials utilizing psychedelic-assisted therapy has thus far demonstrated positive results. Some of the first trials were conducted in people experiencing psychiatric symptoms in relation to a serious or life-threatening illness. One randomized, double-blind trial of 51 participants with a severe cancer diagnosis found extremely promising results for reductions in depression and anxiety for at least six months following dosing: around 60% of the patients were considered in remission from their psychiatric symptoms, and another 20% showed significant symptom reduction (Griffiths et al., 2016). Another randomized control study of 29 cancer patients with illness related anxiety or depression found very similar results—an 80% response rate at 6-month follow-up (Ross et al., 2016). In addition to the reduction in psychiatric symptoms, patients also experienced an increase in quality of life, life meaning, and optimism, and less anxiety about death (Griffiths et al., 2016). These changes are long lasting: a follow-

up study found that between 60 and 80% of participants still demonstrated significant antidepressant or anti-anxiety responses after 4.5 years (Agin-Liebes et al., 2020).

A 2020 meta-analysis analyzed nine studies of clinical trials in which LSD, psilocybin, ayahuasca, or MDMA was combined with integration therapy in order to treat various mental health conditions (Luoma et al., 2020). Results were very promising— the overall reduction in symptoms (PTSD, anxiety/depression associated with life-threatening illness, unipolar depression, or social anxiety) was significant ( $p < .001$ ) and the average effect size was 1.2 (Luoma et al., 2020). This means that someone with one of these conditions who is undergoing psychedelic-assisted therapy has an 80% chance of doing significantly better than someone undergoing a placebo treatment (Luoma et al., 2020). This is especially impressive when compared to the average effect size of traditional mental health treatment— one review found this number to be 0.40 for pharmacological interventions for psychiatric disorders (Huhn et al., 2014).

Although we often discuss psychedelics in a clinical setting, the vast majority of psychedelic use takes place in a recreational context (Dollar, 2021). Survey research has found increases in psychological well-being for recreational users four weeks post-experience (Haijen et al., 2018). According to a survey of over 20,000 participants, lifetime recreational use of psychedelics is not correlated with an increased risk for mental health diagnoses (Johansen & Krebs, 2015). Not all recreational psychedelic experiences are created equal: using psychedelics in a group, with self-expansive intentions, and with plans to integrate the experience predict positive mental health outcomes (Arnaud & Sharpe, 2021). This is not the case with other psychoactive substances: one study found that individuals who used MDMA, cannabis, or stimulant

drugs had worse mental health outcomes than people who didn't partake, while individuals who took psychedelics had no significant difference in mental health outcomes (Rougemont-Bücking et al., 2019).

### **REBUS and various psychiatric illnesses**

Many mental disorders are likely associated with an overreliance on maladaptive predictions (Carhart-Harris & Friston, 2019; Villiger, 2022). These predictions can form slowly, as in the case of depression, or acutely, such as after experiencing trauma (Carhart-Harris & Friston, 2019). Evidence for this claim comes from a recent study of 500 participants: some healthy, and some with depression, anxiety, a substance use disorder, or an eating disorder. Participants completed a task in which they had to guess their heart rate (without feeling their pulse) by tapping a key every time they thought there was a beat. They did this once in a normal state and once while holding their breath, and then were asked to rate how confident they were in their guessing. Healthy controls guessed much more accurately in the breath hold condition than the experimental group did, suggesting those with a psychiatric diagnosis were unable to update their interoceptive predictions as quickly as controls were (Smith et al., 2020).

Below, I present evidence that the following disorders are related to overly strong predictions and discuss research that investigates the potential for psychedelic-assisted therapy as a treatment.

#### ***Maladaptive predictions: Depression***

Recently, much research has investigated the potential of psychedelics to alleviate depressive symptoms. One study found that even non-clinical trips are associated with significant improvements in depressive symptoms four weeks post experience (Nygart et

al., 2022). Recent clinical trials consisting of a psychedelic experience combined with psychological support in patients with treatment resistant depression found significant symptom improvement that was sustained for at least three months (Carhart-Harris et al., 2016; Carhart-Harris et al., 2018). A recent meta-analysis examined the results of seven clinical trials of psychedelic-assisted therapy that included measures of suicidality. Treatment predicted lower suicidality, and there was a large effect size at initial follow-up and a medium effect size at six months post treatment. Additionally, there was no increase in suicidality or dangerous suicide-related events due to the administration of the psychedelic (Zeifman et al., 2022). Further support comes from animal studies, in which both LSD and psilocybin have been shown to lead to a sustained reduction in depressive symptoms in mice (Hibicke et al., 2020).

The REBUS hypothesis provides an explanation for these promising results. Depression is known to be associated with negative expectations for the self and for future world events, and a lack of positive expectations about the future predicts depressive symptoms (Kube et al., 2020). Evidence for the idea of a failure to update maladaptive predictions comes from a study of participants with major depressive disorder or social anxiety who were presented with a variety of interpersonal scenarios. Some scenarios were presented initially in a negative light, and then later information revealed their more positive nature. The level of symptom severity predicted the difficulty people had adjusting their initial negative interpretations. However, these same participants showed no deficits in adjusting initially positive interpretations to be more negative (Everaert et al., 2018).

Another way to assess prediction updating is by measuring set shifting ability, which refers to the speed one can update to rule changes in cognitive tasks (Fuglset, 2019). Deficits in set shifting have been identified in some depressed patients, pointing to a difficulty updating predictions (Lockwood et al., 2002). A meta-analysis of an emotion-related cognitive task found that overall, depressed persons take longer to respond to incongruent stimuli, suggesting a deficit in responding to visual stimuli that are different than expected (Epp et al., 2012). Supporting the idea of a failure to update negative predictions, people with depression have a higher binding potential of 5HT-2A receptors, meaning that serotonin is binding to these receptors less than in healthy controls (Meyer et al., 2003; Bhagwagar et al., 2006). The higher the binding potential of the 2A receptors, the higher the level of dysfunctional attitudes tends to be (Meyer et al., 2003). In general, there is an association between increased binding potential of 5HT-2A receptors and higher rates of personality disorders, as well as the traits of neuroticism and pessimism (Frokajer et al., 2010; Bhagwagar et al., 2006).

Further evidence for the idea that depression is related to an overreliance on predictions comes from studies looking at the connectivity of the DMN, as this brain network is associated with making predictions (Carhart-Harris & Friston, 2019; Vatansever et al., 2017). Individuals with depression have abnormally high connectivity *within* the DMN, which suggests strong predictions (Leibenluft & Pine, 2013). For example, one study had 45 participants (half with major depression) look at negative images and found that individuals with depression failed to reduce DMN activity to the same extent that controls did (Sheline et al., 2009). Similarly, a study of non-medicated adolescents with major depressive disorder found increased DMN activity in both resting

state and emotion processing as compared to controls (Ho et al., 2015). Individuals with depression also have abnormally low connectivity *between* the DMN and executive networks, suggesting inadequate communication of prediction errors (Leibenluft & Pine, 2013). Transcranial magnetic stimulation (a depression treatment involving non-invasive brain stimulation) that alleviates depressive symptoms also restores connectivity of the DMN to normal, supporting the idea that these structural abnormalities are directly related to symptom severity (Mayberg et al., 2005).

Further evidence for a predictive processing model for depression comes from metabolism of the visceromotor region of the brain: depressive symptoms have been found to be preceded by higher than usual metabolism of visceromotor cortices that are part of the DMN (Barrett & Simmons et al., 2015). These cortices are thought to play a role in interoceptive prediction, suggesting that depression is tied to an inaccurate predicting of bodily states (Barrett & Simmons et al., 2015). Specifically, it has been suggested that individuals with depression are constantly predicting future stress, and in response slowing metabolism and reducing activity in order to conserve energy for this predicted stress that never occurs (Barrett & Simmons et al., 2015). Additionally, imaging studies have found that the alpha oscillations of individuals with depression have higher power than in controls, and increases in alpha band activity are linked to more top-down cognition. (Kemp et al., 2010; Jaworska et al., 2012). Thus, depression seems to be related to overly strong reliance on maladaptive predictions, which psychedelic-assisted therapy has the potential to remedy via agonism of 5HT-2A receptors (Johnson et al., 2019; Carhart-Harris & Nutt, 2017).

### ***Maladaptive predictions: Anxiety***

Within the modern wave of research, there are limited studies examining the efficacy of psychedelic-assisted therapy for anxiety, but the existing results are promising. A recent study administered LSD to 42 participants, half of whom had a life-threatening illness and half of whom had an anxiety disorder, such as generalized anxiety, social anxiety, or panic disorder. Results demonstrated significant decreases in anxiety levels and the improvements were maintained at 16 weeks post-administration (Holze et al., 2022). A small study of nine patients with OCD, which is a type of anxiety disorder, found that psilocybin led to significant decreases in symptoms, though a long-term follow up was not conducted (Moreno et al., 2006). Additionally, psychedelic-assisted therapy has been shown to lead to significant decreases in scores on the state-trait anxiety scale in patients who received the treatment for psychological distress related to life threatening illness (Grob et al., 2011; Gasser et al., 2014). This trend was still evident 12 months after psychedelic experience (Gasser et al., 2014). Studies in patients with treatment-resistant depression report a decrease in anxiety in addition to depression (Carhart-Harris et al., 2016).

Studies indicate that maladaptive predictions play a significant role in anxiety-related disorders, which suggests that psychedelic-assisted therapy could continue to prove useful. People with higher levels of trait anxiety tend to overestimate how likely it is that a feared stimulus will be encountered as well as how severe the consequences will be (Okon-Singer & Aue, 2015). For example, one study found that individuals with a phobia of spiders were much more likely to estimate that they would encounter a spider than a snake or bird, while controls showed no such bias (Aue & Hoeppli, 2012). Thus,

fear-related predictions appear to be overactive in individuals with higher levels of anxiety. Another study examined over 100 volunteers and found that in those with higher anxiety levels, predictive priming had a greater impact on their performance in a task designed to assess motion perception, suggesting higher utilization of predictions (Kraus et al., 2020). Additionally, people with higher trait anxiety have slower reaction time and decreased perceptual sensitivity in non-stressful environments but not in stressful situations (Sussman et al., 2016). This may be because anxious individuals are constantly predicting stress, and do not update these predictions even when sensory data is not confirming them (McGovern et al., 2022). Thus, these individuals may do well when stress materializes (hence the lack of response deficits in stressful environments) but the predictions are maladaptive when it does not (hence the diminished perceptual responses in non-stressful environments) (Sussman et al., 2016).

Supporting the idea of an overreliance on stress-related predictions, individuals with anxiety have higher connectivity in the portions of the DMN related to self-referential and emotional processes, which are likely linked to high level predictions (Coutinho et al., 2016). Increases in DMN activity seem to be associated with duration of illness: an imaging study of patients with generalized anxiety disorder found increases in connectivity to the PCC, and the longer the disorder had been present the more significant these neural changes were (Andreescu et al., 2013). Additionally, an imaging study of individuals with social anxiety disorder found higher theta band activity as compared to controls, and theta band activity is thought to be associated with high level predictions (Xing et al., 2017). The REBUS hypothesis postulates that psychedelic-



assisted therapy has the potential to help these individuals by addressing this overreliance on maladaptive predictions.

***Maladaptive predictions: PTSD***

Although there have been several studies examining the efficacy of MDMA for PTSD, clinical trials with classic psychedelics have yet to be conducted. However, the neurological similarities and high co-morbidity of major depressive disorder (MDD) and PTSD suggest that psilocybin could be helpful for PTSD (Kahn et al., 2022). A hallmark of PTSD is a heightened response of the amygdala when viewing certain stimuli, such as fearful faces (Sherin & Nemeroff, 2011). Similar amygdala responses are present in patients with MDD (Arnone et al., 2012). Given the promising results of psilocybin for MDD, this suggests that a similar treatment could be beneficial for PTSD (Kahn et al., 2022).

In individuals with PTSD, predictions related to traumatic events may be weighted too strongly, contributing to flashbacks and stress responses in the presence of a situation that is similar to the trauma (Kube et al., 2020; Wilkinson et al., 2017). The experience of trauma may have a significant effect on predictions, as trauma often threatens one's safety and thus is interpreted as extremely important (Kube et al., 2020). This is supported by the finding that when people are in a state of stress, they do not update their beliefs in response to good news to the extent that they do when not under stress (Garrett et al., 2018). An over-reliance on trauma-related predictions can explain the hallucinations, flashbacks, and visual disturbances that can be present in PTSD (Kube et al., 2020). These symptoms have been conceptualized as overly strong predictions and not enough weight being placed on the actual visual input one is

receiving from the environment (Kube et al., 2020; Corlett et al., 2019; Sterzer et al., 2018).

For example, let's say someone experiences a traumatic car crash. The brain may develop a prediction that driving in cars is dangerous, and this prediction may be weighted heavily due to the emotional significance of the original experience. The individual may experience psychological reactions, visual disturbances, etc. when they enter a car due to this prediction, despite that no current sensory input is supporting these ideas. Thus, a readjustment of high-level predictions via psychedelic-assisted therapy has the potential to alleviate the maladaptive weighting of predictions versus sensory inputs.

#### ***Maladaptive predictions: Addiction***

There have been several clinical trials investigating the effects of classic psychedelics on nicotine and alcohol addiction. A meta-analysis of six randomized control trials examining the efficacy of LSD-assisted psychotherapy for alcoholism found that a single dose of the substance led to a significant reduction in symptoms for up to six months post-treatment (Krebs & Johansen, 2012). Another study looked at 15 participants with severe nicotine addiction (average of six previous quit attempts, 19 cigarettes per day, and smoking duration of 31 years). At a follow-up 6 months after treatment, 80% of the participants had been abstinent for at least seven days, which is more than twice the success rate of other approaches (Johnson et al., 2014).

There is evidence to suggest that the efficacy of these trials is linked to an overreliance on maladaptive predictions that may occur in addiction. Many substances are addictive because they release a flood of dopamine to the brain, which is rewarding (Blum et al., 2012). This is important to prediction formation because dopamine signals

predictability and consistency: it sends the message that whatever behavior caused the release of dopamine will do so again in the future (Friston et al., 2014; Miller et al., 2020). Thus, a predictive processing model of addiction proposes that drug intake leads to the formation of the prediction that the drug will lead to pleasure and reward, and even when sensory input fails to confirm this prediction (such as when an individual has built up a tolerance to a drug), the prediction is not updated (Gu & Filbey, 2017).

This model also explains why people crave drugs. As established previously, the free energy principle entails that people want to minimize the difference between their predicted state and their sensory input (Friston et al., 2010). Individuals with a substance use disorder have strong expectations that no drugs will lead to withdrawal and craving symptoms, so in order to avoid prediction error their bodies pay attention to symptoms that confirm this prediction (Gu & Filbey, 2017).

Supporting this model, evidence suggests that mindfulness therapy can have a significant impact on treating addiction (Houlihan & Brewer, 2016). One study assigned individuals to receive either mindfulness training or the American Lung Association's freedom from smoking treatment. The mindfulness group smoked significantly less than the control group after the four-week treatment period, and were still smoking significantly less at a 17 week follow up (Brewer et al., 2011). Houlihan & Brewer (2016) posit that this effect is due to increased interoceptive awareness that can result from mindfulness interventions, suggesting that reliance on predictions is diminished via mindfulness training.

It may seem counterintuitive to treat drug addiction with another mind-altering substance, but lifetime psychedelic use is associated with lower rates of opioid use

disorder (Jones et al., 2022). Thus, psychedelic-assisted therapy has the potential to aid individuals in adjusting these maladaptive predictions and paying more attention to how taking drugs actually makes them feel— perhaps not as good as predicted.

***Maladaptive predictions: Eating disorders***

Clinical trials assessing the therapeutic potential of psychedelics for eating disorders (EDs) have yet to be conducted, but survey data is promising. For example, a survey of people with a lifetime ED diagnosis who took a psychedelic drug found significant improvements in depression and well-being post experience (Spriggs et al., 2021).

Eating disorders are another psychiatric illness that seem to be associated with inflexible high-level predictions, such as predictions about one’s body in space. Individuals with an ED may be unable to update their conception of their body even when given conflicting sensory inputs (Riva & Dakanalis, 2018). Supporting this, individuals with anorexia turn their body in a way that corresponds with their predicted body size (larger than reality) rather than their actual body size when they are passing through an opening (Keizer et al., 2013).

Individuals with eating disorders seem to have deficits in updating predictions in general. Evidence for this comes from a 2006 study which found that like depressed patients, patients with anorexia nervosa exhibited cognitive deficits in set shifting (Steinglass et al., 2006). Similarly, a 2005 found that women with anorexia, as well as their healthy sisters, were significantly worse at set shifting in two tasks designed to assess perceptual rigidity when compared to controls (Holliday et al., 2005). Therefore, it does not appear that the cognitive deficits seen in individuals with eating disorders come

from reduced cognitive function due to insufficient caloric intake, as healthy family members appear to share these deficits. EDs are known to run in families, and this suggests that there may be genetic component to predictive flexibility which may put some individuals at risk for developing an ED, or potentially other psychiatric illnesses marked by difficulty updating predictions (Meshkova, 2015).

Like anxiety and depression, eating disorders seem to be associated with alterations in the DMN. One study found that people who had recovered from an eating disorder had higher DMN connectivity than controls (Cowdrey et al., 2014). Even though these individuals are recovered, it seems as though the experience of an ED led to an increase in DMN connectivity, which is in line with too much emphasis on high level predictions (Carhart-Harris & Friston, 2019). Psychedelic-assisted therapy has the potential to introduce a window of increased plasticity in which maladaptive predictions can be updated, encouraging healthy eating behaviors and a reduction of psychological symptoms. If someone with anorexia can update the prediction “I am fat,” and understand that they may actually be concerningly thin, they may be able to accept their need for a higher caloric intake and weight gain.

### **Interim conclusion**

The evidence presented thus far provides support for the REBUS hypothesis, as well as for the idea that depression, anxiety, PTSD, addiction, and eating disorders are linked to an overreliance on maladaptive predictions. Psychedelics seem to have the potential to address this by increasing neuroplasticity, and thus psychedelic-assisted therapy is a promising treatment for these specific disorders. In the next section, disorders that may not be appropriate for treatment with psychedelic-assisted therapy are discussed.

## **Part Four: Contraindications and Comparisons**

### **Contraindications and risks of classic psychedelics**

There are three main categories of risk in relation to psychedelic trips, the first being the experience of a “bad trip”, which can be characterized by anxiety, unpleasant thoughts or emotions, and confusion (Johnson et al., 2019). This experience is quite common in recreational settings: 39% of people who had used psilocybin mushrooms recreationally reported that a trip had been one of the top 5 most challenging experiences of their lives. However, of these individuals who experienced difficulty, 84% reported gaining something significant from the experience (Carbonaro et al., 2016). An interview study of individuals who had shared negative psychedelic experiences in online forums found that while these individuals had experienced acute emotions, such as fear, confusion, and distressing visions, 67% reported that the consequences of this “bad trip” were mostly positive, and only 4% reported that the consequences were mostly negative (Johnstad, 2021). Given the importance of setting for psychedelic trips, the risk of extreme negative experiences is likely lower in a therapeutic setting (Hartogsohn, 2017), but this phenomenon has occurred (Holze et al., 2022). In a 2020 trial of LSD for anxiety, one participant (2% of the sample) experienced acute transient anxiety during drug administration. The participant was treated with a benzodiazepine and an antipsychotic medication, which relieved symptoms. No long-lasting effects were observed, and in the second administration the participant was given a lower dose and did not experience a negative reaction, suggesting that a too high dose was the cause of the anxiety (Holze et al., 2022). Some scholars suggest that negative emotions and distressing experiences are a part of the psychedelic experience and not something to be feared. Dyck & Elcock

(2020) argue that the government and other anti-psychedelic forces increased fear surrounding “bad” trips in an effort to create a narrative of psychedelics as substances that induce violence and unpredictable behavior.

Another risk is the short-term physiological symptoms that psychedelic intake can cause. Given the fact that these substances can cause a significant increase in heart rate, people with cardiac conditions should likely be excluded from trials at this time (Johnson et al., 2019).

The final category of risk is related to psychosis and similar disorders, as in rare cases psychedelics have been shown to aggravate or precipitate these conditions (Paparelli et al., 2011). Examples include a case report published in 2021, in which a woman was hospitalized for a psychotic episode that is believed to have been precipitated by the consumption of psychedelic mushrooms. The woman had never experienced mania or psychosis but did have a family history of bipolar disorder (Hendin & Penn, 2021). Other analysis has similarly pointed to bipolar disorder as a risk factor for negative psychedelic experiences (Bosch et al., 2021). One review examined published case reports of classic psychedelics linked to episodes of psychosis and/or mania, and concluded that experience appears to be rare, and most often occurs in recreational settings (Gard et al., 2021). Multiple scholars have concluded that this type of experience is typically tied to a personal or close family history of psychotic illness or mania (dos Santos et al., 2017; Gard et al., 2021).

Psychedelics are agonists of 5HT-2A receptors, and certain antipsychotic drugs act on these receptors too—but as antagonists (Umbricht et al., 2003). Given that these drugs can be helpful for people with schizophrenia or other psychotic disorders, it follows

that psychedelics would be substances to avoid, as these substances are characterized by the opposite: 5HT-2A agonism (Umbricht et al., 2003; Johnson et al., 2019).

Can a predictive processing framework explain why psychedelics are potentially risky for certain disorders and helpful for others? If so, it would make sense if the contraindicated disorders listed above were characterized by an extreme lack of rigid thinking and too little weight placed on high level predictions as opposed to too much. One study examined the ways in which individuals with schizophrenia interpreted unfamiliar semantic metaphors and found that these people tended to make looser associations than controls and demonstrated an increased level of right hemisphere involvement. Right hemisphere involvement in this type of task is associated with more chaotic thinking, so this result provides evidence for a more chaotic style of processing in individuals with this disorder (Faust & Kenett, 2014). This contrasts with the disorders reviewed earlier in this paper, which are characterized by repetitive, ruminative thinking (Carhart-Harris & Friston, 2019; Villiger, 2022).

Further evidence for this idea comes from deficits in the way that individuals with schizophrenia process context dependent auditory and visual information, a phenomenon that has been widely observed (Umbricht et al., 2003). Importantly, the deficits seen in individuals with schizophrenia are similar to the deficits seen in healthy subjects after an administration of ketamine (Umbricht et al., 2003). As we will see later in the paper, ketamine is thought to induce a state of increased neuroplasticity (Aleksandrova & Phillips, 2021), suggesting that individuals with schizophrenia may already have elevated neuroplasticity. Additionally, unmedicated individuals with bipolar disorder have significantly lower alpha oscillation power, which points to less prediction related



cognition (Başar, 2013; Arnal & Giraud, 2012). As established previously, disorders such as depression are characterized by higher connectivity within the DMN (Leibenluft & Pine, 2013). In contrast, evidence points to lower levels of within network connectivity in the DMN in patients with schizophrenia or early-stage psychosis (O’Neill et al., 2019; Skudlarski et al., 2010). While disorders such as depression and eating disorders seem to be related to an inability to update maladaptive beliefs, disorders characterized by mania or psychosis do not appear to be characterized by this kind of cognitive rigidity, and in fact may be characterized by too little rigidity (Shergill et al., 2014). Thus, psychedelics should not be recommended for individuals with a personal or family history of psychotic or manic disorders, but the risk for others appears to be quite low.

### **Comparing SSRIs and psychedelics**

Selective serotonin reuptake inhibitors (SSRIs) and psychedelics are both substances that can treat mental disorders by acting on the serotonin system (Carhart-Harris & Friston, 2019; Celada et al., 2004). SSRIs inhibit the reuptake of serotonin, so levels of the neurotransmitter in the brain are higher (Homberg et al., 2010). These drugs are commonly prescribed to treat conditions characterized by anxious or depressive symptoms, but exactly why the higher serotonin levels can lead to alleviation of symptoms is unclear (Mock, 2020). It has been proposed that the mechanism of action for SSRIs is related to the agonism of 5HT-1A receptors (Haddjeri et al., 1998). However, psychotropic drugs that function specifically as 5HT-1A receptor agonists (e.g. buspirone) have not been successful in treating depression, suggesting that simple agonism is not the mechanism of action for SSRIs (Carr & Lucki, 2011; Blier & Ward, 2003; Howland, 2015). Supporting this, these medications do not work right away: it

typically takes around 4-6 weeks for patients to begin to experience symptom improvement (Tylee & Walters, 2007). There is evidence to suggest that the mechanism of action for SSRIs is not a simple increase in serotonin levels– if it was, symptom improvement would likely occur sooner (Harmer et al., 2009). In individuals with premenstrual dysphoric disorder, SSRIs do provide immediate relief from symptoms, and this disorder is thought to be caused directly by a serotonin deficiency (Halbreich, 2002; Endicott et al., 1999).

Recent evidence suggests increased neuroplasticity may be the mechanism for both psychedelic-assisted therapy and treatment with SSRIs (Albert, 2019; Carhart-Harris & Friston, 2019; Bui et al., 2013; Klöbl et al., 2022). In support of this idea, a recent study had 99 healthy volunteers participate in an associative learning task for three weeks, and then relearn the same content with different associative pairs for another three weeks (Klöbl et al., 2022). Half of the participants received an SSRI during the re-learning portion of the experiment, and brain imaging was performed before and after this period. Individuals in the SSRI group had a higher rate of functional connectivity changes, suggesting that the medication enhanced neuroplasticity (Klöbl et al., 2022). A similar study administered electrical stimulation to participants in order to condition them to associate fear with certain stimuli, and then in a second phase of the experiment conditioned participants to no longer make this association by presenting the feared stimulus repeatedly without the electrical stimulation. The group given an SSRI during this two-week process was able to unlearn the fear association significantly faster than those who had been given a placebo (Bui et al., 2013). The theory that SSRIs provide therapeutic effects by increasing neuroplasticity explains the delayed effect time of these

medications, as well as why individuals with menstrual dysphoric disorder experience immediate relief. SSRIs are known to work best in conjunction with psychotherapy, which may allow people to make the most of the increased neuroplasticity that the medications support (Cuijpers et al., 2014). For some individuals, psychedelics may work when SSRIs have not. Perhaps the effects of psychedelics on neuroplasticity are stronger than that of SSRIs, or perhaps the emotional or spiritual aspects of the psychedelic trip support more extreme or adaptive brain rewiring than an SSRI can. For others, especially those who may have a contraindication to psychedelic-assisted therapy, SSRIs remain a good option, especially when combined with therapeutic interventions.

### **Comparing ketamine to classic psychedelics**

Ketamine is another drug that sometimes falls under the psychedelic umbrella and has seen a resurgence of clinical interest in recent years. I discuss ketamine here for two reasons: it is the only psychedelic that is currently legalized for clinical use, and like classic serotonergic psychedelics, there is evidence to suggest that this drug works via its effects on neuroplasticity (Bonnett, 2022; Johansen et al., 2022). In contrast to classic psychedelics, ketamine is a dissociative psychedelic that acts on the glutaminergic system as well as the opioid system (Price, 2018; Zanos & Gould, 2018). There is a high response rate to ketamine for depressive symptoms, but the relief it provides appears to be short-lived: a meta-analysis of studies examining ketamine for depression found remission rates of 77% four hours post infusion and 43% 72 hours post-infusion, but most patients relapsed within a month (Katalinic et al., 2013). The largest potential for ketamine may be in acute situations such as suicidal ideation, where rapid symptom relief

is needed. Indeed, studies have found ketamine to have a significant positive effect on suicidal ideation (Ballard et al., 2014).

Historically, the dominant view was that the therapeutic effects of ketamine were dependent on its antagonism of NMDA receptors, which are part of the glutaminergic system (Aleksandrova & Phillips, 2021; Price, 2018). However, a recent clinical trial of adults with treatment-resistant depression found that in participants for whom ketamine produced an antidepressant effect, this effect was not observed when the ketamine infusion was preceded by the administration of naltrexone, an opioid antagonist (Williams et al., 2019). Naltrexone is often used to treat alcoholism and opioid use disorder, as this drug binds to and blocks opioid receptors (Singh & Saadabadi, 2022). Thus, ketamine's therapeutic potential may depend primarily on its effects on the opioid system (Price, 2018; Williams et al., 2019).

There is evidence to suggest that like classic psychedelics, ketamine works by increasing neuroplasticity (Aleksandrova & Phillips, 2021). Although the initial mechanisms of ketamine and classic psychedelics are different, both substances have been found to lead to activation of neurons in areas of the brain associated with neuroplasticity, such as the prefrontal cortex (Aleksandrova & Phillips, 2021). Supporting the idea that ketamine works by enhancing neuroplasticity, a recent study examined three treatment groups of individuals with major depression: one that received ketamine infusions and then participated in an associative learning exercise designed to increase self-esteem, one that only received ketamine infusions, and one that received a placebo and then participated in the associative learning (Price et al., 2022). Both groups that received ketamine showed significant initial improvement, but the improvement was

brief in the group that did not participate in the associative learning. By 30 days, their symptoms were similar to the non-ketamine group, whereas the ketamine group that did participate in the associative learning exercises maintained sustained symptom reduction at the 30-day mark. This finding suggests that ketamine enhances neuroplasticity and allows for improvement of maladaptive thinking patterns when learning is emphasized (Price et al., 2022).

The REBUS hypothesis postulates that in classic psychedelics, the increase in neuroplasticity is specifically linked to the updating of maladaptive predictions, and there is some evidence of a similar process with ketamine. One study found that administration of low-dose ketamine led to slower responses to predictive stimuli, suggesting lower utilization of predictions (Mohanta et al., 2020). Additionally, ketamine has been shown to decrease the functional connectivity of the DMN, which is relevant to predictive processing (Scheidegger et al., 2012). As with classic psychedelics, more research is needed to determine the neurobiological mechanisms of ketamine assisted therapy, but at this point results suggest that an increase in neuroplasticity is at play, and prediction updating may be relevant.

## **Part Five: Limitations and Recommendations**

### **Research limitations and recommendations**

While psychedelic-assisted therapy shows promising results for treating a variety of psychiatric conditions, many limitations exist. As discussed previously, psychedelic medicine began long before Western science took interest, yet this origin is often ignored in today's clinical trials (George et al., 2019). A recent review of psychedelic studies found that over 80% of participants were Non-Hispanic White (Michaels et al., 2018).

People of color experience mental health struggles at least as often as Non-Hispanic Whites do, and face more barriers to care (Michaels et al., 2018). Therefore, the underrepresentation of these groups in modern psychedelic research is a cause for concern. Additionally, this research occurs within the Western medical system, a system that has led to oppression and trauma for many indigenous and minority groups (George et al., 2019). The modern psychedelic research community should make a concerted effort to highlight the voices of minority groups that are involved in the field, and to broaden studies to include greater diversity of participants (George et al., 2019). Another limitation in this emerging field is the lack of federal investment in research, and increasing funding could help trials become more equitable (Marks & Cohen, 2021).

In addition to homogeneity of samples in clinical trials, many studies exclude participants on psychiatric medications or have patients stop any medications prior to the psychedelic dosing (Johnson et al., 2014; Carhart-Harris et al., 2016). This is done to help ensure a lack of interaction between psychedelics and other psychiatric medications, but may also lead to self-selected and biased samples (e.g., people who are unable or unwilling to go off of medication are largely not included). Further, there is evidence suggesting that classic psychedelics are not dangerous in combination with certain psychiatric medications, including SSRIs (Malcolm & Thomas, 2021). The interaction of these substances should be investigated further with the hopes of being able to include participants who are on SSRIs and certain other psychotropic medications in trials of psychedelic-assisted therapy.

Additionally, more studies should focus on individuals with multiple psychiatric disorders. Nearly 80% of individuals with major depressive disorder have a co-occurring

mental illness (Melartin et al., 2002), and the effect of psychedelics on these interactions are currently unknown. Randomized controlled trials tend to screen out those with comorbid disorders, thus raising the question of whether they are as effective in real-world scenarios where people have co-occurring mental illnesses. Future trials should research co-occurring disorders, with the exception of individuals who are diagnosed with (or who have a family history of) a manic or psychotic disorder. As discussed above, this population appears to be more susceptible to extreme negative events, such as manic episodes, and should continue to be excluded from the research at this time (Paparelli et al., 2011).

Another weakness of the samples of psychedelic-assisted therapy studies is that they are relatively small (Petranker et al., 2020; Wheeler & Dwyer, 2020). Given the importance of large sample sizes in psychological research (Schweizer & Furley, 2016), efforts should be made to include more participants in psychedelic research. More longitudinal studies should also be conducted, as the majority of studies on classic psychedelics followed up with participants for less than six months after the psychedelic experience (Wheeler & Dwyer, 2020).

There has been a flood of media that portrays psychedelics in a positive light in recent years, and this may contribute to assumptions and biases in participants (Butler et al., 2022; Petranker et al., 2020). Given that participants typically volunteer for psychedelic-assisted therapy trials, they may have an existing positive opinion on these substances (Wheeler & Dyer, 2020). Supporting this idea, individuals with previous psychedelic experiences and an affinity toward psychedelics are greatly overrepresented in randomized control trials, which could be affecting results. This bias could be reduced

by recruiting more participants who have never taken a psychedelic and feel neutral about their potential to improve mental health (Ona et al., 2022).

Further complicating these trials, there are characteristics of psychedelics that make administering placebos difficult (Butler et al., 2022). However, that does not mean efforts should not be made. As Butler et al. (2022) points out, psychedelics are not the only clinical interventions that are challenging in this respect: surgery and physical therapy present similar obstacles. Therapeutic interventions in general often suffer from inadequate elimination of expectancy biases: both therapists and patients tend to know what type of treatment they are receiving (Juul et al., 2020). In the case of psychedelic-assisted therapy, strategies to reduce expectancy biases include randomized controlled trials in which one group is given a much lower dose of a psychedelic, or another substance that produces some level of mind-altering effects (Butler et al., 2022). However, ethical concerns may arise: is it unfair to provide someone with therapy that leads them to believe that they have undertaken a significant psychological experience if they have not? In some cases, acknowledging that expectancy effects may be playing a role may be the best option (Butler et al., 2022).

Psychedelic-assisted therapy is complex, and classic psychedelics have only been studied in controlled clinical trial settings. Results have demonstrated efficacy, but efficacy is not the same as effectiveness: just because an intervention proves statistically significant in clinical trials does not mean results will be mirrored in real-world conditions (Singal et al., 2014). Many studies of psychedelic-assisted therapy do not describe the therapeutic mechanisms utilized in enough detail for providers to replicate them if this treatment is rolled out to a larger group (Wheeler & Dyer, 2020). Some



scholars have even gone so far as to suggest that the knowledge gathered in this field may be largely an illusion (Ona et al., 2022). This is a strong claim, and I believe the evidence presented in this paper does support the efficacy of psychedelic-assisted therapy for increasing neuroplasticity and aiding in the treatment of specific mental health disorders. However, more research is needed: samples should be larger and more diverse, comorbid disorders need to be included, studies should aim to reduce bias, and more longitudinal designs should be implemented. Community-based research that assesses the effects of psychedelics in “real-world” contexts can help answer the question of whether these substances are effective beyond specific clinical settings.

### **Clinical limitations and recommendations**

As noted previously, a major limitation in the field of psychedelic-assisted therapy is the accessibility, or lack thereof, of this treatment (Marks & Cohen, 2021). In general, access to mental health treatment is limited, and many who need treatment are unable to access it (Stuhlmiller & Tolchard, 2009). Cost is often a barrier to treatment, and without insurance covering this service, many Americans will be unable to access it. In countries where recreational psychedelics are legal, private psychedelic retreats cost thousands of dollars: a five-night stay can cost \$6,000 or more (“*Integrative ayahuasca retreats*”, 2022). As psychedelic-assisted therapy becomes integrated into public mental healthcare, it is essential that efforts are made to establish insurance coverage of this treatment, especially Medicaid coverage (Marks & Cohen, 2021). This will help ensure that psychedelic-assisted therapy is not a treatment only for individuals with expendable financial resources.

It is important to approach the integration of psychedelic-assisted therapy with the American healthcare system thoughtfully, as the narrative surrounding these substances will greatly affect what happens in healthcare and culture. When, in the 1960s, psychedelics became associated with the counterculture, government vilification and criminalization followed (Wesson, 2011). One path the narrative surrounding psychedelics could take is of medicalization: these substances appear to be useful in treating psychiatric disorders, and thus they should be administered only at the discretion of mental health professionals. Many people would consider it dangerous if someone could go to the pharmacy and buy over the counter SSRIs in order to medicate oneself—a similar path for psychedelic substances is one option. Given that psychedelics are not appropriate for everyone, an advantage of this approach is decreasing psychedelic usage in individuals at risk for negative experiences (Arnaud & Sharpe, 2021). However, disadvantages exist to this approach. In general, the medicalization of mental disorders can put the onus on individuals to fix themselves instead of acknowledging the role that systemic forces are playing (Noorani, 2019). Further, medicalization of psychedelics will likely restrict access to wealthier individuals, which will perpetuate the marginalization of minority groups within the Western medical system (Marks & Cohen, 2021). Another risk to the medicalization narrative is that psychedelic use already exists outside of the clinic (Dollar, 2021), and buying substances off the black market can lead to uncertainties about the content or potency.

Another approach to the psychedelic movement is decriminalizing or legalizing psychedelic substances. Many support this approach, arguing that it is unethical to limit access to natural substances such as plants and fungi (“*Decriminalize nature*”, 2022).

Many people are already using these substances recreationally, and legalization would allow for people to make informed decisions about what and how much of a substance they are taking. This is important, given that compounds such as opioids, amphetamines, and synthetic cannabinoids can be present in what is sold as LSD (de Souza Boff et al., 2020). Further, studies have found that for many people without a diagnosable psychiatric disorder, these substances can still have significant positive impacts on well-being and quality of life, suggesting that their potential goes beyond treating mental illness (Griffiths et al., 2006; Griffiths et al., 2011; Schmid & Liechti, 2018). These substances are not appropriate for everyone, but legalizing a substance does not mean everyone will use it. Given the non-addictive nature of these drugs and the potential benefits they can have, in many ways it makes more sense for psychedelics to be legalized than substances such as alcohol, a substance for which the addictive potential is high and benefits are scarce (Rusyn & Bataller, 2013). Of course, many people may benefit from psychedelic-assisted therapy in a clinical setting, and an approach of legalization can and should be combined with integration into mental health treatment. A risk of this option is a repeat of what happened in the 1960s, when the non-clinical usage of psychedelics led to prohibition (Yaden et al., 2021).

### **Recommendations for therapists**

A major limitation in the clinical realm of psychedelic-assisted therapy is the lack of standardized training for therapists who are providing this modality of care (Phelps, 2017). Differing therapeutic approaches have the potential to affect the experiences of individuals and the effectiveness of treatment (Hartogsohn, 2017). One possible solution is to create a formalized regulatory body that could provide a psychedelic practitioner

certification, which would allow individuals to acquire the necessary knowledge and skills on their own terms. Opportunities for more formalized training and in-depth learning could be available, and partaking in this could lead to more advanced certifications (Haden et al., 2016). This strategy would create an accessible process that can be tailored to therapists' desires, goals, and capabilities, and would provide assurance for patients looking for a practitioner.

The evidence discussed in this paper and the conclusions reached have important implications for clinicians in the mental health field, whether they are working with individuals utilizing psychedelic substances or utilizing more traditional behavioral health treatments. A key takeaway is the importance of neuroplasticity in treating psychiatric illness. The model of psychiatric disorders as a chemical imbalance is becoming less and less supported, by psychedelic research as well as data on other topics (Pies, 2019). As noted previously, serotonin levels are not systematically low in individuals with depression (Cowen & Browning, 2015), indicating that the differences in brain activity we see in various psychiatric disorders should be regarded more as symptoms than as root causes. Supporting this idea, individuals with five or more adverse childhood experiences are three times more likely to be on psychotropic medications, suggesting that these medications are not addressing the core problem (Anda et al., 2007).

This has important implications for mental health professionals and encourages a shift away from a purely medical model of mental disorders. Blaming depression solely on a chemical imbalance in a patient's brain could be counterproductive if an abusive relationship or traumatic childhood is contributing. We know psychiatric medications

work best in conjunction with psychotherapy, which suggests that therapy allows people to make the most of the increased neuroplasticity mental health medications support (Cuijpers et al., 2014). As the world of mental health treatment continues to evolve and improve, focusing on increasing neuroplasticity instead of fixing chemical imbalances may help people heal in an empowered and lasting way, whether this is done via psychedelic-assisted therapy or other strategies. A recent study found that cognitive behavioral therapy helped increase neuroplasticity and restore brain abnormalities in patients with social anxiety disorder, supporting the idea that medications are not always necessary for creating lasting change (Månsson et al., 2016).

For therapists who do work with psychedelics, the REBUS hypothesis and the concepts discussed here have important implications, one of which being that therapists should consider the physical setting of the psychedelic experience. The REBUS hypothesis postulates that sensory inputs are being weighted at a higher precision than normal, so what these sensory inputs are becomes important. Updated versions of the stress-diathesis model of mental illness argue that being in a state of high sensitivity to one's environment is beneficial if the environment is positive but harmful if it is negative (Branchi, 2011). Supporting this, a recent meta-analysis of clinical psilocybin trials found that a significant predictor of negative experiences was being in an environment with PET scan technology, suggesting that this busy and stressful environment influenced people's trips (Studerus et al., 2012). Thus, therapists should ensure a safe and comfortable environment in which the psychedelic experience takes place.

Another strategy that therapists may be able to utilize in preparation for the psychedelic experience is intention setting. Having clear intentions for a psychedelic

experience has been linked to increased likelihood of having a mystical experience (Haijen et al., 2018), which then predicts positive outcomes (Griffiths et al., 2006). In general, intense focus on a specific task is linked to increased neuroplasticity and improved ability to learn the task (Huberman, 2022). Thus, having specific goals that one focuses on during a trip may increase the likelihood of desired effects. For example, someone with a nicotine addiction could set an intention to focus on their desire to stop smoking, and this focus may help the relevant brain rewiring occur.

### **Conclusion**

In a predictive processing model of cognition, sensory inputs are integrated with high level predictions, and there is incentive to minimize prediction error (Friston, 2010; Walsh et al., 2020). Many psychiatric illnesses appear to be related to a deficit in updating maladaptive predictions, and psychedelic-assisted therapy has the potential to address this (Carhart-Harris & Friston, 2019; Villiger, 2022). Classic psychedelics have a myriad of effects, but their therapeutic potential appears to depend on the agonism of 5HT-2A receptors (Johnson et al., 2019). These receptors are located in brain networks associated with making high-level predictions, such as the DMN, and in structures thought to be responsible for determining what information makes it to conscious awareness, such as the claustrum (Nichols et al., 2016; Puglisi-Allegra & Andolina, 2015). Thus, these substances are thought to lead to less attention being paid to high-level predictions and more attention being paid to sensory input, allowing for the adjustment of predictions (Carhart-Harris & Friston, 2019). This suggests that psychedelic-assisted therapy could be useful for treating depression, anxiety, PTSD, substance use disorders and eating disorders, all of which seem to be related to a failure to update predictions

(Carhart-Harris & Friston, 2019; Epp et al., 2012; Aue & Hoeppli, 2012; Kube et al., 2020; Gu & Filbey, 2017; Steinglass et al., 2006). Indeed, recent clinical trials have demonstrated positive results, though more research is needed (Krebs & Johansen, 2012; Zeifman et al., 2022).

Not every disorder is characterized by overreliance on predictions: disorders such as mania, schizophrenia, psychosis, and bipolar disorder appear to have a more complex relation to predictive processing (Leibenluft & Pine, 2013; Umbricht et al., 2003). Limited case reports suggest that psychedelics may be dangerous for individuals with these specific psychiatric illnesses (dos Santos et al., 2017), so clinical trials are not recommended at this time. For many common mental illnesses, these substances hold great promise, but limitations such as bias and small sample sizes exist. As this treatment modality is integrated into our healthcare system, it is essential that accessibility is prioritized and that the deep roots of these substances are acknowledged and respected.

## References

- Agin-Liebes, G. I., Malone, T., Yalch, M. M., Mennenga, S. E., Ponté, K. L., Guss, J., Bossis, A. P., Grigsby, J., Fischer, S., & Ross, S. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *Journal of Psychopharmacology*, *34*(2), 155–166.  
<https://doi.org/10.1177/0269881119897615>
- Albert, P. R. (2019). Adult neuroplasticity: A new “cure” for major depression? *Journal of Psychiatry and Neuroscience*, *44*(3), 147–150. <https://doi.org/10.1503/jpn.190072>
- Alderson, T., Kehoe, E., Maguire, L., Farrell, D., Lawlor, B., Kenny, R. A., Lyons, D., Bokde, A. L., & Coyle, D. (2017). Disrupted thalamus white matter anatomy and posterior default mode network effective connectivity in amnesic mild cognitive impairment. *Frontiers in Aging Neuroscience*, *9*. <https://doi.org/10.3389/fnagi.2017.00370>
- Aleksandrova, L. R., & Phillips, A. G. (2021). Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. *Trends in Pharmacological Sciences*, *42*(11), 929–942. <https://doi.org/10.1016/j.tips.2021.08.003>
- Anda, R., Brown, D., Felitti, V., Bremner, J., Dube, S., & Giles, W. (2007). Adverse childhood experiences and prescribed psychotropic medications in adults. *American Journal of Prevention Medicine*. *32*(5), 389-94. <https://doi.org/10.1016/j.amepre.2007.01.005>
- Andreescu, C., Sheu, L. K., Tudorascu, D., Walker, S., & Aizenstein, H. (2013). The ages of anxiety-differences across the lifespan in the default mode network functional connectivity in generalized anxiety disorder. *International Journal of Geriatric Psychiatry*, *29*(7), 704–712. <https://doi.org/10.1002/gps.4051>



- Argento, E., Capler, R., Thomas, G., Lucas, P., & Tupper, K. W. (2019). Exploring ayahuasca assisted therapy for addiction: A qualitative analysis of preliminary findings among an indigenous community in Canada. *Drug and Alcohol Review, 38*(7), 781–789.  
<https://doi.org/10.1111/dar.12985>
- Arnal, L., & Giraud, A. (2012). Cortical oscillations and sensory predictions. *Trends in Cognitive Science. 16*(7), 390-398. <https://doi.org/10.1016/j.tics.2012.05.003>
- Arnone D., McKie S., Elliott R., Thomas E.J., Downey D., Juhasz G., Williams S.R., Deakin J.F., Anderson I.M. (2012). Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. *American Journal of Psychiatry. 169*(8), 841-850. <https://doi.org/10.1176/appi.ajp.2012.11121774>
- Aue, T., & Hoeppli, M. (2012). Evidence for an encounter expectancy bias in fear of spiders. *Cognition & Emotion. 26*(4), 727-736. <https://doi.org/10.1080/02699931.2011.602241>
- Ballard, E. D., Ionescu, D. F., Vande Voort, J. L., Niciu, M. J., Richards, E. M., Luckenbaugh, D. A., Brutsché, N. E., Ameli, R., Furey, M. L., & Zarate, C. A. (2014). Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety. *Journal of Psychiatric Research, 58*, 161–166.  
<https://doi.org/10.1016/j.jpsychires.2014.07.027>
- Barrett L.F., & Simmons W.K. (2015). Interoceptive predictions in the brain. *Nature Reviews Neuroscience. 16*(7), 419-429. <https://doi.org/10.1038/nrn3950>
- Başar E. (2013). Brain oscillations in neuropsychiatric disease. *Dialogues in Clinical Neuroscience. 15*(3):291-300. <https://doi.org/10.31887/DCNS.2013>
- Beliveau, V., Ganz, M., Feng, L., Ozenne, B., Højgaard, L., Fisher, P. M., Svarer, C., Greve, D. N., & Knudsen, G. M. (2016). A high-resolution in vivo atlas of the human brain's

serotonin system. *The Journal of Neuroscience*, 37(1), 120–128.

<https://doi.org/10.1523/jneurosci.2830-16.2016>

Belouin S.J., & Henningfield J.E. (2018). Psychedelics: Where we are now, why we got here, what we must do. *Neuropharmacology*. 142, 7-19.

<https://doi.org/10.1016/j.neuropharm.2018.02.018>

Benedek M., Bergner S., Könen T., Fink A., Neubauer A.C. (2011). EEG alpha synchronization is related to top-down processing in convergent and divergent thinking.

*Neuropsychologia*. 49(12), 3505-3511.

<https://doi.org/10.1016/j.neuropsychologia.2011.09.004>

Benedetti, F., Piedimonte, A., & Frisaldi, E. (2018). How do placebos work? *European Journal of Psychotraumatology*, 9(3). <https://doi.org/10.1080/20008198.2018.1533370>

Berkovich-Ohana A., Harel M., Hahamy A., Arieli A., Malach R. (2016). Alterations in task-induced activity and resting-state fluctuations in visual and DMN areas revealed in long-term meditators. *Neuroimage*. 135, 125-34.

<https://doi.org/10.1016/j.neuroimage.2016.04.024>

Bernstein, H.-G., Ortmann, A., Dobrowolny, H., Steiner, J., Brisch, R., Gos, T., & Bogerts, B. (2015). Bilaterally reduced claustral volumes in schizophrenia and major depressive disorder: A morphometric postmortem study. *European Archives of Psychiatry and Clinical Neuroscience*, 266(1), 25–33. <https://doi.org/10.1007/s00406-015-0597-x>

Bhagwagar, Z., Hinz, R., Taylor, M., Fancy, S., Cowen, P., & Grasby, P. (2006). Increased 5-HT(2A) receptor binding in euthymic, medication-free patients recovered from depression: a positron emission study with [(11)C]MDL 100,907. *The American Journal of Psychiatry*. 163(9), 1580-1587. <https://doi.org/10.1176/ajp.2006.163.9.1580>

- Blier, P., & Ward, N. M. (2003). Is there a role for 5-HT1A agonists in the treatment of depression? *Biological Psychiatry*, 53(3), 193–203. [https://doi.org/10.1016/s0006-3223\(02\)01643-8](https://doi.org/10.1016/s0006-3223(02)01643-8)
- Blum, K., Chen, A. L. C., Giordano, J., Borsten, J., Chen, T. J. H., Hauser, M., Simpatico, T., Femino, J., Braverman, E. R., & Barh, D. (2012). The addictive brain: All roads lead to dopamine. *Journal of Psychoactive Drugs*, 44(2), 134–143. <https://doi.org/10.1080/02791072.2012.685407>
- Bonnett, C. (2022, February 8). Are ketamine clinics legal? Klarisana. Retrieved November 1, 2022, from <https://www.klarisana.com/blog/are-ketamine-clinics-legal/>
- Bosch, O.G., Halm, S. & Seifritz, E. (2022) Psychedelics in the treatment of unipolar and bipolar depression. *International Journal of Bipolar Disorders*. 10(18). <https://doi.org/10.1186/s40345-022-00265-5>
- Bouso, J. C., Palhano-Fontes, F., Rodríguez-Fornells, A., Ribeiro, S., Sanches, R., Crippa, J. A., Hallak, J. E. C., de Araujo, D. B., & Riba, J. (2015). Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. *European Neuropsychopharmacology*, 25(4), 483–492. <https://doi.org/10.1016/j.euroneuro.2015.01.008>
- Branchi I. (2011) The double edged sword of neural plasticity: increasing serotonin levels leads to both greater vulnerability to depression and improved capacity to recover. *Psychoneuroendocrinology*. 36(3), 339-351. <https://doi.org/10.1016/j.psyneuen.2010.08.011>

- Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: Emerging methods and principles. *Trends in Cognitive Sciences*, *14*(6), 277–290.  
<https://doi.org/10.1016/j.tics.2010.04.004>
- Bui, E., Orr, S. P., Jacoby, R. J., Keshaviah, A., LeBlanc, N. J., Milad, M. R., Pollack, M. H., & Simon, N. M. (2013). Two weeks of pretreatment with escitalopram facilitates extinction learning in healthy individuals. *Human Psychopharmacology: Clinical and Experimental*, *28*(5), 447–456. <https://doi.org/10.1002/hup.2330>
- Busch, N. A., Dubois, J., & VanRullen, R. (2009). The phase of ongoing EEG oscillations predicts visual perception. *Journal of Neuroscience*, *29*(24), 7869–7876.  
<https://doi.org/10.1523/jneurosci.0113-09.2009>
- Butler, M., Jelen, L., & Rucker, J. (2022). Expectancy in placebo-controlled trials of psychedelics: If so, so what? *Psychopharmacology*, *239*(10), 3047–3055.  
<https://doi.org/10.1007/s00213-022-06221-6>
- Carbonaro, T.M., Bradstreet, M.P., Barrett, F.S., MacLean KA, Jesse R, Johnson MW, & Griffiths RR. (2016). Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of Psychopharmacology*. *30*(12),1268-1278. <https://doi.org/10.1177/0269881116662634>
- Carhart-Harris, R. L., & Friston, K. J. (2019). Rebus and the anarchic brain: Toward a unified model of the brain action of psychedelics. *Pharmacological Reviews*, *71*(3), 316–344.  
<https://doi.org/10.1124/pr.118.017160>
- Carhart-Harris, R. L., & Nutt, D. J. (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, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., Leech, R., Malizia, A. L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R. G., & Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fmri studies with psilocybin. *Proceedings of the National Academy of Sciences*, *109*(6), 2138–2143. <https://doi.org/10.1073/pnas.1119598109>
- Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E. E., Nest, T., Orban, C., Leech, R., Williams, L. T., Williams, T. M., Bolstridge, M., Sessa, B., McGonigle, J., Sereno, M. I., Nichols, D., Hellyer, P. J., ... Nutt, D. J. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proceedings of the National Academy of Sciences*, *113*(17), 4853–4858. <https://doi.org/10.1073/pnas.1518377113>
- Carhart-Harris, R., & Goodwin, G. (2017). The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. *Neuropsychopharmacology* *42*, 2105–2113. <https://doi.org/10.1038/npp.2017.84>
- Carhart-Harris, R.L., Erritzoe, D., Haijen, E. Kaelen, M., Watts, R., (2018). Psychedelics and connectedness. *Psychopharmacology*, *235*, 547–550 (2018). <https://doi.org/10.1007/s00213-017-4701-y>
- Carr, G. V., & Lucki, I. (2010). The role of serotonin receptor subtypes in treating depression: A review of Animal Studies. *Psychopharmacology*, *213*(2-3), 265–287. <https://doi.org/10.1007/s00213-010-2097-z>
- Christensen, M., Lim, C., Saha, S., Plana-Ripoll, O., Cannon, D., Presley, F., Weye, N., Momen, N., Whiteford, H., Iburg, K. & McGrath, J. (2020). The cost of mental disorders: a

systematic review. *Epidemiology and Psychiatric Sciences*. 18(29)

<https://doi.org/10.1017/S204579602000075X>

Close, J. B., Hajien, E. C., Watts, R., Roseman, L., & Carhart-Harris, R. L. (2020). Psychedelics and psychological flexibility – results of a prospective web-survey using the acceptance and action questionnaire II. *Journal of Contextual Behavioral Science*, 16, 37–44.

<https://doi.org/10.1016/j.jcbs.2020.01.005>

Corlett, P. R., Horga, G., Fletcher, P. C., Alderson-Day, B., Schmack, K., & Powers, A. R. (2019). Hallucinations and strong priors. *Trends in Cognitive Sciences*, 23(2), 114–127.

<https://doi.org/10.1016/j.tics.2018.12.001>

Coutinho, J. F., Fernandes, S. V., Soares, J. M., Maia, L., Gonçalves, Ó. F., & Sampaio, A. (2015). Default mode network dissociation in depressive and Anxiety States. *Brain Imaging and Behavior*, 10(1), 147–157.

<https://doi.org/10.1007/s11682-015-9375-7>

Cowdrey, F. A., Filippini, N., Park, R. J., Smith, S. M., & McCabe, C. (2012). Increased resting state functional connectivity in the default mode network in recovered anorexia nervosa.

*Human Brain Mapping*, 35(2), 483–491. <https://doi.org/10.1002/hbm.22202>

Cowen, P. J., & Browning, M. (2015). What has serotonin to do with depression? *World Psychiatry*, 14(2), 158–160. <https://doi.org/10.1002/wps.20229>

Crick, F. C., & Koch, C. (2005). What is the function of the claustrum? *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1458), 1271–1279.

<https://doi.org/10.1098/rstb.2005.1661>

Crum, A. J., & Langer, E. J. (2007). Mind-set matters. *Psychological Science*, 18(2), 165–171.

<https://doi.org/10.1111/j.1467-9280.2007.01867.x>

- Crum, A. J., Corbin, W. R., Brownell, K. D., & Salovey, P. (2011). Mind over milkshakes: Mindsets, not just nutrients, determine ghrelin response. *Health Psychology, 30*(4), 424–429. <https://doi.org/10.1037/a0023467>
- Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds, C. F. (2014). Adding psychotherapy to antidepressant medication in depression and anxiety disorders: A meta-analysis. *World Psychiatry, 13*(1), 56–67. <https://doi.org/10.1002/wps.20089>
- de Souza Boff, B., Silveira Filho, J., Nonemacher, K., Driessen Schroeder, S., Dutra Arbo, M., & Rezin, K. Z. (2020). New psychoactive substances (NPS) prevalence over LSD in blotter seized in state of Santa Catarina, Brazil: A six-year retrospective study. *Forensic Science International, 306*, 110002. <https://doi.org/10.1016/j.forsciint.2019.110002>
- Deakin, J. F. W. (2013). The origins of ‘5-HT and mechanisms of defence’ by Deakin and Graeff: A personal perspective. *Journal of Psychopharmacology, 27*(12), 1084–1089. <https://doi.org/10.1177/0269881113503508>
- Decriminalize nature Oakland. Decriminalize Nature. (2022, August 15). Retrieved November 15, 2022, from <https://www.decriminalizenature.org/>
- dos Santos, R. G., Bouso, J. C., & Hallak, J. E. (2017). Ayahuasca, dimethyltryptamine, and psychosis: A systematic review of human studies. *Therapeutic Advances in Psychopharmacology, 7*(4), 141–157. <https://doi.org/10.1177/2045125316689030>
- dos Santos, R. G., Bouso, J. C., Rocha, J. M., Rossi, G. N., & Hallak, J. E. (2021). The use of classic hallucinogens/psychedelics in a therapeutic context: Healthcare policy opportunities and challenges. *Risk Management and Healthcare Policy, 14*, 901–910. <https://doi.org/10.2147/rmhp.s300656>

- Dyck, E., & Elcock, C. (2020). Reframing bumper trips: Scientific and cultural explanations to adverse reactions to psychedelic drug use. *The Social History of Alcohol and Drugs*, 34(2), 271–296. <https://doi.org/10.1086/707512>
- Ehninger, D., & Kempermann, G. (2007). Neurogenesis in the adult hippocampus. *Cell and Tissue Research*, 331(1), 243–250. <https://doi.org/10.1007/s00441-007-0478-3>
- Endicott, J., Amsterdam, J., Eriksson, E., Frank, E., Freeman, E., Hirschfeld, R., Ling, F., Parry, B., Pearlstein, T., Rosenbaum, J., Rubinow, D., Schmidt, P., Severino, S., Steiner, M., Stewart, D., & Thys-Jacobs, S. (1999). Is Premenstrual Dysphoric Disorder a Distinct Clinical Entity? *Journal of Women's Health & Gender-Based Medicine*, 663-679. <http://doi.org/10.1089/jwh.1.1999.8.663>
- Epp, A. M., Dobson, K. S., Dozois, D. J. A., & Frewen, P. A. (2012). A systematic meta-analysis of the Stroop task in depression. *Clinical Psychology Review*, 32(4), 316–328. <https://doi.org/10.1016/j.cpr.2012.02.005>
- Euler, M. J. (2018). Intelligence and uncertainty: Implications of hierarchical predictive processing for the neuroscience of cognitive ability. *Neuroscience & Biobehavioral Reviews*, 94, 93–112. <https://doi.org/10.1016/j.neubiorev.2018.08.013>
- Everaert, J., Bronstein, M. V., Cannon, T. D., & Joormann, J. (2018). Looking through tinted glasses: Depression and social anxiety are related to both interpretation biases and inflexible negative interpretations. *Clinical Psychological Science*, 6(4), 517–528. <https://doi.org/10.1177/2167702617747968>
- Fabry, R. E. (2017). Betwixt and between: The enculturated predictive processing approach to cognition. *Synthese*, 195(6), 2483–2518. <https://doi.org/10.1007/s11229-017-1334-y>



- Faust, M., & Kenett, Y. N. (2014). Rigidity, chaos and integration: Hemispheric interaction and individual differences in metaphor comprehension. *Frontiers in Human Neuroscience*, 8. <https://doi.org/10.3389/fnhum.2014.00511>
- Fjorback L.O., & Walach H. (2012). Meditation Based Therapies—A Systematic Review and Some Critical Observations. *Religions*, 3(1):1-18. <https://doi.org/10.3390/rel3010001>
- Friston, K. (2010). The free-energy principle: A unified brain theory? *Nature Reviews Neuroscience*, 11(2), 127–138. <https://doi.org/10.1038/nrn2787>
- Friston, K., Kilner, J., Harrison, L. (2006) A free energy principle for the brain. *Journal of Physiology-Paris*, 100(1–3), 70-87. <https://doi.org/10.1016/j.jphysparis.2006.10.001>
- Friston, K., Stephan, K. E., Montague, R., & Dolan, R. J. (2014). Computational psychiatry: The brain as a phantastic organ. *The Lancet Psychiatry*, 1(2), 148–158. [https://doi.org/10.1016/s2215-0366\(14\)70275-5](https://doi.org/10.1016/s2215-0366(14)70275-5)
- Fuglset, T. S. (2019). Set-shifting, central coherence and decision-making in individuals recovered from anorexia nervosa: A systematic review. *Journal of Eating Disorders*, 7(1). <https://doi.org/10.1186/s40337-019-0251-5>
- Gard, D. E., Pleet, M. M., Bradley, E. R., Penn, A., Gallenstein, M. L., Riley, L. S., DellaCrosse, M., Garfinkle, E., Michalak, E. E., & Woolley, J. D. (2021). Evaluating the risk of psilocybin for the treatment of Bipolar depression: A review of the research literature and published case studies. *Journal of Affective Disorders*, 6(100240). <https://doi.org/10.1101/2021.04.02.21254838>
- Garrett, N., Gonzzlez-Garzzn, A., Foulkes, L., Levita, L., & Sharot, T. (2018). Updating beliefs under perceived threat. *SSRN Electronic Journal*. <https://doi.org/10.2139/ssrn.3155415>

Garrison, K. A., Zeffiro, T. A., Scheinost, D., Constable, R. T., & Brewer, J. A. (2015).

Meditation leads to reduced default mode network activity beyond an active task.

*Cognitive, Affective, & Behavioral Neuroscience*, 15(3), 712–720.

<https://doi.org/10.3758/s13415-015-0358-3>

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014).

Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *Journal of Nervous & Mental Disease*,

202(7), 513–520. <https://doi.org/10.1097/nmd.000000000000113>

Gaynes, B. N., Warden, D., Trivedi, M. H., Wisniewski, S. R., Fava, M., & John Rush, A.

(2012). What did star☆D teach us? results from a large-scale, practical, clinical trial for patients with depression. *FOCUS*, 10(4), 510–517.

<https://doi.org/10.1176/appi.focus.10.4.510>

George, J. R., Michaels, T. I., Sevelius, J., & Williams, M. T. (2019). The Psychedelic

Renaissance and the limitations of a white-dominant medical framework: A call for

Indigenous and Ethnic Minority Inclusion. *Journal of Psychedelic Studies*, 4(1), 4–15.

<https://doi.org/10.1556/2054.2019.015>

Griffiths, R. R. , Richards, W. A. , McCann, U., & Jesse, R. (2006). Psilocybin can occasion

mystical-type experiences having substantial and sustained personal meaning and

spiritual significance. *Psychopharmacology (Berl)*, 187(3), 268–283.

<https://doi.org/10.1007/s00213-006-0457-5>

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B.

D., Cosimano, M. P., & Klinedinst, M. A. (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), 1181–1197.  
<https://doi.org/10.1177/0269881116675513>
- Grinspoon, L., & Bakalar, J. B. (1998). Psychedelic drugs reconsidered. Lindesmith Center.
- Grob, C.S., Danforth, A.L., Chopra, G.S., Hagerty, M., McKay, C.R., & Halberstadt, A.L. (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer *Arch. Gen. Psychiatry*. 68(1), 71-79.  
<https://dx.doi.org/10.1001/archgenpsychiatry.2010.116>
- Gu, X., & Filbey, F. (2017). A bayesian observer model of drug craving. *JAMA Psychiatry*, 74(4), 419. <https://doi.org/10.1001/jamapsychiatry.2016.3823>
- Haddjeri, N., Blier, P., & de Montigny, C. (1998). Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT<sub>1a</sub> receptors. *The Journal of Neuroscience*, 18(23), 10150–10156. <https://doi.org/10.1523/jneurosci.18-23-10150.1998>
- Haijen, E. C., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R. E., Hampshire, A. D., Lorenz, R., & Carhart-Harris, R. L. (2018). Predicting responses to psychedelics: A prospective study. *Frontiers in Pharmacology*, 9.  
<https://doi.org/10.3389/fphar.2018.00897>
- Halbreich, U. (2002). Efficacy of intermittent, luteal phase sertraline treatment of premenstrual dysphoric disorder. *Obstetrics & Gynecology*, 100(6), 1219–1229.  
[https://doi.org/10.1016/s0029-7844\(02\)02326-8](https://doi.org/10.1016/s0029-7844(02)02326-8)
- Hall, W. (2022). Why was early therapeutic research on psychedelic drugs abandoned? *Psychological Medicine*, 52(1), 26-31. <https://doi.org/10.1017/S0033291721004207>

- Harmer, C. J., Goodwin, G. M., & Cowen, P. J. (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry*, *195*(2), 102–108. <https://doi.org/10.1192/bjp.bp.108.051193>
- Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law*, *3*. <https://doi.org/10.1177/2050324516683325>
- Heisler, L. K., Chu, H.-M., Brennan, T. J., Danao, J. A., Bajwa, P., Parsons, L. H., & Tecott, L. H. (1998). Elevated anxiety and antidepressant-like responses in serotonin 5-HT<sub>1a</sub> receptor mutant mice. *Proceedings of the National Academy of Sciences*, *95*(25), 15049–15054. <https://doi.org/10.1073/pnas.95.25.15049>
- Hibicke, M., Landry, A., Kramer, H., Talman, Z., & Nichols, C. (2020). Psychedelics, but not ketamine, produce persistent antidepressant-like effects in a rodent experimental system for the study of depression. *ACS Chemical Neuroscience*, *11*(6), 864–871. <https://doi.org/10.1021/acchemneuro.9b00493.s002>
- Ho, T. C., Connolly, C. G., Henje Blom, E., LeWinn, K. Z., Strigo, I. A., Paulus, M. P., Frank, G., Max, J. E., Wu, J., Chan, M., Tapert, S. F., Simmons, A. N., & Yang, T. T. (2015). Emotion-dependent functional connectivity of the default mode network in Adolescent Depression. *Biological Psychiatry*, *78*(9), 635–646. <https://doi.org/10.1016/j.biopsych.2014.09.002>
- Holliday, J., Tchanturia, K., Landau, S., Collier, D., & Treasure, J. (2005). Is impaired set-shifting an endophenotype of anorexia nervosa? *American Journal of Psychiatry* *162*, 2269–2275. <https://doi.org/10.1176/appi.ajp.162.12.2269>

Homberg, J. R., Schubert, D., & Gaspar, P. (2010). New Perspectives on the neurodevelopmental effects of ssris. *Trends in Pharmacological Sciences*, *31*(2), 60–65.

<https://doi.org/10.1016/j.tips.2009.11.003>

Huberman, A. (2022, July 17). How to focus to change your brain. Huberman Lab. Retrieved November 21, 2022, from <https://hubermanlab.com/how-to-focus-to-change-your-brain/>

Huhn, M., Tardy, M., Spineli, L. M., Kissling, W., Förstl, H., Pitschel-Walz, G., Leucht, C., Samara, M., Dold, M., Davis, J. M., & Leucht, S. (2014). Efficacy of pharmacotherapy and psychotherapy for adult psychiatric disorders. *JAMA Psychiatry*, *71*(6), 706.

<https://doi.org/10.1001/jamapsychiatry.2014.112>

Inoshita, T., & Hirano, T. (2018). Occurrence of long-term depression in the cerebellar flocculus during adaptation of optokinetic response. *ELife*. <https://doi.org/10.7554/elife.36209.013>

*Integrative ayahuasca retreats: Costa Rica and Peru*. All-Inclusive Ayahuasca Costa Rica Retreats | Authentic Shipibo Ayahuasca Retreats located in Costa Rica. Spiritual healing at it's best, offering meditation, yoga, exercise and plant medicine ceremonies. (2022, November 29). Retrieved December 2, 2022, from <https://soltara.co/retreats/>

Jaworska, N., Blier, P., Fusee, W., & Knott, V. (2012). Alpha Power, alpha asymmetry and anterior cingulate cortex activity in depressed males and females. *Journal of Psychiatric Research*, *46*(11), 1483–1491. <https://doi.org/10.1016/j.jpsychires.2012.08.003>

Jiang, L., Cao, X., Li, T., Tang, Y., Li, W., Wang, J., Chan, R. C., & Li, C. (2016). Cortical thickness changes correlate with cognition changes after cognitive training: Evidence from a Chinese community study. *Frontiers in Aging Neuroscience*, *8*.

<https://doi.org/10.3389/fnagi.2016.00118>

- Johansen, P.-Ø., & Krebs, T. S. (2015). Psychedelics not linked to mental health problems or suicidal behavior: A population study. *Journal of Psychopharmacology*, 29(3), 270–279. <https://doi.org/10.1177/0269881114568039>
- Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT<sub>2A</sub>R agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology*, 28(11), 983–992. <https://doi.org/10.1177/0269881114548296>
- Johnson, M. W., Hendricks, P. S., Barrett, F. S., & Griffiths, R. R. (2019). Classic psychedelics: An Integrative Review of Epidemiology, therapeutics, mystical experience, and Brain Network function. *Pharmacology & Therapeutics*, 197, 83–102. <https://doi.org/10.1016/j.pharmthera.2018.11.010>
- Johnstad, P. G. (2021). Day trip to hell: A mixed methods study of challenging psychedelic experiences. *Journal of Psychedelic Studies*, 5(2), 114–127. <https://doi.org/10.1556/2054.2021.00155>
- Jones, G., Ricard, J. A., Lipson, J., & Nock, M. K. (2022). Associations between classic psychedelics and opioid use disorder in a nationally-representative U.S. adult sample. *Scientific Reports*, 12(1). <https://doi.org/10.1038/s41598-022-08085-4>
- Juul, S., Gluud, C., Simonsen, S., Frandsen, F. W., Kirsch, I., & Jakobsen, J. C. (2020). Blinding in randomised clinical trials of psychological interventions: A retrospective study of published trial reports. *BMJ Evidence-Based Medicine*, 26(3), 109–109. <https://doi.org/10.1136/bmjebm-2020-111407>
- Kaplan, A. L., Confair, D. N., Kim, K., Barros-Álvarez, X., Rodriguiz, R. M., Yang, Y., Kweon, O. S., Che, T., McCorvy, J. D., Kamber, D. N., Phelan, J. P., Martins, L. C., Pogorelov, V. M., DiBerto, J. F., Slocum, S. T., Huang, X.-P., Kumar, J. M., Robertson, M. J.,

- Panova, O., ... Ellman, J. A. (2022). Bespoke Library docking for 5-HT<sub>2A</sub> receptor agonists with antidepressant activity. *Nature*, *610*(7932), 582–591.  
<https://doi.org/10.1038/s41586-022-05258-z>
- Katalinic, N., Lai, R., Somogyi, A., Mitchell, P. B., Glue, P., & Loo, C. K. (2013). Ketamine as a new treatment for depression: A review of its efficacy and adverse effects. *Australian & New Zealand Journal of Psychiatry*, *47*(8), 710–727.  
<https://doi.org/10.1177/0004867413486842>
- Keizer, A., Smeets, M. A., Dijkerman, H. C., Uzunbajakau, S. A., van Elburg, A., & Postma, A. (2013). Too fat to fit through the door: First evidence for disturbed body-scaled action in anorexia nervosa during locomotion. *PLoS ONE*, *8*(5).  
<https://doi.org/10.1371/journal.pone.0064602>
- Keller, G. B., & Mrsic-Flogel, T. D. (2018). Predictive processing: A canonical cortical computation. *Neuron*, *100*(2), 424–435. <https://doi.org/10.1016/j.neuron.2018.10.003>
- Kemp, A. H., Griffiths, K., Felmingham, K. L., Shankman, S. A., Drinkenburg, W., Arns, M., Clark, C. R., & Bryant, R. A. (2010). Disorder specificity despite comorbidity: Resting EEG alpha asymmetry in major depressive disorder and post-traumatic stress disorder. *Biological Psychology*, *85*(2), 350–354. <https://doi.org/10.1016/j.biopsycho.2010.08.001>
- Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*, *16*(12), 606–617.  
<https://doi.org/10.1016/j.tics.2012.10.007>
- Klimesch, W., Pfurtscheller, G., & Schimke, H. (1992). Pre- and post-stimulus processes in category judgement tasks as measured by event-related desynchronization (ERD). *Journal of Psychophysiology*, *6*(3), 185–203.

- Klöbl, M., Seiger, R., Vanicek, T., Handschuh, P., Reed, M. B., Spurny-Dworak, B., Ritter, V., Godbersen, G. M., Gryglewski, G., Kraus, C., Hahn, A., & Lanzenberger, R. (2022). Escitalopram modulates learning content-specific neuroplasticity of functional brain networks. *NeuroImage*, 247. <https://doi.org/10.1016/j.neuroimage.2021.118829>
- Koch, C. (1993). Computational approaches to cognition: The bottom-up View. *Current Opinion in Neurobiology*, 3(2), 203–208. [https://doi.org/10.1016/0959-4388\(93\)90211-g](https://doi.org/10.1016/0959-4388(93)90211-g)
- Kometer, M., Schmidt, A., Jancke, L., & Vollenweider, F. X. (2013). Activation of serotonin 2A receptors underlies the psilocybin-induced effects on &nbsp; oscillations, N170 visual-evoked potentials, and visual hallucinations. *Journal of Neuroscience*, 33(25), 10544–10551. <https://doi.org/10.1523/jneurosci.3007-12.2013>
- Krebs, T. S., & Johansen, P.-Ø. (2012). Lysergic acid diethylamide (LSD) for alcoholism: Meta-analysis of randomized controlled trials. *Journal of Psychopharmacology*, 26(7), 994–1002. <https://doi.org/10.1177/0269881112439253>
- Kube, T., Schwarting, R., Rozenkrantz, L., Glombiewski, J. A., & Rief, W. (2020). Distorted cognitive processes in major depression: A predictive processing perspective. *Biological Psychiatry*, 87(5), 388–398. <https://doi.org/10.1016/j.biopsych.2019.07.017>
- Laukkonen, R. E., & Slagter, H. A. (2021). From many to (n)one: Meditation and the plasticity of the predictive mind. *Neuroscience & Biobehavioral Reviews*, 128, 199–217. <https://doi.org/10.1016/j.neubiorev.2021.06.021>
- Leibenluft, E., & Pine, D. S. (2013). Resting state functional connectivity and depression: In search of a bottom line. *Biological Psychiatry*, 74(12), 868–869. <https://doi.org/10.1016/j.biopsych.2013.10.001>



- León-Cabrera, P., Pagonabarraga, J., Morís, J., Martínez-Horta, S., Marín-Lahoz, J., Horta-Barba, A., Bejr-Kasem, H., Kulisevsky, J., & Rodríguez-Fornells, A. (2021). Neural signatures of predictive language processing in parkinson's disease with and without mild cognitive impairment. *Cortex*, 141, 112–127.  
<https://doi.org/10.1016/j.cortex.2021.03.032>
- Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive dysfunction in Geriatric Depression. *American Journal of Psychiatry*, 159(7), 1119–1126.  
<https://doi.org/10.1176/appi.ajp.159.7.1119>
- Luoma, J. B., Chwyl, C., Bathje, G., Davis, A., & Lancelotta, R. (2020). A meta-analysis of placebo-controlled trials of psychedelic-assisted therapy. *Journal of Psychoactive Drugs*, 52(4), 289–299. <https://doi.org/10.31234/osf.io/sgujx>
- Magaraggia, I., Kuiperes, Z., & Schreiber, R. (2021). Improving cognitive functioning in major depressive disorder with psychedelics: A dimensional approach. *Neurobiology of Learning and Memory*, 183, 107467. <https://doi.org/10.1016/j.nlm.2021.107467>
- Malcolm, B., & Thomas, K. (2021). Serotonin toxicity of serotonergic psychedelics. *Psychopharmacology*, 239(6), 1881–1891. <https://doi.org/10.1007/s00213-021-05876-x>
- Marks, M., & Cohen, I. G. (2021). Psychedelic therapy: A roadmap for wider acceptance and Utilization. *Nature Medicine*, 27(10), 1669–1671. <https://doi.org/10.1038/s41591-021-01530-3>
- Martin, D. A., & Nichols, C. D. (2016). Psychedelics recruit multiple cellular types and produce complex transcriptional responses within the brain. *EBioMedicine*, 11, 262–277.  
<https://doi.org/10.1016/j.ebiom.2016.08.049>

- McGovern, H. T., De Foe, A., Biddell, H., Leptourgos, P., Corlett, P., Bandara, K., & Hutchinson, B. T. (2022). Learned uncertainty: The free energy principle in anxiety. *Frontiers in Psychology, 13*. <https://doi.org/10.3389/fpsyg.2022.943785>
- Melartin, T. K., Rytsala, H. J., Leskela, U. S., Lestela-Mielonen, P. S., Sokero, T. P., & Isometsa, E. T. (2002). Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *The Journal of Clinical Psychiatry, 63*(2), 126–134. <https://doi.org/10.4088/jcp.v63n0207>
- Meshkova, T. A. (2015). Heredity and Environment in Etiology of Eating Disorders. I. Review of Twin Studies. *Moscow State University of Psychology and Education, 2304–0394*. <https://doi.org/https://doi.org/10.17759/cpse>
- Meyer, J. H., McMain, S., Kennedy, S. H., Korman, L., Brown, G. M., DaSilva, J. N., Wilson, A. A., Blak, T., Eynan-Harvey, R., Goulding, V. S., Houle, S., & Links, P. (2003). Dysfunctional attitudes and 5-HT<sub>2A</sub> receptors during depression and self-harm. *American Journal of Psychiatry, 160*(1), 90–99. <https://doi.org/10.1176/appi.ajp.160.1.90>
- Michaels, T. I., Purdon, J., Collins, A., & Williams, M. (2018). Inclusion of people of color in psychedelic-assisted psychotherapy: A review of the literature. *SSRN Electronic Journal, 18*(245). <https://doi.org/10.2139/ssrn.3311241>
- Miller, M., Kiverstein, J., & Rietveld, E. (2020). Embodying addiction: A predictive processing account. *Brain and Cognition, 138*. <https://doi.org/10.1016/j.bandc.2019.105495>
- Miyazaki, K. W., Miyazaki, K., & Doya, K. (2011). Activation of dorsal raphe serotonin neurons is necessary for waiting for delayed rewards. *Neuroscience Research, 32*(31), 10451–10457. <https://doi.org/10.1016/j.neures.2011.07.1628>

Mock, J. (2020, July 23). *How antidepressants work is a mystery scientists still don't understand.*

Discover Magazine. Retrieved December 4, 2022, from

<https://www.discovermagazine.com/health/how-antidepressants-work-is-a-mystery-scientists-still-dont-understand>

Mohanta, S., Afrasiabi, M., Casey, C., Tanabe, S., Redinbaugh, M. J., Kambi, N. A., Phillips, J.

M., Polyakov, D., Filbey, W., Austerweil, J. L., Sanders, R. D., & Saalman, Y. B.

(2020). Predictive feedback, early sensory representations and fast responses to predicted stimuli depend on NMDA receptors. *Journal of Neuroscience*, *41*(49), 10130–10147.

<https://doi.org/10.1101/2020.01.06.896589>

Moreno, F. A., Wiegand, C. B., Taitano, E. K., & Delgado, P. L. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *The Journal of Clinical Psychiatry*, *67*(11), 1735–1740. <https://doi.org/10.4088/jcp.v67n1110>

Nichols, D. E., Johnson, M. W., & Nichols, C. D. (2016). Psychedelics as medicines: An emerging new paradigm. *Clinical Pharmacology & Therapeutics*, *101*(2), 209–219.

<https://doi.org/10.1002/cpt.557>

Nygart, V. A., Pommerencke, L. M., Haijen, E., Kettner, H., Kaelen, M., Mortensen, E. L., Nutt,

D. J., Carhart-Harris, R. L., & Erritzoe, D. (2022). Antidepressant effects of a psychedelic experience in a large prospective naturalistic sample. *Journal of Psychopharmacology*, *36*(8), 932–942. <https://doi.org/10.1177/02698811221101061>

O'Neill, A., Mechelli, A., & Bhattacharyya S. (2019). Dysconnectivity of Large-Scale

Functional Networks in Early Psychosis: *A Meta-analysis*. *Schizophrenia Bulletin*, *45*(3),

579–590. <https://doi.org/10.1093/schbul/sby094>

- Ona, G., Kohek, M., & Bouso, J. C. (2022). The illusion of knowledge in the emerging field of psychedelic research. *New Ideas in Psychology*, 67, 100967.  
<https://doi.org/10.1016/j.newideapsych.2022.100967>
- Palhano-Fontes, F., Andrade, K. C., Tofoli, L. F., Santos, A. C., Crippa, J. A., Hallak, J. E., Ribeiro, S., & de Araujo, D. B. (2015). The psychedelic state induced by ayahuasca modulates the activity and connectivity of the Default Mode Network. *PLOS ONE*, 10(2).  
<https://doi.org/10.1371/journal.pone.0118143>
- Paparelli, A., Di Forti, M., Morrison, P. D., & Murray, R. M. (2011). Drug-induced psychosis: How to avoid star gazing in schizophrenia research by looking at more obvious sources of light. *Frontiers in Behavioral Neuroscience*, 5.  
<https://doi.org/10.3389/fnbeh.2011.00001>
- Passow, S., Specht, K., Adamsen, T. C., Biermann, M., Brekke, N., Craven, A. R., Ersland, L., Grüner, R., Kleven-Madsen, N., Kvernenes, O. H., Schwarzlmüller, T., Olesen, R. A., & Hugdahl, K. (2015). Default mode network functional connectivity is closely related to metabolic activity. *Human Brain Mapping*, 36(6), 2027–2038.  
<https://doi.org/10.1002/hbm.22753>
- Petranker, R., Anderson, T., & Farb, N. A. (2020). Psychedelic research and the need for transparency - polishing Alice's looking Glass. *Frontiers in Psychology*.  
<https://doi.org/10.31234/osf.io/vgt3r>
- Petri, G., Expert, P., Turkheimer, F., Carhart-Harris, R., Nutt, D., Hellyer, P. J., & Vaccarino, F. (2014). Homological scaffolds of brain functional networks. *Journal of The Royal Society Interface*, 11(101), 20140873. <https://doi.org/10.1098/rsif.2014.0873>

- Phelps, J. (2017). Developing guidelines and competencies for the training of psychedelic therapists. *Journal of Humanistic Psychology*, 57(5), 450–487.  
<https://doi.org/10.1177/0022167817711304>
- Pies, R. (2019). Debunking the two chemical imbalance myths, again. *Psychiatric Times*. Retrieved November 1, 2022, from <https://www.psychiatrictimes.com/view/debunking-two-chemical-imbalance-myths-again>
- Pollan, M. (2019). *How to change your mind: The new science of psychedelics*. Penguin.
- Preller, K. H., Razi, A., Zeidman, P., Stämpfli, P., Friston, K. J., & Vollenweider, F. X. (2019). Effective connectivity changes in LSD-induced altered states of consciousness in humans. *Proceedings of the National Academy of Sciences*, 116(7), 2743–2748.  
<https://doi.org/10.1073/pnas.1815129116>
- Price, K. (2018, August 28). Ketamine's antidepressive effects tied to opioid system in brain. News Center. Retrieved November 10, 2022, from <https://med.stanford.edu/news/all-news/2018/08/ketamines-antidepressive-effects-tied-to-opioid-system-in-brain.html>
- Price, R. B., Spotts, C., Panny, B., Griffio, A., Degutis, M., Cruz, N., Bell, E., Do-Nguyen, K., Wallace, M. L., Mathew, S. J., & Howland, R. H. (2022). A novel, brief, fully automated intervention to extend the antidepressant effect of a single ketamine infusion: A randomized clinical trial. *American Journal of Psychiatry*.  
<https://doi.org/10.1176/appi.ajp.20220216>
- Puglisi-Allegra, S. & Andolina, D. (2015) Serotonin and Stress Coping. *Behavioural Brain Research*, 277, 58-67. <https://doi.org/10.1016/j.bbr.2014.07.052>

- Rikhye, R.V., Gilra, A. & Halassa, M.M. (2018). Thalamic regulation of switching between cortical representations enables cognitive flexibility. *Natural Neuroscience*, 21, 1753–1763. <https://doi.org/10.1038/s41593-018-0269-z>
- Riva, G., & Dakanalis, A. (2018). Altered processing and integration of multisensory bodily representations and signals in eating disorders: A possible path toward the understanding of their underlying causes. *Frontiers in Human Neuroscience*, 12. <https://doi.org/10.3389/fnhum.2018.00049>
- Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (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), 1165–1180. <https://doi.org/10.1177/0269881116675512>
- Rougemont-Bücking, A., Jungaberle, H., Scheidegger, M., Merlo, M. C. G., Grazioli, V. S., Daepfen, J.-B., Gmel, G., & Studer, J. (2019). Comparing mental health across distinct groups of users of psychedelics, MDMA, Psychostimulants, and Cannabis. *Journal of Psychoactive Drugs*, 51(3), 236–246. <https://doi.org/10.1080/02791072.2019.1571258>
- Rusyn, I., & Bataller, R. (2013). Alcohol and toxicity. *Journal of Hepatology*, 59(2), 387-388. <https://doi.org/10.1016/j.jhep.2013.01.035>
- Scheeringa, R., Mazaheri, A., Bojak, I., Norris, D. G., & Kleinschmidt, A. (2011). Modulation of visually evoked cortical fmri responses by phase of ongoing occipital alpha oscillations. *Journal of Neuroscience*, 31(10), 3813–3820. <https://doi.org/10.1523/jneurosci.4697-10.2011>

- Scheidegger, M., Walter, M., Lehmann, M., Metzger, C., Grimm, S., Boeker, H., Boesiger, P., Henning, A., & Seifritz, E. (2012). Ketamine decreases resting state functional network connectivity in healthy subjects: Implications for antidepressant drug action. *PLoS ONE*, 7(9). <https://doi.org/10.1371/journal.pone.0044799>
- Schmid, Y., & Liechti, M. E. (2018). Long-lasting subjective effects of LSD in normal subjects. *Psychopharmacology*, 235(2), 535–545. <https://doi.org/10.1007/s00213-017-4733-3>
- Schweizer, G., & Furley, P. (2016). Reproducible research in sport and exercise psychology: The role of sample sizes. *Psychology of Sport and Exercise*, 23, 114–122. <https://doi.org/10.1016/j.psychsport.2015.11.005>
- Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., Mintun, M. A., Wang, S., Coalson, R. S., & Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, 106(6), 1942–1947. <https://doi.org/10.1073/pnas.0812686106>
- Sheline, Y., Mittler, B., & Mintun, M. (2002). The hippocampus and depression. *European Psychiatry*, 3, 300-305. [https://doi.org/10.1016/s0924-9338\(02\)00655-7](https://doi.org/10.1016/s0924-9338(02)00655-7)
- Shergill, S. S., White, T. P., Joyce, D. W., Bays, P. M., Wolpert, D. M., & Frith, C. D. (2014). Functional magnetic resonance imaging of impaired sensory prediction in Schizophrenia. *JAMA Psychiatry*, 71(1), 28. <https://doi.org/10.1001/jamapsychiatry.2013.2974>
- Sherin, J. E., & Nemeroff, C. B. (2011). Post-traumatic stress disorder: The neurobiological impact of psychological trauma. *Dialogues in Clinical Neuroscience*, 13(3), 263–278. <https://doi.org/10.31887/dcns.2011.13.2/jsherin>

- Singal, A. G., Higgins, P. D., & Waljee, A. K. (2014). A primer on effectiveness and efficacy trials. *Clinical and Translational Gastroenterology*, 5(1).  
<https://doi.org/10.1038/ctg.2013.13>
- Singleton, S. P., Luppi, A. I., Carhart-Harris, R. L., Cruzat, J., Roseman, L., Nutt, D. J., Deco, G., Kringelbach, M. L., Stamatakis, E. A., & Kuceyeski, A. (2021). LSD and psilocybin flatten the brain's energy landscape: Insights from receptor-informed network control theory. *BioRxiv*. <https://doi.org/10.1101/2021.05.14.444193>
- Skudlarski, P., Jagannathan, K., Anderson, K., Stevens, M. C., Calhoun, V. D., Skudlarska, B. A., & Pearlson, G. (2010). Brain connectivity is not only lower but different in schizophrenia: A combined anatomical and functional approach. *Biological Psychiatry*, 68(1), 61–69. <https://doi.org/10.1016/j.biopsych.2010.03.035>
- Smith, J. B., Watson, G. D., Liang, Z., Liu, Y., Zhang, N., & Alloway, K. D. (2019). A role for the claustrum in salience processing? *Frontiers in Neuroanatomy*, 13.  
<https://doi.org/10.3389/fnana.2019.00064>
- Smith, R., Kuplicki, R., Feinstein, J., Forthman, K. L., Stewart, J. L., Paulus, M. P., & Khalsa, S. S. (2020). A bayesian computational model reveals a failure to adapt interoceptive precision estimates across depression, anxiety, eating, and Substance Use Disorders. *PLOS Computational Biology*, 16(12). <https://doi.org/10.1371/journal.pcbi.1008484>
- Sperry, R. W. (1950). Neural basis of the spontaneous optokinetic response produced by visual inversion. *Journal of Comparative and Physiological Psychology*, 43(6), 482–489.  
<https://doi.org/10.1037/h0055479>



- Spriggs, M.J., Kettner, H. & Carhart-Harris, R.L. (2021). Positive effects of psychedelics on depression and wellbeing scores in individuals reporting an eating disorder. *Eating & Weight Disorders*, 26, 1265–1270. <https://doi.org/10.1007/s40519-020-01000-8>
- Steinglass, J. E., Walsh, B., & Stern, Y. (2006). Set shifting deficit in anorexia nervosa. *Journal of the International Neuropsychological Society*, 12(03).  
<https://doi.org/10.1017/s1355617706060528>
- Steriade, M. (2004). Local gating of information processing through the thalamus. *Neuron*, 41(4), 493–494. [https://doi.org/10.1016/s0896-6273\(04\)00076-5](https://doi.org/10.1016/s0896-6273(04)00076-5)
- Sterzer, P., Adams, R. A., Fletcher, P., Frith, C., Lawrie, S. M., Muckli, L., Petrovic, P., Uhlhaas, P., Voss, M., & Corlett, P. R. (2018). The predictive coding account of psychosis. *Biological Psychiatry*, 84(9), 634–643. <https://doi.org/10.1016/j.biopsych.2018.05.015>
- Stuhlmiller, C., & Tolchard, B. (2009). Computer-assisted for Depression & Anxiety: Increasing accessibility to evidence-based mental health treatment. *Journal of Psychosocial Nursing and Mental Health Services*, 47(7), 32–39.  
<https://doi.org/10.3928/02793695-20090527-01>
- Sussman, T. J., Jin, J., & Mohanty, A. (2016). Top-down and bottom-up factors in threat-related perception and attention in anxiety. *Biological Psychology*, 121, 160–172.  
<https://doi.org/10.1016/j.biopsycho.2016.08.006>
- Torgerson, C. M., Irimia, A., Goh, S. Y., & Van Horn, J. D. (2014). The DTI connectivity of the human claustrum. *Human Brain Mapping*, 36(3), 827–838.  
<https://doi.org/10.1002/hbm.22667>
- Tylee, A., & Walters, P. (2007). Onset of action of antidepressants. *BMJ*, 334(7600), 911–912.  
<https://doi.org/10.1136/bmj.39197.619190.80>

- U.S. Department of Health and Human Services. (n.d.). Mental illness. National Institute of Mental Health. Retrieved November 1, 2022, from <https://www.nimh.nih.gov/health/statistics/mental-illness>
- Umbricht, D., Vollenweider, F., & Schmid, L. (2003). Effects of the 5-HT<sub>2A</sub> Agonist Psilocybin on Mismatch Negativity Generation and AX-Continuous Performance Task: Implications for the Neuropharmacology of Cognitive Deficits in Schizophrenia. *Neuropsychopharmacology* 28, 170–181. <https://doi.org/10.1038/sj.npp.1300005>
- Valle, M., Maqueda, A. E., Rabella, M., Rodríguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mañanas, M. À., Barker, S., Friedlander, P., Feilding, A., & Riba, J. (2016). Inhibition of alpha oscillations through serotonin-2a receptor activation underlies the visual effects of ayahuasca in humans. *European Neuropsychopharmacology*, 26(7), 1161–1175. <https://doi.org/10.1016/j.euroneuro.2016.03.012>
- Vatansever, D., Menon, D. K., & Stamatakis, E. A. (2017). Default mode contributions to Automated Information Processing. *Proceedings of the National Academy of Sciences*, 114(48), 12821–12826. <https://doi.org/10.1073/pnas.1710521114>
- Villiger, D. (2022). How psychedelic-assisted treatment works in the bayesian brain. *Frontiers in Psychiatry*, 13. <https://doi.org/10.3389/fpsyt.2022.812180>
- Volgin, D. V., Fay, R., & Kubin, L. (2003). Postnatal development of Serotonin 1B, 2 A and 2C receptors in brainstem motoneurons. *European Journal of Neuroscience*, 17(6), 1179–1188. <https://doi.org/10.1046/j.1460-9568.2003.02545.x>
- Walsh, K. S., McGovern, D. P., Clark, A., & O'Connell, R. G. (2020). Evaluating the neurophysiological evidence for predictive processing as a model of perception. *Annals*

*of the New York Academy of Sciences*, 1464(1), 242–268.

<https://doi.org/10.1111/nyas.14321>

Wang, L., Zobeiri, O.A., & Millar, J.L. (2021). Head movement kinematics are altered during gaze stability exercises in vestibular schwannoma patients. *Scientific Reports*, 11.

<https://doi.org/10.1038/s41598-021-86533-3>

Watts, R. & Luoma, J. (2020). The use of the psychological flexibility model to support psychedelic assisted therapy. *Journal of Contextual Behavioral Science*, 15, 92-102.

<https://doi.org/10.1016/j.jcbs.2019.12.004>

Watts, R., Day, C., Krzanowski, J., Nutt, D., & Carhart-Harris, R. (2017). Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *Journal of Humanistic Psychology*, 57(5), 520–564.

<https://doi.org/10.1177/0022167817709585>

Weber, K., Lau, E. F., Stillerman, B., & Kuperberg, G. R. (2016). The Yin and the Yang of prediction: An fmri study of Semantic Predictive Processing. *PLOS ONE*, 11(3).

<https://doi.org/10.1371/journal.pone.0148637>

Wesson, D. R. (2011). Psychedelic drugs, hippie counterculture, speed and phenobarbital treatment of sedative-hypnotic dependence: A journey to the haight ashbury in the sixties. *Journal of Psychoactive Drugs*, 43(2), 153–164.

<https://doi.org/10.1080/02791072.2011.587708>

Wheeler, S. W., & Dyer, N. L. (2020). A systematic review of psychedelic-assisted psychotherapy for Mental Health: An Evaluation of the current wave of research and suggestions for the future. *Psychology of Consciousness: Theory, Research, and Practice*, 7(3), 279–315. <https://doi.org/10.1037/cns0000237>

- Wilkinson, S., Dodgson, G., & Meares, K. (2017). Predictive processing and the varieties of psychological trauma. *Frontiers in Psychology, 8*.  
<https://doi.org/10.3389/fpsyg.2017.01840>
- Williams, N. R., Heifets, B. D., Bentzley, B. S., Blasey, C., Sudheimer, K. D., Hawkins, J., Lyons, D. M., & Schatzberg, A. F. (2019). Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism. *Molecular Psychiatry, 24*(12), 1779–1786. <https://doi.org/10.1038/s41380-019-0503-4>
- Xing, M., Tadayonnejad, R., MacNamara, A., Ajilore, O., DiGangi, J., Phan, K. L., Leow, A., & Klumpp, H. (2017). Resting-state theta band connectivity and graph analysis in generalized social anxiety disorder. *NeuroImage: Clinical, 13*, 24–32.  
<https://doi.org/10.1016/j.nicl.2016.11.009>
- Yaden, D. B., Yaden, M. E., & Griffiths, R. R. (2021). Psychedelics in psychiatry—keeping the Renaissance from going off the rails. *JAMA Psychiatry, 78*(5), 469.  
<https://doi.org/10.1001/jamapsychiatry.2020.3672>
- Zanos, P., & Gould, T. (2018). Mechanisms of ketamine action as an antidepressant. *Molecular Psychiatry, 23*, 801–811. <https://doi.org/10.1038/mp.2017.255>
- Zanto, T. P., Rubens, M. T., Thangavel, A., & Gazzaley, A. (2011). Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. *Nature Neuroscience, 14*(5), 656–661. <https://doi.org/10.1038/nn.2773>
- Zeifman, R. J., Yu, D., Singhal, N., Wang, G., Nayak, S. M., & Weissman, C. R. (2022). Decreases in suicidality following psychedelic therapy. *The Journal of Clinical Psychiatry, 83*(2). <https://doi.org/10.4088/jcp.21r14057>

Zhang, G., Ásgeirsdóttir, H. N., Cohen, S. J., Munchow, A. H., Barrera, M. P., & Stackman, R. W. (2013). Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6J MICE. *Neuropharmacology*, *64*, 403–413.  
<https://doi.org/10.1016/j.neuropharm.2012.06.007>