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DNA methylation and the opposing NMDAR dysfunction in schizophrenia and major depression disorders: a converging model for the therapeutic effects of psychedelic compounds in the treatment of psychiatric illness

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Abstract

Psychedelic compounds are being increasingly explored as a potential therapeutic option for treating several psychiatric conditions, despite relatively little being known about their mechanism of action. One such possible mechanism, DNA methylation, is a process of epigenetic regulation that changes gene expression via chemical modification of nitrogenous bases. DNA methylation has been implicated in the pathophysiology of several psychiatric conditions, including schizophrenia (SZ) and major depressive disorder (MDD). In this review, we propose alterations to DNA methylation as a converging model for the therapeutic effects of psychedelic compounds, highlighting the N-methyl D-aspartate receptor (NMDAR), a crucial mediator of synaptic plasticity with known dysfunction in both diseases, as an example and anchoring point. We review the established evidence relating aberrant DNA methylation to NMDAR dysfunction in SZ and MDD and provide a model asserting that psychedelic substances may act through an epigenetic mechanism to provide therapeutic effects in the context of these disorders.

INTRODUCTION

Epigenetic modifications, such as DNA methylation and histone modification, describe a collection of genetic changes that alter gene expression without changing the base pair order of the genome. Given their ability to respond to environmental stimuli with lasting effects on gene expression, the field of epigenetics is particularly attractive to researchers studying diseases with environmental influences, and in recent years, epigenetic mechanisms have been increasingly implicated in the pathophysiology of several psychiatric diseases [1, 2]. Amongst the psychiatric diseases to demonstrate epigenetic changes are schizophrenia (SZ) and major depressive disorder (MDD). Despite the differing symptom profiles of these

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two disorders, evidence supports the role of epigenetic modification, and specifically DNA methylation, in the development, presentation, and progression of both SZ and MDD.

DNA methylation is the process of adding a methyl group to cytosine residues in the DNA, which affects the ability of DNA transcription machinery to transcribe the DNA, ultimately resulting in a change in gene expression. As discussed below, DNA methylation induces different effects on gene transcription and subsequent protein expression levels based on the location of methylation along the gene. While DNA methylation of the promoter likely leads to decreased expression [3–5], DNA methylation of the gene body may lead to increased expression levels [6–9]. This versatility allows DNA methylation to be considered for various pathophysiological phenomena and across a diverse set of psychiatric diseases. One of the many phenomena potentially explained by DNA methylation is the dysfunction of the N-methyl D-aspartate receptor (NMDAR), which has been implicated in the pathophysiology of both SZ and MDD, albeit in seemingly opposite directions.

In SZ, NMDAR hypofunction is one of the leading theories of disease etiology and is believed to contribute to cortical hyperactivity and disruptions in other neurotransmitter systems [10]. In MDD, in contrast, the theory of NMDAR hyperactivity has been posited following the observed antidepressant effects associated with various NMDAR antagonists, most notably ketamine [11]. Ketamine's mechanism of therapeutic action has not yet been fully elucidated, however, and some research has suggested that the antidepressant effects may be independent of ketamine's NMDAR inhibition [12]. The rapid onset antidepressant action of ketamine and other NMDAR antagonists lends credibility to the notion of NMDAR dysfunction in MDD, however, the exact nature of this dysfunction involves complex synaptic and circuit mechanisms [13, 14]. NMDAR function is dependent not only on the number and location of the receptors, but also on receptor subunit composition. DNA methylation has the potential to explain NMDAR dysfunction in both SZ and MDD by resulting in altered levels of specific NMDAR subunits, as well as global decreases or increases in NMDAR activity.

In examining the NMDAR dysfunction in MDD, it is difficult not to discuss the recent rise in preclinical research and clinical trials examining the antidepressant actions of psychedelic compounds in the treatment of MDD [15]. Despite having different receptor binding targets, drugs from various classes of psychedelic compounds share many subjective and antidepressant effects, suggesting a common downstream effector. A commonly proposed mechanism for this therapeutic effect is a change in synaptic plasticity [16], a process which involves modulation of NMDAR activity. Thus, there is a connection between the NDMAR dysfunction seen in psychiatric illnesses, including MDD and SZ, and the potential mechanism of action underlying the antidepressant effects of psychedelic compounds. We argue here that this relationship can be explained by a convergent mechanism: epigenetic modification, namely DNA methylation. Additional investigation of the epigenetic effects of psychedelic compounds is needed to fully uncover their therapeutic potential, which may extend to other psychiatric diseases and symptom groups, potentially including the negative symptoms of SZ.

EPIGENETIC MODIFICATIONS: DNA METHYLATION

Epigenetic modifications are alterations to the genome that do not affect the base pair order of the DNA and can occur transiently in response to environmental cues. Since first proposed in 1942 [17], the field of epigenetics has expanded dramatically. Epigenetic modifications have been implicated in the pathophysiology of numerous developmental processes and disease states, including in neuropsychiatric disorders. One of the most well-characterized processes of epigenetic modification, DNA methylation, is a process wherein DNA methyltransferases (DNMTs) transfer a methyl group from S-adenyl methionine (SAM) onto a cytosine residue, forming 5mC [18]. Here, we provide a brief overview of the process of DNA methylation, followed by a review of the role of DNA methylation in the pathophysiology of SZ and MDD.

There are several known DNMT proteins, including DNMT1, DNMT3A, DNMT3B, and DNMT3L (Fig. 1). DNMT1 preserves DNA methylation patterns during DNA replication and cell division using hemimethylated DNA as a template [19]. DNMT3A and DNMT3B function to methylate DNA de novo, i.e., without requiring a hemimethylated template [20]. DNMT3L does not have catalytic activity, but it associates with the de novo methyltransferases (DNMT3A and DNMT3B) to stimulate activity [21]. Though not exclusively, the vast majority of DNA methylation occurs at cytosines that are immediately adjacent to a guanine, so-called CpG sites [22, 23], and the majority of human CpG sites are methylated [24, 25].

There exist stretches of the genome approximately 1 kb in length with marked increases in CpG frequency, known as CpG islands (CGIs) [26]. Despite the high concentration of CpG sites, most CpG islands are unmethylated, potentially due to the tendency toward conversion of 5mC to thymine via deamination, resulting in a germline loss of CpGs outside of CpG islands [27]. Most promoters exist within CpG islands and are unlikely to be methylated [28]. Approximately one third of intragenic CGIs in the human brain are methylated, although the function of this tissue-specific intragenic methylation is currently unknown [29]. Methyl-CpG binding proteins (MeCPs), so called DNA methylation “readers,” recognize methylation marks at CpG dinucleotides to alter gene expression [30]. For example, MeCP2 can associate with co-repressor complexes to induce transcription repression [31, 32], and mutations to the MeCP2 gene (*MECP2*) have been directly associated with the neurological disorder Rett syndrome [33], highlighting the correlation between epigenetic regulation and neurological function.

DNA methylation alters the transcription of a particular genomic sequence, however, the location of the methylation along the gene appears to dictate the nature of this alteration (Fig. 1). DNA methylation in the promoter region of a gene can impair the ability of transcriptional machinery to bind to and transcribe DNA, thus resulting in decreased expression of the gene product (gene repression) [3–5, 34]. However, in actively dividing cells, DNA methylation of the gene body does not interfere with gene transcription, and in fact can result in increased gene expression [6–9]. The three-dimensional chromosomal conformation of the DNA may also be affected by DNA methylation, which could facilitate or inhibit interactions between promoters and enhancers, further influencing genic

expression [35]. DNA methylation may also play a role in transcription product splicing, as increased methylation is observed at the boundaries between exons and introns [36].

DNA METHYLATION IN SZ AND MDD

Genome-wide association studies (GWAS) have identified a number of genetic risk loci for both SZ [37] and MDD [38] that fall within genetic regulatory domains, including non-coding regions and promoters, supporting the notion that aberrant regulation of gene expression and other genetic processes may be a significant contributor in the pathophysiology of both diseases. Epigenetic modification, especially DNA methylation, significantly contributes to gene expression regulation, and thus epigenetic aberrations have been investigated as a possible mechanism underlying the development and pathophysiology of SZ and MDD.

One of the most consistent findings in epigenetic investigations of SZ and SZ-relevant phenotypes is the overexpression of DNMT1 [39–42]. Several studies have found that DNMT1 is overexpressed specifically in the GABAergic interneurons, but not pyramidal neurons, of SZ patients [42–44]. DNMT1 functions by moving a methyl group onto cytosine residues, and treatment with methionine, a methyl-group donor, markedly worsens psychotic symptoms in patients with SZ [45]. Administration of methionine to cortical neuron cultures results in methylation of the *RELN* promoter, as well as subsequent downregulation of reelin and glutamic acid decarboxylase 67 (GAD67) mRNA expression, an effect that was reversed by knockdown of DNMT1 [46]. Thus, administration of methionine likely exacerbates the effects of the already hyperactive DNMTs in SZ by providing an additional substrate.

Several epigenomic studies have found differential DNA methylation patterns in SZ and MDD compared to control samples. SZ- or psychosis-relevant differentially methylated CpGs have been identified in both postmortem prefrontal cortex (PFC) [47] and peripheral blood of living subjects [48, 49]. A recent study identified 66 CpG sites wherein methylation was associated with depression score in monozygotic twins [50]. Additionally, this study identified 19 differentially methylated regions between the depressed and non-depressed pairs, and in the majority, methylation was positively correlated to depression score, indicating a trend of hypermethylation in depression.

Investigators have also utilized animal models and human tissue to interrogate the methylation status of specific genes associated with disease pathology, sometimes yielding mixed results. In human studies, some investigations of DNA methylation in SZ have shown hypermethylation of the *RELN* promoter [51–54] (though others have failed to detect a statistically significant difference [55, 56]) and hypermethylation of the *GAD1* (glutamate decarboxylase 1 gene) promoter in the inferior parietal lobe of postmortem psychotic patients [57]. However, others found hypomethylation of this same gene in repressive chromatin of postmortem SZ tissue [58] and hypomethylation of the membrane-bound catechol-O-methyltransferase (MB-COMT) gene body (*COMT*), with subsequent downregulation of the protein [59–61]. Consistent with dopaminergic hyperactivity in SZ, there was DNA hypermethylation in the gene body of dopamine receptors D3 (*DRD3*)

[62] and D4 (*DRD4*) (males only) [63] but hypomethylation in the promoter regions of D2 (*DRD2*) [64].

Chronic stress is a cornerstone in the study of animal models of depression, and investigations utilizing this model have demonstrated a number of stress-induced epigenetic alterations. A recent meta-analysis showed that chronic unpredictable mild stress (CUMS) is a robust method to elicit anhedonia in animal models [65]. Investigations have shown decreased histone acetylation in the hippocampus of rats exposed to chronic stress [66] and induction of DNMT3A in the nucleus accumbens (NAc) of rats exposed to social defeat stress [67], amongst many others (reviewed in refs. [68, 69]). Furthermore, differential DNA methylation and histone modification of the glial cell-derived neurotrophic factor gene (*GDNF*) reliably predicted response to stress in two distinct mouse lines [70]. Research has also shown that stress is related to DNA methylation changes in several genes in humans, including a glucocorticoid receptor gene (*NR3C1*), a serotonin transporter gene (*SLC6A4*), and *BDNF*, amongst others (reviewed in ref. [71]). Interestingly, acute inhibition of stress-induced DNA methylation using DNMT inhibitors promotes rapid and sustained antidepressant effects associated with increased BDNF-TrkB-mTOR signaling in the PFC [72].

As outlined above, investigations into the epigenetic modifications in SZ and MDD often yield mixed results. These conflicting findings may result from yet undefined disease subtypes underlying varied pathophysiology. A recent study demonstrated decreased methylation of the oxytocin receptor gene (*OXTR*) in both recent onset SZ and ultra-high risk for psychosis cohorts, while hypomethylation was associated with increased negative symptoms in both SZ and psychosis women [73]. This supports the notion that aberrations in DNA methylation at distinct loci may contribute to a subtype of SZ with more pronounced negative symptoms. Further, when SZ patients were divided into two subtypes, one with marked difference in methylation status compared to healthy controls and one with methylation patterns that were relatively similar to healthy controls [74], the differential methylation group demonstrated more severe symptomology and degree of cognitive deficit. The potential role of DNA methylation in the generation of different subtypes of SZ should be further explored, with the weighted contribution to other symptom domains considered.

As in SZ, DNA methylation patterns also help to explain the varied symptom presentations associated with depression. In a 2021 study, methylation profiles differed in the peripheral blood of patients with adult-onset versus late-onset depression, and several CpG sites were identified as potential markers of adult-onset depression [75]. While the age of disease onset may be related to different methylation patterns in depression, epigenetic aging on its own does not appear accelerated in the depressed individual [76]. Epigenetic alterations may also be responsible for sex-specific differences in disease manifestation and symptom presentation. In a subchronic variable defeat stress model, female mice appeared more susceptible to developing depression-like symptoms than their male counterparts and demonstrated greater induction of DNMT3A in the NAc [77]. Interestingly, when DNMT3A was upregulated in the NAc of male mice, it increased their susceptibility to developing depression-like symptoms, while DNMT3A knockdown in female mice showed an increase in resilience to the development of depressive-like symptoms.

Presented above are only a handful of the many known aberrations in DNA methylation that have been identified in SZ and MDD, supporting widespread changes in epigenetic regulation in the pathophysiology of both diseases. Additionally, both SZ and MDD demonstrate dysfunction of the NMDAR, and we propose that this dysfunction may be in part mediated by DNA methylation aberrations. Next, we will briefly review the NMDAR, discuss NMDAR dysfunction in SZ and MDD, and finally present the limited research on DNA methylation of the NMDAR subunit genes in both disorders.

NMDARS

The NMDAR is a class of ionotropic glutamate receptors activated by NMDA, in addition to glutamate [78] and glycine [79]. These receptors are indispensable for synaptic plasticity-dependent processes such as learning and memory and are implicated in a number of psychiatric and neurological disorders. Other non-NMDA ionotropic glutamate receptors include AMPA receptors and kainate receptors. The NMDAR contains two glutamate binding sites and two glycine binding sites [80], and is composed of 2 obligatory GluN1 subunits and 2 GluN2 or GluN3 subunits [81–84]. GluN1 can include up to 8 splice variants as a result of posttranscriptional RNA processing [85, 86]. GluN2 includes 4 variants encoded by the GluN2A-D genes (*GRIN2A-D*) [87, 88], and GluN3 includes 2 variants encoded by the GluN3A-B genes (*GRIN3A-B*) [89]. The genes for the NMDAR subunits are dispersed throughout the genome, spanning five chromosomes (Fig. 2).

NMDARs are moved between synaptic and extrasynaptic sites via rapid lateral translocation [90], and the process of NMDAR trafficking is implicated in long-term depression (LTD) and potentiation (LTP). The subunit composition of NMDARs has significant consequences on receptor function and kinetic profile. NMDAR subunit composition also plays a significant role in the relative contribution of NMDARs to the processes of LTD and LTP. Within a few hours following synaptic activation, NMDA receptors, particularly GluN2A-containing receptors, are preferentially recruited to synapses [91, 92] and thus play a more prominent role in LTP induction, partly due to their faster kinetics [93]. In contrast, extrasynaptic NMDARs are predominately GluN2B-containing [94], which are strongly implicated in LTD [95]. Notably, the process of NMDAR trafficking, and thus synaptic plasticity, is influenced by BDNF levels (reviewed in ref. [96]). BDNF has been shown to increase GluN1, GluN2A, and GluN2B mRNA and protein levels in the hippocampus [97], and the process of hippocampal LTP is mediated in part via signaling of the BDNF receptor TrkB [98].

In addition to their differential contributions to LTP/LTD, the subunit composition of NMDARs follows distinct developmental and brain-region specific patterns (Fig. 2). While the GluN1 subunit is ubiquitously expressed in all NDMARs, GluN2 subunit expression patterns are more variable, with GluN2A subunits being widely distributed throughout the adult brain: GluN2B subunits predominate in the forebrain [99, 100], GluN2C subunits in the cerebellum, and GluN2D subunits in the midbrain and interneuron populations [101–104]. Tri-heteromeric NMDARs (GluN1/GluN2A/GluN2B) are concentrated predominately in the hippocampus and cortex [105–107].

GluN2B and GluN2D subunits are expressed in the embryonic brain, and GluN2A expression increases from birth through development. GluN2A subunits increase in proportion to GluN2B throughout development, and this GluN2B-to-GluN2A subunit transition is critical to normal neurological development [102, 108]. Although GluN2B subunits predominate in the cerebellum at birth, they largely disappear from this region during early postnatal development and are replaced by GluN2C subunits, which, during the same timespan, disappear from forebrain structures and are replaced by GluN2B subunits [102]. GluN2D expression decreases dramatically throughout development [102].

Given their critical role in normal and pathophysiological processing, positive and negative modulators of NMDARs have been well-characterized (reviewed in refs. [109, 110]). Positive modulators of NMDAR function include polyamines, arachidonic acid, pregnenolone sulfate, and CIQ. Negative modulators of NMDAR function include ketamine, D-APV, memantine, MK-801, TCN-201, ifenprodil, pregnanolone sulfate, and QNZ46. These positive and negative modulators have been used to investigate the effects of NMDAR hypo- and hyperfunction on behavior, development, and disease states, and have contributed to our understanding of various neuropsychiatric disorders. Below, we will discuss the role of NDMAR dysfunction SZ and MDD, and we will describe the potential role of DNA methylation in this dysfunction.

NMDAR DYSFUNCTION IN SZ

Although the dopamine hypothesis once reigned as the predominate view of neurotransmitter dysfunction in the pathophysiology of SZ, many experts now argue that dysfunction of the NMDAR-mediated glutamate system may be a more apt explanation, at least for early development and progression of SZ. Evidence of NMDAR dysfunction in SZ dates back to the 1990s, when it was discovered that in healthy control subjects, the NMDAR antagonists ketamine and PCP induced SZ-relevant symptoms [111–114], and these same substances exacerbated symptoms in SZ patients [115, 116]. Since then, details of the glutamate hypothesis of SZ, the notion that NMDAR hypofunction is a core tenet of the pathophysiology of SZ, have been extensively researched and reviewed [10, 100, 117–119].

NMDAR dysfunction in SZ is most often characterized as hypofunction of the NMDARs of GABAergic interneurons, resulting in disinhibition of cortical pyramidal neurons (Fig. 3). NMDAR hypofunction in SZ is supported by numerous postmortem examinations of SZ brain tissue, which have revealed aberrations in several NMDAR subunit protein and mRNA levels, though results related to specific subunit levels have been mixed. A meta-analysis showed decreased GluN1 mRNA expression in the PFC of SZ patients [120], whereas *GRIN2A* was identified as a genetic risk locus for the development of SZ [121, 122]. Decreased activity of the downstream signaling cascades associated with the NMDAR was also found in postmortem examination of the dorsolateral PFC in SZ patients, specifically in the postsynaptic density fraction, despite increased NMDAR density in this same area [123], suggesting NMDAR may be dysfunctional in SZ, rather than reduced in quantity.

Support for NMDAR hypofunction and subsequent cortical disinhibition in the pathophysiology of SZ has also been demonstrated in numerous animal models of psychosis (Table 1). Electrophysiological studies have revealed a number of changes associated with SZ, perhaps the most notable and consistent of which is the increased gamma-band oscillations observed in SZ patients and SZ-relevant animal models [124]. In the healthy brain, parvalbumin (PV)- and somatostatin (SST)-containing interneurons contribute inhibitory inputs to pyramidal cortical neurons to support the maintenance of gamma oscillations [125]. Decreased PV interneuron activity due to NMDAR hypofunction may result in hyperexcitability of the cortex, thus contributing to the alterations in gamma synchrony typically seen in SZ [126]. The NMDAR antagonist ketamine also increases the power of gamma-band oscillations [127, 128], and in a model of NMDAR hypofunction, serine racemase knockout (SRKO) mice demonstrate impaired investigation-elicited gamma power and increased background gamma power, suggesting a deficit in signal-to-noise ratio in the gamma band, which may contribute to impaired cognitive functioning [129]. Finally, SRKO mice exhibited reduced inhibitory synapses onto CA1 pyramidal neurons, which resulted in an increased E/I balance [130]. Each of these studies provide supporting evidence for the concept of NMDAR hypofunction resulting in disinhibition of cortical pyramidal neurons.

The timing of NMDAR hypofunction is critical in the development of SZ or SZ-relevant symptoms, as the age at which NMDAR hypofunction is induced appears to dictate the effects seen and the degree to which SZ-like behaviors are generated. Following administration of the NMDAR antagonist MK-801 on postnatal day 10, mice demonstrated reduced function of PV-containing interneurons, decreased GABA transmission, and decreased levels of GABA-related proteins [50]. Additionally, these mice showed several SZ-relevant behavioral deficits in adolescence. Alvarez et al. investigated the effects of early postnatal NMDAR ablation in cortical and hippocampal interneurons at different developmental stages and found that while cortical hyperactivity occurred in the juvenile mice, the mPFC to hippocampus functional hypoconnectivity was not evident until adolescence [131].

These findings support the sequential contribution of cortical hyperactivity to the later development of SZ-like phenotypes. The GluN2B-to-GluN2A transition in NMDAR composition during development occurs later in the PFC than in other brain regions, as discussed above, and this corresponds to later maturation of this brain region as compared to others [99]. NMDAR hypofunction early in development may exacerbate this delayed transition, and further contribute to the cognitive dysfunction seen in SZ. Interestingly, repeated administration of (R)-ketamine to maternal immune activation-exposed animals during adolescence resulted in a significant reduction in SZ-relevant symptoms in adulthood [132]. This suggests that (R)-ketamine, which contains only the (R) enantiomer of the normally racemic ketamine mixture (discussed below), may have neuroprotective effects when administered during development, and this theory warrants further investigation.

The theory of NMDAR hypofunction in SZ is further supported by the dysfunction of other neurotransmitters seen in SZ, as many of these neurotransmitter systems work synergistically with the glutamatergic system. In our recent review, we argued that the

NMDAR hypofunction seen in SZ was not a result of aberrant neuromodulatory transmitters (e.g., dopamine), but rather that NMDAR hypofunction resulted in the subsequent dysfunction of other systems [100]. The reciprocal relationship between NMDAR-mediated neurotransmission and various other neuromodulatory systems is extensive, and studies investigating NMDAR hypofunction have revealed numerous other neurotransmitter system aberrations, including increased dopamine release in the striatum [133], aberrant BDNF signaling in the PFC [134], and increased serotonin levels in the mPFC [135].

NMDAR DYSFUNCTION IN MDD

Support for NMDAR dysfunction in MDD was first evidenced by the antidepressant effects of various NMDAR antagonists. The discovery of this drug class in the treatment of depression came about serendipitously, when D-cycloserine was administered for the treatment of tuberculosis but additionally resulted in elevated mood [136]. This finding was expounded upon by Trullas and Skolnick, who found that NMDAR antagonists, including the non-competitive antagonist MK-801 and the competitive antagonist AP-7, have antidepressant-like effects in animal models of depression [137]. Since these initial findings, NDMAR antagonists have demonstrated significant antidepressant effects in both preclinical and clinical studies. Notably, the non-competitive NMDAR antagonist ketamine has consistently demonstrated rapid, long-lasting antidepressant effects in numerous clinical populations [138–142] (reviewed in refs. [13, 143]).

Ketamine’s antidepressant mechanism of action is currently an area of active research and has not yet been fully elucidated. Much in the same way that NMDAR hypofunction in SZ is theorized to increase cortical activity via preferential blockade of NMDARs on GABAergic (inhibitory) interneurons, resulting in disinhibition of the cortical pyramidal neurons, ketamine results in increased cortical activity despite blocking excitatory (glutamatergic) neurotransmission (Fig. 3) [144, 145]. It is not clear if this NMDAR blockade is responsible for the antidepressant effects of ketamine, as recent studies have demonstrated the potential for an NMDAR-independent mechanism related to ketamine metabolites [12]. Furthermore, as noted above, the antidepressant effects of ketamine outlast the acute NMDAR blockade of the drug [14].

Ketamine consists of the (R) and (S) enantiomers, commonly referred to as arketamine and esketamine, respectively. (S)-ketamine has significantly higher NMDAR binding affinity than (R)-ketamine [146], and the vast majority of clinical trials investigating individual ketamine enantiomers for the treatment of MDD have focused on (S)-ketamine rather than (R)-ketamine. Despite lower NMDAR binding affinity, (R)-ketamine may have more potent antidepressant effects based on preclinical studies [147–149]. Furthermore, (R)-ketamine produces fewer psychosis-like side effects [147] and has lower abuse liability [150] than (S)-ketamine, and thus may be a more tolerable treatment option. Indeed, in rhesus monkeys, esketamine, but not arketamine, decreased dopamine D2/3 receptor binding in the striatum [151], in line with the increased risk of psychosis-like effects of esketamine compared to arketamine. (R)- and (S)-ketamine also produced differential fMRI responses when administered to conscious rats, with (R)-ketamine mimicking the effects elicited following MK-801 administration [152]. This finding suggests that the antidepressant

mechanism underlying (R)-ketamine is unique from that underlying (S)-ketamine, and that (R)-ketamine may potentially function in an NMDAR-independent manner. However, despite apparently lacking GluN2B subunit specificity, ketamine's antidepressant effects are negated in GluN2B-deficient mice, suggesting a GluN2B-specific role in ketamine's mechanism of action [153].

Given the knowledge that NMDAR antagonism produces antidepressant effects, some researchers have investigated NMDAR hyperactivity as a possible mechanism in the pathophysiology of MDD. Postmortem studies have revealed various aberrations in the expression levels of NMDAR subunits in the brains of patients with MDD [118] (see Table 1).

Several rodent models of depression have also demonstrated stress-related increases in NMDAR subunit expression. These include increased GluN1 expression/mRNA levels in the hippocampus following immobilization stress [154, 155] and increased GluN1 subunit levels in the VTA following varied stress paradigm [156]; increased GluN2A subunit expression in adult rats exposed to maternal separation [157]; increased *GRIN1*, *GRIN2A*, and *GRIN2B* expression in the frontal cortex of BDNF-deficient animals [158]; and increased GluN2A and GluN2B mRNA expression in the hippocampus following chronic restraint stress [159] and chronic corticosterone administration [160]. Of note, chronic stress exposure resulted in increased GluN1 subunit expression, but no significant changes in mRNA levels of GluN2A or GluN2B in rat hippocampus [161]. In animals exposed to chronic unpredictable mild stress, GRIN1 expression was decreased [162]. Chronic stress has also been shown to decrease NMDAR subunit expression (GluN1, GluN2A, and GluN2B) in the PFC, but not the motor cortex, of rats [163].

In summary, these studies of NMDAR subunit aberration in depression, when taken together with studies of antidepressant effects of NMDAR antagonists, suggest that NMDAR hyperactivity may contribute to the symptom profiles seen in MDD. Furthermore, NMDAR subunit dysregulation may contribute to the aberrations in synaptic plasticity seen in MDD, though the exact contributions of NMDAR dysregulation to the pathophysiology of depression are still being elucidated. This concept is further discussed in our section on the therapeutic potential of psychedelics, which may exert their antidepressant functions through NMDAR-mediated changes in LTP and synaptic plasticity (see Fig. 4).

DNA METHYLATION OF NMDAR SUBUNIT GENES

As outlined above, alterations in DNA methylation patterns and aberrations in epigenetic machinery in SZ and MDD have been established by extensive research, much of which is still ongoing. Given the evidence supporting both epigenetic alterations and NMDAR dysfunction in SZ and MDD, it is reasonable to theorize that this NMDAR dysfunction may result from aberrant epigenetic regulation. Still, oddly, relatively few studies have investigated this specific line of questioning. Therefore, we will now focus on the limited research on DNA methylation changes in SZ and MDD associated explicitly with the NMDAR.

In a recent study, hypomethylation of the GRIN2B promoter was found in peripheral blood samples of SZ patients, and methylation at a particular CpG site was correlated positively to cognitive function [164]. However, in a study investigating the relationship between childhood trauma and methylation status at *GRIN1*, *GRIN2A*, and *GRIN2B* in the peripheral blood of patients with SZ, their siblings, and healthy controls, *GRIN1* hypermethylation was found to be correlated to trauma status in siblings but not SZ patients [165]. Rats reared in isolation also demonstrated hypermethylation of *GRIN1* in the PFC and of *GRIN2B* in the hippocampus [166]. Interestingly, subchronic PCP (an NMDAR antagonist) administration results in promoter hypermethylation of the *GRIN1* and *GRIN2B* genes, but not the *GRIN2A* gene, in rodent models [167].

Still, it is unknown exactly *how* epigenetic mechanisms may regulate NMDAR subunits. Repressor element 1-silencing transcription factor (REST) contributes to the GluN2B-to-GluN2A switch seen during neurodevelopment via epigenetic regulation, and both REST expression and methylation of H3K27 at the *GRIN2B* promoter are increased in the methylazoxymethanol (MAM) rodent model of SZ [168]. NMDAR blockade with the competitive antagonist CGP-37849 resulted in aberrant histone acetylation in the mPFC of rodents, suggesting that NMDAR hypofunction and epigenetic alterations could be reciprocal in SZ [169]. Indeed, it is possible that NMDAR hypofunction in early adolescence results in DNA methylation of NDMAR-relevant genes, which perpetuates a state of continued NMDAR hypofunction throughout an individual's life.

An interesting example of higher-order chromatin relevant for SZ was reported for the *GRIN2B* gene locus [35, 117, 170]. Specifically, this higher-order chromatin is dynamically regulated by neuronal activity, and multiple loop-bound intronic and intergenic DNA sequences from the *GRIN2B* transcription start site (TSS) are formed to compete for promoter access to regulate *GRIN2B* expression [35, 170]. In addition to such promoter-enhancer loops, the *GRIN2B* promoter interacts with and is counterbalanced by intragenic repressive chromatin embedded in intron sequences downstream from the TSS [170]. Transcriptional regulation at the *GRIN2B* locus is thus likely engaged with a dynamic and competitive interplay of multiple loop formations involving the *GRIN2B* promoter, which may be further influenced by methylation status at the promoter and distant regulatory sites [170, 171]. Interestingly, these loop-bound sequences interact with the *GRIN2B* promoter and harbor single nucleotide polymorphisms (SNP) implicated in working memory and SZ [170].

In a genome-wide methylation study of 94 maltreated and 96 non-traumatized children, *GRIN1* was identified as one of three genes that predicted depression [172]. Further, in validating these genes in a mouse model of neglect, methylation of *GRIN1*, along with DNA-binding protein inhibitor (*ID3*) and tubulin polymerization-promoting protein (*TPPP*), significantly predicted depression-like behaviors in the elevated plus maze and forced swim test [173]. *GRIN2A* hypermethylation has also been identified in the PFC and hippocampus of depressed individuals compared to healthy controls following examination of postmortem brain tissue [174].

These studies support the role of DNA methylation in the differential regulation of *GRIN2B* gene expression in SZ (Fig. 3). Given the role of GluN2B subunit-containing NMDARs in the induction of LTD, and the known deficits in synaptic plasticity in neuropsychiatric disorders like SZ and MDD, this is particularly interesting. Still, additional studies are needed to understand the role of this differential expression in the pathophysiology of SZ. The differential methylation and subsequent altered expression of the *GRIN2B* gene in SZ are of particular interest given both the GluN2B-to-GluN2A transition during neurodevelopment and the known dysfunction of the PFC, where the GluN2B subunit predominates, in SZ patients. Additionally, more research is needed to elucidate the role of DNA methylation in the expression regulation of other NMDAR subunits. Of note, recent studies have consistently reported the critical role of the *GRIN2A* gene in SZ [121, 122]. Whether and how the *GRIN2A* gene is methylated, and how this process may contribute to the progression of SZ and depression, remain to be determined.

THE THERAPEUTIC POTENTIAL OF PSYCHEDELICS

The recent success of ketamine as a potential treatment for depression has sparked a renewed interest in the use of psychedelic compounds for the treatment of numerous psychiatric disorders. While ketamine may not immediately evoke the essence of a psychedelic compound, given its action as an NMDAR antagonist rather than a serotonin agonist, psychedelic compounds include an array of substances with varying effects and receptor binding targets (see Fig. 4). Psychedelic compounds are generally divided into classes of classic psychedelics, which function as serotonin 2A (5-HT2A) agonists (e.g., psilocybin and LSD); dissociative psychedelics, which function as NMDAR antagonists (e.g., ketamine); entactogens, which function as positive modulators of both the serotonin and dopamine systems (e.g., MDMA); and atypical psychedelics, which do not fit into the above categories (reviewed in ref. [175]). The hallmark psychedelic effects of these compounds generally include profound perceptual and emotional alterations, including euphoria, auditory and visual hallucinations, time distortions, and ego dissolution [176].

Psychedelic compounds have had a complicated history in the medical field, as many early drug experiments were steeped in unethical practices and resulted in a decades-long moratorium on government-funded psychedelic research in the US [175]. In more recent years, psychedelic compounds have again become an appealing area of psychiatric research, as they have shown promise for treating several different psychiatric illnesses, including depression, post-traumatic stress disorder, anxiety, obsessive-compulsive disorder, and substance use disorders (reviewed in ref. [15]). Despite the increase in psychedelic-mediated treatment trials, the mechanism by which these substances elicit their therapeutic effects is still unclear. Given the varied receptor binding targets of psychedelic compounds, a shared downstream effector action is expected, and several theories have been proposed to describe this potential mechanism of psychedelic therapeutic action.

One of the most common changes elicited by psychedelic administration in both animal and human studies is that of increased synaptic plasticity. Both psilocybin [177] and N,N-dimethyltryptamine (DMT) [178] have been shown to increase the density of dendritic spines in the brains of rodents. DMT, LSD, and DOI also increase synaptogenesis in rodents

[179]. Synaptic plasticity has been theorized to underlie the increases in cognitive flexibility observed in human studies of psychedelic compounds [180]. In a recent study of psilocybin for the treatment of MDD, improvements in depressive symptoms were correlated with increases in theta power on subject EEG [181]. Exactly how these observations of neural and cognitive plasticity relate to one another, however, is an active area of research.

One proposed mechanism involves binding psychedelic compounds to the BDNF receptor TrkB. In a 2023 study, Moliner and colleagues found that both LSD and psilocin, the active ingredient in psilocybin, bind to TrkB with greater affinity than non-psychedelic antidepressant compounds and that this TrkB binding is necessary for the synaptic plasticity effects seen following psychedelic administration [182]. This discovery is particularly intriguing because psychedelic-induced TrkB signaling does not require serotonin 5-HT2A receptor signaling, suggesting that the plasticity changes associated with psychedelics may be independent of their hallucinogenic properties. Similarly, it was shown that the behavioral and electrophysiological responses to psilocybin are preserved in mice despite the coadministration of ketanserin, a 5-HT2A/2C receptor antagonist [183].

The idea that the therapeutic mechanism of psychedelic action may be independent of serotonin 2A receptor signaling is particularly attractive, as it helps bridge the gap between different psychedelic subclasses. Despite sharing common subjective and therapeutic effects, not all psychedelic compounds share a common binding target. Most notably, ketamine, a potent dissociative psychedelic with known therapeutic benefits in the treatment of MDD, functions as an NMDAR antagonist. The possibility of a shared downstream effector mechanism of psychedelic action despite varied receptor binding targets was recently supported in a series of studies by Nardou and colleagues, in which it was demonstrated that psychedelic compounds across multiple subclasses consistently function to reopen a critical period of social reward learning [184, 185].

First, Nardou and colleagues found that MDMA could reopen a critical period of social reward learning via oxytocin-dependent LTD synaptic plasticity [185]. Given that MDMA is an empathogenic psychedelic, generally resulting in increased sociability and social reward, the authors then sought to discover if this ability to reopen the social reward learning critical period was specific to MDMA or shared across psychedelics. They proceeded to demonstrate that ketamine, LSD, psilocybin, and ibogaine were all able to reopen to social reward learning critical period in rodents following a single dose [184]. They further established that the duration of the critical period reopening was proportional to the duration of subjective effects typically seen in humans. Theorizing that this critical period reopening may be accomplished via downstream effects on gene expression regulation, they investigated mRNA expression levels following psychedelic administration and found differential expression of several genes associated with the extracellular matrix (ECM). Here, we propose that psychedelic compounds may induce alterations in DNA methylation patterns, resulting in altered expression of genes related to synaptic plasticity, including NMDAR subunit genes, and that these changes in DNA methylation contribute to the therapeutic effects of the drugs (Fig. 4).

The concept of drug-induced epigenetic modifications is not new. It has been well-established that cannabinoid exposure is associated with differential DNA methylation of various genes in peripheral blood [186–188], sperm [189, 190], and brain tissue [191, 192]. Furthermore, it has been shown that in animals with parental THC exposure, there is significant *GRIN2A* hypomethylation in exon 1 and decreased GluN2A gene expression, supporting the notion of drug-induced DNA methylation changes resulting in aberrant gene expression [193]. Differential DNA methylation patterns are also observed in methamphetamine-treated mice compared to control groups [194]. More recently and perhaps most excitingly, widespread DNA methylation changes have been identified in the rodent PFC following repeated administration of the psychedelic compound LSD [195]. It is reasonable to theorize, then, that other substances may also induce changes in DNA methylation, and that these changes may be related to the underlying psychiatric effects of these substances. Here, we discuss briefly the limited research investigating DNA methylation changes associated with psychedelic compounds.

Despite the apparent knowledge gap regarding the mechanism of action underlying ketamine's antidepressant effects, very little research has been done into the epigenetic modifications induced by ketamine treatment. In the chronic despair mouse model of depression, both acute ketamine treatment and chronic antidepressant (imipramine and fluoxetine) treatment produced significant decreases in DNA methylation of the Homer1 (a scaffolding protein associated with synaptic signaling) promoter [196]. This reduction in DNA methylation levels was a reversal of the promoter hypermethylation and decreased expression seen in the chronic despair model prior to treatment. It was also associated with an increase in Homer1 gene expression following treatment. In addition, ketamine treatment, when combined with fear extinction training, produced significant decreases in BDNF promoter DNA methylation in an inescapable foot shock model [197]. This reduction was again a reversal of observed hypermethylation induced by inescapable foot shock prior to treatment. These two studies not only demonstrate the capacity of ketamine to reduce DNA methylation, but they also offer the possibility that ketamine reverses aberrant methylation in psychiatric disease, potentially underlying ketamine's mechanism of antidepressant action. In a mouse model of depression, DOI (2,5-dimethyoxy-4-iodoamphetamine) not only significantly reduced depressive-like symptoms, but also resulted in long-lasting epigenomic changes, including gene clusters related to NDMAR function [198].

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the rapid rise of psychedelic medications for the treatment of various psychiatric disorders, and the known aberrations in DNA methylation observed in these disorders, very little research has been conducted to examine a potential link between the antidepressant effects of psychedelic substances and the epigenetic modifying properties of these substances. We propose that alterations in DNA methylation underlie the antidepressant effects of psychedelic compounds, using the NMDAR genes as a reference point. NMDAR dysfunction is implicated in the pathophysiology of depression, via hyperactivity of the GABAergic interneurons and subsequent hypoactivity of the cortex, supported by the antidepressant properties of the NMDAR antagonist ketamine. This NMDAR hyperactivity

may partly be caused by aberrations in DNA methylation patterns associated with these genes, and treatment with psychedelic compounds may reverse these aberrations.

Further, we described the NMDAR hypofunction that results in decreased activity of GABAergic interneurons and subsequent hyperactivity of the cortex in SZ. Several lines of research have implicated DNA methylation aberrations in the NMDAR dysfunction in SZ. Many psychedelic compounds have been shown to elicit psychosis-like effects in healthy controls and worsen symptoms in patients with SZ when administered acutely. However, there is limited research investigating the changes in DNA methylation patterns observed following the administration of psychedelic compounds to NMDAR-deficient animal models. Psychedelic compounds may have a stabilizing effect on DNA methylation patterns, which could result in reduced symptoms for some psychiatric concerns beyond their known antidepressant effects. Additionally, it is unclear the mechanism by which psychedelic compounds alter DNA methylation patterns. This should be further investigated, as it could offer therapeutic potential for treating SZ, amongst other psychiatric illnesses, if the mechanism could be separated from the acute psychedelic effects of these compounds. For example, the non-hallucinogenic psychedelic analogue tabernanthalog was recently synthesized and demonstrated potential therapeutic effects in the treatment of substance use and depression-like behaviors in rodent models [199].

The age at which NMDAR dysfunction begins, and the age at which psychedelic compounds are administered, may impact the long-term symptom profile of the individual. As discussed above, the NMDAR subunit preponderance is not only brain region-specific, but changes throughout development, most notably in the so-called GluN2B-to-GluN2A subunit transition that occurs early in development. It is unknown how changes in DNA methylation affect this transition, and how interventions aimed at altering DNA methylation levels may ultimately affect development. Furthermore, NMDAR subunits predominate in different ratios based on the specific cell, and the effects of NDMAR subunit epigenetic modification at a cellular level, e.g., pyramidal neurons vs. GABAergic interneurons, have yet to be fully elucidated. Finally, as medicine generally and psychiatric treatment specifically become increasingly more individualized, it raises the question of disease subtypes and SNP-specific genotypes in the pathophysiology of disease, and the effects of methylation status of these disease-specific SNPs should be further explored for diagnostic and treatment purposes.

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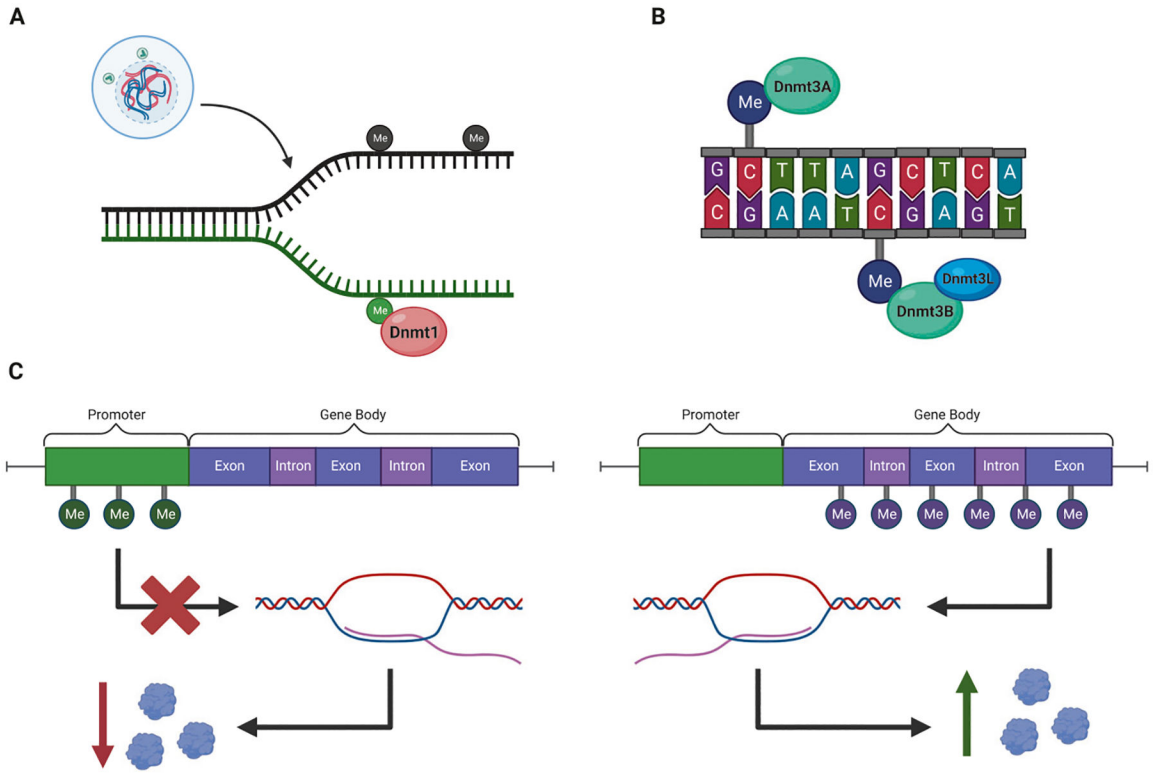

Fig. 1. DNA methylation by DNA methyltransferases.

A DNMT1 preserves DNA methylation patterns during DNA replication and cell division. **B** DNMT3A and DNMT3B perform de novo DNA methylation; DNMT3L acts in association with these DNA methyltransferases to stimulate activity. **C** Increased DNA methylation in the promoter region interferes with gene transcription and results in decreased gene expression. In contrast, increased DNA methylation in the gene body does not interfere with gene transcription and may result in increased gene expression.

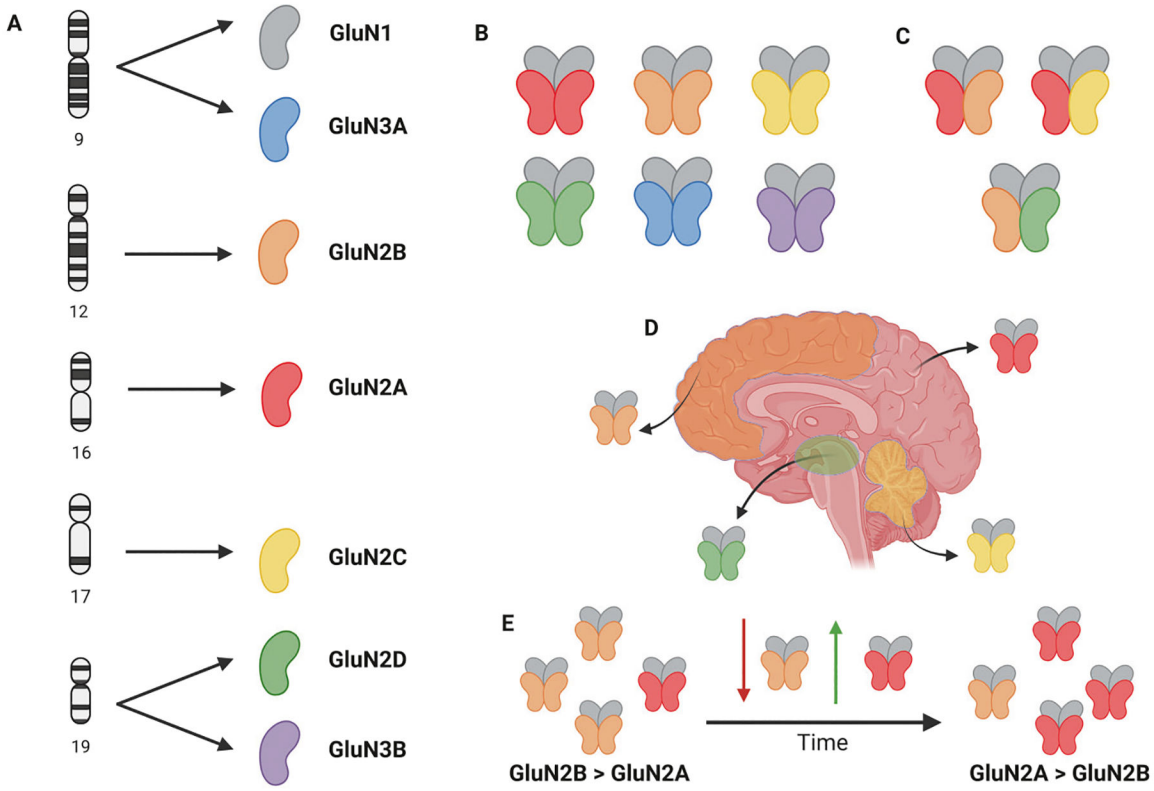

Fig. 2. NMDA receptor subunits.

A Genes for the NMDA receptor subunits are dispersed across five chromosomes – chromosome 9 (GluN1 and GluN3A), chromosome 12 (GluN2B), chromosome 16 (GluN2A), chromosome 17 (GluN2C), and chromosome 19 (GluN2D and GluN3B). **B** Most NMDA receptors are heterodimeric, composed of two obligatory GluN1 subunits and two identical GluN2 or GluN3 subunits. **C** Some heterotrimeric NMDA receptors have been identified, which are composed of two GluN1 subunits and either (1) one GluN2A subunit + one GluN2B subunit, (2) one GluN2A subunit + one GluN2C subunit, or (3) one GluN2B subunit + one GluN2D subunit. **D** The GluN2A subunit is ubiquitously expressed throughout the adult brain, while GluN2B predominates in the forebrain, GluN2C predominates in the cerebellum, and GluN2D predominates in the midbrain. **E** Throughout development, GluN2B subunits are replaced with GluN2A subunits, in what is known as the GluN2B-to-GluN2A switch.

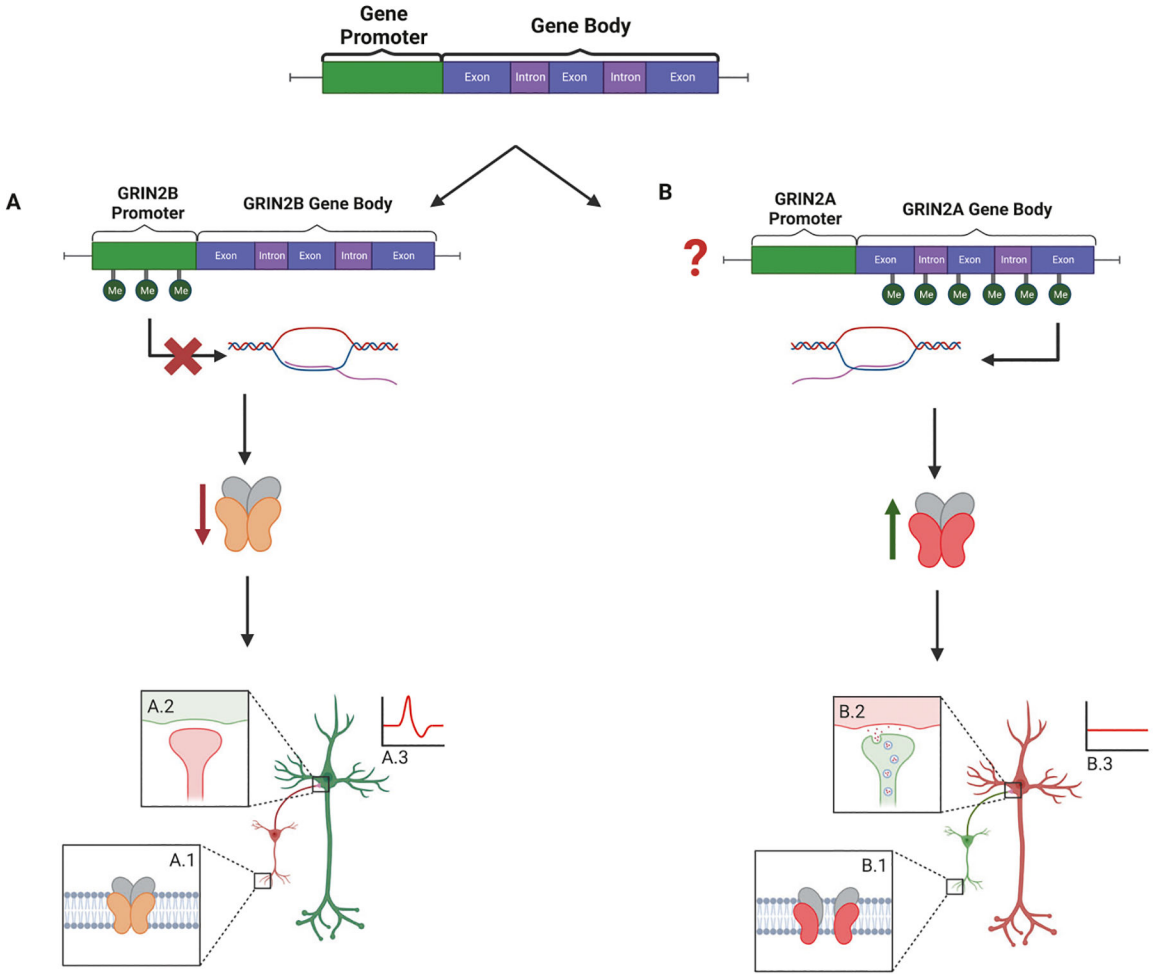

Fig. 3. Proposed mechanisms of NMDAR dysfunction in SZ and MDD.

DNA methylation of the promoter and gene body result in different expression profiles, and this may underlie the opposing directions of NMDAR dysfunction in SZ (hypofunction) and MDD (hyperfunction). **A** DNA methylation of the *GRIN2B* Promoter in SZ. DNA methylation of the *GRIN2B* promoter prevents transcription of the *GRIN2B* gene, resulting in decreased GluN2B expression. This *GRIN2B* promoter hypermethylation may be partially responsible for the NMDAR hypofunction in SZ, demonstrated in Fig. A.1–3. **A.1** NMDA receptors on GABAergic interneurons are hypoactive, preventing the activation of these interneurons. **A.2** The interneuron does not release GABA at the synaptic junction between GABAergic interneuron and pyramidal neuron. **A.3** The pyramidal neuron is disinhibited, resulting in increased firing and cortical hyperexcitability. **B** DNA Methylation of the *GRIN2A* Body in MDD. DNA methylation of the *GRIN2A* gene body facilitates transcription of the *GRIN2A* gene, resulting in increased GluN2A expression. This *GRIN2A* gene body hypermethylation may be partially responsible for the NMDAR hyperfunction proposed in MDD, demonstrated in Fig. B.1–3. **B.1** NMDA receptors on GABAergic interneurons are hyperactive, resulting in activation of these interneurons. **B.2** The interneuron releases GABA at the synaptic junction between GABAergic interneuron

and pyramidal neuron. **B.3** The pyramidal neuron is inhibited, resulting in decreased firing and cortical hypoexcitability.

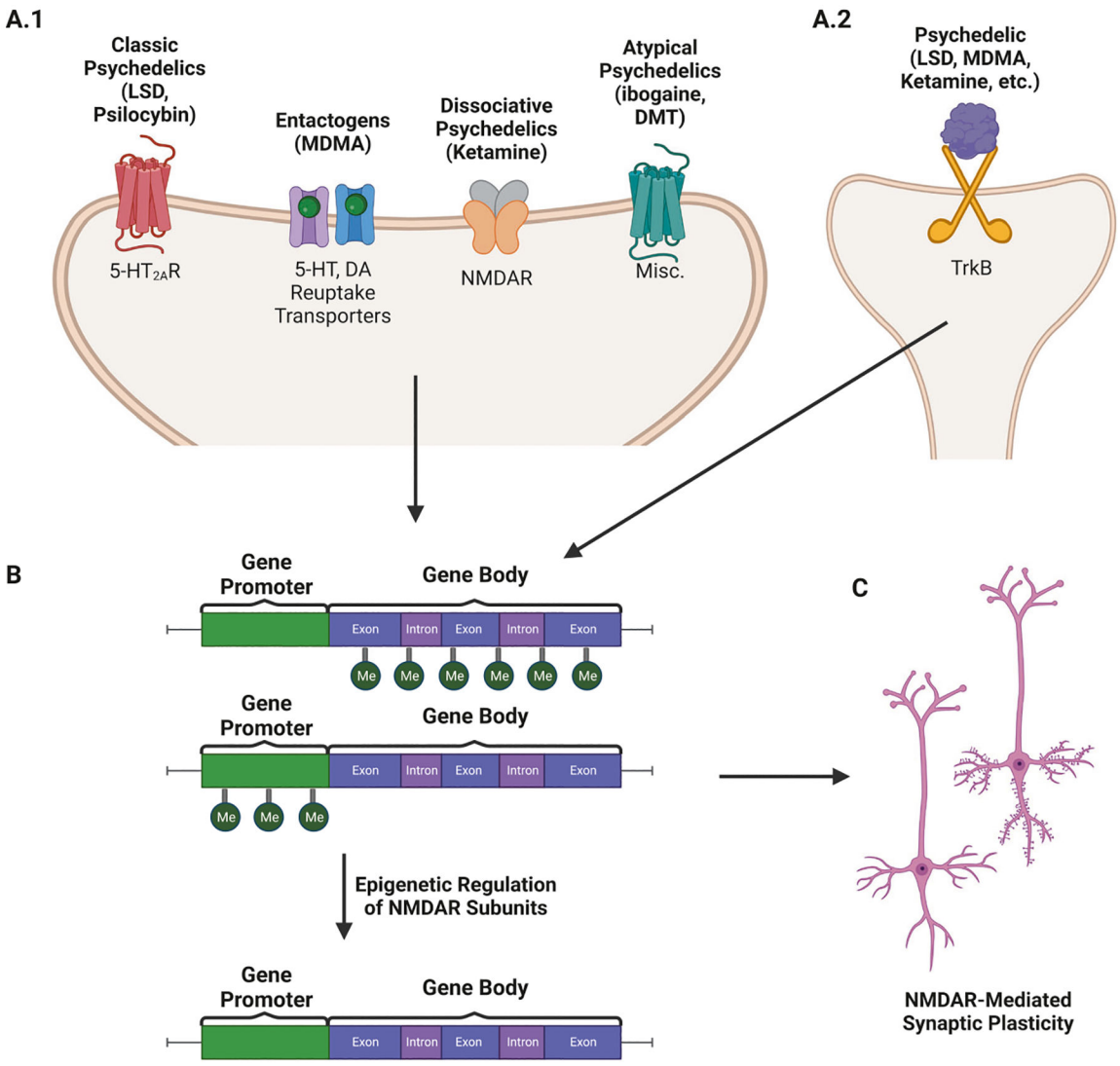

Fig. 4. Psychedelic compounds, mechanisms of action in synaptic plasticity.

A, A.1 Psychedelic compounds include classic psychedelics (psilocybin, LSD), which act as 5HT2A receptor agonists; dissociative psychedelics (ketamine), which act as NMDAR antagonists; entactogens (MDMA), which act as positive modulators of the serotonin and dopamine systems; and atypical psychedelics (ibogaine, DMT), which do not fit into the aforementioned categories. **A.2** In addition to their individual receptor binding targets, psychedelic compounds may also bind to the BDNF receptor TrkB. **B** Despite their varied receptor binding targets, psychedelic compounds may share downstream signaling pathways that ultimately result in changes to, and/or stabilization of, DNA methylation patterns. **C** DNA methylation patterns result in changes to NMDAR subunit expression, ultimately resulting in increased dendritic spine formation and changes to NMDAR-mediated synaptic plasticity, which may underlie the therapeutic effects of psychedelic compounds.

Table 1.

Human and animal studies investigating NMDAR subunit aberrations in SZ and MDD.

Sample/Population studied	Relevant disease	NMDAR subunit(s)/ allele(s) investigated	Methods	Results	Reference
Cre recombinase mice	SZ	GluN1 (GRIN1)	GRIN1 alleles disrupted in ~50% of cortical and hippocampal interneurons in the second postnatal week	GRIN1-deficient mice demonstrated several SZ-relevant behaviors following social isolation	[200]
Cre recombinase mice	SZ	GluN1 (GRIN1)	Amphetamine-induced dopamine changes were investigated in GRIN-1 deficient mice	GRIN1-deficient mice demonstrated dopaminergic disruptions characteristic of SZ - amphetamine increased dopamine in the nucleus accumbens and decreased dopamine in the mPFC	[201]
Cre recombinase mice	SZ	GluN1 (GRIN1)	GRIN1 alleles disrupted in ~50% of cortical and hippocampal interneurons in the second postnatal week	GRIN1-deficient mice demonstrated upregulation of glycogen synthase kinase-3 (GSK3) in GABAergic interneurons, and GSK3B inhibition resulted in decreased SZ-relevant phenotypes in these mice.	[202]
MK-801 treated rats	SZ	GluN2A (GRIN2A), GluN2B (GRIN2B)	Pharmacologic models of SZ were used to investigate levels of GRIN2A- and GRIN2B-targeting micro RNAs (miRNAs)	Elevated levels of GRIN2A/2B-targeting miRNAs were identified in both SZ-relevant models, and decreased expression levels of GluN2A and GluN2B protein were also seen in both models	[203]
Methylazoxy-methanol acetate (MAM) treated rats	SZ	GluN2A (GRIN2A), GluN2B (GRIN2B)			
Postmortem human PFC samples	SZ, MDD	GluN1 isoforms (GRIN1 splice variants)	Postmortem PFC from patients with depression, SZ, or nonpsychiatric healthy controls were assessed for GluN1 splice variant levels	C1 cytosolic segment-containing GluN1 levels were decreased in SZ and increased in MDD	[204]
Postmortem human lateral amygdala samples	MDD	GluN1 (GRIN1), GluN2A (GRIN2A)	GluN1 and GluN2A protein levels were measured in postmortem depressed or nonpsychiatric healthy control samples	GluN2A levels were significantly increased in depressed populations; GluN1 levels were not significantly different	[205]
Postmortem human locus coeruleus and cerebellum samples	MDD	GluN1 (GRIN1), GluN2C (GRIN2C)	GluN1 and GluN2C protein levels were measured in postmortem depressed or nonpsychiatric healthy control samples	GluN2C levels were significantly increased in the locus coeruleus of depressed subjects; GluN1 levels were not significantly different	[206]
Postmortem human locus coeruleus and PFC samples	MDD	All NMDAR subunits (GluN1, GluN2A-D, GluN3A-B)	NMDAR subunit protein levels were measured in postmortem depressed or nonpsychiatric healthy control samples	GluN2B and GluN2C subunits were upregulated in the locus coeruleus, but not the PFC, of depressed subjects	[207]
Postmortem human dorsolateral PFC	MDD	GluN1 (GRIN1), GluN2A-D (GluN2A-D)		GluN1 and GluN2A-D levels were increased in female MDD subjects	[208]
Postmortem human PFC samples	MDD	GluN1 (GRIN1), GluN2A (GRIN2A), GluN2B (GRIN2B)	GluN1, GluN2A, and GluN2B protein levels were measured in postmortem depressed or nonpsychiatric healthy control samples	GluN2A and GluN2B levels were reduced in the PFC of depressed subjects; GluN1 levels were not significantly different	[209]
Postmortem human medial temporal lobe samples	MDD	GluN1 (GRIN1), GluN2A-D (GluN2A-D)	NMDAR subunit protein levels were measured in postmortem samples from SZ, MDD, or bipolar disorder patients, and from nonpsychiatric healthy controls	GluN2A and GluN2B levels were reduced in the PFC of depressed subjects; GluN1 levels were not significantly different	[210]

Sample/Population studied	Relevant disease	NMDAR subunit(s)/ allele(s) investigated	Methods	Results	Reference
Postmortem human dorsolateral PFC	MDD, SZ	GluNI (GRIND, GluN2A-D (GluN2A-D)		GluN1 levels were decreased in MDD, SZ, and bipolar disorder; GluN2A levels were decreased in SZ and MDD; and GluN2C levels were decreased in SZ; GluN2B and GluN2D levels were not significantly different	[211]