Investigating the Neurobiological Basis of Ketamine's Antidepressant and Dissociative Effects: Are They Independent Mechanisms?

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Abstract

Depression presents a significant clinical challenge due to its high prevalence, treatment resistance, and the limitations of conventional therapies. This thesis investigates the neurobiological underpinnings of ketamine's rapid antidepressant effects alongside its medically problematic dissociative properties, with the primary aim of determining whether these effects are mediated by independent mechanisms. A comprehensive review of the literature reveals that ketamine's antidepressant effects involve several distinct mechanisms. One mechanism involves improved top-down regulation via enhanced connectivity between prefrontal and limbic regions, which contributes to better emotional regulation. Separately, ketamine's action is also associated with increased levels of brain-derived neurotrophic factor (BDNF), enhanced opioid signaling, and an upregulation of AMPA receptor activity. In contrast, ketamine-induced dissociation appears to arise primarily from disruptions in working memory and alterations in neural oscillatory patterns, particularly within the default mode network and related brain regions. While short-term correlations exist between dissociative and antidepressant effects, evidence suggests largely independent neurobiological mechanisms. This dissociation between therapeutic and dissociative effects provides a promising framework for developing novel compounds that retain ketamine's antidepressant efficacy while minimizing its dissociative side effects.

Introduction

Depression is a condition that can debilitate people and significantly reduce their quality of life and ability to function as productive members of society (Stecher et al., 2023). Depression rates have steadily increased since the early 2000s, a trend that persisted beyond the COVID-19 pandemic. (Goodwin et al., 2022; Egbert et al., 2021). This issue is highly complex, driven by multifactorial causes, and compounded by the stigma that discourages many individuals with symptoms of depression from seeking help (Drapalski et al., 2013). A major challenge in depression treatment is the limited efficacy of existing therapies (Insel & Wang, 2009). Psychotherapy requires significant time and commitment, with mixed success rates. Antidepressants, while commonly used, have delayed effects and unwanted side effects, making adherence difficult. There is also a subset of people with depression for which the currently available treatments are ineffective. These patients have treatment-resistant depression (TRD), indicating the dire need for novel antidepressant treatments (Rush et al., 2006).

Depression is a complex and heterogeneous condition, meaning that it has multiple contributing factors and symptoms but also that it presents differently for each individual. This complexity has brought on various theories from both biological and psychological perspectives, and these theories are still evolving to this day. The first theory of depression introduced the Monoamine Hypothesis, which states that depression is a result of a deficiency in monoamine

neurotransmitters such as serotonin, dopamine, and norepinephrine. This theory has had extensive scientific debate, and multiple other theories have expanded on it. Importantly, this theory led to the development of the only pharmacological approach to treat depression. A class of the discovered antidepressants, selective serotonin reuptake inhibitors (SSRI), increase serotonin levels and are known to treat a subset of MDD patients (Schildkraut, 1965), and while these are the most known there exist respective variations for dopamine, and norepinephrine. Another biological theory that builds on the limitations of the monoamine hypothesis is that depression is caused by reduced Brain-Derived Neurotrophic Factor (BDNF) levels, which play a critical role in neurogenesis and synaptic plasticity. It is supported by multiple evidence, among them the post-mortem studies that show reduced BDNF in the brains of depressed individuals (Duman & Monteggia, 2006) but also by studies showing that increased BDNF production contributes to the treatment of MDD (Correia et al., 2023). A relevant psychological theory is the Cognitive Theory of depression developed by Aaron Beck, which is the basis of cognitive behavioral therapy. According to this theory, depression is characterized by a cognitive bias that predisposes individuals to develop negative thought patterns, which in turn reinforce feelings of hopelessness, a critical factor in suicidal ideation. This conceptual framework has informed the development of Cognitive Behavioral Therapy (CBT), an intervention widely used in clinical practice today (Beck, 1979). As mentioned earlier these therapies are insufficient as they only work for a subset of MDD patients and require commitment as they take a long time to take effect.

In the last decades, a new class of drugs has been showing potential in treating depression, these are drugs that modulate the glutaminergic system, specifically the N-methyl-D-aspartate (NMDA) receptor (McIntyre & Jain, 2024). Early research has implicated NMDA receptors with memory acquisition, long-term potentiation (Morris et al., 1986), and importantly working memory (Tsien et al., 1996). Ketamine is the main reason glutaminergic drugs are being thought of as potential antidepressants because recent research has provided evidence, including clinical trials, that it is effective in treating depression (Berman et al., 2000; Lapidus et al., 2014). It has also been shown to treat suicidality and anhedonia, and importantly, it is effective in some patients with TRD (Price et al., 2009; Nogo et al., 2022; Murrough et al., 2012). Ketamine primarily acts as an NMDA antagonist with some secondary pharmacological properties that we will explore later.

Ketamine has been widely utilized as an anesthetic in medical settings since the 1970s and has also been used recreationally since the 1980s. The appeal of ketamine as a recreational drug comes from its distinct dissociative and psychedelic-like effects. Ketamine's antidepressant effects seem to solve many of the problems mentioned, with it having rapid and long-lasting antidepressant effects, and treating patients with TRD (Murrough et al., 2012). However, ketamine has limitations of its own, specifically when considering the dissociative effects that it can produce.

Dissociation encompasses a range of subjective experiences. It is a term that can be used in the context of clinical psychology, where it describes a chronic pathological state, but also in

the context of an altered state of consciousness to describe a transient state that changes the quality of perception (Mertens & Daniels, 2021).In this review, we will focus on the transient state of dissociation, which can be defined as “a disruption in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior,” according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). While ketamine is an effective antidepressant medication, the dissociative effects pose a significant challenge in medical settings. Ketamine can induce bizarre altered states of consciousness that could leave some patients vulnerable and, in some cases, produce a traumatic experience (Correia-Melo et al., 2017). This means that practitioners would need to be specifically trained in guiding people through the experience in a safe space. Also, there is a need to educate the patients about this dissociative state before undergoing treatment so that they know what to expect and how to handle the experience. This significantly restricts the accessibility and potential adaptability of the treatments. Currently, there is conflicting research on whether the dissociative effects are a necessity for the antidepressant effects.

Reissmann et al. (2023) conducted a case study on a patient with TRD who received twelve ketamine infusions. The researchers measured the intensity of the Altered State of Consciousness (ASC) produced by the ketamine using the 5D-ASC questionnaire and the Depression scores using the BDI-II. They found a strong correlation between the intensity of the ASCs with the improvement of depression scores, indicating that the antidepressant effects may be dependent on the dissociative effects. But it is also worth mentioning that at the end of the infusions, the specific patient did not see a significant reduction in depression overall, suggesting a more nuanced relationship between the dissociative and antidepressant effects. If we could dissociate the mechanisms behind the antidepressant and dissociative effects of ketamine, we would be confident that it is possible to develop a drug that triggers the exact antidepressant mechanisms as ketamine while also eliminating the medically undesirable dissociative effects. A literature search was conducted to understand whether the dissociative effects are indeed required for the therapeutic effects by answering the following question: What are the mechanisms underlying the antidepressant and dissociative effects of ketamine?

Therapeutic Mechanisms

Before we examine the mechanisms that underlie the antidepressant effects of ketamine, it would also be beneficial to understand what the disruptions are in the brain of an MDD patient. Ramasubbu et al. (2014) show that MDD patients have reduced FC between their amygdala and multiple other regions that belong to the Salience and Central Executive Network which are involved in categorizing important stimuli and cognitive control among other functions (Seeley et al., 2007, Menon & Uddin, 2010). Findings indicate that this contributes to impaired top-down regulation, leading to persistent negative affect and impaired emotion regulation. Impaired

top-down regulation refers to the inability of higher-order brain regions, the Prefrontal Cortex (PFC), to correctly regulate more, evolutionarily older, regions such as the amygdala. The work of Gao et al. (2022) and Nejad et al. (2013) shows that depressed patients during a cognitive control task had reduced activation in the dorsolateral prefrontal cortex (dlPCF) and anterior cingulate cortex (ACC), both areas that are in the PFC and are crucial for cognitive control, which suggests that the neural mechanisms needed to regulate emotions are compromised (impaired top-down control). During emotional viewing tasks, MDD patients only had a heightened and prolonged response in the limbic system when presented with negative stimuli, indicating a cognitive bias. These two processes of impaired cognitive control and negative cognitive bias can be described as a state of emotional dysregulation (disability to downregulate negative emotions) in MDD patients.

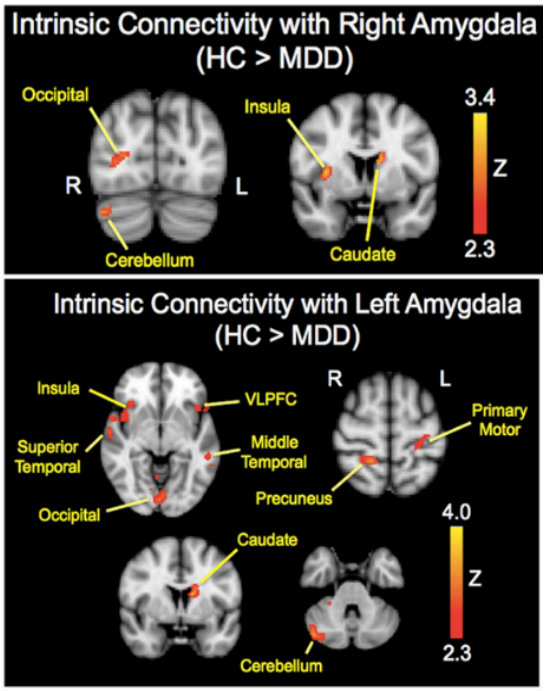

Figure 1. Altered functional connectivity between the right and left amygdala in MDD patients compared to healthy controls. This suggests impaired top-down regulation, contributing to emotional dysregulation. From Ramasubbu, R., Konduru, N., Cortese, F., Bray, S., Gaxiola-Valdez, I., & Goodyear, B. (2014). Reduced Intrinsic Connectivity of Amygdala in Adults with Major Depressive Disorder. *Frontiers in Psychiatry*, *5*. https://doi.org/10.3389/fpsyt.2014.00017

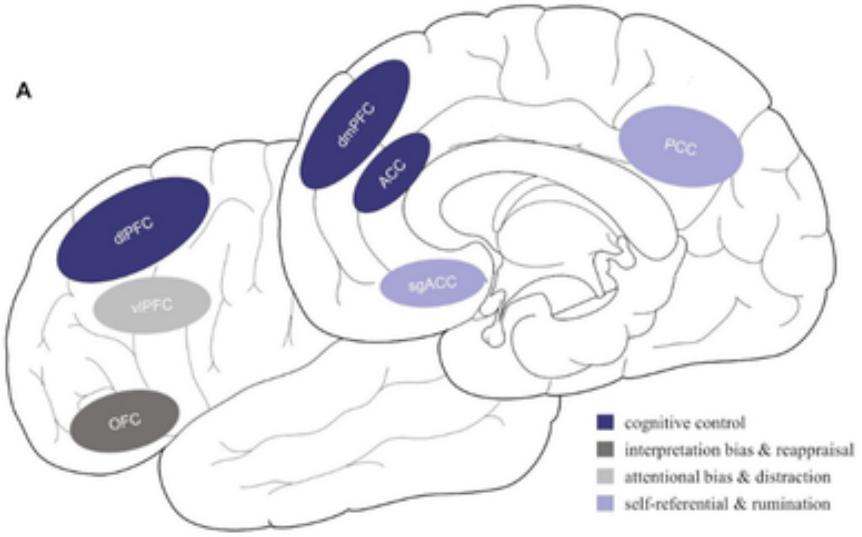

Figure 2. Illustration of key brain regions involved in depression-related cognitive dysfunction and their respective functions. From Gao, W., Yan, X., & Yuan, J. (2022). Neural correlations between cognitive deficits and emotion regulation strategies: understanding emotion dysregulation in depression from the perspective of cognitive control and cognitive biases. *Deleted Journal*, *2*(3), 86–99. https://doi.org/10.1093/psyrad/kkac014

NMDA-Related Mechanisms (Zanos et al., 2018)

First, let's start with two theories relating to the NMDA-dependent antidepressant effects of ketamine: the disinhibition hypothesis and the involvement of extrasynaptic NMDARs. The disinhibition hypothesis postulates that the antidepressant effect occurs due to increased activation in the prefrontal cortex, specifically the medial prefrontal cortex (mPFC). This increased activation occurs because ketamine has a preferentially strong effect on some specific neurons, which are called GABAergic interneurons (Seamans, 2008; Moghaddam et al., 1997). Via directly modulating GABAergic interneurons with optogenetics, Yizhar et al. (2011) showed that they act as “brakes” that inhibit cortical neurons in the mPFC and other corticolimbic areas of the brain, which was also indirectly shown by the work of Moghaddam et al. (1997) by inhibiting them with ketamine. Thus, by stopping the inhibition of the GABAergic neurons, the PFC neurons fire more frequently, increasing the overall activity in these areas. This hypothesis is substantiated by subsequent research that exclusively blocked the GABAergic interneurons and observed similar antidepressant effects (Zanos et al., 2017; Fischell et al., 2015). As mentioned previously, MDD patients show reduced activity in the PFC, which leads to impaired top-down control. Thus, the increased activity in the PFC induced by the inhibition of these interneurons contributes to regulating the top-down control.

The second theory has an end mechanism for the antidepressant action, which has to do with an mTOR-dependent mechanism. Miller et al. (2014) explored this mechanism using

genetically modified mice, which could not produce a specific NMDAR subunit. This subunit is found on specific NMDA receptors located outside the synapse of neurons. Low levels of ambient glutamate tonically activate these NMDARs. This study showed that the absence of these specific NMDARs disinhibits the mTOR pathway, which leads to increased production of BDNF. This suggests that when ketamine inhibits these extrasynaptic NMDARs, it leads to the production of BDNF, which, as mentioned earlier, has been shown to contribute to the treatment of depression. They also showed that in knockout mice lacking extrasynaptic NMDARs, ketamine did not further reduce depressive-like behaviors. This finding indicates that the absence of these receptors prevents ketamine's antidepressant effects, suggesting that extrasynaptic NMDAR inhibition is a necessary contributor to ketamine's therapeutic action.

NMDA Independent Mechanisms

Two NMDAR-independent mechanisms show significant potential in elucidating the underlying basis of antidepressant effects. The first one has to do with a specific metabolite of ketamine called (2S,6S;2R,6R)-hydroxynorketamine (HNK). Zanos et al. (2016) using mice and rat models showed that this specific metabolite not only contributes to the antidepressant effects of ketamine but also is necessary. They determined that HNK works by inducing an adaptation that leads to the upregulation of Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) receptors, the other glutaminergic receptors. While we don't understand how this upregulation results in antidepressant effects, they confirmed that it does by using an AMPA antagonist before HNK administration, which diminished the antidepressant effects. Importantly, they show that HNK does not produce any of the dissociative effects that ketamine induces.

The second mechanism has to do with ketamine's action on the opioid system. Williams et al. (2018) and Williams et al. (2019) used an opioid antagonist before ketamine administration, which resulted in a substantial decrease in the rapid antidepressant and antisuicidal effects of ketamine. This implies that ketamine interacts with opioid antagonists in a way that facilitates the antidepressant effects. Importantly, despite the opioid antagonist disrupting the antidepressant effect, dissociative effects remained present. While we don't understand the full extent of the mechanisms yet, we know that ketamine potentiates the μ-opioid receptor by increasing the effectiveness of opioid-induced signaling (Gupta et al., 2011).

Functional connectivity that underlies Antidepressant Effects

Another technique that can help us understand the acute effects of ketamine on the brain is fMRI, which measures functional connectivity (FC). FC practically measures whether the activity in one brain region is correlated with another, indicating communication. Depending on the experimental design, whether comparing healthy individuals to those with depression or examining participants during specific tasks, we can identify the neural communication pathways that underlie either an antidepressant mechanism or a dissociative state.

First, let's look at a study that followed patients with Major Depressive Disorder (MDD) as they had a series of ketamine infusions (Vasavada et al., 2020). This study measured the FC at baseline, after the first infusion, and after the last infusion to compare the changes in FC. They found significant results showing that FC between the amygdala and the central executive network (CEN) and the right hippocampus and left CEN increased. Additionally, the left amygdala decreased FC with the Salience network (SN), which also predicted improvements in anxiety. The increase of FC between the hippocampus and CEN predicted decreased anhedonia. As previously mentioned, MDD patients have a reduced FC between their amygdala and SN, and CEN contributes to impaired top-down control. Thus, the increased connectivity between these regions contributes to the antidepressant effects by strengthening top-down control.

The final study conducted by Meiering et al. (2024) assessed differences in FC and functional activity (FA) in healthy participants while they were under the influence of ketamine and actively engaged in a task involving negative emotional processing. They found that ketamine decreased the FA of the DMN and the hippocampus while it increased FC between frontal and limbic regions. This increase in FC between frontal and limbic regions is associated with better emotional regulation during negative emotion-processing tasks (Berboth & Morawetz, 2021), still, this effect is acute, according to the study. However, the reduction of FA in the DMN was sustained one day after the ketamine infusion, indicating that this may be part of the long-term antidepressant effects of ketamine. This reduction in FA is potentially one of the antidepressant mechanisms, as we know that for MDD patients, a hyperactive DMN during negative emotional processing is associated with the maladaptive strategy of rumination (Gao et al., 2022); the sustained reduction of activity in the DMN may disrupt this maladaptive strategy.

Dissociative Mechanisms

Now that we have discussed some of the antidepressant mechanisms let's turn to the dissociative mechanisms. As defined previously, dissociation is the disruption of the normal integration of experience and thus perception. Therefore we need to relate how the main function that is associated with NMDA receptors, working memory, is related to perception. Working memory can be thought of as the process that temporarily stores information about the present and facilitates the manipulation of that information to create new mental representations. According to D'Esposito and Postle (2014), working memory is not confined to a single brain system; rather, it emerges from the coordinated activity of a distributed network of neural systems. Additionally, they also found that persistent neural activity is required for working memory. Working memory is directly implicated with perceptions as studies have found working memory operations in the perceptual cortex (Sreenivasan et al., 2014) but also that working memory influences modes of perception such as visual and color perception(Allen et al., 2011, Roussy et al., 2021). It is also helpful to distinguish between two distinct manifestations of

dissociation: depersonalization and derealization. Depersonalization refers to the subjective experience of feeling detached from one's self (including thoughts, emotions, and bodily sensations). In contrast, derealization denotes a perceived disconnection from the external world, making the environment appear unreal or distorted.

NMDA-R antagonists abolish persistent neuron firing, disrupting mental representation

In the last decade, there has been an increase in research on the dissociative effects of ketamine, allowing us to speculate on possible factors that facilitate dissociation. The first contributing factor comes from the research of Wang et al. (2013), which finds that ketamine disrupts normal perception through a disruption in working memory, and Van Vugt et al. (2020), which provides subsequent evidence for the disruption of working memory by ketamine. Both studies were conducted on primates as they provide an accurate model for the human brain since they have similar brain physiology, among other reasons. The researchers focused on specific neurons in the dlPFC (brain region associated with working memory) of primates after disrupting NMDA receptors, and the relevant neurons they focused on are called delay cells. As we have mentioned before, a condition for working memory is the persistent firing of cells, which in this case are these delay cells. Van Vugt et al. (2020) directly disrupted NMDA receptors in the dlPFC, while Wang et al. (2013) used systematic ketamine administration. Both ways achieved a disruption of the NMDA receptor, which resulted in the cessation of the persistent firing of delay cells and the disruption of working memory. As mentioned before, working memory is directly implicated in maintaining the standard flow of perception. This provides a mechanism by which ketamine disrupts standard perception through its impact on working memory.

EEG Behind Dissociative States

The dissociative state induced by ketamine has also been studied in the context of resting brain wave activity by conducting electroencephalography (EEG), which measures the firing frequency of a neuron population. De La Salle et al. (2016) measured the resting brainwave activity of humans while the ketamine was in effect while focusing on the DMN, CEN, and SN. They also used the Clinician-Administered Dissociative States Scale (CADSS), which allowed them to correlate the brainwave activity with the degree of dissociative states. They found a significant decrease in slow frequencies, which include the delta, theta, and alpha waves, and an increase in fast frequencies, which are gamma waves. Most importantly, they found a correlation between a decrease in α-waves and an increase in depersonalization scores.

Vesuna et al. (2020) attempted to find a brain wave mechanism behind the dissociative state more explicitly. To do this, first, they administered ketamine in mice and measured the brain wave activity, but they also used two-photon microscopy to measure with a single-cell resolution a specific layer of neurons in the retrosplenial cortex, which is part of the DMN. They found that ketamine induced a prominent delta-wave frequency in these neurons. Importantly, they were able to establish a causal relationship by inducing a delta-wave frequency in these cells using optogenetics, which in turn produced behaviors associated with dissociative states in the mice. They also supplemented this finding with human correlates. In a patient with focal seizures, a delta rhythm was observed in the same region just before the seizures. Self-reports indicate that this coincided with dissociative experiences. This provides a solid potential mechanism for dissociative states.

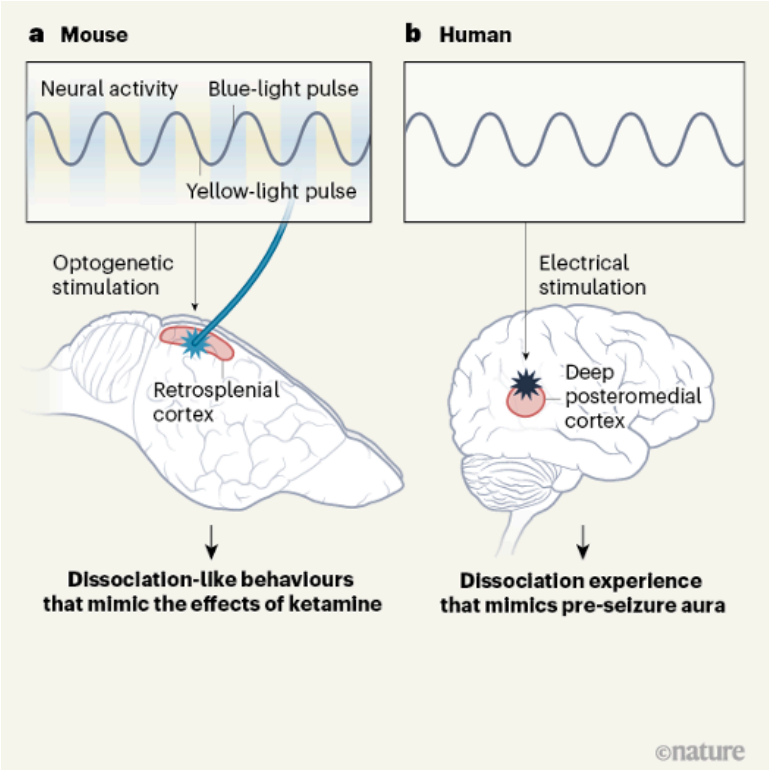

Figure 3. An overview of techniques for eliciting brain oscillations associated with dissociative states. From Solt, K., & Akeju, O. (2020). The brain rhythms that detach us from reality. *Nature*, *586*(7827), 31–32. https://doi.org/10.1038/d41586-020-02505-z

Functional Connectivity and Activity During Dissociative States

In this section, we will examine a study that measures FC in relation to dissociative states. This study comes from the research of Bonhomme et al. (2016), which investigated the

functional connectivity of the brain networks associated with resting during ketamine alteration of consciousness. They controlled this by increasing the dosage stepwise until loss of responsiveness was achieved. They found that the default mode network (DMN) and the salience network (SN) had significant alterations, mostly decreases, in the intranetwork connectivity. As for internetwork connectivity, they found that the DMN increased its connectivity with other regions but also with regions that are usually not connected to it, such as the right sensory cortex. Although the study doesn't directly correlate FC with the intensity of the dissociative experience, we can speculate on how these FC alterations contribute to the dissociative experience by looking at experiential symptoms and the healthy function of these networks. Healthy DMN activity is responsible for maintaining self-referential processes and integration of self-related information; we can thus speculate that the decreased connectivity within the DMN results in symptoms of depersonalization. Ketamine has also been shown to produce very vivid and complex visual hallucinations (Vlisides et al. 2018), and the DMN is responsible for dictating the self-reported level of detail of an experience (Sormaz et al., 2018). This indicates that the changes in the DMN connectivity may facilitate the increased level of visual detail in ketamine-induced dissociative experiences. The increase in functional connectivity between the DMN and sensory cortex could explain the subjective experience of "melting into one's surroundings" (Muetzelfeldt et al., 2008). This is because, under normal conditions, these two regions exhibit an anticorrelated relationship, meaning that as the DMN becomes more active, the sensory cortex shows decreased activity, which is to be expected as the DMN contributes to the perception of the internal world and the sensory cortex to the external world(Buckner et al., 2008, Raichle, 2015, Van Buuren et al., 2010). Thus, the inversion or the anticorrelation contributes to the experience of the two worlds blending.

Conclusion & Discussion

Now that we have examined the mechanisms underlying the dissociative and antidepressant effects of ketamine, we can answer the research question: What are the mechanisms underlying the antidepressant and dissociative effects of ketamine? Starting with the antidepressant effects of ketamine we can see that a prevalent mechanism is establishing a functional top-down regulation. This is shown both by the functional connectivity studies that show enhanced connectivity between the amygdala and the PFC in participants that experience alleviation of depression symptoms and by the strengthening of PFC activity. The antidepressant effects of ketamine depend on some other mechanisms as well: Enhanced BDNF production induced by the inhibition of specific NMDA receptors by ketamine, enhancement of opioid receptor-induced signaling, and the upregulation of AMPA receptors by the ketamine metabolite HNK. The dissociative effects of ketamine have completely different mechanisms. The disruption of working memory plays an important role as it leads to the disruption of normal perception and integration of information. A second mechanism that is also crucial for the

induction of dissociation is the alteration of the firing frequency of a population of neurons in the retrosplenial cortex as it was shown that inducing a delta-wave frequency in these cells induces dissociation. Finally, altered functional connectivity is also a crucial part of the dissociation process as we can explain how specific subjective experiences may arise due to this altered functional connectivity.

Before we answer the initial question, “Are the antidepressant effects of ketamine dependent on the dissociative effects?”, we should examine two studies involving statistical analysis that investigate if a correlation between the dissociative and antidepressant effects of ketamine is present. These are the studies of Echegaray et al. (2023) and Chen et al. (2022) and both of them found no correlation linking the dissociative with the long-term antidepressant effects of ketamine. However, Echegaray et al. (2023) did find a correlation that lasted for the first 24 hours, suggesting that the dissociative effects may contribute to the antidepressant effects but only temporarily.

In the process of examining the mechanisms of ketamine, it has become apparent that the antidepressant effects are independent of the dissociative effects of ketamine as the preceding studies suggest. Two key findings strongly support this conclusion. First, the fact that the ketamine metabolite produces antidepressant effects while not producing dissociative effects (Zanos et al. 2016) indicates that at least some part of the antidepressant effects are completely independent from the dissociative effects. The second finding that supports this is the diminished antidepressant effects following an opioid antagonist (Williams et al. 2018; Williams et al. 2019) while the dissociative effects were present. These findings help solidify our conclusion as we would expect to see a disruption in both effects if the antidepressant effects shared mechanisms with the dissociative effects.

Finally, the only potential overlap between mechanisms was seen with the correlation of decreasing alpha-power with the intensity of dissociative experience observed by De La Salle et al. (2016). It is potentially overlapping with the antidepressant mechanisms as a decrease in alpha waves in MDD patients has been associated with the treatment of depression (Riddle et al., 2021). This could mean that the dissociative effects also have some limited antidepressant properties and may explain the correlation that the case study of Reissmann et al. (2023) found between the intensity of dissociation and better depression scores but also the temporary correlation that Echegaray et al. (2023) found.

These findings suggest that rapid and sustained antidepressant effects can occur independently. Further research is necessary to identify a compound that reliably elicits these effects. Despite the challenges of drug discovery, the ketamine metabolite HNK shows considerable promise. Further investigation into its pharmacological and neurobiological differences from ketamine could guide the development of novel antidepressants. A novel agent that combines these therapeutic benefits without ketamine's dissociative side effects could transform depression treatment, particularly for patients with treatment-resistant depression, by reducing the need for expert supervision and thereby enhancing cost efficiency and accessibility.

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ChatGPT was used as a means for literature search (provided titles and summaries of relevant studies which were cross-checked) and also to rewrite some of my phrases to be more fit without changing the meaning.
Consensus AI was used as a means for literature search.

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