Where and how does neuroplasticity lead to therapeutic changes?

Lorenzo Palm[1]

Supervised by Rutger Boesjes[2] and Martien Kas[3].

[1] Master's in Behavioural and Cognitive Neurosciences, Department of Science and Engineering, University of Groningen

[2] Psychedelic Therapy & Mechanisms group, University Center of Psychiatry (UCP), University Medical Center Groningen (UMCG).

[3] Groningen Institute for Evolutionary Life Sciences (GELIFES), University of Groningen.

ABSTRACT

The neuroplasticity theory of depression posits that the brain's ability to reorganize and form new connections plays a central role in both the development and treatment of depression. Extensive research connects brain atrophy observed in depression with the therapeutic and neuroplastic action of compounds like selective serotonin reuptake inhibitors (SSRIs), ketamine, and classic psychedelics. However, enhanced neuroplasticity can also have detrimental effects, as seen for example in the reward pathways in both addiction and depression.

This review thus addresses two important research questions:

1. Where in the brain does neuroplasticity lead to therapeutic changes?
2. How do these plasticity changes translate into cognitive and emotional well-being?

We begin the essay by examining recent evidence supporting the role of neuroplasticity in psychedelics and other antidepressant treatments. Then, we explore which brain regions are most involved in depression and might benefit from therapeutic neuroplasticity. Finally, we propose a hypothesis on how neuroplasticity could contribute to improvements in behavior, cognition, and emotion by stimulating psychological flexibility, and how this could be investigated in the future.

Table of Contents

INTRODUCTION

The ability of the nervous tissue to modify over the course of an organism's life is referred to as “neuroplasticity”, a term that is gaining traction both as a potential biomarker of neuropsychiatric illnesses and as a target for therapeutics.

Psychedelics, from the Greek words psyché 'soul, mind' and dēleín 'to manifest', are a large family of drugs that are currently being (re-)explored as potential treatments for mental health disorders, precisely because of their strong plasticity-inducing effects. The most studied compounds are the classic psychedelics, such as psilocybin, lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (N,N-DMT), and non-classic psychedelics, such as ketamine and 3,4-Methylenedioxymethamphetamine (MDMA). Sufficient doses of psychedelics reliably induce a transient altered state of consciousness, followed by long-lasting changes in mood, personality, and behavior. Such changes and their underlying biology have been found to endure far longer than the presence of the drug in the organism (Garcia-Romeu et al., 2016). Evidence from contemporary clinical trials has shown that symptom relief produced by these substances surfaces after one or a few treatment sessions, yet it can last for an extended period without re-exposure to the drug. The novelty of psychedelics compared to available mental health medications lies in their rapid onset of action and lasting therapeutic properties.

This interest in psychedelics aligns with mounting evidence of impaired neuroplasticity in disorders such as major depressive disorder (MDD) and chronic stress. Structural and cellular changes, particularly in cortico-limbic regions governing mood and emotion, are characteristic of these conditions, including neuronal loss and synaptic dysfunction (Manji et al., 2000; Price & Duman, 2020). Extensive evidence links for example chronic stress and MDD to brain atrophy in the hippocampus and prefrontal cortex (PFC) (Bora et al., 2012), as well as reduced levels of brain-derived neurotrophic factor (BDNF) and mTORC1 signaling in these two areas (Duman & Aghajanian, 2012; Duman & Monteggia, 2006; Ota et al., 2014). The ENIGMA MDD working group's large-scale meta-analysis, pooling neuroimaging data from over 9,000 individuals across 20 countries, confirmed significant reductions in gray matter in the hippocampus, anterior cingulate cortex, and orbitofrontal cortex in individuals with MDD (Schmaal et al., 2016).

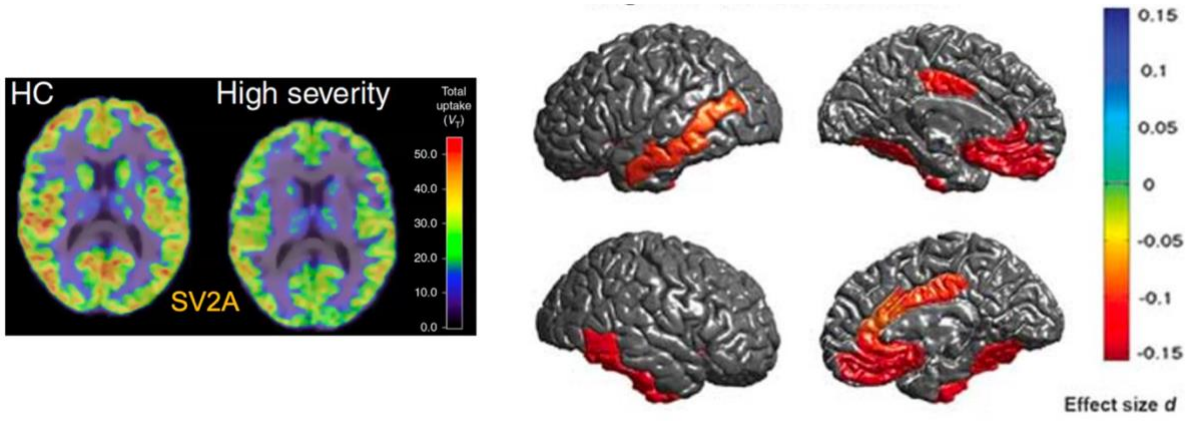


Figure 1: Left: Reduced synaptic density in severe Major Depressive Disorder (MDD) compared to healthy controls (HC). The image illustrates a decrease in synaptic vesicle glycoprotein 2A (SV2A) density, an indirect index of synaptic density (Holmes et al., 2019). Right: Cortical thickness reductions in MDD patients versus HC (Schmaal et al., 2016).

A framework is thus emerging around the idea that psychedelics may rectify these alterations by inducing a heightened state of plasticity which provides a window of opportunity for therapeutical intervention with enduring efficacy (Aleksandrova & Phillips, 2021; Castrén & Antila, 2017; Kavalali & Monteggia, 2020a). It must be noted, however, that psychedelics are not the only plasticity-enhancing pharmacological agents, nor is a heightened state of plasticity an inherently good thing. For example, plasticity within reward circuity has been identified as a mechanism of addiction to compounds such as cocaine (Rossi et al., 2023; Thomas et al., 2008). Currently prescribed antidepressants, like selective-reuptake inhibitors (SSRIs), have also been demonstrated to gradually induce neuroplasticity, which has been shown to correlate with their gradual antidepressant effects (Castrén & Antila, 2017; Tardito et al., 2006).
While numerous reviews on the evidence for plasticity enhancement exists for psychedelics (Aleksandrova & Phillips, 2021; Olson, 2022; Slocum et al., 2022) and other antidepressant treatments (Yates et al., 2021), there has been limited focus on the translational value of what enhanced plasticity really means from a neurocircuitry- and cognitive-perspective. This review thus hopes to investigate where in the brain does enhanced neuroplasticity lead to beneficial effects and how can this be interpreted from a cognitive-behavioral and emotional perspective.

Psychedelics and Neuroplasticity

Ketamine

The non-classic psychedelic ketamine was one of the first compounds whose potential as a treatment for mental illness was investigated in modern trials. At the start of the new millennium, it was found that a single sub-anesthetic dose of ketamine administration resulted in significant antidepressant effects within a few hours (Berman et al., 2000). According to the most recent research, ketamine's therapeutic effects as a standalone treatment for depression and bipolar disorder peak after 24 hours and can last up to a week afterward, with a few additional doses prolonging the effects up to 4 weeks after the last treatment (Walsh et al., 2022). Ketamine is an arylcyclohexylamine, often classified as a non-classic psychedelic, with a marked dose-dependent profile of psychoactive effects, generally referred to as dissociative. In fact, at medium doses ketamine-induced dissociative effects are psychedelic-like, transitioning into anaesthesia as dosage increases. Ketamine acts primarily as an antagonist of

the N-methyl-D-aspartate receptor (NMDAR) expressed on neurons that release glutamate and γ-Aminobutyric acid (GABA). In clinical settings, ketamine is frequently given intravenously in a racemic mixture of its two enantiomers, namely S (+)- and R (-)-ketamine, though both given separately are also psychedelic, and the S (+) enantiomer -esketamine – is now licensed as a medicine. The subjective effects of ketamine are mainly linked to its glutamatergic mechanism of action in cortical regions. Like other NMDAR antagonists, ketamine binds to the intra-channel phencyclidine site of the NMDAR, sitting on the GluN2 subunit. Ketamine binding results in a decrease of the channel opening and a decrease in the amplification of the response to repeated stimulation (Mion & Villevieille, 2013). In frontocortical regions, the administration of ketamine produces an increase in glutamate release. These effects seem paradoxical considering the NMDAR antagonistic properties of the drug, and different mechanistic theories have been proposed. One of the main hypotheses proposes that at sub-anesthetic doses, ketamine preferentially blocks NMDARs expressed on inhibitory GABAergic interneurons, thus disinhibiting the glutamatergic neurons they regulate. The rise in glutamate brought on by ketamine activates postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), releasing Brain-derived neurotrophic factor (BDNF) which activates the Mammalian target of rapamycin (mTOR) via agonism to the Tropomyosin receptor kinase B (TrkB) (Figure 2). In this manner, an autoregulatory feedback loop is initiated, whereby activation of BDNF activates its own transcription via Akt/CREB or MAPK/CREB pathways (Zanos et al., 2018).

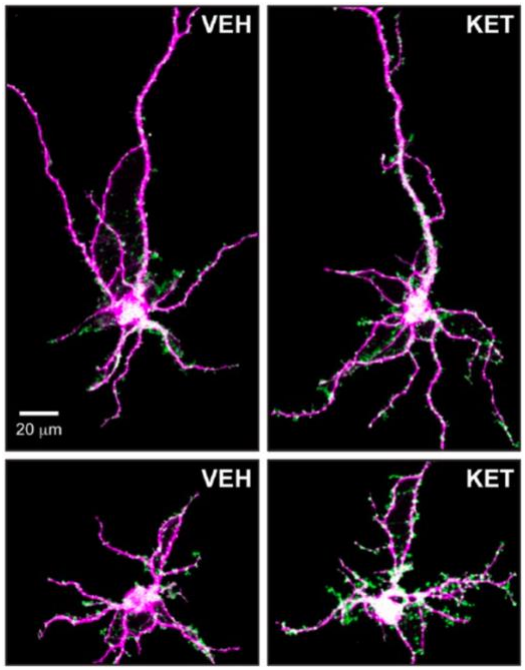


Figure 2: Mature cortical neurons in a culture treated with ketamine show an increase in synapse formation compared to vehicle. In magenta: MAP2 staining for neuronal structures. In green: synapses identified by the overlapping of markers for presynaptic and postsynaptic sites. Picture taken from Olson (2018).

Different studies have shown that rat-derived neurons exposed to medium concentrations of ketamine, corresponding to dissociative sub-anesthetic doses in humans, increased spinogenesis, dendritogenesis, dendritic arbor complexity, and soma size after 72 hours, with lowest concentrations and short periods of exposure having the highest efficacy (Cavalleri et al., 2018; Ly et al., 2018, 2020; Zhang et al., 2020). Structural modifications were found to depend on an AMPAR-BDNF-TrkB-mTOR signalling by a few studies (Cavalleri et al., 2018; Ly et al., 2018, 2020) and the phosphorylation of CRMP2, a downstream target of mTOR, by

one study (Zhang et al., 2020). Additional in-vivo studies found that ketamine increased spine density in the medial prefrontal cortex (mPFC) within 24 hours following administration, an effect associated with the emergence of an antidepressant-like response, which lasted up to 2 weeks after a single sub-anaesthetic dose (Li et al., 2010; Phoumthipphavong et al., 2016; Ruddy et al., 2015a). One of these studies (Li et al. 2010) showed that the antidepressant effects were mediated by mTOR.

Recently, dual laser two-photon glutamate uncaging and imaging was used to resolve the temporal dynamics of the ketamine-induced spinogenesis in the mPFC layer 5 pyramidal neurons. Through the implementation of a powerful set of experiments, using 2-photon imaging and optogenetics, Moda-Sava et al. (2019) established a causal role between the neuroplasticity in the mPFC and antidepressant effects elicited by ketamine. They began by demonstrating the effects of corticosterone and the repeated restraint stress model on the in-vivo reduction of spine density in the mouse's mPFC and on depressive behavior. They then showed that this was subsequently reversed by ketamine administration, which led to spine growth in the mPFC and an increase in antidepressant behavior in 3 different mouse models of depression.

They then went on to use optogenetics to selectively photoablate the ketamine-induced spines in the prefrontal cortex, which led to a significant reduction in antidepressant behavior measured by the tail-suspension test. This causal role between cortical spinogenesis and the antidepressant effects of ketamine has also been corroborated by another study using 2 photon imaging (Wu et al., 2021). This study showed that an administration of a single medium dose of ketamine to mice enhanced glutamate-evoked spinogenesis (i.e., neuron's likelihood to form new spines) 2 and 4 hours after treatment, temporally matching the emergence of ketamine's therapeutic effects. They also showed that after an uncontrollable stress paradigm the probability of glutamate evoking spinogenesis decreased relative to the baseline, with ketamine treatment restoring the baseline potential for plasticity and leading to antidepressant behavior.

However, the effects observed in models of depression were not observed in the wild-type controls. One study found no increase in spine density in the hippocampus 3 hours post-injection of a medium dose of ketamine (Widman et al., 2018). Furthermore, prolonged exposure to high anesthetic doses of ketamine, administration during development, and/or chronic administration of this drug have been found to induce neuronal degeneration and reduce neurogenesis (Brown et al., 2015; Huang et al., 2016; Ruddy et al., 2015b; Zou et al., 2009). These effects contrast the beneficial ones reported above with lower, controlled doses, and underscore caution in considering future dosing and treatment duration with this compound.

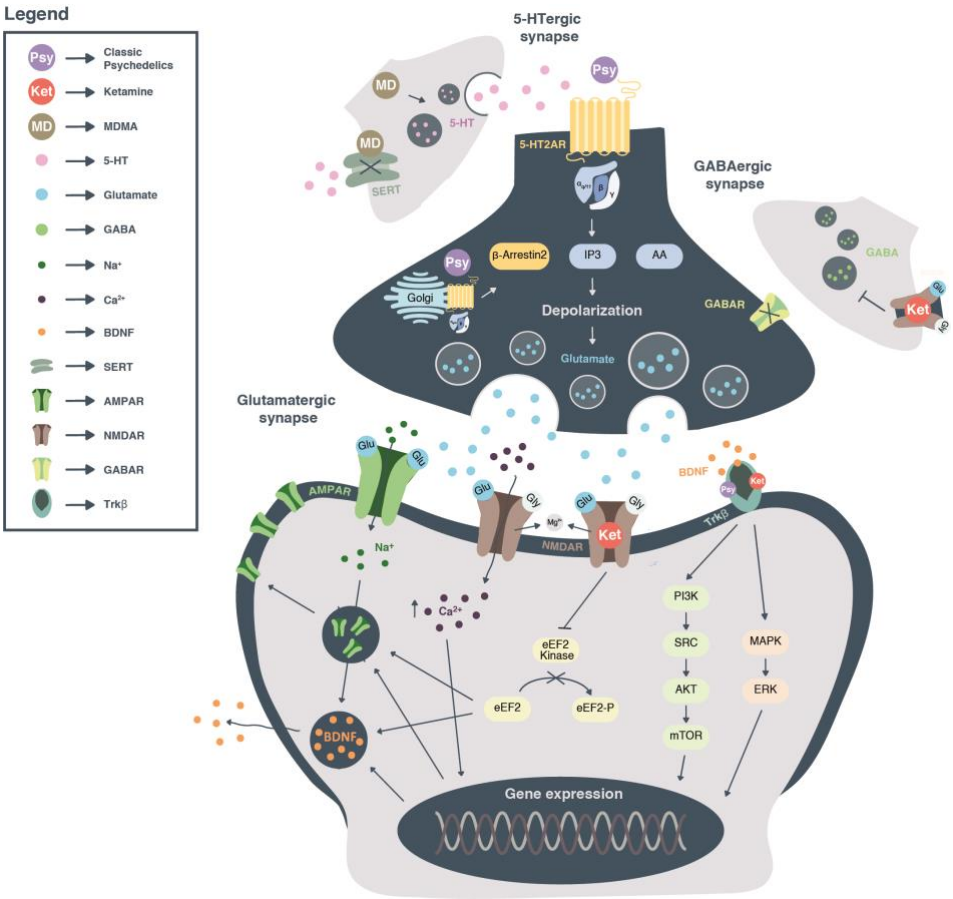


Figure 3: The acute cellular mechanism of classic psychedelics, ketamine and MDMA.

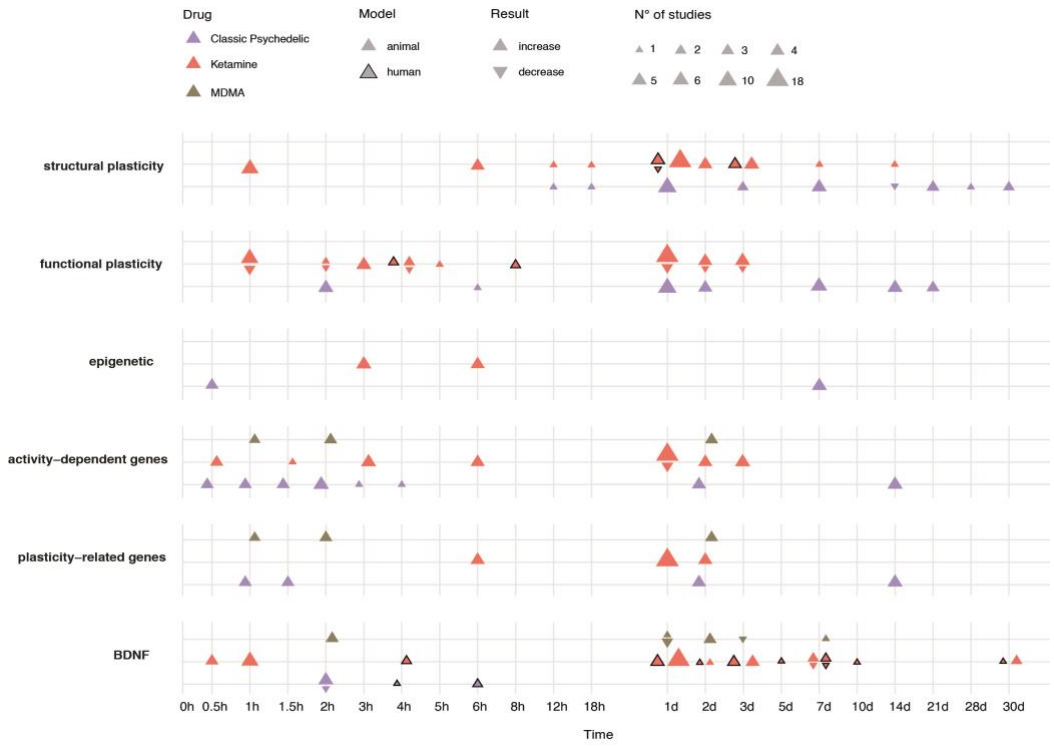


Figure 4: Post-acute neuroplastic effects of psychedelics. Only the findings relative to the neuroplastic effects induced by a single medium dose of a classic psychedelic, ketamine, or MDMA are shown.

Classic Psychedelics

Classic psychedelics have been employed for various mental health conditions, including anxiety, depression, obsessive-compulsive disorder, and substance abuse disorders (Andersen et al., 2021). Rapid and sizable effect sizes that have been maintained for follow-up durations ranging from months to years after the conclusion of therapy are remarkable aspects of these investigations.

Classic psychedelics are defined by their direct activity on the serotonin (5-HT) system, producing alteration of the perception of reality and the sense of self. Despite the pharmacological diversity within classic psychedelics, agonism of the 5-HT receptor type 2A (5-HT2AR) appears to be the primary mechanism via which these drugs' subjective effects are mediated (Nichols, 2016). The 5-HT2AR is a canonical G protein-coupled receptor and is highly conserved across species. The 5-HT2AR is densely expressed in neocortical regions involved in cognition, perception, sensorimotor gating, and mood (Ettrup et al., 2014). In particular, glutamatergic pyramidal neurons in layer V of the prefrontal cortex exhibit a high density of 5-HT2ARs in their apical dendrites, both within the membrane and inside the cell (Vargas et al., 2023). When stimulated by classic psychedelics, 5-HT2AR-expressing glutamatergic neurons initiate a glutamate cycling involving the same AMPAR-BDNF-TrkB-mTORpost-synaptic pathway described for ketamine (Aleksandrova & Phillips, 2021). However, other pathways also exist. For a detailed review see (Slocum et al., 2022).

Currently it is debated whether the activation 5-HT2AR is necessary for the neuroplasticity effects of classic psychedelics. In a recent discovery Vargas et al. (Vargas et al., 2023) showed that the ability of psychedelics to induce dendritogenesis relies on the activation of 5-HT2AR pools located intracellularly rather than on membrane surface. They showed that while molecules that permeate the neuronal plasma membranes such as N,N-DMT and psilocin promote dendritogenesis, their impermeable chemical analogues as well as serotonin (5-HT), can only promote plasticity if experimentally allowed to enter the cell. Also, activation of transmembrane 5-HT2AR alone was found to be not sufficient to induce structural plasticity, but activation of intracellular 5-HTAR was required. The finding was recently confirmed by a computational model of various 5-HT2AR agonists (Palmisano et al., 2024). Vargas et al. also showed that a mice model with ectopic post-synaptic expression of SERT in the medial PFC of mice, allowing 5-HT to access and activate intracellular 5-HT2ARs, have increased spine density and antidepressant-like effects 24 hours after pharmacological stimulation of 5-HT release (Vargas et al., 2023).

Another recent study showed that psychedelics can promote structural neuroplasticity via a 5-HT2AR-independent mechanism. Moliner et al., (2023) observed that rodent-derived cortical neurons treated with equally low concentrations of LSD and psilocin showed increases in dendritic arbor complexity and spinogenesis at 24 hours that were mediated by TrkB expression. The effect persisted after the blockage of 5-HT2ARs. The study suggests a novel mechanism of action of antidepressants, such as classic psychedelics, ketamine, and SSRIs, whereby the allosteric binding to TrkB would promote the dimerization of the receptor and localization near raft-like synaptic cellular membranes, increasing TrkB sensitivity to BDNF binding (i.e., structural meta-plasticity, see Box 1). In this study, psychedelics showed a higher affinity for allosteric binding to TrkB than did SSRIs, potentially accounting for the higher efficacy of the former in inducing neuroplasticity with the proposed mechanism (Moliner et al., 2023).

Using 2-photon imaging, Shao et al. (2021) showed that psilocybin significantly increased spine density and head-width in rats' mPFC, an effect that lasted up to a month from a single-dose injection (Figure. 4). In accordance to what has been found by Moliner et al. (2023), the observed neuroplastic effects were not blocked by partial blockage of the 5-HT2AR (Shao et al., 2021b).
Using Golgi-Cox staining, Ly et al. (2018) were also able to show the impact of classic psychedelics on increased neuritogenesis, spinogenesis, and synaptogenesis in the mPFC of rats (Figure. 4).

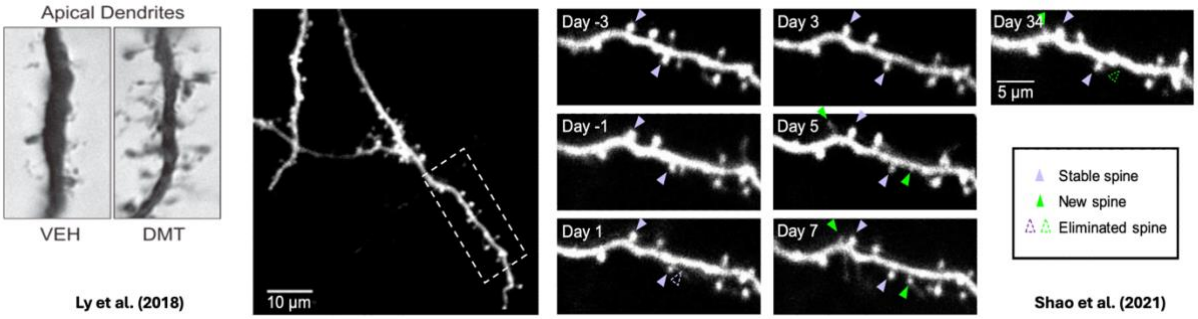
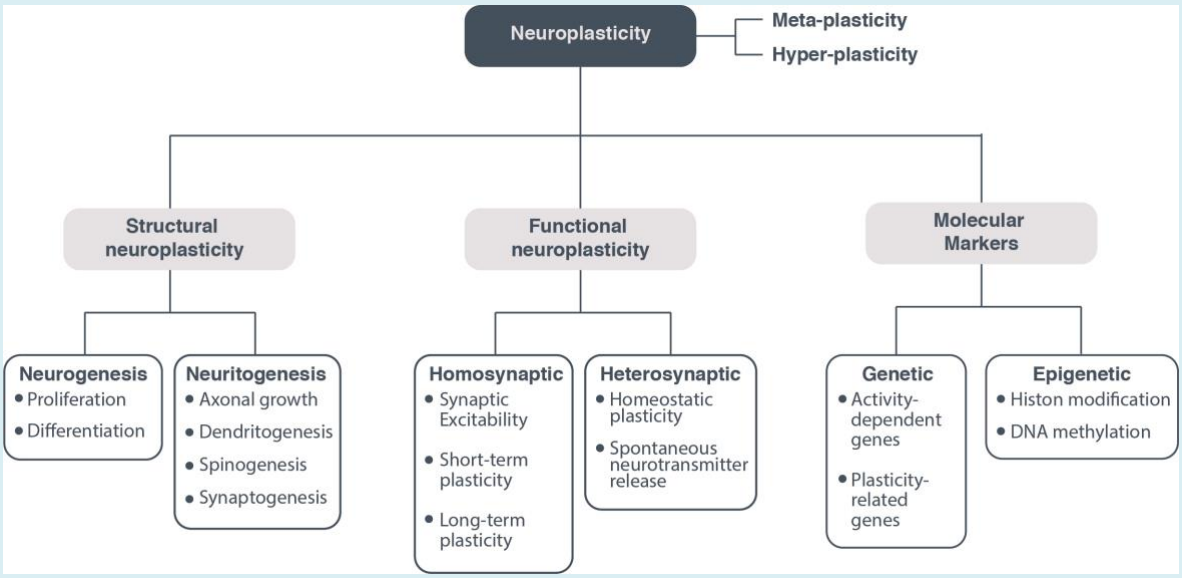


Figure 5: Images from two studies investigating the effect of classic psychedelics on spine density. On the left, the resulst from Ly et al. (2018) showing the effects of DMT vs Vehicle (Golgi-Cox staining) on the spinogenesis of PFC's pyramidal neurons. On the right, the results from Shao et al. 2021 showing the effects of psylocybin on PFC's pyramidal neuron's spine density (using 2-photon imaging) several days after single-dose injection.

Moreover, in the learned helplessness rat model of depression, Shao et al. (2021) found that psylocybin led to a reduction in the number of escape failures, an indicator of antidepressant behavior in mice.

Box 1: **What do we mean for Neuroplasticity?**

Neuroplasticity can be categorized into different types based on whether it entails altering the brain's structure, function, or underlying molecular and genetical mechanisms.



1. Structural Neuroplasticity

Structural neuroplasticity entails the morphological remodeling of the brain. This includes *neurogenesis* **(**the formation of new neurons), *neuritogenesis* **(**the formation of new dendrites (*dendritogenesis*), spines (*spinogenesis*), or axonal elongations) and *synaptogenesis* (the formation of new synapses between neurons). Structural neuroplasticity also involves neuronal apoptosis (cell death) and synaptic pruning, both essential for eliminating unnecessary neurons and synapses (Bernardinelli et al., 2014; Götz & Huttner, 2005). Importantly, pharmacological interventions can either enhance structural changes (referred to as *hyper-plasticity*) or modulate the thresholds of neurons to undergo structural plasticity (known as *meta-plasticity*) (Abraham & Bear, 1996; Nardou et al., 2023).

2. Functional Neuroplasticity

Functional neuroplasticity refers to changes in the efficiency of neural communication. It can be categorized into activity-dependent and activity-independent forms of plasticity. *Activity-dependent plasticity* (or homosynaptic plasticity) occurs when synaptic changes are driven by direct neuronal activity (i.e., 'Hebbian plasticity'). This includes *short-term plasticity*, where synaptic efficacy changes rapidly over milliseconds to minutes (Zucker & Regehr, 2002), and *long-term plasticity*, where synaptic efficacy changes in the timeframe of minutes to hours and underlie learning and memory. Examples of this type include processes such as *long-term potentiation (LTP)* and *long-term depression (LTD*) (Citri & Malenka, 2008). Activity-independent plasticity (or heterosynaptic plasticity) involves mechanisms such as *homeostatic plasticity* and *spontaneous neurotransmitter release*. Homeostatic plasticity refers to the ability of neurons to adjust synaptic or intrinsic excitability via a negative feedback loop to keep firing rates relatively constant within a network (Kavalali & Monteggia, 2020b).

3. Genetic and Molecular Markers

Neuroplasticity is closely linked to changes at the molecular level, including modifications in gene expression. *Activity-dependent genes* are the immediate-early genes such as Arc and c-Fos, which are activated quickly after neuronal stimulation (Lanahan & Worley, 1998). *Plasticity-related genes* encode proteins required for the functional and structural remodelling of neurons, these include BDNF, ERKs, and post-synaptic density proteins (Ehrlich & Josselyn, 2016). Moreover, *epigenetic modifications*, such as histone acetylation and DNA methylation, regulate gene accessibility and are critical for enabling neuroplasticity (Broide et al., 2007; Geng et al., 2021).

Other Antidepressant treatments and Neuroplasticity

Neuroplasticity seems to be a common thread not only among psychedelics, but also among other treatments for psychiatric disorders.

For example, SSRIs' delayed antidepressant effects have been associated with a gradual increase in brain-derived neurotrophic factor (BDNF) expression, both through the mTOR pathway described above for ketamine and classic psychedelics (Duman et al., 2016), as well as through the cyclic-AMP response element-binding protein (CREB) pathway (Nibuya et al., 1995; Tardito et al., 2006).

Moreover, a recent study (Casarotto et al., 2021) provided direct evidence of the link between SSRIs and neuroplasticity. The study demonstrated that the SSRI fluoxetine binds directly to the TrkB receptor, enhancing BDNF signaling through positive allosteric modulation. Behaviorally, BDNF-TRKB signaling elicited by fluoxetine reduced immobility in the forced swimming test, facilitated long-term memory in object location memory test and promoted extinction of conditioned fear in a BDNF-dependent manner. At the same time, BDNF-TRKB signaling failed to produce these behavioral effects in TrkB-mutant mice, indicating the importance of TRKB binding for antidepressant, fear-extinction and memory processes of SSRIs.

Although direct evidence is lacking, also psychotherapy has been associated to BDNF. Perroud et al. (2013) showed for example that intensive dialectical behavioral therapy reduced the methylation status of the BDNF gene, and this change was significantly associated with changes in depressive, impulsivity and hopelessness scores in 115 subjects affected by bordeline personality disorder. Psychotherapy has also been associated to structural grey-matter (GM) changes. As for example a significant reduction in GM volume in the bilateral amygdala has been found after cognitive behavioral theapy for social anxiety disorder (Månsson et al., 2016), even after a year (Månsson et al., 2017).

Even though evidence has been mixed on this, the therapeutic effects of brain stimulation may also be related to neuroplasticity. For example non-invasive brain stimulation has been shown to increases plasticity in cultures of hippocampal neurons of rats (Vlacos et al., 2012, Lenz et al., 2015). Furthermore, Electroconvulsive Therapy (ECT) -a last resort treatment for depression- has been shown to raise BDNF serum levels, which has been proposed to be a marker for ECT treatment response in patients with MDD (Rocha et al., 2016).

Electroconvulsive shock (ECS), an animal model of ECT, has resulted in improvements in anxiety-like and depressive-like behaviors in rodents (Gao et al., 2016; Zhu et al., 2015), and has been related to increases in BDNF mRNA (Altar et al., 2003; Neyazi et al., 2018; Zhang et al., 2016).

Physical activity has also been considered an effective treatment for depression (Hwang et al., 2023; Noetel et al., 2024), and associated to an increase of several neurotrophic factors such as BDNF, glial cell line derived neurotrophic factor (GDNF) and nerve growth factor (NGF) (de Sousa Fernandes et al., 2020).

Neuroplasticity is not always beneficial

It is also notable, however, that in some brain circuits, stress and depression may lead to enhancement of neuroplasticity. For example, studies demonstrate that social defeat stress increases BDNF in the ventral tegmental area-nucleus accumbens (VTA-NAc) pathway[1], and infusion of BDNF in this pathway led to a depression-like phenotype in mice (Eisch et al., 2003; Wook Koo et al., 2016).

[1] ECT has shown to cause a robust reduction in VTA BDNF levels and this reduction was essential for its antidepressant effects on rats (Taliaz et al., 2013).

In humans, a recent neuroimaging study involving 187 participants - scanned repeatedly (up to 62 times) over 1.5 years - consistently found that depression was associated with a two-fold expansion of the Salience/Frontostriatal Network, which included the Nac (Lynch et al., 2024).

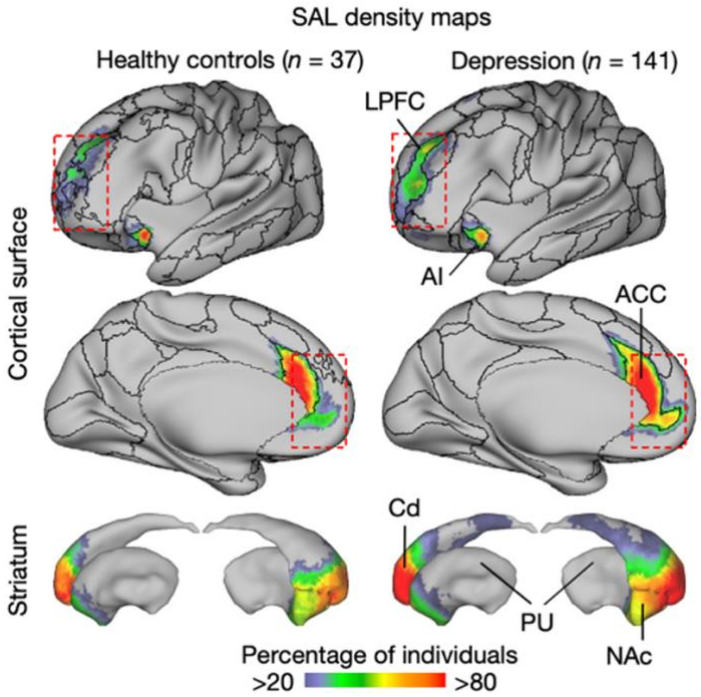


Figure 6: Frontostriatal salience network expansion in individuals in depression. Picture taken from Lynch et al. (2024)

Similarly, in the case of addiction, increased neuroplasticity within the mesolimbic reward pathway (particularly in the VTA and Nac, as seen also in depression) has been shown to underlie addiction to compounds such as cocaine (Kauer & Malenka, 2007).
Hence, given the complexity and duality of neuroplasticity, two key research questions emerge:

1) *Where in the brain does plasticity lead to therapeutic changes?*
2) *How do these plasticity changes contribute to cognitive and emotional well-being?*

The following two chapters will try to answer to these important questions.

1. Where in the brain does plasticity lead to therapeutic changes?

Understanding where neuroplasticity occurs in the brain to produce therapeutic changes in disorders like depression remains largely underexplored. We will therefore present an overview of neuroimaging and neuroanatomical evidence indicating where neuroplasticity may possibly be beneficial for this disorder.

An interesting theory posits that cognitive biases in depression arise from maladaptive bottom-up processes, which are perpetuated by a reduced top-down capacity to engage in cognitive control of maladaptive thoughts (Disner et al., 2011). This has been proposed based on evidence suggesting that an overactivation of limbic structures—such as the amygdala, anterior insula, and hippocampus— suppresses the distribution of blood flow in regions that are ‘higher up’ along the cognitive hierarchy, such as the prefrontal cortex (PFC) (Arnsten, 2009; Drevets & Raichle, 1998). In particular in the dorsolateral prefrontal cortex (DLPFC),

ventromedial prefrontal cortex (VMPFC) and orbitofrontal cortex (OFC), which typically exert top-down control (through the anterior cingulate cortex (Drevets et al., 2008; Mayberg, 2009) over the limbic regions to regulate emotions. This dysregulation results in impaired emotional regulation, a hallmark of major depressive disorder (MDD) (Drevets, 2000). Structural and functional connections between these regions have been explored extensively. Petrides and Pandya (1999), for instance, demonstrated that the DLPFC is structurally connected to the OFC and VMPFC, which, in turn, connects to subcortical regions such as the amygdala, insula, and hippocampus (Ghashghaei & Barbas, 2002). These pathways, particularly the VMPFC-amygdala connections, have been shown to mediate inhibitory control over emotional responses (Delgado et al., 2008; Milad & Quirk, 2002; Ochsner & Gross, 2005); individuals with lesions in the vmPFC, for example, display increased activation in the right amygdala when exposed to aversive pictures compared to healthy subjects (Motzkin et al., 2015).

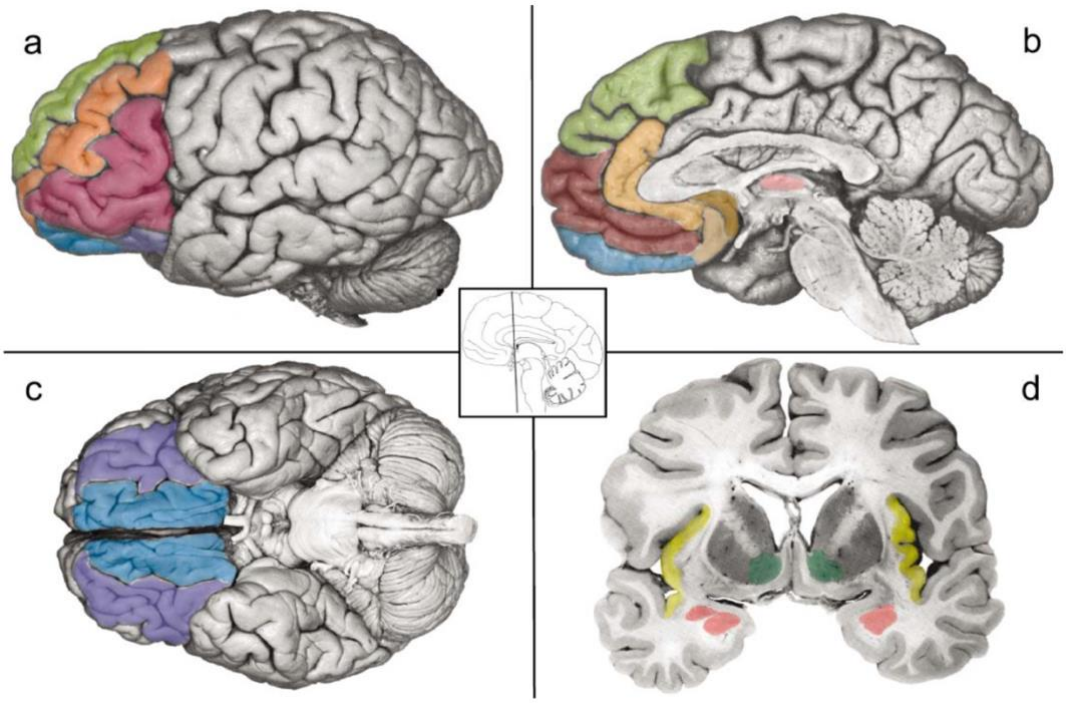


Figure 7: The fronto-limbic network. This network includes two closely connected systems, one responsible for generating the experience of emotion and one for regulating of the emotional experience; both are anchored together by the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC). The OFC (shown in a, b and c in blue and purple) and the VMPFC, in maroon (b), are therefore connected to the anterior insula (d, yellow), subgenual anterior cingulate cortex (b, peach) and amygdala (d, rose), which together form the subcortical system of emotion response. The OFC and VMPFC are also connected to the dorsomedial prefrontal cortex (a, b, green), the ventrolateral prefrontal cortex (VLPFC), shown in red (a), and the dorsolateral prefrontal cortex (a, orange), which together form the prefrontal system involved in the reappraisal of emotions. Picture taken from (Barrett et al., 2007).

However, despite strong theoretical backing, neuroimaging meta-analyses have found to be inconsistent in the detection of one pattern of activation linked to depression (Müller et al., 2017). These inconsistencies suggest that there may not be a single pattern of neural activity underlying depression. Instead, heterogeneous neurocircuitry patterns could be involved, with different brain circuits underlying different depressive symptoms (Tozzi et al., 2024).
In addition to the fronto-limbic network (Figure 6), the default mode network (DMN) is another circuit that has gained attention for its role in depression. A network typically

engaged during rest and self-referential thinking, hyperconnectivity within the DMN has been linked to rumination (Kaiser et al., 2015; Whitfield-Gabrieli & Ford, 2012).
Hypoconnectivity within the cognitive control network (CCN) has also been proposed to underlie the diminished cognitive control and emotion regulation observed in depressed individuals (Kaiser et al., 2015). For a more detailed overview of the networks involved depending on symptomathology see (Tozzi et al., 2024; Williams, 2016).

Given the inconsistent results of neuroimaging studies of depression, and a generally low test-retest reliability of both task and resting-state fMRI measures (Elliott et al., 2020; Noble et al., 2019), a shift in research focus may be necessary. Emerging evidence suggests that moment-to-moment fluctuations in brain activity, often measured as brain signal variability, could represent an interesting paradigm shift. Studies have shown that moment-to-moment changes in brain signal variability have been effective in predicting remission after psychotherapy (Månsson et al., 2022), and it has been linked to better cognitive performance (Garrett et al., 2013). Additionally, there is growing interest in using within-subject longitudinal designs (Lynch et al., 2024), where brain activity is measured repeatedly in individuals over time, rather than focusing solely on group-level comparisons.

2. How do these plasticity changes contribute to cognitive and emotional well-being?

Since it is hard to pinpoint where in the brain do neuroplasticity-increases lead to mental well-being, it is also hard to figure out what effect this has on cognition and behavior.
However, neuroplasticity is the process of forming new synaptic connections, increasing the complexity of neuronal dendrites and generating new neurons. This in turn can be conceptualized as the brain's process of forming new thought patterns and ways of thinking. Cognitively, this can be understood as an increase in flexibility.
Psychological flexibility (or cognitive flexibility) is often classified as an executive function (Poldrack et al., 2011), especially belonging to the subgroup of "mental set-shifting" (or just shifting), which can be broadly conceptualized as switching between different cognitive frameworks depending on the demands of the environment (Scott, 1962).
Psychological Flexibility has been associated as a core feature of mental health (Kashdan, 2010), especially given the evidence that many psychopathologies are characterized by psychological inflexibility or rigidity.
Rumination, for example, a key vulnerability factor for depression (Nolen-Hoeksema et al., 2008), involves repetitive dysfunctional thinking, looping through automatic negative thoughts that create a vicious cycle of cognitive rigidity. Studies have also found that depressed individuals have a bias towards negatively valenced stimuli (Gotlib et al., 2004; Peckham et al., 2010) and eye-tracking technologies have shown that depression is linked to a reduced orientation towards positive stimuli (Armstrong & Olatunji, 2012).
These attentional biases can also be understood as a form of cognitive inflexibility.

Anxiety disorders, phobias and trauma-related disorders are often characterized by experiential avoidance, or, in other words, the unwillingness to live through certain aspects of experience (Hayes et al 1999). The avoidance response then becomes a default way of coping with these experiences, maintaining the disorder over time and contributing to psychological inflexibility.

Similarly, in obsessive-compulsive disorder (OCD), intrusive thoughts are linked to compulsions and rituals that need to be performed to reduce anxiety. These behaviors create a rigid thought-behavior loop, making it difficult for individuals to break free from their compulsive actions.

Exposure psychotherapy challenges the avoidance and thought-behavior loops in these disorders by gradually and systematically exposing individuals to feared stimuli or situations, helping them confront and tolerate distress without resorting to avoidance or compulsions. By encouraging individuals to face their fears, they learn that the distress they experience is manageable and often diminishes over time. It might be argued that this therapy fosters psychological flexibility, as the person gains the ability to interpret and approach certain stimuli in a different and more flexible way, rather than avoidance and fear.

Cognitive-behavioral theories of mood and anxiety disorders posit that they are characterized by distorted core beliefs that people have about themselves, the world or the future. These core beliefs are often absolute, rigid, forming the foundation of the person's worldview. These core beliefs typically revolve around themes such as feelings of worthlessness, unlovability and failure. Core beliefs strongly shape automatic thoughts and how the person interprets the events around him and her. Our view is that neuroplasticity might provide a fertile ground for these core beliefs to be modified and challenged, but only if applied in a context that can steer neuroplasticity towards the neurocircuitries that can facilitate psychological flexibility.

Research on psychedelics is starting to show a link between psychological flexibility and psychedelics (Davis et al., 2020; Doss et al., 2021; Sloshower et al., 2024). This connection may be rooted on corroborated evidence that psychedelics reduce within-network connectivity of common brain networks while enhancing between-network connectivity, arguably making brain behave more flexbily (Daws et al., 2022; Girn et al., 2022; Roseman et al., 2014; Tagliazucchi et al., 2016; Timmermann et al., 2023).
As proposed earlier, brain signal variability may serve as an interesting avenue for future neuroimaging studies on psychopathologies. Research has shown that brain variability increases during task performance compared to rest in younger, faster-performing adults, whereas older and slower-performing adults demonstrate less brain variability overall compared to younger adults (Garrett et al., 2013). Higher variability might reflect a wider range of brain states and transitions between them, allowing for more flexible and optimal responses (McIntosh et al., 2008). This, in turn, might be conceptualized as a flexible transition between typically connected brain networks to a more dynamic state, not bound by rigid patterns of connectivity, as observed when under psychedelic treatment.
In conclusion, a possible hypothesis worth investigating that integrates the evidence reported in this essay might follow the following line of thought: increased neuroplasticity, potentially facilitated by psychedelics, may lead to greater neural proliferation and a more diverse array of connectivity patterns. This expansion in connectivity could be reflected in heightened brain signal variability, which may support increased psychological flexibility and improved mental well-being.

CONCLUSION

To conclude, psychiatry is undergoing significant advancements, with growing evidence positioning psychedelics as promising treatment for several disorders. Beyond their fast antidepressant action, both ketamine and classic psychedelics induce significant structural

plasticity in the brain. This led to a growing interest in the role of neuroplasticity, not only in the development of psychiatric disorders but also in their treatment. Both psychedelics and SSRIs seem to share a common AMPAR-BDNF-TrkB-mTOR molecular pathway (or an even more direct allosteric binding to TrkB-BDNF signaling) that underlies the neuroplastic effects of these compounds. Interestingly, the literature at the moment has mostly shown that these compounds stimulate spinogenesis and dendritogenesis in the rondents' medial prefrontal cortex and, in some studies, in rondents'hippocampus (Lin et al., 2021; Raval et al., 2021; Xu et al., 2020), both regions strongly implicated in depression.

While there seems to be a common thread among antidepressant treatments and neuroplasticity, some plasticity-driven increases may be maladaptive, as it has been shown for addiction and depression in the VTA-NAc pathway, emphasizing the need to identify specific neural circuits where plasticity can support therapeutic outcomes.

Unfortunately, research into which brain regions benefit from neuroplasticity to achieve antidepressant effects remains relatively underexplored, while the study of neuroimaging and neuroanatomy underlying depressive symptoms has been extensively investigated. For example, several networks have been proposed to be involved in the persistence of depression, these include a Fronto-Limbic Network, the Default Mode Network and the Cognitive Control one (among others). Hence, a modulation of neuroplasticity in these regions may provide therapeutic outcomes. Despite this, fMRI has struggled consistently to pinpoint a single pattern of brain activity associated with depression, leading to the suggestion that future studies should shift focus from average BOLD responses to the variability of these responses across time. Given inconsistencies in the proposal of a single region or network that might benefit from therapeutic neuroplasticity, we propose a broader cognitive model of neuroplasticity centered on psychological flexibility. Flexibility has been proposed as a hallmark of mental well-being, based on evidence that many psychopathologies are characterized by rigidity of thought. In conclusion, we integrate the reported information by proposing a potential line of research combining psychedelics, fMRI brain signal variability and assessments of psychological flexibility. This approach could offer deeper insights into how psychedelics influence brain dynamics, and explore the potential of brain signal variability as a biomarker of psychological flexibility and therapeutic neuroplasticity.

5524 words

BIBLIOGRAPHY

Abraham, W. C., & Bear, M. F. (1996). Metaplasticity: The plasticity of synaptic plasticity. *Trends in Neurosciences*, *19*(4), 126–130. https://doi.org/10.1016/S0166-2236(96)80018-X

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

Andersen, K. A. A., Carhart-Harris, R., Nutt, D. J., & Erritzoe, D. (2021). Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatrica Scandinavica*, *143*(2), 101–118. https://doi.org/10.1111/acps.13249

Armstrong, T., & Olatunji, B. O. (2012). Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. *Clinical Psychology Review*, *32*(8), 704–723. https://doi.org/10.1016/j.cpr.2012.09.004

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*(6), 410–422. https://doi.org/10.1038/nrn2648

Barrett, L. F., Mesquita, B., Ochsner, K. N., & Gross, J. J. (2007). The experience of emotion. *Annual Review of Psychology*, *58*, 373–403. https://doi.org/10.1146/annurev.psych.58.110405.085709

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*, *47*(4), 351–354. https://doi.org/10.1016/S0006-3223(99)00230-9

Bernardinelli, Y., Muller, D., & Nikonenko, I. (2014). Astrocyte-Synapse Structural Plasticity. *Neural Plasticity*, *2014*(1), 232105. https://doi.org/10.1155/2014/232105

Broide, R. S., Redwine, J. M., Aftahi, N., Young, W., Bloom, F. E., & Winrow, C. J. (2007). Distribution of histone deacetylases 1-11 in the rat brain. *Journal of Molecular Neuroscience: MN*, *31*(1), 47–58. https://doi.org/10.1007/BF02686117

Brown, B. P., Kang, S. C., Gawelek, K., Zacharias, R. A., Anderson, S. R., Turner, C. P., & Morris, J. K. (2015). In vivo and in vitro ketamine exposure exhibits a dose-dependent induction of activity-dependent neuroprotective protein in rat neurons. *Neuroscience*, *290*, 31–40. https://doi.org/10.1016/j.neuroscience.2014.12.076

Casarotto, P. C., Girych, M., Fred, S. M., Kovaleva, V., Moliner, R., Enkavi, G., Biojone, C., Cannarozzo, C., Sahu, M. P., Kaurinkoski, K., Brunello, C. A., Steinzeig, A., Winkel, F., Patil, S., Vestring, S., Serchov, T., Diniz, C. R. A. F., Laukkanen, L., Cardon, I., … Castrén, E. (2021). Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. *Cell*, *184*(5), 1299-1313.e19. https://doi.org/10.1016/j.cell.2021.01.034

Castrén, E., & Antila, H. (2017). Neuronal plasticity and neurotrophic factors in drug responses. *Molecular Psychiatry*, *22*(8), Article 8. https://doi.org/10.1038/mp.2017.61

Cavalleri, L., Merlo Pich, E., Millan, M. J., Chiamulera, C., Kunath, T., Spano, P. F., & Collo, G. (2018). Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. *Molecular Psychiatry*, *23*(4), 812–823. https://doi.org/10.1038/mp.2017.241

Citri, A., & Malenka, R. C. (2008). Synaptic Plasticity: Multiple Forms, Functions, and Mechanisms. *Neuropsychopharmacology*, *33*(1), 18–41. https://doi.org/10.1038/sj.npp.1301559

Davis, A. K., Barrett, F. S., & Griffiths, R. R. (2020). Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *Journal of Contextual Behavioral Science*, *15*, 39–45. https://doi.org/10.1016/j.jcbs.2019.11.004

Daws, R. E., Timmermann, C., Giribaldi, B., Sexton, J. D., Wall, M. B., Erritzoe, D., Roseman, L., Nutt, D., & Carhart-Harris, R. (2022). Increased global integration in the brain after psilocybin therapy for depression. *Nature Medicine*, *28*(4), 844–851. https://doi.org/10.1038/s41591-022-01744-z

de Sousa Fernandes, M. S., Ordônio, T. F., Santos, G. C. J., Santos, L. E. R., Calazans, C. T., Gomes, D. A., & Santos, T. M. (2020). Effects of Physical Exercise on Neuroplasticity and Brain Function: A Systematic Review in Human and Animal Studies. *Neural Plasticity*, *2020*, 8856621. https://doi.org/10.1155/2020/8856621

Delgado, M. R., Nearing, K. I., LeDoux, J. E., & Phelps, E. A. (2008). Neural Circuitry Underlying the Regulation of Conditioned Fear and Its Relation to Extinction. *Neuron*, *59*(5), 829–838. https://doi.org/10.1016/j.neuron.2008.06.029

Disner, S. G., Beevers, C. G., Haigh, E. A. P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, *12*(8), 467–477. https://doi.org/10.1038/nrn3027

Doss, M. K., Považan, M., Rosenberg, M. D., Sepeda, N. D., Davis, A. K., Finan, P. H., Smith, G. S., Pekar, J. J., Barker, P. B., Griffiths, R. R., & Barrett, F. S. (2021). Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. *Translational Psychiatry*, *11*(1), Article 1. https://doi.org/10.1038/s41398-021-01706-y

Drevets, W. C. (2000). Neuroimaging studies of mood disorders. *Biological Psychiatry*, *48*(8), 813–829. https://doi.org/10.1016/s0006-3223(00)01020-9

Drevets, W. C., & Raichle, M. E. (1998). Suppression of Regional Cerebral Blood during Emotional versus Higher Cognitive Implications for Interactions between Emotion and Cognition. *Cognition and Emotion*, *12*(3), 353–385. https://doi.org/10.1080/026999398379646

Drevets, W. C., Savitz, J., & Trimble, M. (2008). The Subgenual Anterior Cingulate Cortex in Mood Disorders. *CNS Spectrums*, *13*(8), 663–681.

Duman, R. S., & Aghajanian, G. K. (2012). Synaptic dysfunction in depression: Potential therapeutic targets. *Science (New York, N.Y.)*, *338*(6103), 68–72. https://doi.org/10.1126/science.1222939

Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. *Nature Medicine*, *22*(3), 238–249. https://doi.org/10.1038/nm.4050

Duman, R. S., & Monteggia, L. M. (2006). A Neurotrophic Model for Stress-Related Mood Disorders. *Biological Psychiatry*, *59*(12), 1116–1127. https://doi.org/10.1016/j.biopsych.2006.02.013

Ehrlich, D. E., & Josselyn, S. A. (2016). Plasticity-related genes in brain development and amygdala-dependent learning. *Genes, Brain, and Behavior*, *15*(1), 125–143. https://doi.org/10.1111/gbb.12255

Eisch, A. J., Bolaños, C. A., de Wit, J., Simonak, R. D., Pudiak, C. M., Barrot, M., Verhaagen, J., & Nestler, E. J. (2003). Brain-derived neurotrophic factor in the ventral midbrain-nucleus accumbens pathway: A role in depression. *Biological Psychiatry*, *54*(10), 994–1005. https://doi.org/10.1016/j.biopsych.2003.08.003

Elliott, M. L., Knodt, A. R., Ireland, D., Morris, M. L., Poulton, R., Ramrakha, S., Sison, M. L., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2020). What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence

and a Meta-Analysis. *Psychological Science*. https://doi.org/10.1177/0956797620916786

Ettrup, A., da Cunha-Bang, S., McMahon, B., Lehel, S., Dyssegaard, A., Skibsted, A. W., Jørgensen, L. M., Hansen, M., Baandrup, A. O., Bache, S., Svarer, C., Kristensen, J. L., Gillings, N., Madsen, J., & Knudsen, G. M. (2014). Serotonin 2A receptor agonist binding in the human brain with [11C]Cimbi-36. *Journal of Cerebral Blood Flow & Metabolism*, *34*(7), 1188–1196. https://doi.org/10.1038/jcbfm.2014.68

Garcia-Romeu, A., Kersgaard, B., & Addy, P. H. (2016). Clinical Applications of Hallucinogens: A Review. *Experimental and Clinical Psychopharmacology*, *24*(4), 229–268. https://doi.org/10.1037/pha0000084

Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2013). The modulation of BOLD variability between cognitive states varies by age and processing speed. *Cerebral Cortex (New York, N.Y.: 1991)*, *23*(3), 684–693. https://doi.org/10.1093/cercor/bhs055

Geng, H., Chen, H., Wang, H., & Wang, L. (2021). The Histone Modifications of Neuronal Plasticity. *Neural Plasticity*, *2021*(1), 6690523. https://doi.org/10.1155/2021/6690523

Girn, M., Roseman, L., Bernhardt, B., Smallwood, J., Carhart-Harris, R., & Nathan Spreng, R. (2022). Serotonergic psychedelic drugs LSD and psilocybin reduce the hierarchical differentiation of unimodal and transmodal cortex. *NeuroImage*, *256*, 119220. https://doi.org/10.1016/j.neuroimage.2022.119220

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology*, *113*(1), 121–135. https://doi.org/10.1037/0021-843X.113.1.121

Götz, M., & Huttner, W. B. (2005). The cell biology of neurogenesis. *Nature Reviews Molecular Cell Biology*, *6*(10), 777–788. https://doi.org/10.1038/nrm1739

Holmes, S. E., Scheinost, D., Finnema, S. J., Naganawa, M., Davis, M. T., DellaGioia, N., Nabulsi, N., Matuskey, D., Angarita, G. A., Pietrzak, R. H., Duman, R. S., Sanacora, G., Krystal, J. H., Carson, R. E., & Esterlis, I. (2019). Lower synaptic density is associated with depression severity and network alterations. *Nature Communications*, *10*(1), 1529. https://doi.org/10.1038/s41467-019-09562-7

Huang, H., Liu, C.-M., Sun, J., Hao, T., Xu, C.-M., Wang, D., & Wu, Y.-Q. (2016). Ketamine Affects the Neurogenesis of the Hippocampal Dentate Gyrus in 7-Day-Old Rats. *Neurotoxicity Research*, *30*(2), 185–198. https://doi.org/10.1007/s12640-016-9615-7

Hwang, D.-J., Koo, J.-H., Kim, T.-K., Jang, Y.-C., Hyun, A.-H., Yook, J.-S., Yoon, C.-S., & Cho, J.-Y. (2023). Exercise as an antidepressant: Exploring its therapeutic potential. *Frontiers in Psychiatry*, *14*, 1259711. https://doi.org/10.3389/fpsyt.2023.1259711

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry*, *72*(6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Kashdan, T. B. (2010). Psychological Flexibility as a Fundamental Aspect of Health. *Clinical Psychology Review*, *30*(7), 865–878. https://doi.org/10.1016/j.cpr.2010.03.001

Kauer, J. A., & Malenka, R. C. (2007). Synaptic plasticity and addiction. *Nature Reviews Neuroscience*, *8*(11), 844–858. https://doi.org/10.1038/nrn2234

Kavalali, E. T., & Monteggia, L. M. (2020a). Targeting Homeostatic Synaptic Plasticity for Treatment of Mood Disorders. *Neuron*, *106*(5), 715–726. https://doi.org/10.1016/j.neuron.2020.05.015

Kavalali, E. T., & Monteggia, L. M. (2020b). Targeting Homeostatic Synaptic Plasticity for Treatment of Mood Disorders. *Neuron*, *106*(5), 715–726. https://doi.org/10.1016/j.neuron.2020.05.015

Lanahan, A., & Worley, P. (1998). Immediate-early genes and synaptic function. *Neurobiology of Learning and Memory*, *70*(1–2), 37–43. https://doi.org/10.1006/nlme.1998.3836

Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J. M., Iwata, M., Li, X.-Y., Aghajanian, G., & Duman, R. S. (2010). mTOR-Dependent Synapse Formation Underlies the Rapid Antidepressant Effects of NMDA Antagonists. *Science*, *329*(5994), 959–964. https://doi.org/10.1126/science.1190287

Lin, P.-Y., Ma, Z. Z., Mahgoub, M., Kavalali, E. T., & Monteggia, L. M. (2021). A synaptic locus for TrkB signaling underlying ketamine rapid antidepressant action. *Cell Reports*, *36*(7). https://doi.org/10.1016/j.celrep.2021.109513

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Zarandi, S. S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports*, *23*(11), 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022

Ly, C., Greb, A. C., Vargas, M. V., Duim, W. C., Grodzki, A. C. G., Lein, P. J., & Olson, D. E. (2020). Transient Stimulation with Psychoplastogens Is Sufficient to Initiate Neuronal Growth. *ACS Pharmacology & Translational Science*, *4*(2), 452–460. https://doi.org/10.1021/acsptsci.0c00065

Lynch, C. J., Elbau, I. G., Ng, T., Ayaz, A., Zhu, S., Wolk, D., Manfredi, N., Johnson, M., Chang, M., Chou, J., Summerville, I., Ho, C., Lueckel, M., Bukhari, H., Buchanan, D., Victoria, L. W., Solomonov, N., Goldwaser, E., Moia, S., … Liston, C. (2024).

Frontostriatal salience network expansion in individuals in depression. *Nature*, *633*(8030), 624–633. https://doi.org/10.1038/s41586-024-07805-2

Manji, H. K., Moore, G. J., Rajkowska, G., & Chen, G. (2000). Neuroplasticity and cellular resilience in mood disorders. *Molecular Psychiatry*, *5*(6), Article 6. https://doi.org/10.1038/sj.mp.4000811

Månsson, K. N. T., Salami, A., Carlbring, P., Boraxbekk, C.-J., Andersson, G., & Furmark, T. (2017). Structural but not functional neuroplasticity one year after effective cognitive behaviour therapy for social anxiety disorder. *Behavioural Brain Research*, *318*, 45–51. https://doi.org/10.1016/j.bbr.2016.11.018

Månsson, K. N. T., Salami, A., Frick, A., Carlbring, P., Andersson, G., Furmark, T., & Boraxbekk, C.-J. (2016). Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder. *Translational Psychiatry*, *6*(2), e727–e727. https://doi.org/10.1038/tp.2015.218

Månsson, K. N. T., Waschke, L., Manzouri, A., Furmark, T., Fischer, H., & Garrett, D. D. (2022). Moment-to-Moment Brain Signal Variability Reliably Predicts Psychiatric Treatment Outcome. *Biological Psychiatry*, *91*(7), 658–666. https://doi.org/10.1016/j.biopsych.2021.09.026

Mayberg, H. S. (2009). Targeted electrode-based modulation of neural circuits for depression. *The Journal of Clinical Investigation*, *119*(4), 717–725. https://doi.org/10.1172/JCI38454

McClelland, J. L., & O'Reilly, R. C. (n.d.). *Why There Are Complementary Learning Systems in the Hippocampus and Neocortex:InsightsFrom the Successesand Failuresof Connectionist Models of Learning and Memory*. 39.

McIntosh, A. R., Kovacevic, N., & Itier, R. J. (2008). Increased brain signal variability accompanies lower behavioral variability in development. *PLoS Computational Biology*, *4*(7), e1000106. https://doi.org/10.1371/journal.pcbi.1000106

Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, *420*(6911), 70–74. https://doi.org/10.1038/nature01138

Mion, G., & Villevieille, T. (2013). Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). *CNS Neuroscience & Therapeutics*, *19*(6), 370–380. https://doi.org/10.1111/cns.12099

Moda-Sava, R. N., Murdock, M. H., Parekh, P. K., Fetcho, R. N., Huang, B. S., Huynh, T. N., Witztum, J., Shaver, D. C., Rosenthal, D. L., Alway, E. J., Lopez, K., Meng, Y., Nellissen, L., Grosenick, L., Milner, T. A., Deisseroth, K., Bito, H., Kasai, H., & Liston, C. (2019). Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science*, *364*(6436), eaat8078. https://doi.org/10.1126/science.aat8078

Moliner, R., Girych, M., Brunello, C. A., Kovaleva, V., Biojone, C., Enkavi, G., Antenucci, L., Kot, E. F., Goncharuk, S. A., Kaurinkoski, K., Kuutti, M., Fred, S. M., Elsilä, L. V., Sakson, S., Cannarozzo, C., Diniz, C. R. A. F., Seiffert, N., Rubiolo, A., Haapaniemi, H., … Castrén, E. (2023). Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nature Neuroscience*, *26*(6), 1032–1041. https://doi.org/10.1038/s41593-023-01316-5

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry*, *77*(3), 276–284. https://doi.org/10.1016/j.biopsych.2014.02.014

Nardou, R., Sawyer, E., Song, Y. J., Wilkinson, M., Padovan-Hernandez, Y., de Deus, J. L., Wright, N., Lama, C., Faltin, S., Goff, L. A., Stein-O'Brien, G. L., & Dölen, G. (2023). Psychedelics reopen the social reward learning critical period. *Nature*, *618*(7966), 790–798. https://doi.org/10.1038/s41586-023-06204-3

Nibuya, M., Morinobu, S., & Duman, R. S. (1995). Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *Journal of Neuroscience*, *15*(11), 7539–7547. https://doi.org/10.1523/JNEUROSCI.15-11-07539.1995

Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews*, *68*(2), 264–355. https://doi.org/10.1124/pr.115.011478

Noble, S., Scheinost, D., & Constable, R. T. (2019). A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *NeuroImage*, *203*, 116157. https://doi.org/10.1016/j.neuroimage.2019.116157

Noetel, M., Sanders, T., Gallardo-Gómez, D., Taylor, P., Cruz, B. del P., Hoek, D. van den, Smith, J. J., Mahoney, J., Spathis, J., Moresi, M., Pagano, R., Pagano, L., Vasconcellos, R., Arnott, H., Varley, B., Parker, P., Biddle, S., & Lonsdale, C. (2024). Effect of exercise for depression: Systematic review and network meta-analysis of randomised controlled trials. *BMJ*, *384*, e075847. https://doi.org/10.1136/bmj-2023-075847

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking Rumination. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *3*(5), 400–424. https://doi.org/10.1111/j.1745-6924.2008.00088.x

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences*, *9*(5), 242–249. https://doi.org/10.1016/j.tics.2005.03.010

Olson, D. E. (2018). Psychoplastogens: A Promising Class of Plasticity-Promoting Neurotherapeutics. *Journal of Experimental Neuroscience*, *12*. https://doi.org/10.1177/1179069518800508

Olson, D. E. (2022). Biochemical Mechanisms Underlying Psychedelic-Induced Neuroplasticity. *Biochemistry*, *61*(3), 127–136. https://doi.org/10.1021/acs.biochem.1c00812

Ota, K. T., Liu, R.-J., Voleti, B., Maldonado-Aviles, J. G., Duric, V., Iwata, M., Dutheil, S., Duman, C., Boikess, S., Lewis, D. A., Stockmeier, C. A., DiLeone, R. J., Rex, C., Aghajanian, G. K., & Duman, R. S. (2014). REDD1 is essential for stress-induced synaptic loss and depressive behavior. *Nature Medicine*, *20*(5), 531–535. https://doi.org/10.1038/nm.3513

Palmisano, V. F., Agnorelli, C., Fagiolini, A., Erritzoe, D., Nutt, D., Faraji, S., & Nogueira, J. J. (2024). Membrane Permeation of Psychedelic Tryptamines by Dynamic Simulations. *Biochemistry*, *63*(4), 419–428. https://doi.org/10.1021/acs.biochem.3c00598

Peckham, A. D., McHugh, R. K., & Otto, M. W. (2010). A meta-analysis of the magnitude of biased attention in depression. *Depression and Anxiety*, *27*(12), 1135–1142. https://doi.org/10.1002/da.20755

Perroud, N., Salzmann, A., Prada, P., Nicastro, R., Hoeppli, M.-E., Furrer, S., Ardu, S., Krejci, I., Karege, F., & Malafosse, A. (2013). Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. *Translational Psychiatry*, *3*(1), e207–e207. https://doi.org/10.1038/tp.2012.140

Petrides, M., & Pandya, D. N. (1999). Dorsolateral prefrontal cortex: Comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical

connection patterns. *The European Journal of Neuroscience*, *11*(3), 1011–1036. https://doi.org/10.1046/j.1460-9568.1999.00518.x

Phoumthipphavong, V., Barthas, F., Hassett, S., & Kwan, A. C. (2016). Longitudinal Effects of Ketamine on Dendritic Architecture In Vivo in the Mouse Medial Frontal Cortex. *eNeuro*, *3*(2), ENEURO.0133-15.2016. https://doi.org/10.1523/ENEURO.0133-15.2016

Poldrack, R. A., Kittur, A., Kalar, D., Miller, E., Seppa, C., Gil, Y., Parker, D. S., Sabb, F. W., & Bilder, R. M. (2011). The Cognitive Atlas: Toward a Knowledge Foundation for Cognitive Neuroscience. *Frontiers in Neuroinformatics*, *5*. https://doi.org/10.3389/fninf.2011.00017

Price, R. B., & Duman, R. (2020). Neuroplasticity in cognitive and psychological mechanisms of depression: An integrative model. *Molecular Psychiatry*, *25*(3), 530–543. https://doi.org/10.1038/s41380-019-0615-x

Raval, N. R., Johansen, A., Donovan, L. L., Ros, N. F., Ozenne, B., Hansen, H. D., & Knudsen, G. M. (2021). A Single Dose of Psilocybin Increases Synaptic Density and Decreases 5-HT2A Receptor Density in the Pig Brain. *International Journal of Molecular Sciences*, *22*(2), 835. https://doi.org/10.3390/ijms22020835

Rocha, R. B., Dondossola, E. R., Grande, A. J., Colonetti, T., Ceretta, L. B., Passos, I. C., Quevedo, J., & da Rosa, M. I. (2016). Increased BDNF levels after electroconvulsive therapy in patients with major depressive disorder: A meta-analysis study. *Journal of Psychiatric Research*, *83*, 47–53. https://doi.org/10.1016/j.jpsychires.2016.08.004

Roseman, L., Leech, R., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2014). The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. *Frontiers in Human Neuroscience*, *8*, 204. https://doi.org/10.3389/fnhum.2014.00204

Rossi, R., Bærentzen, S. L., Thomsen, M. B., Real, C. C., Wegener, G., Grassi-Oliveira, R., Gjedde, A., & Landau, A. M. (2023). A single dose of cocaine raises SV2A density in hippocampus of adolescent rats. *Acta Neuropsychiatrica*, 1–9. https://doi.org/10.1017/neu.2023.14

Ruddy, R. M., Chen, Y., Milenkovic, M., & Ramsey, A. J. (2015a). Differential effects of NMDA receptor antagonism on spine density. *Synapse (New York, N.Y.)*, *69*(1), 52–56. https://doi.org/10.1002/syn.21784

Ruddy, R. M., Chen, Y., Milenkovic, M., & Ramsey, A. J. (2015b). Differential effects of NMDA receptor antagonism on spine density. *Synapse (New York, N.Y.)*, *69*(1), 52–56. https://doi.org/10.1002/syn.21784

Schmaal, L., Veltman, D. J., van Erp, T. G. M., Sämann, P. G., Frodl, T., Jahanshad, N., Loehrer, E., Tiemeier, H., Hofman, A., Niessen, W. J., Vernooij, M. W., Ikram, M. A., Wittfeld, K., Grabe, H. J., Block, A., Hegenscheid, K., Völzke, H., Hoehn, D., Czisch, M., … Hibar, D. P. (2016). Subcortical brain alterations in major depressive disorder: Findings from the ENIGMA Major Depressive Disorder working group. *Molecular Psychiatry*, *21*(6), Article 6. https://doi.org/10.1038/mp.2015.69

Scott, W. A. (1962). Cognitive Complexity and Cognitive Flexibility. *Sociometry*, *25*(4), 405–414. https://doi.org/10.2307/2785779

Shao, L.-X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021a). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. *Neuron*, *109*(16), 2535-2544.e4. https://doi.org/10.1016/j.neuron.2021.06.008

Shao, L.-X., Liao, C., Gregg, I., Davoudian, P. A., Savalia, N. K., Delagarza, K., & Kwan, A. C. (2021b). Psilocybin induces rapid and persistent growth of dendritic spines in

frontal cortex in vivo. *Neuron*, *109*(16), 2535-2544.e4. https://doi.org/10.1016/j.neuron.2021.06.008

Slocum, S. T., DiBerto, J. F., & Roth, B. L. (2022). Molecular insights into psychedelic drug action. *Journal of Neurochemistry*, *162*(1), 24–38. https://doi.org/10.1111/jnc.15540

Sloshower, J., Zeifman, R. J., Guss, J., Krause, R., Safi-Aghdam, H., Pathania, S., Pittman, B., & D'Souza, D. C. (2024). Psychological flexibility as a mechanism of change in psilocybin-assisted therapy for major depression: Results from an exploratory placebo-controlled trial. *Scientific Reports*, *14*(1), 8833. https://doi.org/10.1038/s41598-024-58318-x

Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S. D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., Bullmore, E., Williams, T., Bolstridge, M., Feilding, A., Nutt, D. J., & Carhart-Harris, R. (2016). Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. *Current Biology: CB*, *26*(8), 1043–1050. https://doi.org/10.1016/j.cub.2016.02.010

Taliaz, D., Nagaraj, V., Haramati, S., Chen, A., & Zangen, A. (2013). Altered brain-derived neurotrophic factor expression in the ventral tegmental area, but not in the hippocampus, is essential for antidepressant-like effects of electroconvulsive therapy. *Biological Psychiatry*, *74*(4), 305–312. https://doi.org/10.1016/j.biopsych.2012.07.025

Tardito, D., Perez, J., Tiraboschi, E., Musazzi, L., Racagni, G., & Popoli, M. (2006). Signaling Pathways Regulating Gene Expression, Neuroplasticity, and Neurotrophic Mechanisms in the Action of Antidepressants: A Critical Overview. *Pharmacological Reviews*, *58*(1), 115–134. https://doi.org/10.1124/pr.58.1.7

Thomas, M. J., Kalivas, P. W., & Shaham, Y. (2008). Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *British Journal of Pharmacology*, *154*(2), 327–342. https://doi.org/10.1038/bjp.2008.77

Timmermann, C., Roseman, L., Haridas, S., Rosas, F. E., Luan, L., Kettner, H., Martell, J., Erritzoe, D., Tagliazucchi, E., Pallavicini, C., Girn, M., Alamia, A., Leech, R., Nutt, D. J., & Carhart-Harris, R. L. (2023). Human brain effects of DMT assessed via EEG-fMRI. *Proceedings of the National Academy of Sciences*, *120*(13), e2218949120. https://doi.org/10.1073/pnas.2218949120

Tozzi, L., Zhang, X., Pines, A., Olmsted, A. M., Zhai, E. S., Anene, E. T., Chesnut, M., Holt-Gosselin, B., Chang, S., Stetz, P. C., Ramirez, C. A., Hack, L. M., Korgaonkar, M. S., Wintermark, M., Gotlib, I. H., Ma, J., & Williams, L. M. (2024). Personalized brain circuit scores identify clinically distinct biotypes in depression and anxiety. *Nature Medicine*, *30*(7), 2076–2087. https://doi.org/10.1038/s41591-024-03057-9

Vargas, M. V., Dunlap, L. E., Dong, C., Carter, S. J., Tombari, R. J., Jami, S. A., Cameron, L. P., Patel, S. D., Hennessey, J. J., Saeger, H. N., McCorvy, J. D., Gray, J. A., Tian, L., & Olson, D. E. (2023). Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science (New York, N.Y.)*, *379*(6633), 700–706. https://doi.org/10.1126/science.adf0435

Walsh, Z., Mollaahmetoglu, O. M., Rootman, J., Golsof, S., Keeler, J., Marsh, B., Nutt, D. J., & Morgan, C. J. A. (2022). Ketamine for the treatment of mental health and substance use disorders: Comprehensive systematic review. *BJPsych Open*, *8*(1), e19. https://doi.org/10.1192/bjo.2021.1061

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annual Review of Clinical Psychology*, *8*, 49–76. https://doi.org/10.1146/annurev-clinpsy-032511-143049

Widman, A. J., Stewart, A. E., Erb, E. M., Gardner, E., & McMahon, L. L. (2018). Intravascular Ketamine Increases Theta-Burst but Not High Frequency Tetanus Induced LTP at CA3-CA1 Synapses Within Three Hours and Devoid of an Increase in Spine Density. *Frontiers in Synaptic Neuroscience*, *10*. https://www.frontiersin.org/articles/10.3389/fnsyn.2018.00008

Williams, L. M. (2016). Precision psychiatry: A neural circuit taxonomy for depression and anxiety. *The Lancet Psychiatry*, *3*(5), 472–480. https://doi.org/10.1016/S2215-0366(15)00579-9

Wook Koo, J., Labonté, B., Engmann, O., Calipari, E. S., Juarez, B., Lorsch, Z., Walsh, J. J., Friedman, A. K., Yorgason, J. T., Han, M.-H., & Nestler, E. J. (2016). Essential Role of Mesolimbic Brain-Derived Neurotrophic Factor in Chronic Social Stress-Induced Depressive Behaviors. *Biological Psychiatry*, *80*(6), 469–478. https://doi.org/10.1016/j.biopsych.2015.12.009

Wu, M., Minkowicz, S., Dumrongprechachan, V., Hamilton, P., & Kozorovitskiy, Y. (2021). Ketamine Rapidly Enhances Glutamate-Evoked Dendritic Spinogenesis in Medial Prefrontal Cortex Through Dopaminergic Mechanisms. *Biological Psychiatry*, *89*(11), 1096–1105. https://doi.org/10.1016/j.biopsych.2020.12.022

Xu, W., Yao, X., Zhao, F., Zhao, H., Cheng, Z., Yang, W., Cui, R., Xu, S., & Li, B. (2020). Changes in Hippocampal Plasticity in Depression and Therapeutic Approaches Influencing These Changes. *Neural Plasticity*, *2020*, 8861903. https://doi.org/10.1155/2020/8861903

Yates, C., Kruse, J. L., Price, J. B., Robertson, A. A. B., & Tye, S. J. (2021). Modulating Neuroplasticity: Lessons Learned from Antidepressants and Emerging Novel Therapeutics. *Current Treatment Options in Psychiatry*, *8*(4), 229–257. https://doi.org/10.1007/s40501-021-00249-9

Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F. R., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., & Gould, T. D. (2018). Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological Reviews*, *70*(3), 621–660. https://doi.org/10.1124/pr.117.015198

Zhang, Z., Zhang, J., Li, J., Zhang, J., Chen, L., Li, Y., & Guo, G. (2020). Ketamine Regulates Phosphorylation of CRMP2 To Mediate Dendritic Spine Plasticity. *Journal of Molecular Neuroscience*, *70*(3), 353–364. https://doi.org/10.1007/s12031-019-01419-4

Zou, X., Patterson, T. A., Divine, R. L., Sadovova, N., Zhang, X., Hanig, J. P., Paule, M. G., Slikker Jr., W., & Wang, C. (2009). Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. *International Journal of Developmental Neuroscience*, *27*(7), 727–731. https://doi.org/10.1016/j.ijdevneu.2009.06.010

Zucker, R. S., & Regehr, W. G. (2002). Short-term synaptic plasticity. *Annual Review of Physiology*, *64*, 355–405. https://doi.org/10.1146/annurev.physiol.64.092501.114547