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Ketamine and Serotonergic Psychedelics: An Update on the Mechanisms and Biosignatures Underlying Rapid-Acting Antidepressant Treatment

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Abstract

The discovery of ketamine as a rapid-acting antidepressant spurred significant research to understand its underlying mechanisms of action and to identify other novel compounds that may act similarly. Serotonergic psychedelics (SPs) have shown initial promise in treating depression, though the challenge of conducting randomized controlled trials with SPs and the necessity of long-term clinical observation are important limitations. This review summarizes the similarities and differences between the psychoactive effects associated with both ketamine and SPs and the mechanisms of action of these compounds, with a focus on the monoaminergic, glutamatergic, gamma-aminobutyric acid (GABA)-ergic, opioid, and inflammatory systems. Both molecular and neuroimaging aspects are considered. While their main mechanisms of action differ—SPs increase serotonergic signaling while ketamine is a glutamatergic modulator—evidence suggests that the downstream mechanisms of action of both ketamine and SPs include mechanistic target of rapamycin complex 1 (mTORC1) signaling and downstream $GABA_A$ receptor activity. The similarities in downstream mechanisms may explain why ketamine, and potentially SPs, exert rapid-acting antidepressant effects. However, research on SPs is still in its infancy compared to the ongoing research that has been conducted with ketamine. For both therapeutics, issues with regulation and proper controls should be addressed before more widespread implementation.

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Keywords

Ketamine; serotonergic psychedelics; depression; rapid-acting therapeutics; biosignatures

1.0 Introduction

Pharmacotherapies developed to treat major depressive disorder (MDD) have historically been unsuccessful for roughly a third of patients (Rush et al., 2006; Trivedi et al., 2006). Furthermore, even when successful at reducing depressive symptoms, these drugs—typically monoaminergic-based antidepressants—have a substantial therapeutic time lag of weeks to months, limited remission rates, and undesirable side effects (Drewiany et al., 2015).

In this context, the recent discovery that sub-anesthetic doses of racemic (*R,S*)-ketamine (hereafter referred to as ketamine), an N-methyl-D-aspartate receptor (NMDAR) antagonist and glutamatergic modulator, have rapid antidepressant effects that occur in a matter of hours dramatically altered the therapeutic landscape (Kishimoto et al., 2016). Ketamine was initially approved by the US Food and Drug Administration (FDA) in 1970 as a rapid-acting general anesthetic. In recent years, multiple randomized, placebo-controlled trials have validated its robust antidepressant effects in individuals with MDD (Alnefeesi et al., 2022; McIntyre et al., 2020), those with treatment-resistant depression (TRD) who had not previously responded to conventional therapeutics (Dai et al., 2022; Zarate et al., 2006), and those with treatment-resistant bipolar depression (Diazgranados et al., 2010; Zarate et al., 2012). These antidepressant effects were found to be sustained well beyond the half-life of the drug and its peak pharmacokinetic exposure in the body, suggesting that its effects are maintained via a timely activation of signaling cascades in the brain. One meta-analysis demonstrated that ketamine's antidepressant effects peaked at 24 hours post-infusion and faded after 10 to 12 days (Kishimoto et al., 2016). These findings led the FDA to approve intranasal esketamine (Spravato)—the (*S*)-enantiomer of ketamine—for adults with TRD in 2019, and for adults with MDD and acute suicidal ideation or behavior in 2020 (U.S. Food & Drug Administration, 2019) under a Risk Evaluation and Management Schedule (REMS). This agent has also been approved by the European Union for the same indications.

Despite its encouraging antidepressant profile, concerns regarding the use of ketamine as an antidepressant persist, particularly given its potential for abuse and the unknown effects of its long-term use in clinical settings (Kokane et al., 2020; Liu et al., 2016). Ketamine also generates a transient psychoactive state that peaks around 40 minutes post-infusion, including changes in perception, mood, thought, and self-awareness, which necessitate its administration under medical supervision (Acevedo-Diaz et al., 2019; Kraus et al., 2017; Sassano-Higgins et al., 2016). Nevertheless, the re-purposing of ketamine from an anesthetic to an antidepressant created a paradigm shift, sparking a surge in research to develop and/or repurpose other therapeutic compounds with rapid and robust actions and similar behavioral and biological effects (Kadriu et al., 2020).

The most prominent example is research into the effects of so-called "classic" psychedelics, including lysergic acid diethylamide-25 (LSD), psilocybin and its active metabolite psilocin, 2,5-Dimethoxy-4-iodoamphetamine (DOI), N,N-dimethyltryptamine (DMT), 5-methoxy-

DMT (5-MeO-DMT), and the related empathogen 3,4-methylenedioxy-methamphetamine (MDMA) (Carhart-Harris and Goodwin, 2017). Coined by Osmond in 1957, the word “psychedelic” is often used interchangeably with the terms “hallucinogen” and “psychotomimetic” in the literature. In this manuscript, we refer to this class of drugs as serotonergic psychedelics (SPs), which reflects both their primary mechanism of action as 5-HT2A receptor agonists and their unique effects on the ego and consciousness (Carhart-Harris et al., 2012; Johnson et al., 2019; Mason et al., 2020; Rucker et al., 2018). Depending on the agent, psychoactive states will alternatively be referred to as psychedelic, psychotomimetic, or dissociative (Nichols, 2016). The term psychedelic refers to diverse agents that alter a person’s thoughts, feelings, and awareness of their own surroundings; in contrast, the term psychotomimetic reflects an alteration of behavior or personality that mimics psychosis, and the term dissociative references a state in which a disconnection or lack of continuity exists between a person’s thoughts, memories, or feelings. SPs produce both psychedelic and psychotomimetic states, whereas ketamine appears to induce primarily transient psychotomimetic and dissociative states.

In the 1950s and 1960s, over 1000 clinical research papers explored the therapeutic effects of SPs, particularly with regard to treating addiction, but they often lacked scientific rigor, including failure to incorporate control groups or blinding, report adverse effects, and validate outcome measures (Carhart-Harris and Goodwin, 2017). In 1967, research into SPs was brought to an abrupt halt when they were classified as Schedule I drugs (indicating that they had no medical value and were highly addictive), a decision that stemmed from concerns regarding their non-clinical use (Rucker et al., 2018) and the potential harm associated with their ability to engender life-altering experiences. However, there has been a recent resurgence of interest in clinical and preclinical SP research, especially with psilocybin; indeed, recent findings suggest that just one or two doses of SPs may persistently mitigate the symptoms of MDD and anxiety, as well as alcohol and tobacco addiction, more effectively than conventional treatments (Agin-Liebes et al., 2020; Carhart-Harris et al., 2018; Griffiths et al., 2016; Muttoni et al., 2019; Nichols et al., 2017; Ross et al., 2016). This work led the FDA to designate psilocybin as a “breakthrough therapy” in 2018 for TRD and again in 2019 for MDD.

Despite proposed parallels, much remains unknown about the convergent and divergent mechanisms of ketamine and SPs, particularly given the comparative dearth of properly controlled clinical trials and experiments investigating the therapeutic effects of SPs. While clinical trials of ketamine have consistently proven that it effectively targets TRD, properly controlled studies of SPs are still in their infancy, and many more unanswered clinical and mechanistic questions surround their use. Nevertheless, the rapid recent pace of new studies focusing on the effects of SPs requires that the literature in this area be regularly updated. This paper, which updates recent findings in this area (Kadriu et al., 2021), will review the molecular, imaging, and behavioral data believed to underlie the distinct and overlapping mechanisms of both therapeutics with the goal of informing future research into rapid-acting antidepressants. Unravelling the mechanism of antidepressant action that underlies both ketamine and SPs would dramatically expand our understanding of psychiatric disorders and have important implications for drug development. Towards this end, the manuscript explores the potential role of psychotomimetic or psychedelic effects in antidepressant

efficacy, the divergent main mechanisms of these two therapeutic compounds, their potential common downstream targets, and regulatory issues that must be considered for both.

2.0 The Convergent and Divergent Mechanisms of Ketamine and SPs

2.1 An overview of the major mechanisms of action of ketamine and SPs

While initially thought to primarily exert its antidepressant effects through NMDAR antagonism, research suggests that ketamine has several potentially relevant mechanisms of antidepressant action (Yang et al., 2019; Zanos et al., 2018a). Currently, two main NMDAR-related hypotheses exist for ketamine's effects: the disinhibition hypothesis and the direct inhibition hypothesis (Miller et al., 2016). The disinhibition hypothesis states that, at subanesthetic doses, ketamine preferentially antagonizes NMDARs on gamma-aminobutyric acid (GABA)-ergic interneurons. Blockade of these inhibitory interneurons increases firing of excitatory pyramidal neurons, which increases glutamate release and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) transmission; this, in turn, activates integral synaptic signaling pathways that contribute to ketamine's therapeutic effects (Gerhard et al., 2020). The direct inhibition hypothesis posits that ketamine's antagonism of NMDARs on excitatory pyramidal neurons lessens tonic NMDAR activation by circulating glutamate, which subsequently increases protein synthesis by decreasing suppression of eukaryotic elongation factor 2 (eEF2) (Autry et al., 2011; Nosyreva et al., 2013). Interestingly, the preliminary efficacy of (*R*)-ketamine—which is a less potent NMDAR antagonist—has spurred research into NMDAR-independent mechanisms of ketamine. This NMDAR-independent mechanism, which is thought to be mediated via AMPAR activation, activates a downstream BDNF-TrkB cascade to promote excitatory signaling in the cortex and hippocampus (Yang et al., 2019; Zanos et al., 2018a). Although the mechanisms underlying ketamine's NMDAR-independent effects on AMPAR transmission remain unclear, ketamine and (2*R*,6*R*)-HNK have been shown to upregulate the expression and phosphorylation of GluA1 independent of NMDAR antagonism (Li et al., 2022b; Yao et al., 2018; Zanos et al., 2016). Recent research also found increased cyclic adenosine monophosphate (cAMP)-induced phosphorylation of cAMP response element-binding protein (CREB) after ketamine administration, even after NMDAR knockout. This CREB phosphorylation increased BDNF release, which can activate the downstream BDNF-TrkB cascade to increase excitatory signaling (Wray et al., 2019). In addition to its glutamatergic mechanisms, evidence suggests that ketamine is also a monoamine reuptake inhibitor, a modulator of opioid receptor (mu, delta, kappa) activity, a dopamine receptor agonist, and a muscarinic receptor antagonist, among other mechanisms of action (Matveychuk et al., 2020).

Broadly, SPs interact with a variety of serotonergic receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_4, 5-HT_5, and 5-HT_6) and, with less affinity, some non-serotonergic receptors (e.g., dopamine receptors, certain trace amine receptors, kappa opioid receptors, sigma receptors, etc) (reviewed in (McClure-Begley and Roth, 2022; Slocum et al., 2022)). Their psychedelic activity is believed to be primarily mediated by 5-HT_{2A} receptor agonism (López-Giménez and González-Maeso, 2018; Rolland et al., 2014). The overlapping pharmacology of SPs (i.e., 5-HT_{2A} binding) was also demonstrated

in a recent clinical trial that found that participants could not differentiate between the psychedelic experiences produced by LSD or psilocybin, except for their duration (Holze et al., 2022). Mechanistic and genetic rodent studies have shown that abolishing 5-HT_{2A} receptor activity prevents the antidepressant-like effects of SPs on behavior and structural plasticity (Ly et al., 2018; Pędzich et al., 2022). On the other hand, antidepressant-like behavioral and electrophysiological responses to psilocybin were not blocked by the 5-$HT_{2A/2C}$ receptor antagonist ketanserin, though this experiment should be repeated with an antagonist that is more selective for the 5-HT_{2A} receptor, such as volinanserin (Hesselgrave et al., 2021). In addition, the selective 5-HT_{2A} receptor agonist DOI had no antidepressant-like effects in an LPS-induced mouse model of depression, but it did increase dendritic spine density (Qu et al., 2022). Interestingly, a non-psychedelic analog studied with the same LPS mouse model had antidepressant-like effects that were not associated with 5-HT_{2A}R agonism (Qu et al., 2022). For a summary of hypothesized mechanisms underlying the antidepressant effects of ketamine and SPs, please see Table 1.

2.2 Psychoactive Effects

In the development of novel, rapid-acting antidepressant agents, one key question of interest is how pharmacotherapies that appear to work through diverse mechanisms nevertheless exert similar—and perhaps equally rapid-acting—effects. Broadly, ketamine's antidepressant effects peak at 24 hours; depressive symptom reduction has been reported within one hour and can last upwards of two weeks (Hashimoto, 2019). Initial trials exploring the ability of SPs to reduce depressive symptoms found an effect within one day (Palhano-Fontes et al., 2019; Sanches et al., 2016), but this result has not always been replicated (Grob et al., 2011). However, this may be due to differences in participant population (e.g., individuals with recurrent depression or TRD vs. those with late-stage cancer) or the SP used (e.g., ayahuasca vs. psilocybin). A recent Phase 2 trial found reduced Montgomery-Asberg Depression Rating Scale (MADRS) scores in participants with TRD three weeks after an acute dose of psilocybin (Goodwin et al., 2022a). While not analyzed, MADRS scores were also reduced at Day 2 after psilocybin administration. Overall, however, most research exploring the effects of SPs on depressive symptoms has focused on longer time-points (Romeo et al., 2020), and further research is necessary to determine the extent to which SPs can be classified as a rapid-acting antidepressant.

Although they target different neurotransmitter systems, both ketamine and SPs similarly induce psychoactive states. These psychoactive experiences, however, appear to be mediated via different mechanisms: NMDAR antagonism for ketamine and 5-HTR agonism for SPs. It is important to note at the outset that most research conducted in SPs is classified as qualitative or quasi-experimental, in sharp contrast to ketamine, whose therapeutic effects have often been assessed via randomized controlled trials.

Initial research for ketamine focused on its underlying mechanisms of action, not the role of its psychoactive effects, particularly because it induces only mild and fleeting psychoactive effects at antidepressant doses (around 0.5 mg/kg). At these sub-anesthetic doses, approximately 80% of individuals with TRD report dissociative symptoms in response to ketamine, including "feeling strange, weird, or bizarre", and 50% report stronger

psychoactive effects such as a sensation of “floating” (Acevedo-Diaz et al., 2020b); however, these effects are transient, peaking around 40 minutes post-infusion and dissipating shortly thereafter (Acevedo-Diaz et al., 2020b). Interestingly, initial reports regarding subjective experiences after (*R*)-ketamine administration have differentiated its effects from those of (*S*)-ketamine, with very few psychotomimetic effects reported in early clinical trials (Zhang et al., 2022).

In contrast, SPs are often administered at much higher doses than the minimum needed to produce a psychedelic effect (e.g., ~0.3 mg/kg for psilocybin, ~1.67 mg/kg for DMT) (Knudsen, 2023; Sanches et al., 2016). Although ketamine and certain SPs (such as psilocin) have similar half-lives (~2.5 hours), the higher doses needed for SPs to exert their therapeutic effects typically lead to much stronger and longer-lasting psychoactive and psychotomimetic effects. While the timing of these effects varies widely between SPs due to differences in plasma half-lives, the psychoactive effects of most SPs can last for hours—for example, approximately six hours for psilocybin (Passie et al., 2002) and up to 12 hours for LSD (Dolder et al., 2015); in contrast, some SPs have extremely strong but very transient effects—for example, the effects of DMT only last from five to 30 minutes (Strassman and Qualls, 1994).

Across cultures and contexts, “mystical-type experiences” are commonly reported after SP administration, including reports of bliss, connection, acceptance, transcendence of space and time, and sacredness (Johnson et al., 2019). For example, 4.5 years after a single treatment, 71–100% of patients with life-threatening cancer treated with psilocybin attributed reductions in depressive and anxiety symptoms to the treatment (Agin-Liebes et al., 2020), though these measures were self-reported, and 39% of the patients had also received psychotherapy in the interim period. It should also be noted that SPs are not always significantly more effective than traditional antidepressants such as escitalopram (Carhart-Harris et al., 2021), and the varied results warrant further exploration.

The degree to which psychoactive effects and therapeutic efficacy are linked for each of these compounds remains unclear. The association between ketamine’s efficacy and its psychoactive effects appears to be weak, and most data indicate that its psychotomimetic effects are not related to its antidepressant outcomes (Acevedo-Diaz et al., 2020a; Ballard and Zarate, 2020). Furthermore, one recent study found no interaction between reported adverse events post-ketamine and later MADRS scores (Greenwald et al., 2021). This lack of association between ketamine’s dissociative and antidepressant effects, as well as the effects of other NMDAR antagonists, suggests that some of ketamine’s antidepressant effects may be NMDAR-independent. In contrast, the psychoactive effects induced by SPs appear to be dose-dependent and to correlate with self-reported positive persistent effects in healthy volunteers, as assessed via a non-validated scale (the Persistent Effects Questionnaire) (Barrett and Griffiths, 2018; McCulloch et al., 2022). In addition, the “quality” of psychedelic experience after psilocybin administration, as assessed through the Altered States of Consciousness Questionnaire, predicted future reduction of depressive symptoms measured by the QIDS-SR (Self-Reported Quick Inventory of Depressive Symptoms) (QIDS-SR) at five weeks (Roseman et al., 2018). A recent systematic review across disorders that included TRD and substance use disorder found parallel results—

namely, that the intensity of the acute psychedelic experience (measured through various scales) was the most significant predictor of future treatment response (Romeo et al., 2021). In contrast, recent literature reviews that included non-psychedelic analogs such as 6-MeO-isoDMT have suggested that the psychedelic experience is not necessary for antidepressant effects (Olson, 2020). Nevertheless, further validation is needed of both the scales used to assess psychedelic experience as well as the precise nature of this association in participants diagnosed with depression.

Another key point is that therapeutic milieu may play a confounding role in the psychoactive differences between ketamine and SPs. First introduced in 1965, the concepts of set (referring to mindset) and setting (the location in which the SPs are administered) (Hartogsohn, 2017) became heavily intertwined in SP research. It should be noted from the outset that the effects of set and setting on ketamine administration have rarely been studied or considered. Ketamine is usually offered in stringent clinical settings, though recent qualitative studies suggest that treatment environment may affect participant experience, particularly a strong therapeutic alliance with the prescribing clinician (Griffiths et al., 2021). In contrast, SPs are often administered after extensive preparation, often involving long discussions between the participant and practitioner of what to expect after administration of the SP, in a carefully orchestrated space designed to be soothing (Johnson et al., 2008; Schatzberg, 2020). It is important to note that the more stringent administration of ketamine has led to more conclusive evidence of its antidepressant effects, given that set and setting vary so widely in trials of the therapeutic effects of SPs (Golden et al., 2022).

Given the psychoactive effects of both ketamine and SPs, considerable research has sought to identify similarly effective compounds that lack these psychoactive effects. However, efforts to develop ketamine-like drugs that mirror its antidepressant effects but lack its dissociative effects have, to date, proven largely unsuccessful (Kadriu et al., 2020). With regard to SPs, microdosing—the act of taking sub-psychedelic doses—has generated significant interest. Nevertheless, the COMPASS Pathways Phase 2b trial found that a 25mg dose of psilocybin (considered a “macrodose”) was significantly more effective than a 1mg “microdose” in reducing depressive symptoms three weeks later, though the higher dose was also associated with more adverse events on the first day (61% vs. 38%) (Goodwin et al., 2022b). Other studies found that non-psychedelic levels of psilocybin/LSD lowered levels of self-reported depression and anxiety symptoms as assessed via the Depression, Anxiety, Stress Scale-21 (DASS-21), but this was in the general population and not in those diagnosed with depression or anxiety (Rootman et al., 2022). A placebo-controlled crossover trial in the general population found similar results, with reduced anxiety and stress symptoms in response to non-psychedelic doses of psilocybin versus placebo as assessed through the DASS-21 (Marschall et al., 2022); however, that study excluded those previously diagnosed with any psychiatric disorder.

As noted previously, research into the efficacy of SPs in TRD is still in its infancy. In comparison, a meta-analysis that reviewed a decade of ketamine trials found clinical response rates (defined as a 50% reduction in depressive scale scores) of 36.5% within 24 hours, a percentage that rose to 47.6% over two to seven days. Remission, defined as the absence of depressive symptoms, was found in 18% of the TRD participants within

24 hours and 28.2% within two to seven days (Marcantoni et al., 2020). Although there is less clinical research to draw on when determining the efficacy of SPs in TRD, one small, open-label trial of psilocybin in conjunction with psychological support found that 67% of patients (8/12 participants) met criteria for remission at one week (Carhart-Harris et al., 2016a); results were not provided for earlier timepoints. In a larger trial, the response rate at Week 3 was between 18–37% depending on dose (1–25 mg). Remission rates at Week 3 ranged from 8–29%, again in a dose-dependent manner (Goodwin et al., 2022a), suggesting the importance of proper dosing in SP research. Although trials to determine the effects of SPs in TRD are growing, it is important to note that much previous research has focused primarily on the impact of SPs on depressive symptoms, and efficacy rates could change when SPs are used in a TRD population.

2.3 The Monoaminergic System

Traditional antidepressants are based on the monoaminergic hypothesis of depression, which suggests that a depletion of serotonin, norepinephrine, and/or dopamine underlies depressive symptomatology. While the depletion of these monoamines is a consistent finding in MDD (Delgado, 2000; Hamon and Blier, 2013), the upregulation of monoamines after treatment does not consistently parallel the alleviation of depressive symptoms (Hirschfeld, 2000; Liu et al., 2017). mGlu2/3 antagonists, whose antidepressant-like effects are similar to those of ketamine, appear to mediate their actions by increasing the firing of 5-HT neurons as well as via 5-HT release (Chaki and Fukumoto, 2019).

In addition to its glutamatergic effects, ketamine appears to indirectly modulate monoaminergic neurotransmission. In the prefrontal cortex (PFC) of mice, ketamine, its enantiomers, and/or its metabolites increased extracellular levels of serotonin, dopamine, and norepinephrine (Ago et al., 2019). This transient increase in monoamine levels appeared to be mediated through glutamatergic projections from the medial PFC (mPFC) into the dorsal raphe and locus coeruleus (López-Gil et al., 2019). Serotonin depletion through a tryptophan hydroxylase inhibitor also blocked the antidepressant-like effects of (*S*)-ketamine in an animal model (du Jardin et al., 2018). In preclinical and clinical PET studies, 5-HT_{1B} receptor binding and serotonin transporter (SERT) occupancy were found to be increased in most, but not all, studies (Spies et al., 2018; Tiger et al., 2020; Yamanaka et al., 2014). However, the role of the serotonergic system in the antidepressant actions of (*R*)-ketamine are less clear; for instance, at least one study found that 5-HT depletion had no effect on (*R*)-ketamine's behavioral antidepressant-like effects (Zhang et al., 2018).

Behaviorally, ketamine effectively targets the motivational dysfunction believed to be related to dopamine reward circuits (Abdallah et al., 2017b; Mkrtchian et al., 2021); clinical trials found that it was particularly successful in ameliorating anhedonia, a symptom rarely improved by traditional antidepressants (Ballard et al., 2017; Lally et al., 2014; Nogo et al., 2022). Briefly, anhedonia is considered a core symptom of depression and a predictor of worse course of illness and treatment response (McMakin et al., 2012; Morris et al., 2009; Uher et al., 2012). Historically, traditional antidepressants have more effectively treated increased negative affect than decreased positive affect (Uher et al., 2012). Thus, while traditional antidepressants can improve symptoms such as a depressed

mood, which can improve depressive scale scores and classify patients as “responders” or “remitters”, anhedonia often remains a residual issue (Landen et al., 2005; McCabe et al., 2010; Nierenberg et al., 1999; Price et al., 2009), a distinction that underscores ketamine’s unique effects on anhedonic symptoms. With regard to dopaminergic pathways in particular, preclinical studies found that the Drd1 antagonist SCH39166 blocked the behavioral effects of repeated ketamine administration (Hare et al., 2019).

More recently, ketamine was found to restore multiple behaviors dampened by stress in mice, an effect blocked by inhibiting dopaminergic signaling (Wu et al., 2021a; Wu et al., 2021b). Activation of Drd1 after ketamine administration also increased cortical spinogenesis in parallel timing to ketamine’s behavioral effects (Wu et al., 2021a). High-dose ketamine was also found to dose-dependently increase Drd1 expression in the PFC and hippocampus in a mouse model of schizophrenia by inhibiting related microRNAs (Li et al., 2022a). Lastly, repeated administration of ketamine increased the firing activity of dopaminergic and norepinephrinergic—but not serotonergic—neurons (Iro et al., 2021). Interestingly, the actions of (*R*)-ketamine were not blocked by the Drd1 antagonist SCH-23390, suggesting that (*R*)-ketamine may have dopaminergic-independent effects (Chang et al., 2020). Collectively, these results suggest that monoaminergic signaling contributes to ketamine’s antidepressant effects, though it is probably not the main mechanism underlying its rapid-acting impact, especially in light of (*R*)-ketamine’s 5-HT- and dopaminergic-independent antidepressant-like effects.

In contrast, SPs have clear direct actions on monoaminergic neurotransmission and bind directly to serotonin, dopamine, and norepinephrine receptors. The pharmacology of these various compounds is quite complex and has recently been reviewed in great detail (Inserra et al., 2021). As mentioned above, the main mechanism of action of SPs is agonism of various 5-HT receptors. LSD, DMT, and 5-MeO-DMT may also affect the SERT (Kyzar and Kalueff, 2016; Rickli et al., 2015), though *in vitro* work reported no interaction between LSD and the SERT (Blough et al., 2014; Rickli et al., 2015). Novel research that seeks to develop non-psychedelic analogues is focusing on β-arrestin-biased ligands, which have lower transduction efficacy for the 5-HT_{2A} receptor, the primary mediator of psychedelic activity (Cao et al., 2022). Further supporting the role of transporters in antidepressant response to SPs, novel monoamine transporter ligands ((2-Aminopropyl)benzo[β]thiophenes) also stimulate a behavioral head-twitch response that mimics psychedelic activity (Rudin et al., 2022).

The degree to which SPs mediate dopaminergic transmission is less clear. In larger amounts, LSD can decrease dopaminergic firing activity, which may account for the psychotic symptoms associated with high doses (De Gregorio et al., 2016). Nevertheless, the reinforcing effects of dopamine may also be associated with greater abuse liability (Berke and Hyman, 2000). Some research even suggests that DMT, psilocybin, and mescaline may convert into dopamine after ingestion, adding another layer of complexity to the impact of SPs on monoaminergic transmission (Fitzgerald, 2021).

2.4 The Glutamatergic System

Both ketamine and SPs are believed to increase neurite outgrowth, synapse formation, and synaptic connections by facilitating changes in neuroplasticity (Aleksandrova and Phillips, 2021). These neuroplastic changes are driven by glutamatergic signaling (primarily in the PFC), with increases in AMPAR activation, a burst of glutamate release, and activation of the mechanistic target of rapamycin (mTOR) signaling pathway contributing to the antidepressant effects of both ketamine and SPs (Aleksandrova and Phillips, 2021). While ketamine and SPs have different primary mechanisms of action, both NMDAR antagonism and 5-HTR agonism activate mTOR downstream, increasing protein synthesis and excitatory activity. Another potential overlapping downstream target is the dephosphorylation of eukaryotic elongation factor 2 (eEF2), which can directly upregulate protein synthesis that contributes to synaptogenesis. This increase in dendritic outgrowth and synaptogenesis from both ketamine and SPs could lay the foundation for their longer-lasting antidepressant effects by reversing both structural and functional synaptic deficits associated with stress and depression. For a more in-depth overview of the impact of ketamine and SPs on indicators of neuroplasticity, see (Aleksandrova and Phillips, 2021; Kadriu et al., 2021).

As an anesthetic, ketamine functions primarily as a non-competitive NMDAR antagonist through an open channel block mechanism (MacDonald et al., 1987). Recent cryo-electron microscope studies of human NMDAR structures found that esketamine appears to bind between the channel gate and the selectivity filter and to move between two locations in the binding pocket (Zhang et al., 2021c). As noted above, the two main mechanistic hypotheses of ketamine (disinhibition and direct inhibition) both center on ketamine's effects on the glutamatergic system. The disinhibition hypothesis postulates that ketamine acts by favorably binding to NMDARs that express the GluN1/GluN2C, which are preferentially expressed on GABAergic interneurons, therefore blocking the inhibitory activity on excitatory pyramidal neurons in the cortex. Updated research supports this theory, demonstrating that ketamine's antidepressant effects stem from its ability to preferentially bind to NMDARs on GABAergic interneurons, an effect that is blocked by NMDAR-GluN2B knockdown on Gad1-expressing neurons (Pothula et al., 2021).

The premise of the direct inhibition hypothesis is that ketamine inhibits NMDARs located on post-synaptic terminals, altering cellular signaling pathways that influence protein expression (Miller et al., 2016). Interestingly, nitrous oxide (a non-competitive NMDAR inhibitor) was recently shown to have electrophysiological antidepressant effects similar to those of ketamine in rodents (Izumi et al., 2022). NMDAR antagonism has also been associated with ketamine's dissociative effects (Lodge and Mercier, 2015; Moghaddam et al., 1997).

Research into the effects of SPs on NMDARs is more mixed. Changes in NMDAR function are known to impact 5-HT2AR expression, which could contribute to the action of SPs. In a mouse model of schizophrenia, NMDAR blockade increased 5-HT2A excitability in the cortex, an effect potentially mediated through the NMDAR-subunit Grin1 and the Gαq protein pathway (Nakao et al., 2022). In a chronic stress animal model, psilocybin greatly increased AMPA/NMDA ratios in hippocampal slices compared to those treated with vehicle or ketanserin (an anti-hypertensive agent used to study the serotonergic system), an

effect that was significantly correlated with anhedonic behavior in the sucrose preference test (Hesselgrave et al., 2021). Ibogaine, a psychedelic alkaloid, also appears to be a potential NMDAR antagonist, and this mechanism plays a primary role in its use as a treatment for substance use disorders (Underwood et al., 2021). Another study also found increased NR2A levels after psilocybin administration, though that study also noted that psilocybin was not associated with behavioral antidepressant-like effects (Wotjas et al., 2022). In contrast, repeated administration of LSD did not potentiate synaptic response to NMDAR agonists or increase NMDA currents (De Gregorio et al., 2018).

Despite evidence that both ketamine and SPs may work through NMDARs, the low concentrations needed for ketamine to exert antidepressant effects has cast doubt on how necessary NMDAR inhibition is in this regard (Zanos et al., 2016). It is likely that ketamine inhibits only a fraction (less than half at physiological conditions) of NMDARs, even at peak drug concentrations (Dravid et al., 2007; Zhao et al., 2012), and therapeutic concentrations of the ketamine metabolite (2*R*,6*R*)-hydroxynorketamine (HNK) did not block NMDAR function (Lumsden et al., 2019). In addition, other NMDAR antagonists have not been able to fully mimic ketamine's antidepressant effects; as one example, MK-801 (a structural analog that has been heavily researched) had non-sustainable antidepressant effects in rodents (Autry et al., 2011; Piva et al., 2021; Yang et al., 2016; Zanos et al., 2016). NMDAR antagonists such as memantine, lanicemine, and many others have had little clinical success despite early preclinical evidence (Kadriu et al., 2020; Pochwat et al., 2019). Nevertheless, NMDAR antagonists may still be clinically useful. For instance, a recent meta-analysis found that memantine, despite failing in clinical trials, effectively treated depressive symptoms in those with mood disorders (Hsu et al., 2022). Rapastinel also showed promise in Phase 2 clinical trials for use in TRD, although Phase 3 clinical trials were negative, potentially due to problems with study design (Kato and Duman, 2020). In addition, a recent proof-of-concept study found that the novel intravenous NR2B antagonist MIJ821 had antidepressant effects in individuals with TRD and caused few psychotomimetic side effects (Ghaemi et al., 2021). Finally, dextromethorphan in combination with bupropion was recently FDA-approved to treat MDD (Majeed et al., 2021).

More recently, attention has turned to the AMPAR-mediated mechanisms that may underlie the actions of both ketamine and SPs. The role of AMPAR transmission in the effects of rapid-acting antidepressants has been extensively described (Abdallah et al., 2016; Alt et al., 2006; Kadriu et al., 2019; Zanos and Gould, 2018; Zanos et al., 2018b). Briefly, inhibition of GABA signaling disinhibits glutamate release from excitatory pyramidal neurons. The increased glutamate binds to post-synaptic AMPARs, which increase brain-derived neurotrophic factor (BDNF) release through a rise in Ca^{2+} influx. BDNF then binds to tropomyosin-related kinase B (TrkB) which, through downstream signaling molecules, activates the mTOR complex 1 (mTORC1). This transient activation upregulates proteins related to increased excitatory transmission, such as post-synaptic density-95, Synapsin I, and increased membrane insertion of GluA1.

Many preclinical studies support this mechanism of action for ketamine (Li et al., 2010; Zanos et al., 2016; Zhou et al., 2014). There has also been a drive to classify the actions of ketamine's enantiomers and metabolites, particularly (*R*)-ketamine and (2*R*,6*R*)-HNK

(Hess et al., 2022). Notably, the actions of (*R*)-ketamine, which induced longer-lasting antidepressant effects in a chronic stress model, appeared to depend on AMPA and TrkB activation. (*S*)-ketamine, in turn, activated mTOR independently of TrkB activation (Rafało-Ulińska and Pałucha-Poniewiera, 2022). The inactivation of eukaryotic initiation factor 4E-binding proteins (4E-BPs) through mTOR is essential for the antidepressant-like effects of both ketamine and (2*R*,6*R*)-HNK (Aguilar-Valles et al., 2021). Recent research into the role of mTORC1 on ketamine's effects have produced somewhat unexpected results. Specifically, rapamycin (which inhibits the actions of mTOR) prolonged ketamine's antidepressant effects in participants with TRD (Abdallah et al., 2020). A recent clinical trial similarly found that pre-treatment with rapamycin prolonged ketamine's antidepressant, but not anti-suicidal, effects (Averill et al., 2022). This may be due, in part, to rapamycin's anti-inflammatory effects in the periphery, which could contribute to ketamine's antidepressant effects (Attur et al., 2000; Chen et al., 2013). Preclinical studies also found that (*R*)-ketamine had mTOR-independent antidepressant-like effects in a chronic stress model, where administration of (*R*)-ketamine, but not (*S*)-ketamine, significantly attenuated phosphorylation of extracellular signal-regulated kinase (ERK) (Yang et al., 2018b). Further research also identified the ERK-NRBP1-CREB-BDNF signaling pathway in microglia as important to (*R*)-ketamine's sustained effects (Yao et al., 2022).

Evidence similarly suggests that the therapeutic effects of SPs are mediated through mTORC1 activation (Aleksandrova and Phillips, 2021; Kadriu et al., 2021; Vollenweider and Preller, 2020; Vollenweider and Smallridge, 2022). For instance, sustained AMPAR and mTOR activation was found to be necessary for SP-induced neuronal growth in cortical cultures (Ly et al., 2020). Proteomic analyses in human brain organoids also found that LSD increased mTOR activation (Ornelas et al., 2022), further supporting the importance of mTOR in neural plasticity in humans. Finally, a metabolomics study also found increased mTOR-related signaling after ayahuasca consumption (Madrid-Gambin et al., 2022). In contrast, elevated plasma levels of BDNF, which are generally associated with increased mTOR-related signaling, were not observed in healthy volunteers following administration of LSD or psilocybin (Holze et al., 2022). Nevertheless, there is a paucity of clinical research regarding how necessary mTORC1 is to the therapeutic effects of SPs, and no registered clinical trials are presently investigating this important question.

Finally, while ionotropic glutamatergic transmission is clearly essential for the antidepressant effects of both ketamine and SPs, metabotropic glutamate receptors (mGluRs) may also play an important role (Chaki, 2021; Musazzi, 2021). mGluR levels have consistently been linked to stress vulnerability (Peterlik et al., 2016), and mGluR2/3 antagonism has been an area of particular interest in drug discovery. mGluR2/3 antagonists were found to exert similar antidepressant-like effects to ketamine, potentially through their interactions with the serotonergic system (Chaki and Fukumoto, 2019), and have shown early promise as rapid-acting antidepressants (Pilc et al., 2022). Interestingly, (2*R*,6*R*)-HNK was found to exert mGlu2R-dependent antidepressant effects (Zanos et al., 2019). Another recent study found that while ketamine did not alter mRNA or the protein expression of ionotropic glutamate receptors, both chronic stress and ketamine administration altered mGluR2 expression (Elhussiny et al., 2021). Co-administration of ketamine and an mGluR2/3 antagonist also sustained antidepressant response in animal

models (Pałucha-Poniewiera et al., 2021; Rafało-Ulińska et al., 2022). In contrast, few studies have examined the effects of SPs on mGluRs. mGluR2/3 agonists inhibited the effects of DOI in mice, as it appears that mGluR2s and 5-HT_{2A}Rs form a G-protein coupled receptor complex particularly important for the head-twitch response (Benvenga et al., 2018; Delille et al., 2012; Gewirtz et al., 2002; Kłodzinska et al., 2002). However, these findings are preliminary, and more research is needed to determine whether mGluRs play a role in the antidepressant response associated with SPs.

2.5 The GABAergic system

A large body of evidence links depression with GABAergic signaling deficiencies (Duman et al., 2019), and the disinhibition hypothesis of ketamine's mechanism of action relatedly posits that GABAergic neurotransmission dysfunction is involved in the pathophysiology of depression (Zanos and Gould, 2018). Overall, MDD is associated with GABAergic deficits that coincide with homeostatic-like reductions in glutamatergic neurotransmission and can be rescued by rapid-acting antidepressants (Ren et al., 2016). A similar mechanism may underlie, at least to some extent, the mechanism of action of SPs. Indeed, excitatory pyramidal cells are regulated by GABAergic interneurons that express serotonin receptors (Nichols, 2016). Cortical GABAergic interneurons are abundant, but only 13–46% of them express the 5-HT_{2A}R compared to 86–100% of excitatory cells in layers II-IV of the human and monkey cortex (De Almeida and Mengod, 2007).

Considerable research has examined how ketamine may influence GABAergic signaling. Studies suggest that ketamine upregulates $GABA_A$ receptor activity in the cortex and hippocampus (Wang et al., 2017), increases turnover of hippocampal GABA (Silberbauer et al., 2020), and increases GABA release in the mPFC (Pham et al., 2020). Other compounds that upregulate $GABA_A$ receptor activity by preferentially binding to the delta subunit also have antidepressant properties, including the progesterone metabolite allopregnanolone (brexanolone) (Lüscher and Möhler, 2019), which was FDA-approved to treat postpartum depression in 2019 (Pinna et al., 2022). Negative $GABA_A$ receptor allosteric modulators also exert antidepressant effects by strengthening excitatory synapses without ketamine's adverse effects (Fischell et al., 2015). Muscimol and high doses of benzodiazepines, both of which increase $GABA_A$ receptor transmission, were found to dampen ketamine's antidepressant effects (Andrashko et al., 2020; Fuchikami et al., 2015), a finding paralleled by results showing that increased activation of $GABA_A$ receptors decreased antidepressant response to ketamine (Pham et al., 2020). Regardless of the implicated mechanisms, ketamine rapidly alleviates deficits in synaptic GABAergic markers as well as the frequency of inhibitory post-synaptic currents in the mPFC induced by stress, perhaps by transiently releasing large amounts of glutamate and/or directly facilitating the plasticity of GABAergic interneurons (Ghosal et al., 2020).

With regard to SPs, psilocybin has been found to raise both GABA and glutamate levels in the mPFC and to inhibit glutamate release in the hippocampus by acting on serotonin receptors located on GABAergic interneurons (Carhart-Harris and Nutt, 2017; Mason et al., 2020). Stress-induced alterations in GABAergic circuitry in the ventral tegmental area, a dopaminergic region strongly associated with reward and addiction, were normalized by

5-HT_{2A}R agonists (Kimmey et al., 2019), suggesting that SPs would have similar actions. However, the therapeutic effects of SPs are more likely to be related to their direct action on excitatory pyramidal neurons than on their ability to mediate GABAergic interneurons. In support of this notion, the pharmaco-electroencephalogram response to LSD was found to be similar between $GABA_A$ receptor δ subunit knockout mice and wildtype controls (Grotell et al., 2021).

Given that the balance between inhibitory and excitatory neurotransmission needs to be appropriately maintained to prevent psychiatric disturbances, additional research is needed to elucidate how GABAergic signaling contributes to the rapid and sustained antidepressant effects of ketamine and—even more so—to that of SPs. For instance, it would be interesting to evaluate whether ketamine and SPs recover levels of the enzyme glutamate decarboxylase (GAD) in cortical and limbic brain centers, like the hippocampus, which is sensitive to excitotoxicity (Gruenbaum et al., 2022). GAD converts glutamate into GABA in a single step, quickly distinguishing excitatory from inhibitory signals, and low GAD levels are associated with chronic stress and depression (Miyata et al., 2021). $GABA_B$ receptors are another pharmacological target of interest; generally, $GABA_B$ receptor agonists are pro-depressive whereas antagonists are anti-depressive (Jacobson et al., 2018). It is unknown whether SPs work via $GABA_B$ receptors, but administration of the $GABA_B$ receptor agonist baclofen prevented the antidepressant-like effects of ketamine in a mouse model, further suggesting that $GABA_B$ receptor inhibition may have beneficial effects (Rosa et al., 2016).

2.6 Opioid System

There has been a resurgence of interest regarding the role of the opioid system in MDD (Perez-Caballero et al., 2020), in part due to observations that ketamine's antidepressant effects may require the activation of certain opioid receptors (Williams et al., 2019; Williams et al., 2018). The opioid system is highly dysregulated in depression; for instance, a reduction in mu-opioid receptor availability was associated with treatment-resistance and with the improper processing of social cues (Peciña et al., 2019). The efficacy of low-dose buprenorphine, an opioid partial agonist, further implicates the opioid system in antidepressant treatment (Peciña et al., 2019). Self-medication with opioid agonists has also been repeatedly observed in individuals with depression, and associations are frequently found between depressive symptoms and opioid misuse (Rogers et al., 2021).

Recent research suggests that ketamine interacts significantly with the mu-opioid receptor and has weak affinity for the kappa-opioid receptor (Bonaventura et al., 2021). This affinity to opioid receptors is only a five- to 20-fold difference less than ketamine and its enantiomers' affinity for the NMDAR. Some preclinical research found that opioid antagonists abolish ketamine's rapid-acting antidepressant effects, though an opiate agonist alone is not sufficient to induce a parallel antidepressant effect (Klein et al., 2020; Zhang et al., 2021a). However, other preclinical studies found that naltrexone had no effect on ketamine's antidepressant-like effects in a chronic social defeat stress model (Zhang and Hashimoto, 2019). Despite ketamine's weak affinity for kappa-opioid receptors, blockade of these with a high-affinity and selective short-acting kappa-opioid receptor antagonist (LY2444296) abolished the antidepressant effects of both ketamine and its metabolite

(2*R*,6*R*)-HNK (Wulf et al., 2022). In addition, administration of an opioid antagonist (naltrexone) blocked ketamine's antidepressant effects in participants with TRD (Williams et al., 2019; Williams et al., 2018). A current clinical trial is building on this work to correlate naltrexone's blockade of antidepressant effects with neuroimaging data (NCT04977674), and other clinical trials are investigating adjunctive ketamine use in combination with buprenorphine or methadone for the treatment of opioid use disorder and comorbid depression (NCT04177706, NCT05051449).

Very little is known about the link between SPs and the opioid system. The plant alkaloid ibogaine has strong psychedelic properties and affinity for kappa-opioid receptors (Wasko et al., 2018). SP binding to mu-opioid and kappa-opioid receptors has also been found to correlate positively with subjective "therapeutic component scores", though it is important to note that mu-opioid receptor binding also correlated positively with self-reported measures of dependence (Zamberlan et al., 2018). SPs may also inadvertently modulate the addiction circuitry related to opioid use disorders, with preliminary research showing early success (reviewed in (Lee et al., 2022)). As an example, a single dose of ibogaine was effective against opioid dependence 12 months later (Noller et al., 2018). Nevertheless, significantly more research on the effects of SPs on the opioid system is needed to corroborate these findings.

2.7 Inflammation

Evidence suggests that stress-induced pro-inflammatory states in the central nervous system may contribute to the pathology of TRD (Yang et al., 2018a). Greater inflammatory responses have typically been associated with a more severe course of illness, higher chance of recurrence, and worse treatment outcomes (Suneson et al., 2021), though not always (Kofod et al., 2022). These inflammatory findings have been paralleled in preclinical research, which found that administration of the endotoxin lipopolysaccaharide (LPS) triggers "depressive-like" behaviors in rodents (Zhao et al., 2020). Peripheral blood mononuclear cells from individuals with MDD stimulated with LPS *ex vivo* had greater reactivity than cells of healthy volunteers, a response that also correlated with greater amygdala activation (Boukezzi et al., 2022).

Inflammatory markers such as tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), interleukin 1β (IL-1β), interleukin 6 (IL-6), and interleukin 8 (IL-8) have consistently been found to be upregulated in both animal models of depression and individuals diagnosed with MDD (Haapakoski et al., 2015; Köhler et al., 2017; Kubera et al., 2011; Wang and Miller, 2018). CRP appears to play a particularly important role, as it has been able to predict subsequent depressive symptoms (Valkanova et al., 2013) and distinguish TRD participants from treatment-responsive, unmedicated participants as well as healthy volunteers (Chamberlain et al., 2019). A positron emission tomography (PET) imaging study also reported increased binding of translocator protein 18kDa (TSPO), a biomarker of inflammation, in the PFC and anterior cingulate cortex of individuals currently experiencing a major depressive episode (Meyer et al., 2020).

Two potential mediators of these inflammatory responses are the hypothalamic-pituitary-adrenal (HPA) axis and the kynurenine pathway. Overactivation of the HPA axis is

characteristic of depression and chronic stress (Stetler and Miller, 2011), and hypersecretion of corticotropin-releasing hormone (CRH) can cause hypercortisolism and decreased reward-system responsivity of the dopaminergic system (Gold and Chrousos, 2002). Indicators of HPA axis hyperactivity are also strongly associated with somatic symptoms, which are reported more often in TRD than MDD (Iob et al., 2020).

The kynurenine pathway, a major modulator of glutamatergic and serotonergic signaling, is also heavily impacted by inflammation (Kowalczyk et al., 2019). Tryptophan-2,3-dioxygenase (TDO) is the kynurenine pathway's main enzyme and catabolizes tryptophan, the precursor for serotonin synthesis. TDO is induced in pro-inflammatory states (Chen and Guillemin, 2009), leading to a tryptophan depletion that can cause depressive symptoms in vulnerable persons (Wichers et al., 2005). The products of the kynurenine pathway are also biologically active, with kynurenic acid (KA) acting as a neuroprotective agent (Foster et al., 1984) and quinolinic acid (QA) as an endogenous neurotoxin (Lugo-Huitrón et al., 2013). Altered ratios of KA and QA have repeatedly been found in participants with depression (Allen et al., 2018; Doolin et al., 2018; Moaddel et al., 2018; Zhou et al., 2018). Considerable research has examined the role of the kynurenine pathway in depression and inflammation; we refer the interested to reader to (Kowalczyk et al., 2019) for a more in-depth discussion.

Ketamine appears to have mixed results on markers of inflammation (see (Johnston et al., submitted) for a recent review). In a mouse model of ulcerative colitis, (*R*)-ketamine, but not (*S*)-ketamine, decreased blood IL-6 levels, an anti-inflammatory effect blocked by administration of a TrkB antagonist, suggesting that ketamine might have anti-inflammatory effects (Fujita et al., 2021). Preclinically, (*R*)-ketamine also significantly attenuated levels of splenomegaly, central and peripheral measures of pro-inflammatory cytokines, and cognitive impairment in mice administered LPS (Zhang et al., 2021b). Interestingly, Wistar rats subjected to maternal deprivation had increased levels of pro-inflammatory cytokines that were reversed in a sex-dependent manner by ketamine or ketamine in combination with either/both electroconvulsive stimulation (ECS) and the selective serotonin reuptake inhibitor (SSRI) escitalopram (Abelaira et al., 2022). However, certain measures of inflammation did not respond to ketamine, including catalase activity and carbonyl levels in the PFC and hippocampus of female rats (Abelaira et al., 2022). Clinical studies have echoed these sex-dependent preclinical results, finding that lower baseline levels of IL-8 predicted treatment response to ketamine in females but not males with depression (Kruse et al., 2021).

Ketamine also affects both the HPA axis and kynurenine pathway. In an animal model of depression, ketamine restored hippocampal glucocorticoid receptor expression, thus helping to restore the HPA axis's negative feedback loop (Wang et al., 2019). Ketamine also reduced levels of corticosterone and adrenocorticotropic hormone (ACTH) after LPS injection (Besnier et al., 2017). Clinically, it seems that ketamine promotes an early burst of cortisol in healthy volunteers (Hergovich et al., 2001; Khalili-Mahani et al., 2015), though exploration of this phenomenon in individuals with TRD is needed. Ketamine may also mediate the effects of QA, the pro-inflammatory byproduct of the kynurenine pathway that binds to NMDARs via NMDAR blockade (Miller, 2013; Walker et al., 2013). Ketamine

restored the decreased KYN:tryptophan ratio both clinically (Moaddel et al., 2018) and in a chronic unpredictable mild stress model (Wang et al., 2015). Increased KA levels after ketamine administration also correlated with MADRS score reductions at Days 1, 13, and 26 post-ketamine (Zhou et al., 2018).

Some studies suggest that ketamine acts on the reactivity of the immune system to aversive stimuli such as stressors. For example, ketamine demonstrated prophylactic effects against chronic stressors, preventing stress-induced behavioral changes (Brachman et al., 2016) as well as resilience against LPS- or TNF-α-induced depressive-like behaviors associated with the NLRP3 inflammasome pathway (Camargo et al., 2021). A recent proof-of-concept study found that a pre-stress ketamine infusion in healthy volunteers significantly decreased levels of salivary cortisol and alpha amylase (Costi et al., 2022). It should be noted that chronic, high-frequency ketamine use may increase neurogenic and IgE inflammation to contribute to urological toxicity (Ng et al., 2021), but this has only been observed in ketamine abusers and not at antidepressant doses.

Compared to their antidepressant (or antidepressant-like) effects, research on the anti-inflammatory effects of SPs is still in its infancy, but some information can be extrapolated from other disorders (see (Saeger and Olson, 2022) for a recent review of the anti-inflammatory effects of SPs on various neurodegenerative disorders). SPs appear to produce strong anti-inflammatory effects by binding to 5-HT_{2A} receptors on immune cells (Flanagan and Nichols, 2018), where activation was found to lessen airway inflammation in a mouse model of asthma (Flanagan et al., 2019a) and vascular inflammation in a high fat diet model (Flanagan et al., 2019b). Microglia also express receptors targeted by SPs, including 5-HT_{2A}, 5-HT_{2B}, 5-$HT_{7,}$ and sigma-1 receptors (Jia et al., 2018; Turkin et al., 2021). Recent studies have also found associations between lifetime self-reported SP use and lower rates of heart disease, diabetes, body mass index, and hypertension (Simonsson et al., 2021a; Simonsson et al., 2021b; Simonsson et al., 2021c). Further research is needed to explore the potential mechanisms underlying these broad anti-inflammatory outcomes, including potential lifestyle confounders not listed in these studies, such as diet, socioeconomic status, and age.

With regard to the link between SPs, depression, and inflammation in particular, very little recent research has been published (we refer the interested reader to (Flanagan and Nichols, 2018; Flanagan and Nichols, 2022; Kadriu et al., 2021) for an overview of previous work). Briefly, the 5-$HT2_A$ receptor is expressed in many immune tissues, including the spleen and circulating lymphocytes. SPs appear to have strong anti-inflammatory effects due their action on the 5-$HT2_A$ receptor, decreasing levels of cytokines and TNF-α within hours of administration (Pelletier & Segel, 2009). DOI, in particular, was found to provide a prophylactic effect against TNF-α administration, preventing cytokine and chemokine upregulation (Martin & Nichols, 2013). Interestingly, activation of the 5-HT_{2A} receptor by serotonin is primarily pro-inflammatory, leading Flanagan and Nichols to propose that the effects of SPs may be explained by functional selectivity or by the ability of the receptor to use different conformations to activate differing effector pathways (Flanagan and Nichols, 2018). In recent pre-print reports, researchers found that psilocybin decreased TNF-α secretion (Smedfors et al., 2022) and that both psilocin and DMT decreased levels of TLR4,

p65, and CD80 after LPS challenge in microglial cell lines (Kozłowska et al., 2021). In LPS-treated macrophage cells, psilocybin treatment decreased levels of TNF-α, IL-1β, IL-6, and cyclooxygenase-2 (COX-2) (Nkadimeng et al., 2021). In a chronic stress mouse model of PTSD, both DMT and "pharmahuasca" (DMT+harmaline) decreased reactive oxygen species (ROS) and inflammatory gene expression (Kelley et al., 2022). DMT also decreased TNF-α and IL1-β levels and increased IL-10 levels in an *in vivo* model of ischemic brain injury (Nardai et al., 2020). While SPs play a large role in the serotonergic system, to the best of our knowledge, no research has explored their impact on the kynurenine pathway. As a precursor of serotonin itself, tryptophan is uniquely placed to affect the impact of SPs and could be an area of future interest. Preliminary research has also investigated the role of the HPA axis in healthy volunteers, finding increased cortisol and ACTH in plasma during the peak psychedelic effects of psilocybin (Hasler et al., 2004). However, long-term measures in participants with depression are needed to determine the role of HPA axis function in the effect of SPs, and further research is needed more broadly to determine the role of SPs in treating inflammation-associated depression. The hypothesized convergent and divergent mechanisms of ketamine and SPs can be viewed in Figure 1.

3.0 Imaging and pharmacodynamic biosignatures of ketamine and SPs

Developing sensitive and reliable neurophysiological and neuroimaging biomarkers for MDD—and TRD in particular—is critical to improving diagnosis and treatment selection, especially in the context of novel therapeutics such as ketamine and SPs. Conversely, understanding the mechanisms by which novel, rapid-acting therapeutics impact macroscopic brain activity (as recorded by neurophysiological techniques such as electroencephalography (EEG) or magnetoencephalography (MEG) or by hemodynamic response using functional magnetic resonance imaging (fMRI)) can help develop the next generation of rapid-acting antidepressants that lack dissociative or psychotomimetic effects, improving treatment tolerability and effectiveness. Dysregulated neuroplasticity in vulnerable brain regions, including the PFC and hippocampus, is implicated in the pathophysiology of MDD (Liu et al., 2017; Price and Duman, 2020), and facilitation of adaptive neuroplasticity might be a convergent mechanism for the antidepressant efficacy of both ketamine and SPs (Aleksandrova and Phillips, 2021). This section reviews the evidence for convergent neuroplasticity mechanisms from MEG and EEG studies of long-term potentiation (LTP) and gamma power, as well as fMRI studies examining resting-state connectivity.

Neurophysiologically, synaptic efficacy has been examined using tasks that measure LTP, such as amplitude changes of sensory evoked potentials to visual, auditory, and somatosensory stimulation. In a double-blind, placebo-controlled trial, ketamine enhanced visual sensory evoked potentials three to four hours post-ketamine administration compared to an active placebo (remifentanil) in individuals with MDD, potentially reflecting increased synaptic efficacy concomitant with the drug's antidepressant effects (though there was no association between the evoked potential changes and treatment response) (Sumner et al., 2020a). In addition to LTP, shorter-term plasticity has been measured using event-related response EEG tasks that take advantage of deviance detection in the context of repeated visual or auditory stimuli, for example using a mismatch negativity (MMN) task.

In a second double-blind, placebo-controlled trial, ketamine significantly increased the MMN event-related response three to four hours after infusion in individuals with MDD (Sumner et al., 2020b), though this increase was not associated with treatment response and contradicts a host of studies suggesting that ketamine attenuates MMN response during drug administration in healthy volunteers (Rosburg and Kreitschmann-Andermahr, 2016; Rosch et al., 2019; Schmidt et al., 2012). Ketamine has also been found to alter the amplitude and latency of a number of additional ERP components in healthy volunteers during the MMN task (for a review, see (Schwertner et al., 2018)).

In contrast to ketamine, few studies have been conducted to assess the effects of SPs on the MMN response, and existing studies indicate mixed findings in healthy volunteers. For example, while a few studies found that psilocybin did not acutely attenuate the auditory or visual MMN response in healthy volunteers (Schmidt et al., 2012; Schmidt et al., 2013; Umbricht et al., 2003), at least one study reported that psilocybin reduced the MMN response to tactile oddball stimuli (Duerler et al., 2021). In contrast to psilocybin, DMT was found to blunt the auditory MMN response in healthy volunteers (Heekeren et al., 2008), and LSD was found to blunt several event-related potential responses to oddball neutral and angry faces in healthy volunteers (Murray et al., 2022). Further research is needed to elucidate the effects of SPs on MMN response, particularly in individuals with MDD, in order to clarify whether SPs upregulate short- and long-term plasticity mechanisms that mirror ketamine’s proposed mechanisms of action.

Another emerging area of neurophysiological interest is gamma rhythms, particularly gamma power, as a biomarker or endophenotype for MDD. Findings suggest that gamma can distinguish individuals with MDD from healthy volunteers, as well as distinguish subtypes of depression (e.g., bipolar disorder from unipolar depression) (Fitzgerald and Watson, 2018). Gamma rhythms have been found to correlate with action potential generation (Watson et al., 2018), emerge from the coordinated interaction of glutamatergic excitation and GABAergic inhibition (Buzsáki and Wang, 2012), and robustly increase following ketamine administration (Gilbert and Zarate, 2020). In randomized, double-blind, crossover trials in individuals with TRD, ketamine significantly increased gamma (30–50 Hz) power immediately and at two hours post-infusion compared to active placebo (midazolam) (de la Salle et al., 2022), and at six to nine hours following ketamine administration compared to saline placebo (Nugent et al., 2019a; Nugent et al., 2019b); gamma power changes were consistently associated with antidepressant response (de la Salle et al., 2022; Nugent et al., 2019a; Nugent et al., 2019b).

To date, few studies have investigated the effects of SPs on oscillatory power, particularly gamma. In animal work, psilocybin increased local field potential power in the anterior cingulate cortex (ACC) in low (35–55 Hz) and high (65–120 Hz) gamma (at trend levels) while decreasing power in the lower frequency bands including delta, theta, and alpha (Golden and Chadderton, 2022). In healthy volunteers, LSD significantly reduced gamma power during resting-state recordings (Murray et al., 2022) while also reducing power in the lower frequency bands including theta, alpha, and beta (Carhart-Harris et al., 2016b; Murray et al., 2022). As with LTP changes, more work is needed to determine whether SPs have

shared downstream mechanisms with ketamine that increase cortical excitability and gamma power.

Resting-state functional connectivity changes measured with fMRI are another method to examine changes in synaptic plasticity following ketamine and SP administration. In particular, systems-level dysregulation in the default mode network (DMN), including regions such as the ACC, posterior cingulate cortex (PCC), and mPFC is implicated in MDD (Marchetti et al., 2012; Sheline et al., 2010), with findings suggesting reduced connectivity in MDD participants relative to healthy volunteers within these regions (Abdallah et al., 2017a; Kraus et al., 2020). In an open-label study of individuals with TRD, ketamine increased global brain connectivity in the PFC at one day post-infusion (Abdallah et al., 2017a). Another randomized, double-blind, crossover trial found that ketamine increased DMN and insula connectivity in individuals with TRD at two days post-infusion, normalizing connectivity between these regions to levels seen in healthy volunteers at baseline (Evans et al., 2018). A separate randomized, double-blind, crossover study found that ketamine increased PFC and striatal connectivity in individuals with TRD at two days post-infusion, normalizing connectivity levels to those seen in healthy volunteers; in addition, this increase was associated with sustained improvements in anhedonia—defined as loss of interest or pleasure—in those with TRD (Mkrtchian et al., 2021). Interestingly, an open-label study of repeated ketamine dosing in individuals with MDD found that ketamine also modulated connectivity between limbic regions and other resting-state network nodes of the salience and central executive networks at one day after the first and fourth ketamine infusions (Vasavada et al., 2021).

Studies of resting-state functional connectivity in SPs also indicate that these drugs increase network connectivity in regions of the DMN and modulate connectivity between the DMN and other regions implicated in the pathophysiology of depression. For example, increased functional connectivity within the DMN was observed one day following open-label psilocybin administration in individuals with TRD, accompanied by decreased cerebral blood flow in the temporal cortex, including the amygdala (Carhart-Harris et al., 2017). In addition, increased ACC and PCC connectivity was found post-psilocybin administration, though this did not correlate with change in depression scores; in that study, increased ventromedial PFC and bilateral inferior lateral parietal cortex connectivity and decreased parahippocampal and PFC connectivity predicted treatment response at five weeks (Carhart-Harris et al., 2017). A double-blind, randomized, placebo-controlled trial of psilocybin found reduced brain network modularity at three weeks following drug administration in individuals with MDD, indicating greater brain network integration that was associated with treatment response (Daws et al., 2022). Finally, an open-label study of ayahuasca also found increased ACC and PCC connectivity, as well as increased ACC and right mesial temporal lobe limbic structure connectivity, one day after ayahuasca ingestion in healthy volunteers (Sampedro et al., 2017).

4.0 Limitations, Considerations, and Regulatory Issues

Regulatory issues are associated with the use of both ketamine and SPs for the treatment of MDD. However, given that ketamine has been approved at high doses for anesthetic use with

few associated harms for nearly 60 years (Peltoniemi et al., 2016), such issues are an order of magnitude larger for SPs.

As noted above, in light of concerns about ketamine's abuse potential, FDA approval for ketamine only extends to the specific use of intranasal esketamine under a REMS monitoring agreement (U.S. Food & Drug Administration, 2019). However, despite the precautions around ketamine/esketamine's potential abuse liability and misuse outside of clinical supervision (Liu et al., 2016), it remains unclear whether the subanesthetic doses of ketamine used to exert antidepressant effects are enough to spur abuse (Simmler et al., 2022). In high—not antidepressant—doses, ketamine has been associated with disruptions in learning and memory as well as urinary dysfunction (Liu et al., 2016; Schifano et al., 2021), and can also mimic and induce symptoms of psychosis, particularly in those at high risk for psychosis or individuals diagnosed with schizophrenia (Lahti et al., 1995). A recent meta-analysis found that even antidepressant-dose ketamine was associated with psychosis-like symptoms in healthy volunteers and participants with schizophrenia (Beck et al., 2020), suggesting that it is not an ideal candidate for use in some neuropsychiatric disorders.

Although SPs have been used for centuries, particularly in traditional medicine practices, concerns about their therapeutic use persist, as evidenced by their classification as Schedule I substances. In one survey of individuals who had ever used SPs, 13% endorsed at least one harm associated with SP use (cigarette smoking and problematic marijuana use were the two most frequently-reported problems), and these participants benefited less from the experience than those who reported no harm (Raison et al., 2022); nevertheless, it is important to specify that this study examined naturalistic use of SPs and may thus not reflect harms associated with SP administration in a clinical setting. SP dose can also impact their adverse event profile; specifically, high doses associated with antidepressant effects appear to cause more adverse events than low doses (Goodwin et al., 2022a). Other survey-based studies found that psychedelic experiences were associated with long-term improvements in mental well-being in the general population, even following a single lifetime use (Mans et al., 2021). Adverse effects linked to therapeutic SP use include psychological distress and prolonged psychosis, both of which can carry significant risks for participants (Carbonaro et al., 2016; Martinotti et al., 2018); nevertheless, in clinical settings, these effects often resolve after drug effects have dissipated (Johnson et al., 2019; Johnson et al., 2008) and are thought to fall within acceptable limits (Reiff et al., 2020). Given the serotonergic mediation of neural plasticity, the higher serotonin levels associated with SP use can also bring about mixed effects (e.g., improved recovery capacity but increased vulnerability to depression) (Branchi, 2011).

Administration of SPs may also contribute to serotonin toxicity. While an increase in serotonin is characteristic of psychedelic action, SPs alone pose a low risk for serotonin toxicity. However, combining SPs with therapeutics such as monoamine oxidase inhibitors (MAOIs) may increase risk, particularly for ayahuasca, the brew containing the MAO-A isozyme inhibitor harmine, which prolongs the effects of DMT (Malcolm and Thomas, 2022). Symptoms of serotonin toxicity include fluctuating vital signs, agitation, muscle rigidity, and seizure activity. Use of certain SPs has also been linked to neurological and

cognitive impairments through cytotoxicity and oxidative stress (Malcolm and Thomas, 2022).

Participant inclusion issues may also bias the results of SP research, given that a high proportion of research participants have previously used SPs (36–56% compared to 11.5% in the US general population) (McClure-Begley and Roth, 2022), though use of SPs as self-medication may play a role in this higher proportion. Researchers also found that mystical-type experiences were more likely in those who were ranked higher in the undefined personality traits of “openness” and “acceptance” (Aday et al., 2021), which suggests that including individuals who have previously used SPs and have positive expectations surrounding their use may confound study results. Another key point is that most trials of SPs are still open-label, long-term follow-up, or retrospective analyses (Berkovitch et al., 2021; Carhart-Harris et al., 2018). Placebo-controlled studies are necessary, though many challenges are associated with conducting a proper randomized, controlled clinical trial for SPs; these include resolving the role of psychoactive effects in the mechanism of action behind the antidepressant effects of SPs and the need for a comparator psychedelic compound that works through different mechanisms (Aday et al., 2022; Muthukumaraswamy, 2021). For instance, in early ketamine randomized clinical trials, midazolam (McGirr et al., 2015), a benzodiazepine that produces similar side effects to ketamine, provided adequate blinding. However, it should be noted that while ketamine produces psychotomimetic effects such as dissociation, these are mild compared to those of SPs and can thus be more easily controlled for with an appropriate placebo. In this context, an interesting future solution could be the use of SP microdosing (defined as doses that have no psychedelic effects), which could be placebo-controlled. Early microdose randomized clinical trials have begun for psilocybin (NCT05227742).

5.0 Future Research Directions

Rapid-acting antidepressants have led to a paradigm shift in neuropsychiatry and reinvigorated the search for novel pharmacological approaches to disorders such as MDD. However, research into how rapid-acting antidepressants mechanistically affect the underlying psychopathology of neuropsychiatric disorders is in its earliest stages. Novel innovations and approaches, such as PsychLight—a biosensor capable of detecting psychedelic potential in novel compounds by measuring endogenous 5-HT activity in awake mice—should help shed light on the underlying mechanisms of SPs and other potential rapid-acting antidepressants (Cameron et al., 2021; Dong et al., 2021). In addition, identifying compounds that have SP- and ketamine-like attributes (i.e., upregulation of neurotrophic signaling) but lack hallucinogenic properties may be an effective strategy for developing therapies that allow widespread clinical use. Non-psychedelic analogues, such as tabernanthalog (Cameron et al., 2021), could also help mitigate some of the negative psychoactive effects associated with SP and ketamine administration. In addition, the further development of (*R*)-ketamine as an antidepressant has shown promise, both in terms of its potentially reduced side effect profile and preclinical and early clinical therapeutic efficacy versus (*S*)-ketamine (Wei et al., 2022; Zhang et al., 2022); nevertheless, it should be noted that the evidence for (*R*)-ketamine, though promising, is relatively limited compared to (*S*)-ketamine, and additional clinical work is needed to fully ascertain (*R*)-ketamine’s

precise therapeutic profile. Most recently, results from a Phase 2a double-blind, randomized, placebo-controlled, multicenter clinical trial of (*R*)-ketamine (PCN-101) (NCT05414422) for TRD found that this agent failed to meet its primary endpoint, showing no significant change from baseline MADRS scores at 24 hours, despite an overall positive safety profile (Atai Life Sciences, 2022).

Further research is also still needed to clarify whether SPs can truly be classified as rapid-acting antidepressants, given that most research in this area has focused on the impact of acute SP administration on longer time courses (Romeo et al., 2020). In addition, the ability of SPs to ameliorate symptoms in TRD patients needs further investigation; though several studies showed initial promise (Carhart-Harris et al., 2016a; Goodwin et al., 2022a), others found no difference between response rates to SPs and monoaminergic-based antidepressants (Carhart-Harris et al., 2021). With the recent surge in interest in SPs, future studies should also be able to examine the varying impacts of different SPs.

Another area for future research is sex differences. Although prevalence rates of MDD are two- to three-fold higher in females than males, few studies have addressed potential sex differences with regard to ketamine, and almost none have done so for SPs. Notably, no apparent sex differences have emerged in clinical studies of ketamine for depression (Freeman et al., 2019) though both clinical and preclinical studies suggest that there may be some mechanistic differences (reviewed in (Ponton et al., 2022)). One systematic review found no apparent sex differences in clinical studies of SPs for depression (Aday et al., 2021), though preliminary preclinical work suggests that there may be sex differences in amygdala reactivity (Effinger et al., 2022) and prepulse inhibition of startle reactions after SP administration (Vohra et al., 2022). In addition, lack of inclusion of certain racial and ethnic minorities in research regarding both ketamine and SPs limits conclusions that can be made about therapeutic benefits. For example, recent research found that while psilocybin use conferred lower reports of distress amongst white participants, there were significantly lower associations for participants from different racial and ethnic minorities (Grant and Nock, 2022).

Both ketamine and SPs are being investigated for disorders other than depression, and we expect that future work in this area will expand. Specifically, randomized clinical trials found that ketamine and its enantiomers can be successfully used to target alcohol and other substance use disorders (Worrell and Gould, 2021), anxiety spectrum disorders (such as PTSD and social anxiety disorder) (Whittaker et al., 2021), and suicidal ideation (Wilkinson et al., 2018), among others. In contrast to the more robust evidence available for ketamine, most of the findings for SPs are anecdotal. These promising preliminary results nevertheless suggest that SPs may be useful in treating disorders characterized by maladaptive cognitive distortions, like OCD and anorexia nervosa (Foldi et al., 2020; Moreno et al., 2006; Spriggs et al., 2021). Given that SPs also preliminarily appear to mitigate tobacco, alcohol, cannabis, stimulant, and opioid use (Davis et al., 2018; Garcia-Romeu et al., 2019; Johnson et al., 2014; Jones and Nock, 2022; Noller et al., 2018), the anti-addictive potential of SPs also warrants additional investigation.

Despite the disparity in the number of rigorous studies conducted, comparing the mechanistic differences between ketamine and SPs can provide valuable insight into the mechanism of action underlying rapid-acting antidepressants. The most promising convergent mechanism between ketamine and SPs is activation of the mTORC1 pathway and the resultant changes in neuroplasticity. In addition, agonism of the mu-opioid and kappa-opioid receptors may contribute to some of the similarities observed between ketamine and SPs. Differences between the psychedelic and psychotomimetic effects of these compounds, as well as the success of some preliminary non-psychedelic analogues, suggests that the therapeutic experience itself does not fully mediate antidepressant effects. Disparities also exist with regard to how these compounds affect the monoaminergic system, and the evidence is quite mixed regarding how both ketamine and SPs mediate this system, leading to doubts that the monoaminergic system is necessary for rapid-acting antidepressant effects.

Elucidating the mechanisms responsible for the antidepressant effects of both ketamine and SPs is necessary for developing effective treatment approaches, including mechanistically novel pharmacotherapeutics. As the evidence reviewed above makes clear, significantly more research has been conducted with regard to the mechanisms of action that underlie ketamine's antidepressant effects compared to SPs. Nevertheless, we expect that further research into SPs will be forthcoming.

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Dr. Zarate is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R*,*S*)-ketamine metabolites in the treatment of depression and neuropathic pain; and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and post-traumatic stress disorders. He has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government. Dr. Kadriu is now a full-time employee of Jazz Pharmaceuticals.

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Highlights

- Ketamine and psychedelics have different initial mechanisms of action
- Parallel downstream mechanisms may account for therapeutic similarities
- Monoamines, opioid and sigma receptors, and inflammation are all promising targets
- More research on psychedelics is needed compared to ketamine
- Consideration of regulatory issues is crucial to implementation

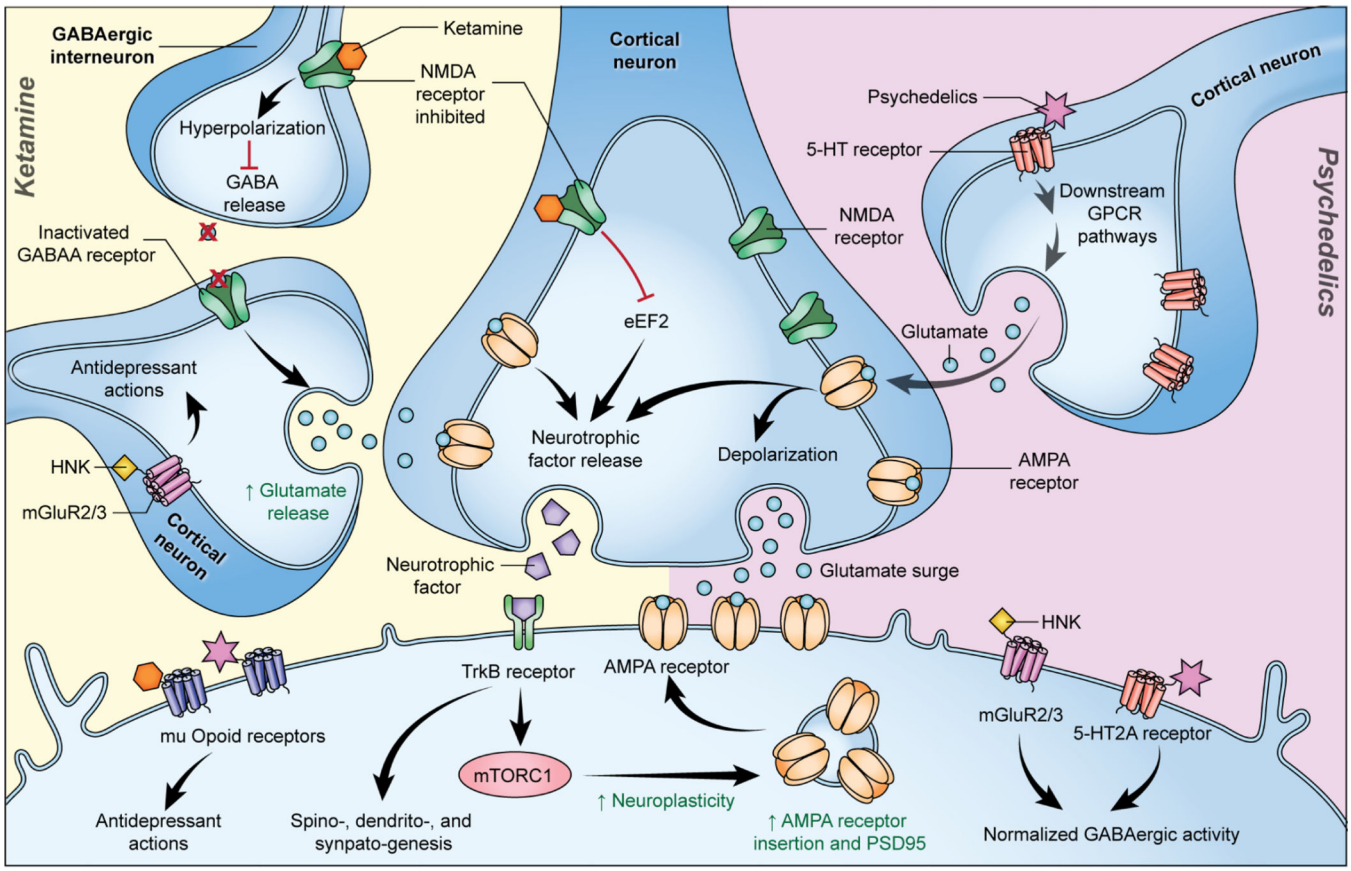

Figure 1. Hypothesized convergent and divergent mechanisms of ketamine and serotonergic psychedelics (SPs).

Ketamine increases glutamate release into the synapse through preferential blockade of NMDARs on GABAergic interneurons (disinhibition hypothesis) or other methods. This glutamate “surge” leads to downstream signaling that transiently activates mTORC1, increasing synaptic protein translation of PSD-95, AMPARs, and others. SPs trigger this glutamate surge through downstream GPCR pathways after 5-HT receptor activation, which leads to parallel mTORC1 activation and subsequent increases in synaptic protein translation. Other proposed mechanisms of antidepressant effects include binding to mu-opioid receptors and normalizing GABAergic activity through either mGluR2/3 (ketamine/(2*R*,6*R*)-HNK) or post-synaptic 5-HT2A receptors (SPs). Figure is approximate for illustrative purposes. Abbreviations: 5-HT: 5-hydroxytryptamine; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GPCR: G protein-coupled receptors; HNK: hydroxynorketamine; mGluR: metabotropic glutamate receptor; mTORC1: mechanistic target of rapamycin complex 1; PSD-95: postsynaptic density protein 95.

Table 1.

Hypothesized mechanisms underlying the antidepressant actions of ketamine and psychedelics.

Mechanism	Area of Effect	Ketamine	Psychedelics
Serotonergic Signaling	Expression	Ketamine increased extracellular levels of 5-HT in the PFC (Ago et al., 2019; López-Gil et al., 2019)	
		5-HT depletion blocked the effects of (*S*)-ketamine (du Jardin et al., 2018)	
		5-HT depletion did not block the effects of (*R*)-ketamine (Zhang et al., 2018)	
	5-HT Receptors	Ketamine increased 5-HT1B receptor binding (Spies et al., 2018; Tiger et al., 2020; Yamanaka et al., 2014)	Non-hallucinogenic analogues of psychedelics (Cao et al., 2022) and novel monoamine transporter ligands (Rudin et al., 2022) exerted antidepressant effects via 5-HT receptors
			Antidepressant and antidepressant-like effects were reportedly primarily mediated through 5-HT2A receptor activation (Cao et al., 2022; López-Giménez and González-Maeso, 2018; Ly et al., 2018; Pędzich et al., 2022; Rolland et al., 2014)
			Behavioral response to psilocybin was not blocked by ketanserin (a 5-HT2A/2C receptor antagonist)
			DOI (a selective 5-HT2A receptor antagonist) did not have antidepressant-like effects
	SERT binding	Ketamine increased SERT binding ((Spies et al., 2018; Tiger et al., 2020; Yamanaka et al., 2014)	Increased occupancy with LSD and 5-MeO-DMT administration (Kyzar and Kalueff, 2016; Rickli et al., 2015), but no interactions with LSD (Blough et al., 2014; Rickli et al., 2015)
Dopaminergic Signaling	Expression	Chemogenetic inhibition of dopamine signaling blocked ketamine's antidepressant-like effects (Wu et al., 2021a; Wu et al., 2021b)	DMT, psilocybin, and mescaline may convert to dopamine after ingestion (Fitzgerald, 2021)
	Dopaminergic Receptors	Drd1 activation mediated the antidepressant-like behavioral effects of ketamine and increased cortical spinogenesis (Hare et al., 2019; Wu et al., 2021a). Drd1 expression also increased after ketamine administration (Li et al., 2022a)	
		(*R*)-ketamine had Drd1-activation independent effects (Chang et al., 2020)	
	Firing activity	Ketamine increased the firing activity of dopaminergic neurons (Iro et al., 2021)	In high doses, LSD increased dopaminergic firing activity (De Gregorio et al., 2016)
Glutamatergic Signaling	Glutamate surge	Glutamate "surge" (reviewed in (Kadriu et al., 2021))	Glutamate "surge" (reviewed in (Kadriu et al., 2021))
	NMDAR-related effects	An extensive literature describes the role of NMDAR antagonism in ketamine's antidepressant effects, particularly on GABA-ergic interneurons (reviewed in (Miller et al., 2016; Zanos and Gould, 2018))	Psilocybin increased AMPAR/NMDAR ratios in hippocampal slices (Hesselgrave et al., 2021)
		(*R*)-ketamine and (2*R*,6*R*)-HNK appeared to have NMDAR-independent effects (Dravid et al., 2007; Lumsden et al., 2019; Zhao et al., 2012)	Ibogaine may antagonize NMDARs (Underwood et al., 2021)

Mechanism	Area of Effect	Ketamine	Psychedelics
			Psilocybin increased NR2A expression but was not associated with an antidepressant response (Wotjas et al., 2022)
	AMPAR-related effects	Ketamine upregulated mTORC1 signaling via increased AMPAR activation (Aguilar-Valles et al., 2021; Li et al., 2010; Rafało-Ulińska and Pałucha-Poniewiera, 2022; Zanos et al., 2016; Zhou et al., 2014)	Psychedelics upregulated mTORC1 signaling via increased AMPAR activation (Ly et al., 2020; Madrid-Gambin et al., 2022; Ornelas et al., 2022; Vollenweider and Preller, 2020; Vollenweider and Smallridge, 2022)
		(2*R*,6*R*)-HNK had mGluR2-dependent antidepressant-like effects (Zanos et al., 2019)	
		(*R*)-ketamine increased ERK signaling, particularly on microglia, which mediated its antidepressant-like effects (Yang et al., 2018b; Yao et al., 2022)	
	mGluR-related effects	Co-administration of ketamine and an mGluR2/3 antagonist sustained antidepressant-like response (Pałucha-Poniewiera et al., 2021; Rafało-Ulińska et al., 2022)	mGluR2/3 agonists inhibited the effects of DOI in mice (Benvenga et al., 2018)
GABAergic signaling	Expression	Ketamine increased hippocampal GABA turnover (Silberbauer et al., 2020) and GABA release (Pham et al., 2020)	Psychedelics increased GABA expression in the mPFC (Carhart-Harris and Nutt, 2017; Mason et al., 2020)
	Receptors	$GABA_A$ receptor activity was upregulated by ketamine (Wang et al., 2017)	LSD did not affect EEG response in $GABA_A$ receptor delta subunit knockout mice (Grotell et al., 2021)
		Benzodiazepines (which also increase $GABA_A$ receptor activity) decreased ketamine's antidepressant effects (Andrashko et al., 2020; Fuchikami et al., 2015)	
	Signaling	Ketamine rescued deficits in synaptic GABA-ergic markers and the frequency of inhibitory post-synaptic currents in the mPFC (Ghosal et al., 2020)	Stress-induced alterations in GABA-ergic circuitry were reversed by 5-HT2aR agonists in the VTA (Kimmey et al., 2019)
Opioid system	Receptors	Ketamine had a strong affinity for the mu-opioid receptor and weak affinity for the kappa opioid receptor (Bonaventura et al., 2021)	Psychedelic binding to mu- and kappa-opioid receptors correlated with "therapeutic component scores" (Zamberlan et al., 2018)
		Opioid receptor antagonists abolished ketamine's (and its metabolites') rapid-acting antidepressant effects in clinical and preclinical models (Klein et al., 2020; Williams et al., 2019; Williams et al., 2018; Wulf et al., 2022; Zhang et al., 2021a)	Mu-opioid receptor binding after psychedelic administration correlated with self-report dependence measures (Zamberlan et al., 2018)
Inflammation	Cytokines	(*R*)-, but not (*S*)-ketamine reduced blood IL-6 levels in a model of ulcerative colitis (Fujita et al., 2021)	Psilocybin, LSD, and DOI reduced levels of cytokines and TNF-α (Kozłowska et al., 2021; Nardai et al., 2020; Nkadimeng et al., 2021; Smedfors et al., 2022; Yu et al., 2008)
		(*R*)-ketamine reduced central and peripheral levels of pro-inflammatory cytokines in mice administered LPS (Zhang et al., 2021b)	
		Ketamine decreased levels of pro-inflammatory cytokines in a sex-dependent manner after maternal deprivation (Abelaira et al., 2022)	
		Baseline IL-8 levels predicted treatment response to ketamine in females but not males (Kruse et al., 2021)	
		Ketamine had prophylactic effects against upregulation of inflammatory markers after stress exposure (Brachman et al., 2016; Camargo et al., 2021; Costi et al., 2022)	DOI had prophylactic effects against TNF-alpha administration, preventing the upregulation of pro-inflammatory cytokines (Nau et al., 2013)

Mechanism	Area of Effect	Ketamine	Psychedelics
	HPA-axis signaling	Ketamine restored glucocorticoid receptor expression in the hippocampus (Wang et al., 2019)	Short-term increases in cortisol and ACTH were observed during the peak hallucinogenic effects of psilocybin (Hasler et al., 2004)
		Corticosterone and ACTH levels were reduced by ketamine after LPS injection (Besnier et al., 2017)	
	Kynurenic signaling	Ketamine restored the KYN:tryptophan ratio (Moaddel et al., 2018; Wang et al., 2015)	
		Increased kynurenic acid post-ketamine correlated with treatment response (Zhou et al., 2018)	

5-HT: 5-hydroxytryptamine; 5-Meo-DMT: 5-methoxy-N,N-dimethyltryptamine; ACTH: adrenocorticotropic hormone; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; DOI: 2,5-Dimethoxy-4-iodoamphetamine; Drd1: dopamine receptor D1; ERK: extracellular signal-related kinase; GABA: gamma aminobutyric acid; HNK: hydroxynorketamine; IL: interleukin; KYN: kynurenine; LPS: lipopolysaccharide; LSD: lysergic acid diethylamide; mGluR: metabotropic glutamate receptor; mPFC: medial prefrontal cortex; mTORC1: mechanistic target of rapamycin complex 1; NMDAR: *N*-methyl-D-aspartate receptor; PFC: prefrontal cortex; SERT: serotonin transporter; TNF-α: tumor necrosis factor alpha; VTA: ventral tegmental area