



## Review

# Pharmacological Mechanism of Ketamine in Suicidal Behavior Based on Animal Models of Aggressiveness and Impulsivity: A Narrative Review

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**Citation:** Nguyen, T.M.L.; Jollant, F.; Triteschler, L.; Colle, R.; Corruble, E.; Gardier, A.M. Pharmacological Mechanism of Ketamine in Suicidal Behavior Based on Animal Models of Aggressiveness and Impulsivity. *Pharmaceuticals* **2023**, *16*, 634. <https://doi.org/10.3390/ph16040634>

Academic Editors: Ana Lúcia S. Rodrigues and Anderson Camargo

Received: 6 March 2023

Revised: 12 April 2023

Accepted: 14 April 2023

Published: 21 April 2023



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**Abstract:** Around 700,000 people die from suicide each year in the world. Approximately 90% of suicides have a history of mental illness, and more than two-thirds occur during a major depressive episode. Specific therapeutic options to manage the suicidal crisis are limited and measures to prevent acting out also remain limited. Drugs shown to reduce the risk of suicide (antidepressants, lithium, or clozapine) necessitate a long delay of onset. To date, no treatment is indicated for the treatment of suicidality. Ketamine, a glutamate NMDA receptor antagonist, is a fast-acting antidepressant with significant effects on suicidal ideation in the short term, while its effects on suicidal acts still need to be demonstrated. In the present article, we reviewed the literature on preclinical studies in order to identify the potential anti-suicidal pharmacological targets of ketamine. Impulsive-aggressive traits are one of the vulnerability factors common to suicide in patients with unipolar and bipolar depression. Preclinical studies in rodent models with impulsivity, aggressiveness, and anhedonia may help to analyze, at least in part, suicide neurobiology, as well as the beneficial effects of ketamine/esketamine on reducing suicidal ideations and preventing suicidal acts. The present review focuses on disruptions in the serotonergic system (5-HT<sub>B</sub> receptor, MAO-A enzyme), neuroinflammation, and/or the HPA axis in rodent models with an impulsive/aggressive phenotype, because these traits are critical risk factors for suicide in humans. Ketamine can modulate these endophenotypes of suicide in human as well as in animal models. The main pharmacological properties of ketamine are then summarized. Finally, numerous questions arose regarding the mechanisms by which ketamine may prevent an impulsive-aggressive phenotype in rodents and suicidal ideations in humans. Animal models of anxiety/depression are important tools to better understand the pathophysiology of depressed patients, and in helping develop novel and fast antidepressant drugs with anti-suicidal properties and clinical utility.

**Keywords:** ketamine; suicide; antidepressant; aggressiveness; impulsivity; endophenotype

## 1. Introduction

Approximately 9% of people report having suicidal thoughts at some time in their life, and 3% actively attempt suicide [1]. Suicidal thought is 1.5 times more prevalent in women than in men, and is particularly frequent in adolescents and young adults [1]. Suicide is the leading cause of preventable mortality all over the world [2]. Every year, nearly 700,000 people in the world take their own lives, where more than two-thirds are from low- and middle-income countries. Suicide was the fourth most significant cause of death among 15–29 year olds worldwide in 2019 [3]. In addition, 10 to 20 times more people than this attempted suicide, with a significant burden at individual and collective levels. Suicidal behavior is a major public health problem worldwide.

Suicidal ideation is a prevalent symptom of many mental diseases [4]. About 90% of people who die from suicide have a history of mental disorder [5], and more than two-thirds of attempts or deaths happen during a major depressive episode (MDE) [6]. Although MDE is treatable with pharmacotherapy, up to one-third of patients do not respond to a prescribed first-line antidepressant and may remain at risk of suicide [7,8]. Furthermore, treatment-resistant depression (TRD) has been identified as a risk factor for (attempted) suicide [9]. TRD is defined as a failure of two successive antidepressant treatments of adequate dosage and duration (i.e., at least eight weeks). The estimated incidences of attempted and completed suicides in TRD patients are 4.66 and 0.47 per 100 patients per year, respectively, which are twice and ten times higher than in people suffering from non-resistant depression [10].

We recently published a review article concerning the interest of ketamine in the prevention of suicidal ideation, specifying its clinical interest [11]. It is difficult to model TRD in rodents. However, we need to develop reliable treatment response predictors to guide personalized antidepressant strategies in these patients. Thus, efforts have been made to establish a peripheral biomarker signature of response/non-response to chronic antidepressant or electroconvulsivotherapy (ECT) in animal models of anxiety/depression [12]. Thus, using a proteomic approach, the peripheral signatures of an antidepressant response (Flx-R) or non-response (Flx-NR) to chronic fluoxetine (Flx) treatment were described in the blood cells of a corticosterone (CORT) model of anxiety/depression in mice [13]. Among Flx-treated mice, one-third of them did not show a 50% decrease in emotionality score, thus defining CORT/Flx-NR. The emotionality score was based on the analysis of complementary behavioral tests of anxiety/depression [14]. Similarly, the proteomic analysis revealed a signature of 33 peripheral proteins associated with a response to ECT, which is known as a highly effective treatment that induces rapid improvement in depressive symptoms [15]. These proteins (7 down- and 26 up-regulated) are involved in regulating pathways that participate in depressive disorder etiology. Other animal models exist that represent other traits of TRD, e.g., rats exposed to maternal deprivation, which induces a depressive-like behavior. A single dose of ketamine administered during the adult phase could reverse behavioral effects and neural damage induced by this stressor in adulthood rats [16,17].

Additional risk factors for suicidal behaviors in humans are difficult to model in rodents. These include a family history of suicide (e.g., genetic factors), childhood maltreatment, recent stressful events, and access to lethal means in case of suicidal ideas, among others [18]. Some factors may contribute more to the emergence of suicidal ideas (mental disorders, mental pain, hopelessness, and ruminations), while others may facilitate the transition from suicidal ideas to an act (impulsivity/aggression, risky decision making, as well as alcohol and substance use or disorder). Moreover, some factors may be considered long-term vulnerability factors (e.g., early developmental events and certain personality traits) while others are stress/precipitating factors (e.g., recent adverse events, acute phase of a mental disorder). Overall, it is currently postulated that negative events occurring in vulnerable people may increase the risk of developing intense mental pain, which, in turn, facilitate the emergence of a suicidal state and, in some but not all people, the transition to a suicidal act.

To date, very few medications have been shown to be effective in treating acute suicidal crises or preventing suicidal acts. Since classical monoaminergic antidepressant drugs (SSRI, SNRI) display a long delay of action, rapidly acting drugs may be useful to prevent suicide and reduce the risk of suicide attempts. Can preclinical studies help analyze drugs' beneficial effects on preventing suicidal ideation? Impulsivity may be both a trait and a state in depressed suicide attempters [19]. Impulsive–aggressive behavior is one of the vulnerability factors common to suicide, MDE, and bipolar disorder (BD) patients that can be modeled in rodents.

Thus, this narrative review focuses first on the pathogenesis and neurobiology of suicide by describing the role of neurotransmitters (serotonin, cytokines, glutamate) and brain circuits underlying this phenotype. Then, we describe rodent models of impulsivity/aggressiveness. Finally, we summarize the pharmacological potentials of ketamine that could explain its anti-suicidal properties. As a fast-acting antidepressant, ketamine/esketamine may offer relief in the immediate term in patients with suicide ideation in TRD. The electronic database PubMed was searched for publications from 2000 to 2022, using the search terms 'suicidal behavior' AND/OR 'animal models of aggressiveness and impulsivity'.

## 2. The Pathogenesis and Neurobiology of Suicide

The development of suicide risks is complex; it involves multiple systems and neurological circuits with interacting contributions from genetic, biological, psychological, clinical, social, and environmental factors [20–25]. Understanding these factors might help to detect high-risk individuals and assist in treatment selection [26].

The link between disrupted serotonin expression and suicide attempts or suicide, despite the discrete differences in serotonin receptors and transporter expression between patients with depression and those who exhibit suicide ideation or suicidal behaviors, were described twenty years ago [27]. However, it is unclear to what extent altered serotonin signaling in people who die by suicide can be distinguished from changes associated with depression [26]. Indeed, these two phenotypes often occur together. Evidence shows that low serotonin is associated with personality traits linked to suicidality, such as impulsive aggression [28].

The dysfunction in additional neurotransmitter systems and their molecular alterations have also been implicated in depression and suicide. For example, changes in glutamate and the GABA receptor subunit gene expression in the brains of suicide victims with major depressive disorders (MDD) have yielded some initial promising results [29]. In addition, treatments for severe depression and suicide ideation that target the glutamate pathway, such as ketamine, carry much hope [4].

Furthermore, recent findings indicate that the pathogenesis of mood disorders and suicide involves the abnormal plasticity of neural circuits [30,31]. Indeed, it has been argued that mood disorders and suicide are caused by the brain's inability to respond appropriately to environmental stimuli, which is due to reduced synaptic and structural plasticity. The role of consistent changes in gene expression in synaptic and structural plasticity was investigated in the postmortem brains of suicide subjects [31–33]. Furthermore, changes in synaptic circuitry, synaptic connectivity, and dendritic morphology have also been identified during depression and suicidality [34,35].

In addition, a meta-analysis of 18 studies comprising 1,743 subjects found evidence of aberrant inflammatory cytokine (IL-1 $\beta$  and IL-6) levels in the blood, cerebrospinal fluid, and the postmortem brain samples of patients with suicidal behavior [36]. Thus, using the brain tissue and blood from the postmortem cohorts of MDD patients who died by suicide is of great interest in identifying at-risk patients [37]. Next, such an identification of biomarkers will require validation in prospective clinical cohorts.

Suicide neurobiology is poorly understood. The majority of the literature focuses on the brain serotonergic system, the hypothalamic–pituitary–adrenal (HPA) axis, and immune-inflammatory modulators [20]. The serotonergic system has been the most

investigated and is related to suicide risk, whether directly or indirectly, through its function in mood disorders, impulsivity, and aggression [20].

### 3. Pharmacological Interventions on Suicidal Behavior

To date, very few medications have been shown to be effective in treating acute suicidal crises or preventing suicidal acts. Lithium salts (Li<sup>+</sup>) are the only mood stabilizer that has demonstrated efficacy in suicide prevention [38]. By its specific action on the serotonergic system, treatment with Li<sup>+</sup> significantly reduces impulsive–aggressive behavior. Long-term treatment with Li<sup>+</sup> seems to reduce suicidal ideation, suicidal behaviors, and death by suicide in BD. The extent to which Li<sup>+</sup> treatment prevents suicide in patients with affective disorder needs to be further investigated [39], thus reinforcing the importance of finding “anti-suicide” drug treatments. To date, no treatment has been indicated for the treatment of suicidal ideation.

The majority of pharmacological approaches regarding the treatment and prevention of suicide are focused on the treatment of psychiatric disorders [20]. Suicidal ideation frequently requires rapid intervention, yet very few treatments successfully reduce suicidal thoughts, and none are fast-acting [40]. The long delay in the clinical antidepressant efficacy observed with both pharmacotherapy (such as with SSRI–SNRI) and electroconvulsive therapy (ECT) further raises the suicidal risk [4,41]. Curbing suicidal ideation would be the ideal strategy for preventing the emergent self-harm that accounts for the majority of deaths associated with depression [4].

Recently, intravenous (IV) ketamine has been shown to reduce, within hours, the suicidal ideation in MDE and BD [11,42,43] (see below).

### 4. An Approach of Impulsivity–Aggressiveness in Rodents

A simple definition of impulsive behavior is the tendency to act prematurely without foresight. For example, such motor impulsive behavior is evident following acute morphine consumption [44]. Cognitive and psychological changes, such as a lack of impulse control, can also be observed [44]. Regulating impulsive behaviors in preclinical studies is considered in clinical conditions, and is labeled as ‘impulsive–compulsive disorders’ [45]. In rodent models, the evidence generally supports a higher impulsive behavior in males when compared with females [46]. However, data from human studies are less uniform, with reports of increased impulsive action in both males and females [47].

Although animal models are essential for research, rodents do not engage in suicidal behavior that is amenable to translational studies (see [48] for a review). However, experimental research can consider the mechanisms by which drugs might be associated with potential “adverse effects” such as suicidal ideation. Many components that are implicated in the neurobiology of suicidal behaviors, as well as the neurobiology of circuits delineated as relevant to ideation in humans, may be studied in animal models. Most of them are only intended to recapitulate some of the aspects of neurobiology that are implicated in human psychiatric disorders, rather than in the disorder itself [49]. By investigating traits that show strong cross-species parallels in addition to associations with suicide in humans, animal models might elucidate the mechanisms by which drugs are associated with suicidal thinking and behavior. Traits linked with suicide in humans that can be successfully modeled in rodents include aggressiveness, impulsivity, and irritability [48].

Despite limitations in determining suicidal intent in animals, animal models can be used to study the neurobiological components of suicidal behaviors and its related circuits in humans. Several biomarkers (endophenotypes) have been measured in rodents that are correlated with symptoms of MDD and suicidal risk factors, at least in part because of shared underlying genetic influences. Endophenotypes such as microRNAs, neurotransmitter system abnormalities (serotonin—Table 1), HPA axis dysfunction, as well as endocrine and neuroimmune changes lead to aggressiveness, impulsivity, and decision-making deficits [50] (Table 1). The molecular pathways related to suicidal behavior can be investigated in animal models, providing insights into the neurobiology of suicidal

behaviors in humans [49]. Some studies have started to identify the neural substrates and circuit-level contributions to dysregulated impulsivity [51].

MicroRNAs (miRNAs) are a type of noncoding RNA that play a role in neural plasticity and higher brain functioning [52,53] (Table 1). Several miRNAs have been found to regulate genes involved in the neurobiology of suicidal behavior [54,55]. Thus, early childhood stress is linked to the miR-16 upregulation and subsequent downregulation of the brain-derived neurotrophic factor (BDNF) gene in the hippocampus, in which depression-like behaviors were induced by maternal deprivation or chronic unpredictable stress in rats [54]. MiRNA dysregulation has also been linked to aggressive behavior and psychiatric disorders, such as bipolar disorder, depression, and schizophrenia, as well as suicide in people with no psychiatric diagnosis [56]. Smalheiser et al. (2014) showed that adaptive miRNA expression in the frontal cortex in response to shocks is blunted in rats exhibiting learned helplessness, which is a risk factor for suicidal behavior in humans [57]. The active reorganization of gene expression networks in those rats may have resulted in a persistent phenotype, thus emphasizing the importance of determining the role of miRNAs in regulating gene expression in neuronal circuits after stressful life events.

The serotonergic system has been involved for a long time in impulsive/aggressive behavior. In the 2000s, reducing levels of 5-HT in the central nervous system was associated with increases in impulsive behavior in both humans [58] and rodents [59] (Table 1). For example, the 5-HT system may play a role in controlling impulsive aggression through decreasing the latency to attack in male mice [60] (Table 1). Starting in the mid-1990s, genetic manipulation techniques were used to identify the specific receptor populations that modulate aggression and impulsivity in mice [61]. In the mid-2000s, conditional knock-out/knockdown approaches, which selectively delete specific genes in a tissue or brain region of scientific interest, were used. For example, Htr1b null mice exhibit increased aggression and impulsivity (Table 1) [61,62]. The adolescent expression of forebrain 5-HT<sub>1B</sub> heteroreceptors influences aggressive behavior; however, in a distinct set of 5-HT<sub>1B</sub> receptors, it modulates impulsive behavior during adulthood [63]. In some cases, as with 5-HT<sub>2B</sub>R, animal models give results that converge with those obtained in humans. Further, 5Htr2b-knockout mice exhibit increased impulsivity and enhanced locomotor activity, while a particular polymorphism, i.e., a 5-HT<sub>2B</sub>R premature stop codon identified in the Finnish population, predisposes one to severe impulsivity [64]. By contrast, the single-nucleotide polymorphism of other members of the 5-HT system, such as the tryptophan hydroxylase genes TPH2 and the 5-HT<sub>1A</sub>R gene, were inconsistently linked to a higher risk of suicide [49,65]. However, the monoamine oxidase A (MAO-A) story, an enzyme that degrades serotonin and norepinephrine, is interesting. In adult transgenic mice with a MAO-A gene deletion, enhanced aggression in males was observed [66] (Table 1). Interestingly, a complete and selective deficiency of MAO-A enzymatic activity was found in five men of a Dutch family who were affected by a syndrome of borderline mental retardation and abnormal behavior including impulsive aggression [67].

Tryptophan degradation provides another hypothesis (i.e., the kynurenine pathway). L-tryptophan (L-Trp) is metabolized by the enzyme tryptophan hydroxylase to form serotonin. However, L-Trp in the body mainly breaks down into kynurenine metabolites and nicotinamide adenosine dinucleotide [68]. An imbalance in this pathway, particularly in the production of the metabolites kynurenic acid and quinolinic acid, has been associated with changes in glutamate neurotransmission and neuroinflammation, potentially contributing to mood disorders and suicidal behavior [68]. Plasma kynurenine levels were found to be elevated in suicide attempters with major depressive disorders when compared with either non-suicidal depressive patients or controls with no history of depression [69] (Table 1). However, these results have since been challenged by others [70]. In animal models of stress (foot shocks), kynurenine levels were found to be increased in the plasma and brain [71]; however, this 20-year-old data will need to be replicated.

An additional hypothesis suggests that suicide pathogenesis is associated with neuroinflammation. Most of the influence of the brain on the immune system goes through

the HPA axis (Table 1). Both stress and depression have been associated with impaired immune function. Thus, depression is now thought to be associated with the activation of some aspects of cellular immunity, resulting in the hypersecretion of proinflammatory cytokines and in the hyperactivity of the HPA axis [72] (Table 1). Evidence suggests that the underlying neurobiology of suicidal behavior involves increases in inflammatory biomarkers in both the CNS and the peripheral systems of individuals with a history of suicidal behavior. Increased cytokine levels, such as IL-4, IL-13, IL-1, IL-6, and TNF, have been reported in postmortem brain samples [24], as well as in the blood samples of patients who died by suicide or attempted suicide [73–75]. For example, IL-6 is elevated in the CSF of suicide attempters and is related to symptom severity [76]. In rodents, interactions between the HPA axis and the immune system were explored under stress conditions, e.g., a rat model of chronic tail restraint (Table 1). Restraints were increased in IL-1 $\beta$  with no changes in adrenocorticotropin (ACTH) and corticosterone (CORT) levels [77]. However, a naturalistic (predator) stressor failed to modify IL-1 $\beta$ , IL-1 receptor antagonist, IL-1 receptor type I, or TNF- $\alpha$  mRNA levels in rat prefrontal cortexes and hypothalamuses [78]. The hypothalamic expression of IL-1 $\beta$  and IL-2 mRNA was altered during repeated cold stress [79]. Thus, the changes in inflammatory cytokines in rodent models under stressful conditions are highly heterogeneous. It is now necessary to explore the changes in brain cytokines in rodent models of impulsivity/aggressiveness because these preclinical data are missing. One can, however, find some studies on the exacerbation of endophenotypes linked to suicidal behavior (aggression) in animal models. Interestingly, mice lacking the TNF receptor did not exhibit aggressive behavior in the resident–intruder test, suggesting that TNF also exerts a role in aggressive behavior [80]. Cytokines may have very specific effects on the brain, and further research is necessary to fully understand their impact.

Activation of the kynurenine pathway may cause subsequent serotonin depletion and the stimulation of glutamate neurotransmission. Some changes are accompanied by decreased BDNF levels in the brain (*see below*), which is linked to impaired neuroplasticity and cognitive deficits [81] (Table 1).

**The HPA axis/stress and glucocorticoid receptor:** It is now apparent that adaptive changes result from the chronic stress and depression that lead to a hypoactivity of the glucocorticoid receptors (GR) on immune cells and in the limbic regions of the brain (Table 1). In the late 1990s and early 2000s, questions were raised about the epigenetic modifications of the GR gene in the hippocampus by maternal behavior and licking/grooming as responses to early life stress [82] (Table 1). However, these responses have not been fully reproduced in other models in rodents [82,83]. Postmortem brain samples from suicide victims revealed altered epigenetic regulation (i.e., DNA methylation patterns) on the GR gene in the hippocampus of those with a history of childhood abuse [84–86]. This suggests a possible mechanism by which early life adversity may increase the risk of suicide. Lamontagne et al. (2022) also highlighted the candidate endophenotypes of suicide risks, such as sleep disturbances, changes in the 5-HT<sub>2A</sub> receptor expression associated with suicide in humans and chronic stress in animals, as well as effects of ketamine [87]. These mechanisms are complementary to those summarized here. The pathophysiology of stress is a factor involved in the onset of suicidal ideation and suicide risk. Evidence from animal models suggests that the rapid-acting mechanism of ketamine effectively rescues one from the chronic-stress-induced pathologies linked to suicide risk. Both reviews agree in emphasizing the critical need to examine the temporal dynamics of this risk factor.

The relationship between gonadal hormones and suicidal behavior is marked by gender differences [88] (Table 1). In men, lower testosterone levels are associated with an increased risk of depression and suicide attempts, while higher testosterone is linked to increased aggression [89–91]. Women are more likely to attempt suicide when estrogen and progesterone levels are low [92]. Preclinical rodent studies have suggested that administering progesterone, or both estrogen and progesterone, decreased impulsivity in female rats, whereas low testosterone levels decreased impulsive behavior in male rats [46,93]

(Table 1). Thus, both clinical and preclinical research agree that gonadal hormones influence suicide-related endophenotypes and the vulnerability to suicide.

**Cognitive traits—impulsivity-aggressiveness:** Indicators of aggression and impulsivity have consistently been associated with suicidal behavior and with a familial transmission of suicide behavior, i.e., “a heritable suicide phenotype” [94,95]. Suicide attempters have higher levels of lifetime impulsive aggression than those found in controls according to retrospective and prospective studies [96–98]. The impulsivity is likely to persist over time and may predispose people to suicidal behavior later in life [99]. Impulsive aggression can also be evaluated in rodent behavioral tasks such as decreased inhibitory control, inability to delay reward, and impaired decision making.

After the above, the role of ketamine in these developments starts.

## 5. Main Pharmacological Properties of Ketamine

**(R,S)-, (S)- and @-ketamine:** (*R,S*)-ketamine was first described in 1965 and used as a general anesthetic and veterinary analgesic drug since 1970 [100–103]. (*R,S*)-ketamine has multiple properties and indications, e.g., for both acute and chronic pain treatment [104].

A 2019 meta-analysis reported that IV (*R,S*)-ketamine (0.5 mg/kg infused over 40 min) reduced suicidal ideation, but no evidence of efficacy was found for other routes of administration [105]. In 2019, an intranasal (IN) spray of esketamine was approved, along with oral antidepressant drugs, as a fast-acting antidepressant by the drug agencies US FDA and European EMA [106,107]. In this indication, esketamine, in combination with an SSRI or an SNRI, constitutes an alternative for adult patients under 65 years of age for the treatment of characterized resistant major depressive episodes—if they are severe and/or a contraindication, or resistant to ECT—who have not responded to at least two different classes of antidepressant drugs. It can be prescribed in the USA for TRD in adults, as well as to treat depressive symptoms in adults with MDE and acute and severe suicidal ideation. However, IN esketamine has moderate effects on depression *versus* a placebo, and it has not shown convincing effects on suicidal ideation to date. Indeed, a recent review pointed out that the results from clinical trials did not demonstrate the antisuicidal effects of esketamine in patients with baseline suicidality [108]. By contrast, ketamine rapidly decreased the severity of suicide ideation and depressive symptoms, but these effects were short-lasting.

Since its discovery in the sixties, many pharmacological properties of ketamine (binding to a glutamate NMDAR, signaling pathways, etc.) have been described. Here is a short summary of them:

(*R,S*)-ketamine is a racemic mixture containing equal parts of (*R*)-ketamine (or arketamine) and (*S*)-ketamine (or esketamine). (*R,S*)-ketamine is a non-competitive antagonist of the *N*-methyl-D-aspartate receptor (NMDA-R). (*R*)-ketamine (or arketamine) [109] has displayed longer-lasting antidepressant-like effects than (*S*)-ketamine in preclinical models of anxiety/depression mice [110,111]; this was despite its four times lower affinity to NMDA-R when compared to (*S*)-ketamine [111]. (*S*)-ketamine is considered to have twice the therapeutic index of racemic ketamine, which means that theoretically adverse effects should be reduced when only half of the usual racemic dose is administered [112]. However, a direct comparison between esketamine (*S*-ketamine), arketamine (*R*-ketamine) enantiomers, and racemic ketamine, specifically regarding their antidepressant efficacy in animal models [113] and in clinical trials are still necessary [114–116].

The pharmacological properties of (*R,S*)-ketamine describe a powerful NMDA-R antagonist *in vitro*,  $EC_{50} = 760$  nM *in vivo*, and  $ED_{50} = 4.4$  mg/kg in rodents' cortex or hippocampus [117,118]. Glutamate is the major excitatory neurotransmitter in the central nervous system. Under physiological conditions, and in the presence of  $Mg^{2+}$ , the NMDA channel is closed, which theoretically should inhibit the ability of (*R,S*)-ketamine to bind to its phencyclidine-like site. However, an electrophysiological *in vitro* study performed in cultured hippocampal neurons has shown that (*R,S*)-ketamine can still block NMDA-R and



reduce post-synaptic currents under physiological conditions (i.e., in the presence of  $Mg^{2+}$ ) [119]. These data suggest that (*R,S*)-ketamine readily exceeds the physiologic capacity of the NMDA-R's  $Mg^{2+}$ -dependent voltage gating to impede ion flow through the receptor channel.

**NMDA-R subunits:** (*R,S*)-ketamine blocks NMDAR on GABA-Gad1 interneurons as well as the subtypes of interneurons expressing somatostatin (Sst) or parvalbumin (Pvalb) in order to induce glutamate release and the indirect activation of excitatory synapses [120,121]. Behavioral studies using cell-type-specific knockdown in the medial prefrontal cortex (mPFC) demonstrated that NMDAR-GluN2B knockdown on Gad1-expressing neurons blocks the antidepressant effects of ketamine in mice [121]. These results provide evidence for initial cellular triggers, neuronal cell types, and the specific NMDA-GluN2B receptor subtype involved in the antidepressant actions of (*R,S*)-ketamine.

Another NMDA-R antagonist, such as memantine, does not inhibit the phosphorylation of eukaryotic elongation factor-2 (eEF2) kinase or increase the BDNF protein expression, which are the essential determinants of ketamine-mediated antidepressant effects [119].

**(*R,S*)-ketamine and AMPA receptor:** The downstream activation of the AMPA receptor (AMPA-R) seems to play an important role in the prefrontal cortex and hippocampal neurons, thus leading to fast ketamine-induced antidepressant effects. NBQX, an AMPA-R antagonist, blocks the neurochemical and behavioral effects of a single, subanesthetic dose of ketamine [122,123]. However, (*R*)-ketamine and (*S*)-ketamine remodel neurotransmission and connectivity through different mechanisms. (*R*)-ketamine strongly activates the prefrontal serotonergic system through an AMPA-receptor-independent mechanism, while (*S*)-ketamine-induced serotonin and dopamine release are activated through the AMPA-receptor-dependent mechanism [124]. These findings provide a neurochemical basis for the underlying pharmacological differences between ketamine enantiomers and their metabolites.

**(2*R,6R*)-hydroxynorketamine, the primary brain metabolite of (*R,S*)-ketamine:** (2*R,6R*)-HNK would have antidepressant-like effects via a mechanism that does not involve a direct inhibition of NMDA-R but for its potential binding to AMPA-R and AMPA-R agonist properties [125]. (*R,S*)-ketamine rapidly and stereoselectively metabolizes into several metabolites, e.g., (*S*)-ketamine is metabolized to (*S*)-norketamine and (2*S,6S*; 2*S,6S*)-HNK (in human: [112]; in rodents: [126,127]). Preclinical studies have indicated that HNKs display antidepressant-like activity in rodent models of anxiety/depression [125]. However, the pharmacological properties of (2*R,6R*)-HNK and its contribution to the actions of (*R,S*)-ketamine are still up for debate [128–133]. We are waiting for the results of clinical trials regarding (2*R,6R*)-HNK and its potential therapeutic applications in TRD [131].

**The opioid receptor activation hypothesis:** In the 1980s, the role of mu, kappa, and sigma opiate/phencyclidine (PCP) receptors was investigated [134,135]. Recently, Williams et al. (2018) showed that ketamine's acute antidepressant effect requires opioid receptor activation in adults with TRD [136]. Furthermore, this action may play a role in the anti-suicidality effects of ketamine [137]. This hypothesis attracted attention, but these two studies involved only 12–14 patients who had received one pre-treatment dose of naltrexone. Although the dissociative effects of ketamine do not seem to be mediated by the opioid receptor signaling [138], further studies are requested before drawing a solid conclusion. Importantly, George (2018) emphasizes that “TRD is a chronic and recurring illness, and little is known whether ketamine may become a chronic treatment” [139].

**The BDNF and mTOR/TrkB receptors:** Beyond NMDA-R antagonism, it has been shown that downstream mechanisms regulating synaptic plasticity involve a cascade of postsynaptic intracellular events that are activated by (*R,S*)-ketamine, which increases the phosphorylation of the mechanistic target of rapamycin (mTOR) [140–142] and the expression of synaptic proteins (eEF2 kinase, BDNF, its high-affinity TrkB receptor, synapsin 1, PSD95, etc.). These findings suggest that the activation of the mTOR signaling



pathways is necessary for the ketamine-induced synaptogenesis in mPFC pyramidal neurons, usually 24 h after a single (*R,S*)-ketamine dose in rodents [122]. Several studies performed in rodents used rapamycin (or sirolimus, intracerebroventricular, i.c.v., 10 mg/mL, 2  $\mu$ L), which is an mTORC1 inhibitor of rapamycin complex 1, to block the antidepressant effects of ketamine [122,142]. However, a single dose of rapamycin failed to achieve this in depressed patients [143]. These discrepancies suggest that an i.c.v. injection of rapamycin is requested to affect a network in the prefrontal /hippocampal circuit. In summary, (*R,S*)-ketamine may exert acute changes in synaptic plasticity, leading to a sustained strengthening of excitatory synapses, thus leading to its fast antidepressant action [144,145].

**mPFC vs. hippocampus:** In the mPFC and hippocampus, ketamine blocks NMDA-R, which ultimately induces the activation of BDNF release and therefore the activation of its high-affinity receptor TrkB. However, between these two brain regions, the mechanisms seem to differ. In the hippocampus, an NMDA-R blockade by ketamine induces a deactivation of eEF2 kinase (also called CaMKII, which suppresses BDNF release), which is necessary for the de-repression of BDNF, post-synaptic AMPA-R activation, and ketamine antidepressant-like activity [146]. By contrast, the signaling cascade induced by ketamine in the mPFC goes through the activation of mTOR, then to BDNF release [122,147]. A link between ketamine mTOR in the hippocampus, or eEF2 in the mPFC, is currently missing. Lisa Monteggia's group recently suggested that the deactivation of eEF2 kinase is requested for the initiation of the ketamine antidepressant effect [146]. It is possible that despite different signaling pathways being involved in the effects of ketamine in the cortex and hippocampus, they could converge to synaptogenesis (a kind of synergistic effect in the cortex–hippocampus circuitry).

**Excitatory/inhibitory balance:** The balance of excitation/inhibition synaptic transmission (E/I balance) is now under investigation in mPFC and in the hippocampus for two main reasons:

i—neurophysiology-pathology: this is its role in the regulation of the cortex–hippocampus neurocircuit function in rodents [148] and its dysregulation in various brain pathologies (schizophrenia: [149]; cognition: [150]; anxiety: [151]). For example, the E/I balance is known to regulate the function of cortex–hippocampus neurocircuits in rodents [152]. The E/I imbalance can result in synaptic deficits, which play an essential role in depression/anxiety [153]. Thus, changes in E/I balance may be a biomarker of the pathophysiology developed in rodent models of anxiety/depression.

ii—pharmacology: E/I balance can be modified by a pharmacological treatment, thus being a biomarker of drug efficacy. We recently found an imbalance of excitatory to inhibitory input toward increased excitatory activity in the mPFC of ketamine-treated mice [154]. Our data agree with Huang and Liston (2017) [155], showing a rapid and transient increase in global glutamate activity (i.e., glutamate release by mPFC glutamatergic axon terminals) in the cortex following ketamine administration.

Over the past decade, accumulating evidence has revealed that dysfunctions in the E/I balance in the mPFC are implicated in the pathology of depression [156,157]. Evidence from the literature has demonstrated that parvalbumin-positive interneurons (PV), the most abundant subtype of the total population of cortical GABAergic interneurons, are the major regulators of E/I balance in the mPFC. Depending on the route of administration (intravenous, intraperitoneal, intranasal), (*R,S*)-ketamine may influence brain E/I balance through a potentiation of glutamatergic synaptic excitation, thus inducing a sustained antidepressant-like brain state [151,158,159]. The divergent pharmacological modulatory effects of (*R*)-ketamine, (*S*)-ketamine, and (*R,S*)-HNK metabolites on the E/I imbalance in various brain regions are still a matter of debate [138,160].

**The disinhibition hypothesis of pyramidal cells in the prefrontal cortex:** There are several hypotheses for ketamine's mechanism of action. The main hypothesis is the disinhibition of pyramidal cells via a decreased output of fast-spiking GABAergic interneurons in the mPFC and hippocampus [120,161–163]. It has been proposed as a key mechanism

that triggers (*R,S*)-ketamine's antidepressant response. A low dose of (*R,S*)-ketamine blocks the NMDA-Rs located on GABA interneurons in the mPFC, resulting in decreased inhibitory inputs and increased small excitatory post-synaptic currents (sEPSCs) on layer V neurons [120] or in increased glutamate release in the mPFC [164]. However, different in vitro/in vivo protocols have been used to test this hypothesis. When using in vitro electrophysiology in the dorsal hippocampus slices in naive rats, ketamine reduced the inhibitory input onto pyramidal cells and increased the synaptically driven pyramidal cell excitability at the single-cell and population levels [163]. By contrast, when using in vivo microdialysis in a mouse model of anxiety/depression, ketamine increased GABA release in the mPFC at 24 h post-administration [165]. Chronic stress yielding a depressed phenotype may explain these discrepancies [166]. The route of ketamine administration could be another important factor. We recently found that the intranasal administration of (*R,S*)-ketamine induced a dose-dependent increase in cortical glutamate release, but not in a GABA release as opposed to a systemic ketamine dose, suggesting that ketamine metabolites produced in the liver following an IP injection may induce a GABAergic action [154]. Furthermore, major depression is associated with low plasma and cerebrospinal fluid GABA concentrations in depressed patients [167]. Thus, this hypothesis needs to be further investigated by comparing the E/I balance in the mPFC versus the hippocampus. The role of the connectivity between the ventral hippocampus and mPFC was recently highlighted using the optogenetic activation of this circuit [168].

## 6. Pharmacological Potentials of Ketamine Action in Suicide Behavior

Early studies in 2014 used pharmacologic approaches that have been considered potential treatments to reduce suicide risk, namely by reducing suicide deaths, attempts, and ideation [40]. The protective effects of lithium salts, clozapine, antidepressants, antipsychotics, and ECT were evaluated to decrease the risk of engaging in suicidal behavior [49]. However, despite inconsistent findings regarding drug efficacy in the reduction in suicidality in both unipolar and bipolar depression [49], the discovery of new targets for the treatment of suicide ideations is necessary. We need to better understand the underlying pathophysiology of suicidal thoughts and the brain regions/circuits/connectivity involved in responses to (*R,S*)-ketamine.

Although ECT is a gold-standard therapy for TRD, ketamine has arisen as an (experimental) alternative over the last two decades with the benefit of rapid onset action and relief from depressive, anxious, and anhedonic symptoms, including suicidal ideations [169]. The short-term efficacy of ketamine in TRD has been confirmed in randomized, double-blind, placebo-controlled trials [170]. Patients with MDD having active suicidal ideation with intent require immediate treatment. A single IV subanesthetic dose of ketamine is assumed to have rapid effects on suicidality in TRD, and acute improvements in suicidality can be sustained with repeated ketamine infusions [171].

Recently, two clinical trials demonstrated the rapid and robust efficacy of an esketamine nasal spray in reducing depressive symptoms in severely ill patients with major depressive disorder who were having active suicidal ideation with intent [172,173]. A meta-analysis of five randomized, double-blind clinical trials with 744 MDD patients with TRD comparing adjunctive IN esketamine to an adjunctive placebo confirmed the rapidity and efficacy of esketamine (with respect to MADRS score change, response, and remission) in treating an imminent risk of suicide [174]. Strikingly, its anti-suicidal and antidepressant benefits in patients with suicidal ideations may be independent of one another. Esketamine's antidepressant activity may last longer than its anti-suicide effect [175]. Another meta-analysis corroborates the efficacy of both IN and IV ketamine administration for the treatment of MDD, but suggests no difference between either route of delivery [115]. However, this assertion was challenged [116]: In the absence of head-to-head studies directly comparing the efficacy of IN esketamine to that of IV ketamine, valid conclusions regarding comparative efficacy should be taken with caution. Existing data from clinical trials were obtained by using markedly differing study designs and patient populations.

The fast-acting antidepressant activity of (*R,S*)-ketamine as a glutamatergic NMDA-R antagonist makes it a valuable research tool for understanding the neurobiology of antidepressant and anti-suicidal responses. “Old data” suggest that (*R,S*)-ketamine may have anti-aggressive properties [176], but this requires further investigation. Disruptions in the glutamate–glutamine cycle were found in the underlying pathology of multiple suicide-related psychiatric conditions such as major depressive disorder [177]. Recently, studies performed in experimental animal models demonstrated that glutamate plays a key role in aggressiveness and impulsivity [177,178]. Thus, efforts to describe neural correlates of suicidal ideation must continue.

Little is known about the mechanism of action and the biomarkers of the response to (*R,S*)-ketamine in the treatment of suicidal thoughts (see [179] for a review). Knowing that the dose of (*R,S*)-ketamine administered in patients with TRD is similar to that used in patients with suicidal ideation (0.5 mg/kg intravenously perfused over 40 min), it can be assumed that the treatment of suicidality with ketamine potentially goes through similar signaling pathways, i.e., the disinhibition hypothesis, synaptogenesis, and the BDNF/mTOR/eEF2 pathways behind NMDA-R/AMPA-R.

## 7. Conclusions

In summary, whether (*R,S*)-ketamine-esketamine effects on impulsivity and aggressiveness are relevant to suicidal behavior remains to be confirmed in preclinical studies. Identification of the mechanisms of pathophysiology, suicide risk factors of neuropsychological vulnerabilities, cognitive deficits, the endophenotypes of sub-groups of patients presenting with suicide ideations/suicidality, as well as the role of critical interactions between genetic and epigenetic factors associated with suicidal behavior may help to solve this issue. Studies of deficits in the balance of motivational and inhibitory processes may be key factors to solve these issues [180]. In addition, neural and behavioral motivational processes highlight the importance of reward circuitry in ketamine's mechanism of action in motivational symptoms [181]. Further studies should be conducted to identify other neural substrates and circuit-level contributions to dysregulated impulsivity. Thus, anhedonia was associated with specific neural circuits in response to (*R,S*)-ketamine, and suicidal ideation may be related to symptoms of anhedonia that are independent of depressive symptoms [182].

The present review should be read in light of the following limitations. Some endophenotypes have been selected (i.e., the 5-HT system and cytokines), but the list is not exhaustive. Certainly, ketamine is the first new treatment for depression in 60 years, with an original mechanism of action, but its effects on suicidal ideation need to be confirmed. To date, there are no studies on the risk/prevention of suicidal acts and mortality, and the long-term adverse effects, particularly the influence of events of abuse, are unknown [41]. Due to the dissociative/psychotomimetic effects of ketamine, the need for its IV infusion requires an acute hospitalization of patients with MDD.

Regarding animal models, efforts must focus on the biomarker identification of (*R,S*)-ketamine response in rodents, including electrophysiological and imaging studies; metabolic, immune, and neurotrophic biomarkers; and the role of neuroinflammation and microglial cells. None of these biomarkers are ready for clinical use in the subgroups of depressed patients with suicidal ideations, nor in those having a co-morbidity, such as those with anxiety, neuroinflammation, metabolic symptoms [183].

However, a key question still remains regarding the potential abuse liability of (*R*)-ketamine versus (*S*)-ketamine (in rodents: [138]). Is it necessary to limit the ketamine affinity at opioid receptors and the dopamine tone in various brain regions (mPFC, nucleus accumbens, basal ganglia) to reduce its adverse effects? (i.e., a favorable risk/benefit ratio). Before being engaged in the second generation of serotonergic and/or glutamatergic antidepressants, e.g., psilocybin (a 5-HT<sub>2A</sub> receptor agonist), additional studies must be undertaken to examine the dopaminergic activity linked to addiction, abuse liability, and drug dependency [184]. Understanding the pharmacology of (*R,S*)-ketamine and its

enantiomers could allow the development of analogous, but safer drugs [185]. Thus, there are concerns about safety and long-term outcomes of glutamatergic antidepressant drugs because the benefit/risk ratio is a relevant question in clinical practice [172]. In the future, there should be more specific molecules, with direct or indirect glutamatergic mechanisms of action for efficacy, but with fewer adverse effects.

**Table 1.** Endophenotypes of suicidal behavior as studied in animal models and humans.

Targets	Rodents	Humans
MicroRNAs	MiRNA expression in the frontal cortex following shocks is blunted in rats exhibiting learned helplessness [57].	MiRNA dysregulation is linked to aggressive behavior and psychiatric disorders, as well as to suicide in people with no psychiatric diagnosis [56].
L-Trp and serotonin system	Extracellular 5-HT and 5-HIAA levels in the mPFC are negatively correlated with levels of aggression in rats [59].	Low CSF 5-HIAA levels and the dysregulation of the 5-HT system are associated with aggression and impulsivity in humans [58].
L-Trp and kynurenine pathway	Plasma and brain kynurenine levels are increased by foot shocks in rats [71].	Plasma kynurenine levels are higher in the CSF of suicide attempters than in healthy people [69,81].
MAO-A	MAO-A deficiency is associated with aggressive behavior [66].	MAO-A deficiency is associated with the disturbed regulation of impulsive aggression [67].
5-HT <sub>1B</sub> receptor	Htr1b null mice exhibit increased aggression and impulsivity [61,62]. 5-HT <sub>1B</sub> R knockout mice show increased aggression and impulsivity, and 5-HT <sub>1B</sub> R polymorphisms are associated with aggression [63].	Adult aggression is determined by forebrain 5-HT <sub>1B</sub> heteroreceptors. Impulsive behavior is modulated by a different population of 5-HT <sub>1B</sub> heteroreceptors [186].
BDNF	Heterozygous BDNF <sup>+/-</sup> mice, conditional BDNF knockout mice, and mutant mice with a specific disruption of <i>Bdnf</i> promoter I exhibited enhanced inter-male aggression [187].	BDNF protein levels in the prefrontal cortex, hippocampus, and amygdala are lower in the postmortem brain of individuals who died by suicide [188]. BDNF Val/Met is related to the suicidal behavior of bipolar patients [189].
HPA axis	Increased maternal licking/grooming is linked to an attenuation of the response to stressful stimuli in rats [82].	DNA methylation patterns on the GR gene are altered in the hippocampus of suicide victims with a history of childhood abuse [84,85].
Cytokines	IL-1, IL-2, and TNF increase aggression in rodents [80,190–192].	IL-4, IL-13, IL-1, IL-6, and TNF increase in the post-mortem brain samples and blood samples of patients who died by suicide or attempted suicide [73–75].
Glutamate	Extracellular glutamate clearance decreases in nandrolone decanoate-induced aggressive behavior in mice [193].	The AMPA glutamate receptor subtype increases in the caudate nucleus of schizophrenics and nonpsychotic suicides [194].
Gonadal hormones	Administering progesterone or both estrogen and progesterone decreases impulsivity in female rats. Low testosterone levels decrease impulsive behavior in male rats [46,93].	Lower testosterone levels increase the risk of depression and suicide attempts. Higher testosterone levels increase aggression in men [89–91]. Lower estrogen and progesterone levels are linked to attempted suicide in women [92].
Microbial pathogens	Latent <i>T. gondii</i> infection reduces and reverses the innate fear of cat odor and other stimuli that precede predation [195].	Suicidal behavior, aggression, and impulsivity are linked to chronic <i>T. gondii</i> infection in both healthy people and psychiatric patients [196,197].

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

### Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	Serotonin
ACTH	Adrenocorticotropin
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AMPA-R	AMPA receptor
BD	Bipolar disorder
BDNF	Brain-derived neurotrophic factor
CORT	Corticosterone
CNS	Central nervous system
CSF	Cerebrospinal fluid
ECT	Electroconvulsive therapy
eEF2	Eukaryotic elongation factor-2
EMA	European Medical Agency
E/I balance	Excitatory/inhibitory balance
FDA	Food Drug Administration
Flx	Fluoxetine
GABA	$\gamma$ -aminobutyric acid
GLT-1	Glutamate transporter
GR	Glucocorticoid receptor
HNK	Hydroxynorketamine metabolite
HPA	Hypothalamic–pituitary–adrenal
i.c.v.	Intracerebroventricular
IL	Interleukin
IN	Intranasal
IP	Intraperitoneal
IV	Intravenous
L-Trp	L-Tryptophan
MDD	Major depressive disorders
MDE	Major depressive episode
miRNAs	MicroRNAs
mPFC	Medial prefrontal cortex
mTOR	Mechanistic target of rapamycin
NMDAR	N-methyl-D-aspartate receptor
PCP	Phencyclidine
PV	Parvalbumin-positive interneuron
Pvalb	Parvalbumin
SNRI	Selective norepinephrine serotonin reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
Sst	Somatostatin
<i>T. gondii</i>	<i>Toxoplasma gondii</i>
TNF	Tumor necrosis factor
TRD	Treatment-resistant depression
TrkB	High-affinity receptor of BDNF

## References

- Borges, G.; Nock, M.K.; Haro Abad, J.M.; Hwang, I.; Sampson, N.A.; Alonso, J.; Andrade, L.H.; Angermeyer, M.C.; Beautrais, A.; Bromet, E.; et al. Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. *J. Clin. Psychiatry* **2010**, *71*, 1617–1628. <https://doi.org/10.4088/JCP.08m04967blu>.
- Rockett, I.R.; Regier, M.D.; Kapusta, N.D.; Coben, J.H.; Miller, T.R.; Hanzlick, R.L.; Todd, K.H.; Sattin, R.W.; Kennedy, L.W.; Kleinig, J.; et al. Leading causes of unintentional and intentional injury mortality: United States, 2000–2009. *Am. J. Public Health* **2012**, *102*, e84–e92. <https://doi.org/10.2105/ajph.2012.300960>.
- World Health Organization. *Suicide in the World: Global Health Estimates*; World Health Organization: Geneva, Switzerland, 2019.
- Rajkumar, R.; Fam, J.; Yeo, E.Y.; Dawe, G.S. Ketamine and suicidal ideation in depression: Jumping the gun? *Pharmacol. Res.* **2015**, *99*, 23–35. <https://doi.org/10.1016/j.phrs.2015.05.003>.
- Arsenault-Lapierre, G.; Kim, C.; Turecki, G. Psychiatric diagnoses in 3275 suicides: A meta-analysis. *BMC Psychiatry* **2004**, *4*, 37. <https://doi.org/10.1186/1471-244X-4-37>.
- Coryell, W.; Young, E.A. Clinical predictors of suicide in primary major depressive disorder. *J. Clin. Psychiatry* **2005**, *66*, 412–417. <https://doi.org/10.4088/jcp.v66n0401>.
- Pfeiffer, P.N.; Kim, H.M.; Ganoczy, D.; Zivin, K.; Valenstein, M. Treatment-resistant depression and risk of suicide. *Suicide Life-Threat. Behav.* **2013**, *43*, 356–365. <https://doi.org/10.1111/sltb.12022>.
- Phillips, J.L.; Norris, S.; Talbot, J.; Hatchard, T.; Ortiz, A.; Birmingham, M.; Owoeye, O.; Batten, L.A.; Blier, P. Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression. *Neuropsychopharmacology* **2020**, *45*, 606–612. <https://doi.org/10.1038/s41386-019-0570-x>.
- Bergfeld, I.O.; Mantione, M.; Figee, M.; Schuurman, P.R.; Lok, A.; Denys, D. Treatment-resistant depression and suicidality. *J. Affect. Disord.* **2018**, *235*, 362–367. <https://doi.org/10.1016/j.jad.2018.04.016>.
- Braun, C.; Bschor, T.; Franklin, J.; Baethge, C. Suicides and Suicide Attempts during Long-Term Treatment with Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients with Major Depressive Disorder. *Psychother. Psychosom.* **2016**, *85*, 171–179. <https://doi.org/10.1159/000442293>.
- Jollant, F.; Colle, R.; Nguyen, T.M.L.; Corruble, E.; Gardier, A.M.; Walter, M.; Abbar, M.; Wagner, G. Ketamine and esketamine in suicidal thoughts and behaviors: A systematic review. *Ther. Adv. Psychopharmacol.* **2023**, *13*, 20451253231151327. <https://doi.org/10.1177/20451253231151327>.
- David, D.J.; Samuels, B.A.; Rainer, Q.; Wang, J.W.; Marsteller, D.; Mendez, I.; Drew, M.; Craig, D.A.; Guizard, B.P.; Guilloux, J.P.; et al. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron* **2009**, *62*, 479–493. <https://doi.org/10.1016/j.neuron.2009.04.017>.
- Mendez-David, I.; Boursier, C.; Domergue, V.; Colle, R.; Falissard, B.; Corruble, E.; Gardier, A.M.; Guilloux, J.-P.; David, D.J. Differential Peripheral Proteomic Biosignature of Fluoxetine Response in a Mouse Model of Anxiety/Depression. *Front. Cell. Neurosci.* **2017**, *11*, 237. <https://doi.org/10.3389/fncel.2017.00237>.
- Guilloux, J.P.; Seney, M.; Edgar, N.; Sibille, E. Integrated behavioral z-scoring increases the sensitivity and reliability of behavioral phenotyping in mice: Relevance to emotionality and sex. *J. Neurosci. Methods* **2011**, *197*, 21–31. <https://doi.org/10.1016/j.jneumeth.2011.01.019>.
- Lebeau, R.H.; Mendez-David, I.; Kucynski-Noyau, L.; Henry, C.; Attali, D.; Plaze, M.; Colle, R.; Corruble, E.; Gardier, A.M.; Gaillard, R.; et al. Peripheral proteomic changes after electroconvulsive seizures in a rodent model of non-response to chronic fluoxetine. *Front. Pharmacol.* **2022**, *13*, 993449. <https://doi.org/10.3389/fphar.2022.993449>.
- Réus, G.Z.; de Moura, A.B.; Borba, L.A.; Abelaira, H.M.; Quevedo, J. Strategies for Treatment-Resistant Depression: Lessons Learned from Animal Models. *Mol. Neuropsychiatry* **2019**, *5*, 178–189. <https://doi.org/10.1159/000500324>.
- Réus, G.Z.; Carlessi, A.S.; Titus, S.E.; Abelaira, H.M.; Ignácio, Z.M.; da Luz, J.R.; Matias, B.I.; Bruchchen, L.; Florentino, D.; Vieira, A.; et al. A single dose of S-ketamine induces long-term antidepressant effects and decreases oxidative stress in adulthood rats following maternal deprivation. *Dev. Neurobiol.* **2015**, *75*, 1268–1281. <https://doi.org/10.1002/dneu.22283>.
- Fazel, S.; Wolf, A.; Chang, Z.; Larsson, H.; Goodwin, G.M.; Lichtenstein, P. Depression and violence: A Swedish population study. *Lancet Psychiatry* **2015**, *2*, 224–232. [https://doi.org/10.1016/S2215-0366\(14\)00128-X](https://doi.org/10.1016/S2215-0366(14)00128-X).
- Corruble, E.; Damy, C.; Guelfi, J.D. Impulsivity: A relevant dimension in depression regarding suicide attempts? *J. Affect. Disord.* **1999**, *53*, 211–215. [https://doi.org/10.1016/s0165-0327\(98\)00130-x](https://doi.org/10.1016/s0165-0327(98)00130-x).
- Al Jurdi, R.K.; Swann, A.; Mathew, S.J. Psychopharmacological Agents and Suicide Risk Reduction: Ketamine and Other Approaches. *Curr. Psychiatry Rep.* **2015**, *17*, 81. <https://doi.org/10.1007/s11920-015-0614-9>.
- Turecki, G.; Brent, D.A.; Gunnell, D.; O'Connor, R.C.; Oquendo, M.A.; Pirkis, J.; Stanley, B.H. Suicide and suicide risk. *Nat. Rev. Dis. Prim.* **2019**, *5*, 74. <https://doi.org/10.1038/s41572-019-0121-0>.
- Bernal, M.; Haro, J.M.; Bernert, S.; Brugha, T.; de Graaf, R.; Bruffaerts, R.; Lépine, J.P.; de Girolamo, G.; Vilagut, G.; Gasquet, I.; et al. Risk factors for suicidality in Europe: Results from the ESEMED study. *J. Affect. Disord.* **2007**, *101*, 27–34. <https://doi.org/10.1016/j.jad.2006.09.018>.
- Brent, D.A.; Mann, J.J. Family genetic studies, suicide, and suicidal behavior. *Am. J. Med. Genet. Part C Semin. Med. Genet.* **2005**, *133C*, 13–24. <https://doi.org/10.1002/ajmg.c.30042>.
- Tonelli, L.H.; Stiller, J.; Rujescu, D.; Giegling, I.; Schneider, B.; Maurer, K.; Schnabel, A.; Möller, H.J.; Chen, H.H.; Postolache, T.T. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. *Acta Psychiatr. Scand.* **2008**, *117*, 198–206. <https://doi.org/10.1111/j.1600-0447.2007.01128.x>.



25. Mitra, R.; Sapolsky, R.M.; Vyas, A. Toxoplasma gondii infection induces dendritic retraction in basolateral amygdala accompanied by reduced corticosterone secretion. *Dis. Model. Mech.* **2013**, *6*, 516–520. <https://doi.org/10.1242/dmm.009928>.
26. Turecki, G.; Brent, D.A. Suicide and suicidal behaviour. *Lancet* **2016**, *387*, 1227–1239. [https://doi.org/10.1016/s0140-6736\(15\)00234-2](https://doi.org/10.1016/s0140-6736(15)00234-2).
27. Arango, V.; Underwood, M.D.; Mann, J.J. Serotonin brain circuits involved in major depression and suicide. *Prog. Brain Res.* **2002**, *136*, 443–453. [https://doi.org/10.1016/s0079-6123\(02\)36037-0](https://doi.org/10.1016/s0079-6123(02)36037-0).
28. Yanowitch, R.; Coccaro, E.F. The neurochemistry of human aggression. *Adv. Genet.* **2011**, *75*, 151–169. <https://doi.org/10.1016/b978-0-12-380858-5.00005-8>.
29. Sequeira, A.; Mamdani, F.; Ernst, C.; Vawter, M.P.; Bunney, W.E.; Lebel, V.; Rehal, S.; Klempan, T.; Gratton, A.; Benkelfat, C.; et al. Global Brain Gene Expression Analysis Links Glutamatergic and GABAergic Alterations to Suicide and Major Depression. *PLoS ONE* **2009**, *4*, e6585. <https://doi.org/10.1371/journal.pone.0006585>.
30. Leistedt, S.J.; Linkowski, P. Brain, networks, depression, and more. *Eur. Neuropsychopharmacol.* **2013**, *23*, 55–62. <https://doi.org/10.1016/j.euroneuro.2012.10.011>.
31. Ota, K.T.; Duman, R.S. Environmental and pharmacological modulations of cellular plasticity: Role in the pathophysiology and treatment of depression. *Neurobiol. Dis.* **2013**, *57*, 28–37. <https://doi.org/10.1016/j.nbd.2012.05.022>.
32. Dwivedi, Y.; Rizavi, H.S.; Roberts, R.C.; Conley, R.C.; Tamminga, C.A.; Pandey, G.N. Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J. Neurochem.* **2001**, *77*, 916–928. <https://doi.org/10.1046/j.1471-4159.2001.00300.x>.
33. Dwivedi, Y.; Rizavi, H.S.; Zhang, H.; Mondal, A.C.; Roberts, R.C.; Conley, R.R.; Pandey, G.N. Neurotrophin receptor activation and expression in human postmortem brain: Effect of suicide. *Biol. Psychiatry* **2009**, *65*, 319–328. <https://doi.org/10.1016/j.biopsych.2008.08.035>.
34. McEwen, B.S. Effects of adverse experiences for brain structure and function. *Biol. Psychiatry* **2000**, *48*, 721–731. [https://doi.org/10.1016/s0006-3223\(00\)00964-1](https://doi.org/10.1016/s0006-3223(00)00964-1).
35. Honer, W.G. Assessing the machinery of mind: Synapses in neuropsychiatric disorders. *J. Psychiatry Neurosci.* **1999**, *24*, 116–121.
36. Black, C.; Miller, B.J. Meta-Analysis of Cytokines and Chemokines in Suicidality: Distinguishing Suicidal Versus Nonsuicidal Patients. *Biol. Psychiatry* **2015**, *78*, 28–37. <https://doi.org/10.1016/j.biopsych.2014.10.014>.
37. Mamdani, F.; Weber, M.D.; Bunney, B.; Burke, K.; Cartagena, P.; Walsh, D.; Lee, F.S.; Barchas, J.; Schatzberg, A.F.; Myers, R.M.; et al. Identification of potential blood biomarkers associated with suicide in major depressive disorder. *Transl. Psychiatry* **2022**, *12*, 159. <https://doi.org/10.1038/s41398-022-01918-w>.
38. Benard, V.; Vaiva, G.; Masson, M.; Geoffroy, P.A. Lithium and suicide prevention in bipolar disorder. *L'Encephale* **2016**, *42*, 234–241. <https://doi.org/10.1016/j.encep.2016.02.006>.
39. Nabi, Z.; Stansfeld, J.; Plöderl, M.; Wood, L.; Moncrieff, J. Effects of lithium on suicide and suicidal behaviour: A systematic review and meta-analysis of randomised trials. *Epidemiol. Psychiatr. Sci.* **2022**, *31*, e65. <https://doi.org/10.1017/s204579602200049x>.
40. Griffiths, J.J.; Zarate, C.A., Jr.; Rasimas, J.J. Existing and novel biological therapeutics in suicide prevention. *Am. J. Prev. Med.* **2014**, *47*, S195–S203. <https://doi.org/10.1016/j.amepre.2014.06.012>.
41. Jick, H.; Kaye, J.A.; Jick, S.S. Antidepressants and the risk of suicidal behaviors. *JAMA* **2004**, *292*, 338–343. <https://doi.org/10.1001/jama.292.3.338>.
42. Grunebaum, M.F.; Galfalvy, H.C.; Choo, T.H.; Keilp, J.G.; Moitra, V.K.; Parris, M.S.; Marver, J.E.; Burke, A.K.; Milak, M.S.; Sublette, M.E.; et al. Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. *Am. J. Psychiatry* **2018**, *175*, 327–335. <https://doi.org/10.1176/appi.ajp.2017.17060647>.
43. Price, R.B.; Iosifescu, D.V.; Murrough, J.W.; Chang, L.C.; Al Jurdi, R.K.; Iqbal, S.Z.; Soleimani, L.; Charney, D.S.; Foulkes, A.L.; Mathew, S.J. Effects of ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression. *Depress. Anxiety* **2014**, *31*, 335–343. <https://doi.org/10.1002/da.22253>.
44. Moazen, P.; Azizi, H.; Salmanzadeh, H.; Semnani, S. Adolescent morphine exposure induces immediate and long-term increases in impulsive behavior. *Psychopharmacology* **2018**, *235*, 3423–3434. <https://doi.org/10.1007/s00213-018-5051-0>.
45. Higgins, G.A.; Brown, M.; St John, J.; MacMillan, C.; Silenieks, L.B.; Thevarkunnel, S. Effects of 5-HT(2C) receptor modulation and the NA reuptake inhibitor atomoxetine in tests of compulsive and impulsive behaviour. *Neuropharmacology* **2020**, *170*, 108064. <https://doi.org/10.1016/j.neuropharm.2020.108064>.
46. Jentsch, J.D.; Taylor, J.R. Sex-related differences in spatial divided attention and motor impulsivity in rats. *Behav. Neurosci.* **2003**, *117*, 76–83. <https://doi.org/10.1037//0735-7044.117.1.76>.
47. Colzato, L.S.; van den Wildenberg, W.P.; Van der Does, A.J.; Hommel, B. Genetic markers of striatal dopamine predict individual differences in dysfunctional, but not functional impulsivity. *Neuroscience* **2010**, *170*, 782–788. <https://doi.org/10.1016/j.neuroscience.2010.07.050>.
48. Malkesman, O.; Pine, D.S.; Tragon, T.; Austin, D.R.; Henter, I.D.; Chen, G.; Manji, H.K. Animal models of suicide-trait-related behaviors. *Trends Pharmacol. Sci.* **2009**, *30*, 165–173. <https://doi.org/10.1016/j.tips.2009.01.004>.
49. Gould, T.D.; Georgiou, P.; Brenner, L.A.; Brundin, L.; Can, A.; Courtet, P.; Donaldson, Z.R.; Dwivedi, Y.; Guillaume, S.; Gottesman, I.I.; et al. Animal models to improve our understanding and treatment of suicidal behavior. *Transl. Psychiatry* **2017**, *7*, e1092. <https://doi.org/10.1038/tp.2017.50>.

50. Meehan, A.J.; Lewis, S.J.; Fazel, S.; Fusar-Poli, P.; Steyerberg, E.W.; Stahl, D.; Danese, A. Clinical prediction models in psychiatry: A systematic review of two decades of progress and challenges. *Mol. Psychiatry* **2022**, *27*, 2700–2708. <https://doi.org/10.1038/s41380-022-01528-4>.
51. Ballard, E.D.; Lally, N.; Nugent, A.C.; Furey, M.L.; Luckenbaugh, D.A.; Zarate, C.A., Jr. Neural correlates of suicidal ideation and its reduction in depression. *Int. J. Neuropsychopharmacol.* **2014**, *18*, pyu069. <https://doi.org/10.1093/ijnp/pyu069>.
52. Alural, B.; Genc, S.; Haggarty, S.J. Diagnostic and therapeutic potential of microRNAs in neuropsychiatric disorders: Past, present, and future. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2017**, *73*, 87–103. <https://doi.org/10.1016/j.pnpbp.2016.03.010>.
53. Dwivedi, Y. Pathogenetic and therapeutic applications of microRNAs in major depressive disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2016**, *64*, 341–348. <https://doi.org/10.1016/j.pnpbp.2015.02.003>.
54. Bai, M.; Zhu, X.; Zhang, Y.; Zhang, S.; Zhang, L.; Xue, L.; Yi, J.; Yao, S.; Zhang, X. Abnormal hippocampal BDNF and miR-16 expression is associated with depression-like behaviors induced by stress during early life. *PLoS ONE* **2012**, *7*, e46921. <https://doi.org/10.1371/journal.pone.0046921>.
55. Issler, O.; Haramati, S.; Paul, E.D.; Maeno, H.; Navon, I.; Zwang, R.; Gil, S.; Mayberg, H.S.; Dunlop, B.W.; Menke, A.; et al. MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity. *Neuron* **2014**, *83*, 344–360. <https://doi.org/10.1016/j.neuron.2014.05.042>.
56. Smalheiser, N.R.; Lugli, G.; Zhang, H.; Rizavi, H.; Cook, E.H.; Dwivedi, Y. Expression of microRNAs and other small RNAs in prefrontal cortex in schizophrenia, bipolar disorder and depressed subjects. *PLoS ONE* **2014**, *9*, e86469. <https://doi.org/10.1371/journal.pone.0086469>.
57. Smalheiser, N.R.; Zhang, H.; Dwivedi, Y. Enoxacin Elevates MicroRNA Levels in Rat Frontal Cortex and Prevents Learned Helplessness. *Front. Psychiatry* **2014**, *5*, 6. <https://doi.org/10.3389/fpsy.2014.00006>.
58. Schweighofer, N.; Bertin, M.; Shishida, K.; Okamoto, Y.; Tanaka, S.C.; Yamawaki, S.; Doya, K. Low-serotonin levels increase delayed reward discounting in humans. *J. Neurosci.* **2008**, *28*, 4528–4532. <https://doi.org/10.1523/jneurosci.4982-07.2008>.
59. van Erp, A.M.; Miczek, K.A. Aggressive behavior, increased accumbal dopamine, and decreased cortical serotonin in rats. *J. Neurosci.* **2000**, *20*, 9320–9325. <https://doi.org/10.1523/jneurosci.20-24-09320.2000>.
60. Chiavegatto, S.; Dawson, V.L.; Mamounas, L.A.; Koliatsos, V.E.; Dawson, T.M.; Nelson, R.J. Brain serotonin dysfunction accounts for aggression in male mice lacking neuronal nitric oxide synthase. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 1277–1281. <https://doi.org/10.1073/pnas.98.3.1277>.
61. Saudou, F.; Amara, D.A.; Dierich, A.; LeMeur, M.; Ramboz, S.; Segu, L.; Buhot, M.C.; Hen, R. Enhanced aggressive behavior in mice lacking 5-HT1B receptor. *Science* **1994**, *265*, 1875–1878. <https://doi.org/10.1126/science.8091214>.
62. Pattij, T.; Broersen, L.M.; Peter, S.; Olivier, B. Impulsive-like behavior in differential-reinforcement-of-low-rate 36 s responding in mice depends on training history. *Neurosci. Lett.* **2004**, *354*, 169–171. <https://doi.org/10.1016/j.neulet.2003.10.004>.
63. Nautiyal, K.M.; Tanaka, K.F.; Barr, M.M.; Tritschler, L.; Le Dantec, Y.; David, D.J.; Gardier, A.M.; Blanco, C.; Hen, R.; Ahmari, S.E. Distinct Circuits Underlie the Effects of 5-HT1B Receptors on Aggression and Impulsivity. *Neuron* **2015**, *86*, 813–826. <https://doi.org/10.1016/j.neuron.2015.03.041>.
64. Bevilacqua, L.; Doly, S.; Kaprio, J.; Yuan, Q.; Tikkanen, R.; Paunio, T.; Zhou, Z.; Wedenoja, J.; Maroteaux, L.; Diaz, S.; et al. A population-specific HTR2B stop codon predisposes to severe impulsivity. *Nature* **2010**, *468*, 1061–1066. <https://doi.org/10.1038/nature09629>.
65. Donaldson, Z.R.; le Francois, B.; Santos, T.L.; Almli, L.M.; Boldrini, M.; Champagne, F.A.; Arango, V.; Mann, J.J.; Stockmeier, C.A.; Galfalvy, H.; et al. The functional serotonin 1a receptor promoter polymorphism, rs6295, is associated with psychiatric illness and differences in transcription. *Transl. Psychiatry* **2016**, *6*, e746. <https://doi.org/10.1038/tp.2015.226>.
66. Cases, O.; Seif, I.; Grimsby, J.; Gaspar, P.; Chen, K.; Pournin, S.; Müller, U.; Aguet, M.; Babinet, C.; Shih, J.C.; et al. Aggressive behavior and altered amounts of brain serotonin and norepinephrine in mice lacking MAOA. *Science* **1995**, *268*, 1763–1766. <https://doi.org/10.1126/science.7792602>.
67. Brunner, H.G.; Nelen, M.; Breakefield, X.O.; Ropers, H.H.; van Oost, B.A. Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A. *Science* **1993**, *262*, 578–580. <https://doi.org/10.1126/science.8211186>.
68. Maes, M.; Leonard, B.E.; Myint, A.M.; Kubera, M.; Verkerk, R. The new ‘5-HT’ hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2011**, *35*, 702–721. <https://doi.org/10.1016/j.pnpbp.2010.12.017>.
69. Sublette, M.E.; Galfalvy, H.C.; Fuchs, D.; Lapidus, M.; Grunebaum, M.F.; Oquendo, M.A.; Mann, J.J.; Postolache, T.T. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. *Brain Behav. Immun.* **2011**, *25*, 1272–1278. <https://doi.org/10.1016/j.bbi.2011.05.002>.
70. Dahl, J.; Andreassen, O.A.; Verkerk, R.; Malt, U.F.; Sandvik, L.; Brundin, L.; Ormstad, H. Ongoing episode of major depressive disorder is not associated with elevated plasma levels of kynurenine pathway markers. *Psychoneuroendocrinology* **2015**, *56*, 12–22. <https://doi.org/10.1016/j.psyneuen.2015.02.011>.
71. Pawlak, D.; Takada, Y.; Urano, T.; Takada, A. Serotonergic and kynurenic pathways in rats exposed to foot shock. *Brain Res. Bull.* **2000**, *52*, 197–205. [https://doi.org/10.1016/s0361-9230\(00\)00252-5](https://doi.org/10.1016/s0361-9230(00)00252-5).
72. Leonard, B.E. Editorial: Stress, depression and the immune system. *Stress Med.* **2000**, *16*, 133–137. [https://doi.org/10.1002/\(SICI\)1099-1700\(200004\)16:3<133::AID-SMI876>3.0.CO;2-9](https://doi.org/10.1002/(SICI)1099-1700(200004)16:3<133::AID-SMI876>3.0.CO;2-9).

73. Steiner, J.; Bielau, H.; Brisch, R.; Danos, P.; Ullrich, O.; Mawrin, C.; Bernstein, H.G.; Bogerts, B. Immunological aspects in the neurobiology of suicide: Elevated microglial density in schizophrenia and depression is associated with suicide. *J. Psychiatr. Res.* **2008**, *42*, 151–157. <https://doi.org/10.1016/j.jpsychires.2006.10.013>.
74. Ducasse, D.; Olié, E.; Guillaume, S.; Artéro, S.; Courtet, P. A meta-analysis of cytokines in suicidal behavior. *Brain Behav. Immun.* **2015**, *46*, 203–211. <https://doi.org/10.1016/j.bbi.2015.02.004>.
75. Janelidze, S.; Mattei, D.; Westrin, Å.; Träskman-Bendz, L.; Brundin, L. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. *Brain Behav. Immun.* **2011**, *25*, 335–339. <https://doi.org/10.1016/j.bbi.2010.10.010>.
76. Lindqvist, D.; Janelidze, S.; Hagell, P.; Erhardt, S.; Samuelsson, M.; Minthon, L.; Hansson, O.; Björkqvist, M.; Träskman-Bendz, L.; Brundin, L. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol. Psychiatry* **2009**, *66*, 287–292. <https://doi.org/10.1016/j.biopsych.2009.01.030>.
77. Mekaouche, M.; Givalois, L.; Barbanel, G.; Siaud, P.; Maurel, D.; Malaval, F.; Bristow, A.F.; Boissin, J.; Assenmacher, I.; Ixart, G. Chronic restraint enhances interleukin-1-beta release in the basal state and after an endotoxin challenge, independently of adrenocorticotropin and corticosterone release. *Neuroimmunomodulation* **1994**, *1*, 292–299. <https://doi.org/10.1159/000097179>.
78. Plata-Salamán, C.R. Central nervous system mechanisms contributing to the cachexia-anorexia syndrome. *Nutrition* **2000**, *16*, 1009–1012. [https://doi.org/10.1016/s0899-9007\(00\)00413-5](https://doi.org/10.1016/s0899-9007(00)00413-5).
79. Tanebe, K.; Nishijo, H.; Muraguchi, A.; Ono, T. Effects of chronic stress on hypothalamic Interleukin-1beta, interleukin-2, and gonadotrophin-releasing hormone gene expression in ovariectomized rats. *J. Neuroendocrinol.* **2000**, *12*, 13–21. <https://doi.org/10.1046/j.1365-2826.2000.00414.x>.
80. Patel, A.; Siegel, A.; Zalcman, S.S. Lack of aggression and anxiolytic-like behavior in TNF receptor (TNF-R1 and TNF-R2) deficient mice. *Brain Behav. Immun.* **2010**, *24*, 1276–1280. <https://doi.org/10.1016/j.bbi.2010.05.005>.
81. Erhardt, S.; Lim, C.K.; Linderholm, K.R.; Janelidze, S.; Lindqvist, D.; Samuelsson, M.; Lundberg, K.; Postolache, T.T.; Träskman-Bendz, L.; Guillemin, G.J.; et al. Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology* **2013**, *38*, 743–752. <https://doi.org/10.1038/npp.2012.248>.
82. Weaver, I.C.; Cervoni, N.; Champagne, F.A.; D'Alessio, A.C.; Sharma, S.; Seckl, J.R.; Dymov, S.; Szyf, M.; Meaney, M.J. Epigenetic programming by maternal behavior. *Nat. Neurosci.* **2004**, *7*, 847–854. <https://doi.org/10.1038/nn1276>.
83. Meaney, M.J. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu. Rev. Neurosci.* **2001**, *24*, 1161–1192. <https://doi.org/10.1146/annurev.neuro.24.1.1161>.
84. McGowan, P.O.; Sasaki, A.; D'Alessio, A.C.; Dymov, S.; Labonté, B.; Szyf, M.; Turecki, G.; Meaney, M.J. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat. Neurosci.* **2009**, *12*, 342–348. <https://doi.org/10.1038/nn.2270>.
85. Labonté, B.; Yerko, V.; Gross, J.; Mechawar, N.; Meaney, M.J.; Szyf, M.; Turecki, G. Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. *Biol. Psychiatry* **2012**, *72*, 41–48. <https://doi.org/10.1016/j.biopsych.2012.01.034>.
86. Turecki, G.; Meaney, M.J. Effects of the Social Environment and Stress on Glucocorticoid Receptor Gene Methylation: A Systematic Review. *Biol. Psychiatry* **2016**, *79*, 87–96. <https://doi.org/10.1016/j.biopsych.2014.11.022>.
87. Lamontagne, S.J.; Ballard, E.D.; Zarate, C.A., Jr. Effects of stress on endophenotypes of suicide across species: A role for ketamine in risk mitigation. *Neurobiol. Stress* **2022**, *18*, 100450. <https://doi.org/10.1016/j.ynstr.2022.100450>.
88. Nock, M.K.; Borges, G.; Bromet, E.J.; Cha, C.B.; Kessler, R.C.; Lee, S. Suicide and suicidal behavior. *Epidemiol. Rev.* **2008**, *30*, 133–154. <https://doi.org/10.1093/epirev/mxn002>.
89. Shores, M.M.; Sloan, K.L.; Matsumoto, A.M.; Moceri, V.M.; Felker, B.; Kivlahan, D.R. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch. Gen. Psychiatry* **2004**, *61*, 162–167. <https://doi.org/10.1001/archpsyc.61.2.162>.
90. Shores, M.M.; Moceri, V.M.; Sloan, K.L.; Matsumoto, A.M.; Kivlahan, D.R. Low testosterone levels predict incident depressive illness in older men: Effects of age and medical morbidity. *J. Clin. Psychiatry* **2005**, *66*, 7–14. <https://doi.org/10.4088/jcp.v66n0102>.
91. Archer, J. Testosterone and human aggression: An evaluation of the challenge hypothesis. *Neurosci. Biobehav. Rev.* **2006**, *30*, 319–345. <https://doi.org/10.1016/j.neubiorev.2004.12.007>.
92. Baca-Garcia, E.; Diaz-Sastre, C.; Ceverino, A.; Perez-Rodriguez, M.M.; Navarro-Jimenez, R.; Lopez-Castroman, J.; Saiz-Ruiz, J.; de Leon, J.; Oquendo, M.A. Suicide attempts among women during low estradiol/low progesterone states. *J. Psychiatr. Res.* **2010**, *44*, 209–214. <https://doi.org/10.1016/j.jpsychires.2009.08.004>.
93. Llana, D.C.; Frye, C.A. Progestogens and estrogen influence impulsive burying and avoidant freezing behavior of naturally cycling and ovariectomized rats. *Pharmacol. Biochem. Behav.* **2009**, *93*, 337–342. <https://doi.org/10.1016/j.pbb.2009.05.003>.
94. Melhem, N.M.; Brent, D.A.; Ziegler, M.; Iyengar, S.; Kolko, D.; Oquendo, M.; Birmaher, B.; Burke, A.; Zelazny, J.; Stanley, B.; et al. Familial pathways to early-onset suicidal behavior: Familial and individual antecedents of suicidal behavior. *Am. J. Psychiatry* **2007**, *164*, 1364–1370. <https://doi.org/10.1176/appi.ajp.2007.06091522>.
95. Turecki, G. Dissecting the suicide phenotype: The role of impulsive-aggressive behaviours. *J. Psychiatry Neurosci. JPN* **2005**, *30*, 398–408.
96. Brent, D.A.; Johnson, B.A.; Perper, J.; Connolly, J.; Bridge, J.; Bartle, S.; Rather, C. Personality disorder, personality traits, impulsive violence, and completed suicide in adolescents. *J. Am. Acad. Child Adolesc. Psychiatry* **1994**, *33*, 1080–1086. <https://doi.org/10.1097/00004583-199410000-00003>.

97. Oquendo, M.A.; Galfalvy, H.; Russo, S.; Ellis, S.P.; Grunebaum, M.F.; Burke, A.; Mann, J.J. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am. J. Psychiatry* **2004**, *161*, 1433–1441. <https://doi.org/10.1176/appi.ajp.161.8.1433>.
98. Swann, A.C.; Dougherty, D.M.; Pazzaglia, P.J.; Pham, M.; Steinberg, J.L.; Moeller, F.G. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *Am. J. Psychiatry* **2005**, *162*, 1680–1687. <https://doi.org/10.1176/appi.ajp.162.9.1680>.
99. Winstanley, C.A.; Eagle, D.M.; Robbins, T.W. Behavioral models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. *Clin. Psychol. Rev.* **2006**, *26*, 379–395. <https://doi.org/10.1016/j.cpr.2006.01.001>.
100. Chen, J.T.; Chen, R.M. Mechanisms of ketamine-involved regulation of cytochrome P450 gene expression. *Expert Opin. Drug Metab. Toxicol.* **2010**, *6*, 273–281. <https://doi.org/10.1517/17425250903505108>.
101. Craven, R. Ketamine. *Anaesthesia* **2007**, *62* (Suppl. 1), 48–53. <https://doi.org/10.1111/j.1365-2044.2007.05298.x>.
102. Hijazi, Y.; Boulieu, R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. *Drug Metab. Dispos.* **2002**, *30*, 853–858. <https://doi.org/10.1124/dmd.30.7.853>.
103. Domino, E.F. Taming the ketamine tiger. 1965. *Anesthesiology* **2010**, *113*, 678–684. <https://doi.org/10.1097/ALN.0b013e3181ed09a2>.
104. Barrett, W.; Buxhoeveden, M.; Dhillon, S. Ketamine: A versatile tool for anesthesia and analgesia. *Curr. Opin. Anaesthesiol.* **2020**, *33*, 633–638. <https://doi.org/10.1097/aco.0000000000000916>.
105. Dadiomov, D.; Lee, K. The effects of ketamine on suicidality across various formulations and study settings. *Ment. Health Clin.* **2019**, *9*, 48–60. <https://doi.org/10.9740/mhc.2019.01.048>.
106. Mahase, E. Esketamine is approved in Europe for treating resistant major depressive disorder. *BMJ* **2019**, *367*, l7069. <https://doi.org/10.1136/bmj.l7069>.
107. US Food and Drug Administration. *FDA News Release. FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression; Available Only at a Certified Doctor's Office or Clinic*; US Food and Drug Administration: Silver Spring, MD, USA, 2019.
108. Siegel, A.N.; Di Vincenzo, J.D.; Brietzke, E.; Gill, H.; Rodrigues, N.B.; Lui, L.M.W.; Teopiz, K.M.; Ng, J.; Ho, R.; McIntyre, R.S.; et al. Antisuiicidal and antidepressant effects of ketamine and esketamine in patients with baseline suicidality: A systematic review. *J. Psychiatr. Res.* **2021**, *137*, 426–436. <https://doi.org/10.1016/j.jpsychires.2021.03.009>.
109. Zhang, J.-C.; Yao, W.; Hashimoto, K. Arketamine, a new rapid-acting antidepressant: A historical review and future directions. *Neuropharmacology* **2022**, *218*, 109219. <https://doi.org/10.1016/j.neuropharm.2022.109219>.
110. Fukumoto, K.; Toki, H.; Iijima, M.; Hashihayata, T.; Yamaguchi, J.I.; Hashimoto, K.; Chaki, S. Antidepressant Potential of (R)-Ketamine in Rodent Models: Comparison with (S)-Ketamine. *J. Pharmacol. Exp. Ther.* **2017**, *361*, 9–16. <https://doi.org/10.1124/jpet.116.239228>.
111. Hashimoto, K. Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective. *Psychiatry Clin. Neurosci.* **2019**, *73*, 613–627. <https://doi.org/10.1111/pcn.12902>.
112. Muller, J.; Pentyala, S.; Dilger, J.; Pentyala, S. Ketamine enantiomers in the rapid and sustained antidepressant effects. *Ther. Adv. Psychopharmacol.* **2016**, *6*, 185–192. <https://doi.org/10.1177/2045125316631267>.
113. Chang, L.; Zhang, K.; Pu, Y.; Qu, Y.; Wang, S.M.; Xiong, Z.; Ren, Q.; Dong, C.; Fujita, Y.; Hashimoto, K. Comparison of antidepressant and side effects in mice after intranasal administration of (R,S)-ketamine, (R)-ketamine, and (S)-ketamine. *Pharmacol. Biochem. Behav.* **2019**, *181*, 53–59. <https://doi.org/10.1016/j.pbb.2019.04.008>.
114. Bahji, A.; Vazquez, G.H.; Zarate, C.A., Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *J. Affect. Disord.* **2021**, *278*, 542–555. <https://doi.org/10.1016/j.jad.2020.09.071>.
115. Meiering, M.S.; Weigner, D.; Gärtner, M.; Schäfer, T.; Grimm, S. Does route of administration affect antidepressant efficacy of ketamine? A meta-analysis of double-blind randomized controlled trials comparing intravenous and intranasal administration. *J. Psychiatr. Res.* **2022**, *156*, 639–646. <https://doi.org/10.1016/j.jpsychires.2022.10.062>.
116. Drevets, W.C.; Popova, V.; Daly, E.J.; Borentain, S.; Lane, R.; Cepeda, M.S.; Mathews, M.; Manji, H.K.; Canuso, C.M. Comments to Drs. Bahji, Vazquez, and Zarate. *J. Affect. Disord.* **2021**, *283*, 262–264. <https://doi.org/10.1016/j.jad.2021.01.046>.
117. Lord, B.; Wintmolders, C.; Langlois, X.; Nguyen, L.; Lovenberg, T.; Bonaventure, P. Comparison of the ex vivo receptor occupancy profile of ketamine to several NMDA receptor antagonists in mouse hippocampus. *Eur. J. Pharmacol.* **2013**, *715*, 21–25. <https://doi.org/10.1016/j.ejphar.2013.06.028>.
118. Murray, F.; Kennedy, J.; Hutson, P.H.; Elliot, J.; Huscroft, I.; Mohnen, K.; Russell, M.G.; Grimwood, S. Modulation of [3H]MK-801 binding to NMDA receptors in vivo and in vitro. *Eur. J. Pharmacol.* **2000**, *397*, 263–270. [https://doi.org/10.1016/s0014-2999\(00\)00263-6](https://doi.org/10.1016/s0014-2999(00)00263-6).
119. Gideons, E.S.; Kavalali, E.T.; Monteggia, L.M. Mechanisms underlying differential effectiveness of memantine and ketamine in rapid antidepressant responses. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 8649–8654. <https://doi.org/10.1073/pnas.1323920111>.
120. Gerhard, D.M.; Pothula, S.; Liu, R.J.; Wu, M.; Li, X.Y.; Girgenti, M.J.; Taylor, S.R.; Duman, C.H.; Delpire, E.; Picciotto, M.; et al. GABA interneurons as the cellular trigger for ketamine's rapid antidepressant actions. *J. Clin. Invest.* **2020**, *130*, 1336–1349. <https://doi.org/10.1172/jci130808>.
121. Pothula, S.; Kato, T.; Liu, R.-J.; Wu, M.; Gerhard, D.; Shinohara, R.; Sliby, A.-N.; Chowdhury, G.M.I.; Behar, K.L.; Sanacora, G.; et al. Cell-type specific modulation of NMDA receptors triggers antidepressant actions. *Mol. Psychiatry* **2021**, *26*, 5097–5111. <https://doi.org/10.1038/s41380-020-0796-3>.

122. Li, N.; Lee, B.; Liu, R.J.; Banasr, M.; Dwyer, J.M.; Iwata, M.; Li, X.Y.; Aghajanian, G.; Duman, R.S. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* **2010**, *329*, 959–964. <https://doi.org/10.1126/science.1190287>.
123. Pham, T.H.; Mendez-David, I.; Defaix, C.; Guiard, B.P.; Tritschler, L.; David, D.J.; Gardier, A.M. Ketamine treatment involves medial prefrontal cortex serotonin to induce a rapid antidepressant-like activity in BALB/cJ mice. *Neuropharmacology* **2017**, *112*, 198–209. <https://doi.org/10.1016/j.neuropharm.2016.05.010>.
124. Ago, Y.; Tanabe, W.; Higuchi, M.; Tsukada, S.; Tanaka, T.; Yamaguchi, T.; Igarashi, H.; Yokoyama, R.; Seiriki, K.; Kasai, A.; et al. (R)-Ketamine Induces a Greater Increase in Prefrontal 5-HT Release Than (S)-Ketamine and Ketamine Metabolites via an AMPA Receptor-Independent Mechanism. *Int. J. Neuropsychopharmacol.* **2019**, *22*, 665–674. <https://doi.org/10.1093/ijnp/pyz041>.
125. Zanos, P.; Moaddel, R.; Morris, P.J.; Georgiou, P.; Fischell, J.; Elmer, G.I.; Alkondon, M.; Yuan, P.; Pribut, H.J.; Singh, N.S.; et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* **2016**, *533*, 481–486. <https://doi.org/10.1038/nature17998>.
126. Williams, M.L.; Mager, D.E.; Parenteau, H.; Gudi, G.; Tracy, T.S.; Mulheran, M.; Wainer, I.W. Effects of protein calorie malnutrition on the pharmacokinetics of ketamine in rats. *Drug Metab. Dispos.* **2004**, *32*, 786–793. <https://doi.org/10.1124/dmd.32.8.786>.
127. Can, A.; Zanos, P.; Moaddel, R.; Kang, H.J.; Dossou, K.S.S.; Wainer, I.W.; Cheer, J.F.; Frost, D.O.; Huang, X.-P.; Gould, T.D. Effects of Ketamine and Ketamine Metabolites on Evoked Striatal Dopamine Release, Dopamine Receptors, and Monoamine Transporters. *J. Pharmacol. Exp. Ther.* **2016**, *359*, 159. <https://doi.org/10.1124/jpet.116.235838>.
128. Abdallah, C.G. (2R,6R)-Hydroxynorketamine (HNK) plasma level predicts poor antidepressant response: Is this the end of the HNK pipeline? *Neuropsychopharmacology* **2020**, *45*, 1245–1246. <https://doi.org/10.1038/s41386-020-0668-1>.
129. Chaki, S.; Yamaguchi, J.I. Now is the time for (2R,6R)-hydroxynorketamine to be viewed independently from its parent drug. *Pharmacol. Biochem. Behav.* **2018**, *175*, 24–26. <https://doi.org/10.1016/j.pbb.2018.09.005>.
130. Collingridge, G.L.; Lee, Y.; Bortolotto, Z.A.; Kang, H.; Lodge, D. Antidepressant Actions of Ketamine Versus Hydroxynorketamine. *Biol. Psychiatry* **2017**, *81*, e65–e67. <https://doi.org/10.1016/j.biopsych.2016.06.029>.
131. Farmer, C.A.; Gilbert, J.R.; Moaddel, R.; George, J.; Adejo, L.; Lovett, J.; Nugent, A.C.; Kadriu, B.; Yuan, P.; Gould, T.D.; et al. Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression. *Neuropsychopharmacology* **2020**, *45*, 1398–1404. <https://doi.org/10.1038/s41386-020-0663-6>.
132. Riggs, L.M.; Aracava, Y.; Zanos, P.; Fischell, J.; Albuquerque, E.X.; Pereira, E.F.R.; Thompson, S.M.; Gould, T.D. (2R,6R)-hydroxynorketamine rapidly potentiates hippocampal glutamatergic transmission through a synapse-specific presynaptic mechanism. *Neuropsychopharmacology* **2020**, *45*, 426–436. <https://doi.org/10.1038/s41386-019-0443-3>.
133. Zanos, P.; Moaddel, R.; Morris, P.J.; Georgiou, P.; Fischell, J.; Elmer, G.I.; Alkondon, M.; Yuan, P.; Pribut, H.J.; Singh, N.S.; et al. Zanos et al. reply. *Nature* **2017**, *546*, E4–E5. <https://doi.org/10.1038/nature22085>.
134. Smith, D.J.; Bouchal, R.L.; deSanctis, C.A.; Monroe, P.J.; Amedro, J.B.; Perrotti, J.M.; Crisp, T. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* **1987**, *26*, 1253–1260. [https://doi.org/10.1016/0028-3908\(87\)90084-0](https://doi.org/10.1016/0028-3908(87)90084-0).
135. Zukin, S.R.; Brady, K.T.; Slifer, B.L.; Balster, R.L. Behavioral and biochemical stereoselectivity of sigma opiate/PCP receptors. *Brain Res.* **1984**, *294*, 174–177. [https://doi.org/10.1016/0006-8993\(84\)91326-x](https://doi.org/10.1016/0006-8993(84)91326-x).
136. Williams, N.R.; Heifets, B.D.; Blasey, C.; Sudheimer, K.; Pannu, J.; Pankow, H.; Hawkins, J.; Birnbaum, J.; Lyons, D.M.; Rodriguez, C.I.; et al. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. *Am. J. Psychiatry* **2018**, *175*, 1205–1215. <https://doi.org/10.1176/appi.ajp.2018.18020138>.
137. Williams, N.R.; Heifets, B.D.; Bentzley, B.S.; Blasey, C.; Sudheimer, K.D.; Hawkins, J.; Lyons, D.M.; Schatzberg, A.F. Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism. *Mol. Psychiatry* **2019**, *24*, 1779–1786. <https://doi.org/10.1038/s41380-019-0503-4>.
138. Bonaventura, J.; Lam, S.; Carlton, M.; Boehm, M.A.; Gomez, J.L.; Solís, O.; Sánchez-Soto, M.; Morris, P.J.; Fredriksson, I.; Thomas, C.J.; et al. Pharmacological and behavioral divergence of ketamine enantiomers: Implications for abuse liability. *Mol. Psychiatry* **2021**, *26*, 6704–6722. <https://doi.org/10.1038/s41380-021-01093-2>.
139. George, M.S. Is There Really Nothing New Under the Sun? Is Low-Dose Ketamine a Fast-Acting Antidepressant Simply Because It Is An Opioid? *Am. J. Psychiatry* **2018**, *175*, 1157–1158. <https://doi.org/10.1176/appi.ajp.2018.18070800>.
140. Duman, R.S.; Shinohara, R.; Fogaça, M.V.; Hare, B. Neurobiology of rapid-acting antidepressants: Convergent effects on GluA1-synaptic function. *Mol. Psychiatry* **2019**, *24*, 1816–1832. <https://doi.org/10.1038/s41380-019-0400-x>.
141. Miller, O.H.; Yang, L.; Wang, C.C.; Hargroder, E.A.; Zhang, Y.; Delpire, E.; Hall, B.J. GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. *eLife* **2014**, *3*, e03581. <https://doi.org/10.7554/eLife.03581>.
142. Yang, C.; Ren, Q.; Qu, Y.; Zhang, J.C.; Ma, M.; Dong, C.; Hashimoto, K. Mechanistic Target of Rapamycin-Independent Antidepressant Effects of (R)-Ketamine in a Social Defeat Stress Model. *Biol. Psychiatry* **2018**, *83*, 18–28. <https://doi.org/10.1016/j.biopsych.2017.05.016>.
143. Abdallah, C.G.; Averill, L.A.; Gueorguieva, R.; Goktas, S.; Purohit, P.; Ranganathan, M.; Sherif, M.; Ahn, K.-H.; D’Souza, D.C.; Formica, R.; et al. Modulation of the antidepressant effects of ketamine by the mTORC1 inhibitor rapamycin. *Neuropsychopharmacology* **2020**, *45*, 990–997. <https://doi.org/10.1038/s41386-020-0644-9>.

144. Pham, T.H.; Gardier, A.M. Fast-acting antidepressant activity of ketamine: Highlights on brain serotonin, glutamate, and GABA neurotransmission in preclinical studies. *Pharmacol. Ther.* **2019**, *199*, 58–90. <https://doi.org/10.1016/j.pharmthera.2019.02.017>.
145. Zanos, P.; Gould, T.D. Mechanisms of ketamine action as an antidepressant. *Mol. Psychiatry* **2018**, *23*, 801–811. <https://doi.org/10.1038/mp.2017.255>.
146. Autry, A.E.; Adachi, M.; Nosyreva, E.; Na, E.S.; Los, M.F.; Cheng, P.F.; Kavalali, E.T.; Monteggia, L.M. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* **2011**, *475*, 91–95. <https://doi.org/10.1038/nature10130>.
147. Nosyreva, E.; Szabla, K.; Autry, A.E.; Ryazanov, A.G.; Monteggia, L.M.; Kavalali, E.T. Acute suppression of spontaneous neurotransmission drives synaptic potentiation. *J. Neurosci.* **2013**, *33*, 6990–7002. <https://doi.org/10.1523/jneurosci.4998-12.2013>.
148. Tatti, R.; Haley, M.S.; Swanson, O.K.; Tselha, T.; Maffei, A. Neurophysiology and Regulation of the Balance Between Excitation and Inhibition in Neocortical Circuits. *Biol. Psychiatry* **2017**, *81*, 821–831. <https://doi.org/10.1016/j.biopsych.2016.09.017>.
149. Wada, M.; Noda, Y.; Iwata, Y.; Tsugawa, S.; Yoshida, K.; Tani, H.; Hirano, Y.; Koike, S.; Sasabayashi, D.; Katayama, H.; et al. Dopaminergic dysfunction and excitatory/inhibitory imbalance in treatment-resistant schizophrenia and novel neuromodulatory treatment. *Mol. Psychiatry* **2022**, *27*, 2950–2967. <https://doi.org/10.1038/s41380-022-01572-0>.
150. Ferguson, B.R.; Gao, W.J. PV Interneurons: Critical Regulators of E/I Balance for Prefrontal Cortex-Dependent Behavior and Psychiatric Disorders. *Front. Neural Circuits* **2018**, *12*, 37. <https://doi.org/10.3389/fncir.2018.00037>.
151. Fuchs, T.; Jefferson, S.J.; Hooper, A.; Yee, P.H.; Maguire, J.; Luscher, B. Disinhibition of somatostatin-positive GABAergic interneurons results in an anxiolytic and antidepressant-like brain state. *Mol. Psychiatry* **2017**, *22*, 920–930. <https://doi.org/10.1038/mp.2016.188>.
152. Just, N.; Sonnay, S. Investigating the Role of Glutamate and GABA in the Modulation of Transthalamic Activity: A Combined fMRI-fMRS Study. *Front. Physiol.* **2017**, *8*, 30. <https://doi.org/10.3389/fphys.2017.00030>.
153. Yin, Y.-Y.; Wang, Y.-H.; Liu, W.-G.; Yao, J.-Q.; Yuan, J.; Li, Z.-H.; Ran, Y.-H.; Zhang, L.-M.; Li, Y.-F. The role of the excitation:inhibition functional balance in the mPFC in the onset of antidepressants. *Neuropharmacology* **2021**, *191*, 108573. <https://doi.org/10.1016/j.neuropharm.2021.108573>.
154. Nguyen, T.M.L.; Defaix, C.; Mendez-David, I.; Tritschler, L.; Etting, I.; Alvarez, J.-C.; Choucha, W.; Colle, R.; Corruble, E.; David, D.J.; et al. Intranasal (R, S)-ketamine delivery induces sustained antidepressant effects associated with changes in cortical balance of excitatory/inhibitory synaptic activity. *Neuropharmacology* **2023**, *225*, 109357. <https://doi.org/10.1016/j.neuropharm.2022.109357>.
155. Huang, B.S.; Liston, C. Cortex-wide optical imaging and network analysis of antidepressant effects. *Brain A J. Neurol.* **2017**, *140*, 2074–2078. <https://doi.org/10.1093/brain/awx166>.
156. Page, C.E.; Coutellier, L. Prefrontal excitatory/inhibitory balance in stress and emotional disorders: Evidence for over-inhibition. *Neurosci. Biobehav. Rev.* **2019**, *105*, 39–51. <https://doi.org/10.1016/j.neubiorev.2019.07.024>.
157. Zhang, B.; Yang, X.; Ye, L.; Liu, R.; Ye, B.; Du, W.; Shen, F.; Li, Q.; Guo, F.; Liu, J.; et al. Ketamine activated glutamatergic neurotransmission by GABAergic disinhibition in the medial prefrontal cortex. *Neuropharmacology* **2021**, *194*, 108382. <https://doi.org/10.1016/j.neuropharm.2020.108382>.
158. Ren, Z.; Pribyl, H.; Jefferson, S.J.; Shorey, M.; Fuchs, T.; Stellwagen, D.; Luscher, B. Bidirectional Homeostatic Regulation of a Depression-Related Brain State by Gamma-Aminobutyric Acidergic Deficits and Ketamine Treatment. *Biol. Psychiatry* **2016**, *80*, 457–468. <https://doi.org/10.1016/j.biopsych.2016.02.009>.
159. Yizhar, O.; Fenno, L.E.; Prigge, M.; Schneider, F.; Davidson, T.J.; O’Shea, D.J.; Sohal, V.S.; Goshen, I.; Finkelstein, J.; Paz, J.T.; et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* **2011**, *477*, 171–178. <https://doi.org/10.1038/nature10360>.
160. Shim, I. Distinct functions of S-ketamine and R-ketamine in mediating biobehavioral processes of drug dependency: Comments on Bonaventura et al. *Mol. Psychiatry* **2022**. <https://doi.org/10.1038/s41380-022-01629-0>.
161. Miller, O.H.; Moran, J.T.; Hall, B.J. Two cellular hypotheses explaining the initiation of ketamine’s antidepressant actions: Direct inhibition and disinhibition. *Neuropharmacology* **2016**, *100*, 17–26. <https://doi.org/10.1016/j.neuropharm.2015.07.028>.
162. Ali, F.; Gerhard, D.M.; Sweasy, K.; Pothula, S.; Pittenger, C.; Duman, R.S.; Kwan, A.C. Ketamine disinhibits dendrites and enhances calcium signals in prefrontal dendritic spines. *Nat. Commun.* **2020**, *11*, 72. <https://doi.org/10.1038/s41467-019-13809-8>.
163. Widman, A.J.; McMahon, L.L. Disinhibition of CA1 pyramidal cells by low-dose ketamine and other antagonists with rapid antidepressant efficacy. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E3007–E3016. <https://doi.org/10.1073/pnas.1718883115>.
164. Moghaddam, B.; Adams, B.; Verma, A.; Daly, D. Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J. Neurosci.* **1997**, *17*, 2921–2927. <https://doi.org/10.1523/jneurosci.17-08-02921.1997>.
165. Pham, T.H.; Defaix, C.; Xu, X.; Deng, S.X.; Fabresse, N.; Alvarez, J.C.; Landry, D.W.; Brachman, R.A.; Denny, C.A.; Gardier, A.M. Common Neurotransmission Recruited in (R,S)-Ketamine and (2R,6R)-Hydroxynorketamine-Induced Sustained Antidepressant-like Effects. *Biol. Psychiatry* **2018**, *84*, e3–e6. <https://doi.org/10.1016/j.biopsych.2017.10.020>.
166. Perrine, S.A.; Ghodoussi, F.; Michaels, M.S.; Sheikh, I.S.; McKelvey, G.; Galloway, M.P. Ketamine reverses stress-induced depression-like behavior and increased GABA levels in the anterior cingulate: An 11.7 T 1H-MRS study in rats. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2014**, *51*, 9–15. <https://doi.org/10.1016/j.pnpbp.2013.11.003>.
167. Sanacora, G.; Mason, G.F.; Rothman, D.L.; Krystal, J.H. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *Am. J. Psychiatry* **2002**, *159*, 663–665. <https://doi.org/10.1176/appi.ajp.159.4.663>.



168. Carreno, F.R.; Donegan, J.J.; Boley, A.M.; Shah, A.; DeGuzman, M.; Frazer, A.; Lodge, D.J. Activation of a ventral hippocampus-medial prefrontal cortex pathway is both necessary and sufficient for an antidepressant response to ketamine. *Mol. Psychiatry* **2016**, *21*, 1298–1308. <https://doi.org/10.1038/mp.2015.176>.
169. Mathew, S.J.; Wilkinson, S.T.; Altinay, M.; Asghar-Ali, A.; Chang, L.C.; Collins, K.A.; Dale, R.M.; Hu, B.; Krishnan, K.; Kellner, C.H.; et al. Electroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study protocol. *Contemp. Clin. Trials* **2019**, *77*, 19–26. <https://doi.org/10.1016/j.cct.2018.12.009>.
170. Iqbal, S.Z.; Mathew, S.J. Ketamine for depression clinical issues. *Adv. Pharmacol.* **2020**, *89*, 131–162. <https://doi.org/10.1016/bs.apha.2020.02.005>.
171. Price, R.B.; Nock, M.K.; Charney, D.S.; Mathew, S.J. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol. Psychiatry* **2009**, *66*, 522–526. <https://doi.org/10.1016/j.biopsych.2009.04.029>.
172. Fu, D.J.; Ionescu, D.F.; Li, X.; Lane, R.; Lim, P.; Sanacora, G.; Hough, D.; Manji, H.; Drevets, W.C.; Canuso, C.M. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). *J. Clin. Psychiatry* **2020**, *81*, 19m13191. <https://doi.org/10.4088/JCP.19m13191>.
173. Ionescu, D.F.; Fu, D.J.; Qiu, X.; Lane, R.; Lim, P.; Kasper, S.; Hough, D.; Drevets, W.C.; Manji, H.; Canuso, C.M. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int. J. Neuropsychopharmacol.* **2021**, *24*, 22–31. <https://doi.org/10.1093/ijnp/pyaa068>.
174. Papakostas, G.I.; Salloum, N.C.; Hock, R.S.; Jha, M.K.; Murrough, J.W.; Mathew, S.J.; Iosifescu, D.V.; Fava, M. Efficacy of Esketamine Augmentation in Major Depressive Disorder: A Meta-Analysis. *J. Clin. Psychiatry* **2020**, *81*, 19r12889. <https://doi.org/10.4088/JCP.19r12889>.
175. Capuzzi, E.; Caldiroli, A.; Capellazzi, M.; Tagliabue, I.; Marcatili, M.; Colmegna, F.; Clerici, M.; Buoli, M.; Dakanalis, A. Long-Term Efficacy of Intranasal Esketamine in Treatment-Resistant Major Depression: A Systematic Review. *Int. J. Mol. Sci.* **2021**, *22*, 9338.
176. Takahashi, R.N.; Morato, G.S.; Monteiro-de-Lima, T.C. Effects of ketamine on experimental animal models of aggression. *Braz. J. Med. Biol. Res.* **1984**, *17*, 171–178.
177. Jimenez-Trevino, L.; Gonzalez-Blanco, L.; Alvarez-Vazquez, C.; Rodriguez-Revuelta, J.; Saiz Martinez, P.A. Glutamine and New Pharmacological Targets to Treat Suicidal Ideation. In *Behavioral Neurobiology of Suicide and Self Harm*; Baca-Garcia, E., Ed.; Springer International Publishing: Cham, Switzerland, 2020; pp. 179–196.
178. Nordman, J.C. Anger management: Mechanisms of glutamate receptor-mediated synaptic plasticity underlying animal aggression. *Int. J. Biochem. Cell Biol.* **2022**, *142*, 106120. <https://doi.org/10.1016/j.biocel.2021.106120>.
179. Reinstatler, L.; Youssef, N.A. Ketamine as a potential treatment for suicidal ideation: A systematic review of the literature. *Drugs RD* **2015**, *15*, 37–43. <https://doi.org/10.1007/s40268-015-0081-0>.
180. Desrochers, S.S.; Spring, M.G.; Nautiyal, K.M. A Role for Serotonin in Modulating Opposing Drive and Brake Circuits of Impulsivity. *Front. Behav. Neurosci.* **2022**, *16*, 791749. <https://doi.org/10.3389/fnbeh.2022.791749>.
181. Mkrtchian, A.; Evans, J.W.; Kraus, C.; Yuan, P.; Kadriu, B.; Nugent, A.C.; Roiser, J.P.; Zarate, C.A. Ketamine modulates fronto-striatal circuitry in depressed and healthy individuals. *Mol. Psychiatry* **2021**, *26*, 3292–3301. <https://doi.org/10.1038/s41380-020-00878-1>.
182. Ballard, E.D.; Wills, K.; Lally, N.; Richards, E.M.; Luckenbaugh, D.A.; Walls, T.; Ameli, R.; Niciu, M.J.; Brutsche, N.E.; Park, L.; et al. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. *J. Affect. Disord.* **2017**, *218*, 195–200. <https://doi.org/10.1016/j.jad.2017.04.057>.
183. Kadriu, B.; Greenwald, M.; Henter, I.D.; Gilbert, J.R.; Kraus, C.; Park, L.T.; Zarate, C.A. Ketamine and Serotonergic Psychedelics: Common Mechanisms Underlying the Effects of Rapid-Acting Antidepressants. *Int. J. Neuropsychopharmacol.* **2021**, *24*, 8–21. <https://doi.org/10.1093/ijnp/pyaa087>.
184. Carhart-Harris, R.L.; Bolstridge, M.; Rucker, J.; Day, C.M.J.; Erritzoe, D.; Kaelen, M.; Bloomfield, M.; Rickard, J.A.; Forbes, B.; Feilding, A.; et al. Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *Lancet Psychiatry* **2016**, *3*, 619–627. [https://doi.org/10.1016/S2215-0366\(16\)30065-7](https://doi.org/10.1016/S2215-0366(16)30065-7).
185. Grunebaum, M.F.; Galfalvy, H.C.; Choo, T.H.; Parris, M.S.; Burke, A.K.; Suckow, R.F.; Cooper, T.B.; Mann, J.J. Ketamine metabolite pilot study in a suicidal depression trial. *J. Psychiatr. Res.* **2019**, *117*, 129–134. <https://doi.org/10.1016/j.jpsychires.2019.08.005>.
186. Zouk, H.; McGirr, A.; Lebel, V.; Benkelfat, C.; Rouleau, G.; Turecki, G. The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2007**, *144b*, 996–1002. <https://doi.org/10.1002/ajmg.b.30521>.
187. Chang, C.-H.; Su, C.-L.; Gean, P.-W. Mechanism underlying NMDA blockade-induced inhibition of aggression in post-weaning socially isolated mice. *Neuropharmacology* **2018**, *143*, 95–105. <https://doi.org/10.1016/j.neuropharm.2018.09.019>.
188. Sonal, A.; Raghavan, V. Brain derived neurotrophic factor (BDNF) and suicidal behavior: A review of studies from Asian countries. *Asian J. Psychiatry* **2018**, *33*, 128–132. <https://doi.org/10.1016/j.ajp.2018.03.004>.
189. Kim, B.; Kim, C.Y.; Hong, J.P.; Kim, S.Y.; Lee, C.; Joo, Y.H. Brain-Derived Neurotrophic Factor Val/Met Polymorphism and Bipolar Disorder. *Neuropsychobiology* **2008**, *58*, 97–103. <https://doi.org/10.1159/000162356>.

190. Bhatt, S.; Bhatt, R.; Zalcman, S.S.; Siegel, A. Role of IL-1 beta and 5-HT2 receptors in midbrain periaqueductal gray (PAG) in potentiating defensive rage behavior in cat. *Brain Behav. Immun.* **2008**, *22*, 224–233. <https://doi.org/10.1016/j.bbi.2007.07.011>.
191. Hassanain, M.; Zalcman, S.; Bhatt, S.; Siegel, A. Interleukin-1 beta in the hypothalamus potentiates feline defensive rage: Role of serotonin-2 receptors. *Neuroscience* **2003**, *120*, 227–233. [https://doi.org/10.1016/s0306-4522\(03\)00264-1](https://doi.org/10.1016/s0306-4522(03)00264-1).
192. Bhatt, S.; Siegel, A. Potentiating role of interleukin 2 (IL-2) receptors in the midbrain periaqueductal gray (PAG) upon defensive rage behavior in the cat: Role of neurokinin NK(1) receptors. *Behav. Brain Res.* **2006**, *167*, 251–260. <https://doi.org/10.1016/j.bbr.2005.09.011>.
193. Kalinine, E.; Zimmer, E.R.; Zenki, K.C.; Kalinine, I.; Kazlauckas, V.; Haas, C.B.; Hansel, G.; Zimmer, A.R.; Souza, D.O.; Müller, A.P.; et al. Nandrolone-induced aggressive behavior is associated with alterations in extracellular glutamate homeostasis in mice. *Horm. Behav.* **2014**, *66*, 383–392. <https://doi.org/10.1016/j.yhbeh.2014.06.005>.
194. Noga, J.T.; Hyde, T.M.; Herman, M.M.; Spurney, C.F.; Bigelow, L.B.; Weinberger, D.R.; Kleinman, J.E. Glutamate receptors in the postmortem striatum of schizophrenic, suicide, and control brains. *Synapse* **1997**, *27*, 168–176. [https://doi.org/10.1002/\(SICI\)1098-2396\(199711\)27:3<168::AID-SYN2>3.0.CO;2-B](https://doi.org/10.1002/(SICI)1098-2396(199711)27:3<168::AID-SYN2>3.0.CO;2-B).
195. Vyas, A.; Kim, S.K.; Giacomini, N.; Boothroyd, J.C.; Sapolsky, R.M. Behavioral changes induced by Toxoplasma infection of rodents are highly specific to aversion of cat odors. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 6442–6447. <https://doi.org/10.1073/pnas.0608310104>.
196. Coccaro, E.F.; Lee, R.; Groer, M.W.; Can, A.; Coussons-Read, M.; Postolache, T.T. Toxoplasma gondii infection: Relationship with aggression in psychiatric subjects. *J. Clin. Psychiatry* **2016**, *77*, 334–341. <https://doi.org/10.4088/JCP.14m09621>.
197. Cook, T.B.; Brenner, L.A.; Cloninger, C.R.; Langenberg, P.; Igibide, A.; Giegling, I.; Hartmann, A.M.; Konte, B.; Friedl, M.; Brundin, L.; et al. “Latent” infection with Toxoplasma gondii: Association with trait aggression and impulsivity in healthy adults. *J. Psychiatr. Res.* **2015**, *60*, 87–94. <https://doi.org/10.1016/j.jpsychires.2014.09.019>.

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