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NMDA receptor hypofunction for schizophrenia revisited: perspectives from epigenetic mechanisms

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Abstract

Schizophrenia (SZ) is a neurodevelopmental disorder with cognitive deficits manifesting during early stages of the disease. Evidence suggests that genetic factors in combination with environmental insults lead to complex changes to glutamatergic, GABAergic, and dopaminergic systems. In particular, the N-methyl-D-aspartate receptor (NMDAR), a major glutamate receptor subtype, is implicated in both the disease progression and symptoms of SZ. NMDARs are critical for synaptic plasticity and cortical maturation, as well as learning and memory processes. In fact, any deviation from normal NMDAR expression and function can have devastating consequences. Surprisingly, there is little evidence from human patients that direct mutations of NMDAR genes contribute to SZ. One intriguing hypothesis is that epigenetic changes, which could result from early insults, alter protein expression and contribute to the NMDAR hypofunction found in SZ. Epigenetics is referred to as modifications that alter gene transcription without changing the DNA sequence itself. In this review, we first discuss how epigenetic changes to NMDAR genes could contribute to NMDAR hypofunction. We then explore how NMDAR hypofunction may contribute to epigenetic changes in other proteins or genes that lead to synaptic dysfunction and symptoms in SZ. We argue that NMDAR hypofunction occurs in early stage of the disease, and it may consequentially initiate GABA and dopamine deficits. Therefore, targeting NMDAR dysfunction during the early stages would be a promising avenue for prevention and therapeutic intervention of cognitive and social deficits that remain untreatable. Finally, we discuss potential questions regarding the epigenetic of SZ and future directions for research.

Keywords

NMDA receptor hypofunction; prefrontal cortex; development; schizophrenia; epigenetics

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Conflicts of Interests

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Introduction

Schizophrenia (SZ) is a severe mental illness that affects approximately 1% of the population and confers devastating consequences for the affected person as well as their family members. Patients with SZ suffer from a combination of positive, negative, and cognitive symptoms that severely impact interpersonal relationships as well as the ability to function in society. Despite decades of intense basic and clinical research, the exact etiology of SZ remains unknown. Still, SZ is recognized as a neurodevelopmental disorder, and the pathophysiological process involves multiple disrupted brain circuits and neurotransmitter systems that are closely related to the onset of symptoms (Jaaro-Peled et al., 2010; Lewis and Gonzalez-Burgos, 2008; Weinberger, 1987). Although psychosis emerges late in adolescence or early adulthood, the earliest cognitive symptoms are evident much earlier (Costa et al., 2006; Crow, 2007; Niwa et al., 2010; Walsh et al., 2008).

For over the past 50 years, the dopamine (DA) model has been the leading neurochemical hypothesis of SZ. This model has proven heuristically valuable, with all current medications for SZ functioning to primarily block DA receptor subtype D2 (Gray and Roth, 2007; Tamminga and Lahti, 1996). However, cognitive dysfunction is a core feature of SZ that strongly correlates with functional outcome, and current therapeutics do not adequately address this aspect of the disease. Therefore, it is unlikely that dopaminergic dysfunction, on its own, can fully account for the wide range of symptoms and neurocognitive deficits seen in SZ. The key to forestalling the disorder is to detect and prevent early stages of risk and prodrome with novel therapeutic targets for early treatment (Insel, 2010; Lieberman et al., 2006). It is thus critical to understand the early developmental changes that contribute to the progression of SZ.

The N-methyl-D-aspartate (NMDA) receptor-mediated glutamatergic model provides a critical alternate approach for conceptualizing the brain abnormalities associated with SZ (Harrison and Weinberger, 2005; Lewis and Moghaddam, 2006; Lisman et al., 2008). Although it remains unclear what changes induce the onset of cognitive dysfunction, NMDAR hypofunction appears to be a convergence point for progression and symptoms of SZ, especially for cognitive deficits (Cohen et al., 2015; Coyle, 2006; Lisman et al., 2008; Marek, 2010; Moghaddam, 2003; Nakazawa et al., 2017; Snyder and Gao, 2013). NMDARs are crucial in synaptic plasticity, learning and memory, and proper neuronal functioning. Importantly, NMDARs contribute to circuit formation for early postnatal stages of brain development, which is otherwise known as the “critical developmental window.” Numerous studies have indicated that the maturation of brain circuitry is usually coincident with the NMDAR subunit switch (e.g., GluN2B-to-GluN2A and GluN3A-to-GluN3B) that occurs at the onset of the critical period of development (Monaco et al., 2015; Monyer et al., 1994; Quinlan et al., 1999; Roberts et al., 2009; Sheng et al., 1994; Snyder et al., 2013; Wang and Gao, 2009; Wang et al., 2008). The NMDAR subunit shift marks the transition from juvenile to “adult” neural processing (Dumas, 2005; Henson et al., 2010) and the switch makes the NMDARs extremely vulnerable to genetic and environmental risk factors (Brenhouse et al., 2008; Spear, 2000). It is likely that convergent mechanisms target NMDAR, which in turn contribute to negative symptoms and neurocognitive dysfunction directly (Lau and Zukin, 2007), as well as to positive symptoms via dysregulation of brain DA systems indirectly.

Still the question remains, how do early life experiences influence genes to alter the course of normal brain development. SZ is most likely due to a complex interaction between environmental risk factors and genetic susceptibility (Harrison and Weinberger, 2005). The high heritability rate of SZ points to a strong genetic component for the disease (Cardno and Gottesman, 2000). Indeed, recent genome-wide association studies (GWAS) have identified 108 genetic risk loci in post-mortem SZ tissue (Ripke, 2014) that have an important role for many patients (Birnbaum and Weinberger, 2017; Coelewij and Curtis, 2018; Weinberger, 2017). Yet, the genetic mutations discovered are unlikely to account for all SZ cases or for the complex symptomology present (Rodriguez-Murillo et al., 2012). Further, GWAS studies indicate only a familial liability close to 20%, suggesting that some other mechanisms aside from simple genetic mutation contribute to the heritability rate for SZ (Agerbo et al., 2015). The answer may be epigenetics, which has been gaining attention for its role in mental illness. During the past two decades, understanding of epigenetic processes in chromatin stability, gene regulation, response to environmental factors, and disease states has grown rapidly (Allis and Jenuwein, 2016). Epigenetic mechanisms tightly control gene expression and repression without any alteration to the DNA sequence, and importantly may provide a mechanism for the missed heritability in SZ (Akbarian, 2014; Trerotola et al., 2015).

Epigenetic mechanisms for SZ - *epigenetic changes to NMDAR genes contribute to NMDAR hypofunction*

Epigenetics is a complex biological process that regulates access to DNA and thus the ease with which genes can be transcribed. Negatively charged DNA is packaged around an octamer of positively charged histones (H), termed H2A, H2B, H3, and H4 to form a nucleosome, a unit of chromatin. Nucleosomes are connected by linker DNA which is stabilized by H1. In addition to packaging DNA, chromatin provides a scaffold for proteins to interact with DNA, including transcriptional machinery as well as repressor proteins. While once thought to be static, it is now known that chromatin in and of itself is a dynamic structure contributing to the accessibility of DNA (Maeshima et al., 2016). Chromatin is further regulated by alterations to DNA through methylation and post-translational modification of histones.

DNA methylation is a process involving the addition of a methyl group to cytosines within DNA. This occurs most frequently at CpG dinucleotides, regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases (Bayraktar and Kreutz, 2018). DNA methylation is catalyzed by related DNA methyl transferases (DNMTs) that include DNMT1, DNMT3A, DNMT3B, and DNMT3L (Guidotti et al., 2011; Zhubi et al., 2009). These modifications alter gene transcription and can be highly stable and heritable. However, evidence also suggests that DNA methylation patterns can be dynamically regulated in response to learning and memory or life experience (Day and Sweatt, 2011). In contrast, histone modification is a more dynamic and complex process with a myriad of post-translational modifications occurring in concert (Peterson and Laniel, 2004). These include ubiquitylation, acetylation, methylation, and sumoylation of lysines, phosphorylation of serines and threonines, and acetylation and methylation of arginines.

This multitude of modifications on chromatin either constrict or loosen the physical attraction/interaction between DNA and histone amino-acid tails, leading to changes in gene transcription. Regulation of histone tails is more readily reversible than DNA methylation and likely plays an important role in plasticity processes and diseases (Christopher et al., 2017). However, a fundamental question raised is when and how epigenetic changes contribute to SZ, and more specifically how they result in NMDAR hypofunction during the early stages of the disease.

There are many ways in which epigenetics could contribute to the SZ disease process. Firstly, there could be global alterations to epigenetic machinery such as histone deacetylases (HDACs) or DNMTs. Data suggest alterations in the expression of various methyltransferases and demethylases in SZ (Morishita et al., 2015). Further, several studies examining DNA methylation in SZ patients found evidence for hypomethylation in specific human populations (Melas et al., 2012; Shimabukuro et al., 2007). However, there is also evidence for hypermethylation in distinct cellular populations (Veldic et al., 2004; Zhubi et al., 2009), supporting the notion that global methylation changes could occur in a brain region or neuronal population-specific manner. For example, one report found that DNMT1 mRNA and protein levels are significantly increased in the telencephalic GABAergic interneurons of SZ patients (Veldic et al., 2004), while another showed overexpression of DNMT3A in distinct GABAergic interneuron populations, and overexpression of both DNMT1 and DNMT3A in peripheral blood lymphocytes (Zhubi et al., 2009). Interestingly, levels of DNMT3A are altered in the prefrontal cortex (PFC) following chronic defeat stress (Elliot and Chapman, 2016; Hammels et al., 2015a; Hammels et al., 2015b). Moreover, prenatal stress, a risk factor in SZ, alters DNMT1 and DNMT3a protein levels, leading to a reduced number of GABAergic interneurons and altered circuit function (Matrisciano et al., 2013). Similarly, early life stress altered plasticity of GABAergic synapses onto ventral tegmental area dopamine neurons via epigenetic mechanisms involving HDACs (Authement et al., 2015). Bahari-Javan and colleagues demonstrated that early life stress increased HDAC1 levels, resulting in altered PFC development and SZ-like phenotypes (Bahari-Javan et al., 2017).

Interestingly, a recent neuroimaging study found reduced expression of HDACs in the dorsolateral prefrontal cortex of SZ patients and this correlated with cognitive deficits (Gilbert et al., 2018). The same group previously showed reduced HDAC2 mRNA levels in the dorsal lateral prefrontal cortex (PFC) of SZ patients (Schroeder et al., 2017). These findings are especially interesting because in mice, HDAC2 expression has been shown to regulate dendritic spines, long-term potentiation, and performance on cognitive tasks (Guan et al., 2009), and HDAC2 was enriched in the promoter of NMDAR subunits compared to HDAC1. However, in this study, HDAC2 knockout mice had increased long-term potentiation (LTP) and improved performance on certain cognitive tasks, which is contradictory to the human study. Future studies are needed to better understand changes to HDACs in normal development and disease models. Still together, these data demonstrate that life experiences can alter epigenetics, impacting the development of brain regions important in SZ and targeting epigenetic machinery may hold therapeutic value (Collier et al., 2016; Ovenden et al., 2018).

Another possibility is that specific SZ-related genes may be epigenetically regulated. SZ human post-post-mortem studies demonstrate epigenetic modifications on several important genes. This includes hypermethylation of the *REELIN* promoter (Abdolmaleky et al., 2005; Grayson et al., 2005) and DNA methylation changes in the HTR2A, encoding the serotonin receptor type 2A (Cheah et al., 2017) and catechol-O-methyltransferase (*COMT)* promoter (Gao et al., 2017). Further, SZ patients had a reduction in the activating histone marker H3K4me3 on the glutamate decarboxylase (*GAD)* 1 promoter, which regulates GAD67 γ-aminobutyric acid (GABA) synthesis enzyme expression and this corresponded to reduced GAD1 mRNA levels (Huang et al., 2007). Of note, this change was found only in females while the methylation changes for *COMT* were driven by male patients. Together these data point to the possibility of sex differences in SZ epigenetics.

Given the importance of NMDARs both for normal cognitive function and their role in SZ, understanding if and how they are epigenetically regulated is of particular interest. Several studies have demonstrated that NMDAR epigenetic regulation contributes to normal brain development and plasticity processes. Specifically, histone methylation at gene promoters is associated with developmental regulation and region-specific expression of ionotropic and metabotropic glutamate receptors in human brain (Stadler et al., 2005). As listed in Table 1, there is a close association with HDAC2 and the promoter of *Grin2a and Grin2b* (Graff et al., 2012; Guan et al., 2009; Qin et al., 2018). Further, in the prefrontal cortex, distal regulatory *Grin2b* sequences are controlled by H3K4me and H3K9me and this is highly associated with the maintenance of working memory (Bharadwaj et al., 2014) and affective and motivational behaviors via setbd1, which encodes an H3K9 methyltransferase (Jiang et al., 2010).

Epigenetic regulation of NMDAR has been found with environmental insults and in mental illness. Prenatal Bisphenol A (a chemical used to make plastic for food container) exposure, which is linked to neurodevelopment disorders, alters *Grin2b* methylation in both mice and humans (Alavian-Ghavanini et al., 2018b), suggesting that environmental exposures could impact epigenetic regulation of NMDARs. Interestingly, these results are sex-specific and suggest that epigenetic regulation may differ in a sex-specific and cellular specific manner. Epigenome-wide methylation analysis in major depressive disorder, found *Grin2a* to be hypermethylated in both human PFC and hippocampus (Kaut et al., 2015). Yet, analysis of NMDAR mRNA levels in post-mortem brain tissue of patients with SZ has resulted in conflicting findings with some studies reporting increases, decreases, or no change in transcript levels (Coyle et al., 2012). This inconsistency hinders our ability to identify whether the pathophysiological mechanisms underlying SZ are a direct result of diminished NMDAR subunit proteins (Weickert et al., 2013). Still, while the use of post-mortem brain tissue provides a specific link to SZ, it only allows for analysis of a very specific examination of adult tissue and misses any potential changes that occur earlier in brain development. Nevertheless, evidence suggests that NMDA receptor subunits, especially GRIN2B, are bidirectionally regulated by different epigenetic markers under various conditions (Table 1), including DNA methylation and histone methylation and acetylation (Table 1, Figure 1).

In particular, the higher order of chromatin relevant to the *GRIN2B* gene locus was recently reported (Bharadwaj et al., 2014). As shown in Figure 1, it is possible that multiple intronic and intergenic DNA sequences, up to 450kb downstream from the *GRIN2B/Grin2b* transcription start site (TSS), for example, could compete for access to the TSS. These sequences are loaded with multiple transcription factors and are in physical proximity to the *GRIN2B/Grin2b* transcription start site (Bharadwaj et al., 2014). Interestingly, the sequences interacting with the *GRIN2B* promoter appeared to harbor single nucleotide polymorphisms (SNP) and are implicated with liability for working memory and SZ (Bharadwaj et al., 2014). Therefore, epigenetic markers associated with DNA methylation or histone modification may target the *GRIN2B* promoter and carry disease-associated sequence polymorphisms. This consequently may either facilitate or repress expression in a highly dynamic and activity-dependent manner for access to the *GRIN2B* promoter sequences (Bharadwaj et al., 2014). Importantly, this *GRIN2B* higher order chromatin study and others (Table 1) have provided a deeper insight into the understanding of the neurobiology of and novel treatment avenues for common psychiatric disease (Rajarajan et al., 2018).

Interestingly and importantly, epigenetic regulation of NMDARs is known to be an important factor in the critical developmental period of the NMDAR subunit switch through repressor element 1-silencing transcription factor (REST). Historically, REST was thought to only play a critical role early in neuronal differentiation, brain development, and neurodegenerative diseases (Hwang and Zukin, 2018; Tamminga and Zukin, 2015). However, REST is now known to be involved in synaptic plasticity, normal aging, and disease processes (Lu et al., 2014; Rodenas-Ruano et al., 2012). REST binds within the promoter region of target genes and recruits co-repressor CoREST and mSin3 that recruit multiple proteins and possess enzymes that catalyze the posttranslational modifications of histone tails (Andres et al., 1999). These include, but are not limited to, multiple HDACs, histone methyltransferases, and DNMTs (Qureshi and Mehler, 2009). While it has been known that REST functions during embryogenesis to epigenetically regulate many genes, including Grin2b, Zukin and colleagues discovered an important role for REST in mature neurons (Rodenas-Ruano et al., 2012; Schoenherr and Anderson, 1995). They found that REST is activated at a critical window of time in hippocampal neurons, possibly through the actions of the prion protein, and acts to repress Grin2b expression via epigenetic remodeling (Rodenas-Ruano et al., 2012; Song et al., 2018). Thus, under normal physiological conditions, epigenetics plays a fundamental role in regulating NMDAR levels leaving open the possibility that this process could be dysregulated in SZ.

Studies from SZ animal models indicate that NMDAR subunit levels are reduced in a brain region and developmental time window specific manner (Gulchina et al., 2017; Snyder and Gao, 2013). Using the prenatal methylazoxymethanol acetate (MAM) prenatal exposure model, we found reduced expression of NMDAR subunits in the juvenile hippocampus that altered NMDAR function during this critical stage of development. We also recently demonstrated that GluN2B expression and function are compromised in PFC of this SZ model. Further, this protein loss during the juvenile period is correlated with an aberrant increase in the epigenetic transcriptional repressor REST and the repressive histone marker H3K27me3 at the Grin2b promoter, as assayed by chromatin immunoprecipitation (ChIP)-quantitative polymerase chain reaction (Gulchina et al., 2017). These studies provide

evidence that epigenetic regulation of NMDARs could contribute to the disease process of SZ (Figure 2).

NMDAR hyopfunctionality induces epigenetic changes in other proteins and/or genes that lead to synaptic dysfunction and symptoms in SZ

In addition to epigenetic regulation of NMDARs themselves, it is important to consider the consequence of NMDAR hypofunction to epigenetic processes. Neuronal activity is translated into transcription alterations in a variety of genes, dependent upon the type and duration of stimulation (Flavell and Greenberg, 2008). These changes are critical both for the normal development of neuronal networks but also for incorporating sensory experiences in postnatal life. Kyrke-Smith and Williams recently proposed that neuronal network function, particularly for synaptic plasticity, is dependent upon proper expression of a wide variety of proteins regulated through epigenetic changes (Kyrke-Smith and Williams, 2018). The mechanism(s) by which this occurs is a very active area of research, but data suggest that epigenetic changes together with NMDARs play a critical role (Jarome and Lubin, 2014; Tyssowski et al., 2018). Calcium influx through NMDARs activates a calcium calmodulin-dependent kinase II (CaMKII)- cAMP response element-binding protein (CREB)-P signalling pathway that alters levels of H3K27ac to control dendritogenesis (Bustos et al., 2017). In another example, contextual fear conditioning led to a rapid, time-dependent increase in histone H3 phosphorylation in hippocampal area CA1. Interestingly, this was blocked by MK801, an NMDAR antagonist (Chwang et al., 2006). Similarly, NMDAR activation in hippocampal slices increased ERK2 and acetylation of histone 3 (Levenson et al., 2004). Neuronal stimulation induced long-term potentiation, which requires NMDAR activation, increased expression of HDAC1 as well as the HDAC interacting protein DnaJ Heat Shock Protein Family (Hsp40) Member B5 (Ryan et al., 2012).

Based on these data, it is reasonable to hypothesize that alterations to glutamatergic synaptic transmission, due to NMDAR hypofunction as in SZ, could contribute to a disruption in network functioning and/or improper network formation. For example, ablation of NMDARs during postnatal development led to epigenetic repression of Kv1.1-type potassium channels, altering neuronal excitability and impairing dendritic maturation (Frangeul et al., 2017). Further, inhibiting NMDAR activity prevented increases in histone H3 acetylation and phosphorylation in striatal tissue extracts (Li et al., 2004). Conversely, NMDAR blockade with MK-801 increased phosphorylation of histone 3 (H3) at serine 10 in the medial PFC, which is associated with chromatin relaxation and increased probability of gene expression (Mackowiak et al., 2013). Together these data suggest that any increase or decrease in NMDAR function will impact epigenetic processes, resulting in an alteration in normal synapse and circuit function.

One of the most important properties of the NMDA receptor is their calcium permeability. Along with changes to cellular excitability, NMDAR hypofunction also leads to drastic alterations in calcium influx and cellular signalling. Evidence indicates that the activity of epigenetic machinery could be impacted by the changes to calcium influx. Calcium is the

critical second messenger that allows synapse to nucleus communication to alter gene transcription (Bading, 2013). NMDAR mediated calcium influx, along with calcium from voltage-gated calcium channels (VGCC) engages a variety of signalling cascades to transmit information about neuronal activity in the dendrites to the nucleus (Bading, 2013). Data suggests a high fidelity between synaptic activation and the nuclear calcium signal which can be disrupted by NMDAR or VGCC blockade {Bengtson, 2010 #39226}. Once in the nucleus, calcium can lead to activation of CREB-CREB binding protein (CBP) dependent transcription. Interestingly, CBP partially functions as a histone acetyltransferase (HAT) as well as associates with many HATs to regulate chromatin and thus gene transcription (Chan and La Thangue, 2001). Additionally, epigenetic machinery itself can be targeted by calcium-induced signaling cascades. For example, DNMTs undergo post-translational modifications, which likely regulate their functional activity (Denis et al., 2011). DNMTs are phosphorylated by protein kinase C and protein kinase B (AKT) among others (Denis et al., 2011). Interestingly, calcium entry through NMDARs can trigger activation of CaMKII and subsequently AKT (Sutton and Chandler, 2002). Thus, it is possible that reduced NMDAR function, as seen in SZ, will affect protein kinase activation that may, in turn, alter DNMT functionality or expression. In fact, NMDAR mediated calcium entry is critical for both short-term and long-term synaptic plasticity. Therefore, alteration of NMDAR function could consequentially regulate other proteins or genes that are critically involved in synaptic functions (Figure 3).

Brain-derived neurotrophic factor (BDNF) is a neurotrophic that is involved in neurodevelopment, synaptogenesis, and neuroplasticity (Angelucci et al., 2005; Poo, 2001). Recent work confirmed that reduced BDNF levels in humans are significantly associated with SZ (Rodrigues-Amorim et al., 2018). Interestingly, epigenetic regulation of BDNF itself is suggested to play a role in psychiatric disorders, including SZ (Ikegame et al., 2013; Mitchelmore and Gede, 2014). In the hippocampus, BDNF secretion in response to activity requires activation of calcium-responsive transcription factors and is at least partially dependent on calcium influx through NMDARs (Kolarow et al., 2007; Tao et al., 2002). In hippocampal cultures, NMDA stimulation and resulting calcium influx, increased phosphorylation of MeCp2 leading to increased BDNF mRNA levels (Zhou et al., 2006). Work by Lipsky's group expanded these findings with CHIP to show that NMDA activation results in multiple epigenetic changes to the BDNF promoter, including a decrease in histone H3 at lysine 9 dimethylation (H3K9me2) and increases in H3K4me2 and H3K9/14 acetylation (H3AcK9/14) (Tian et al., 2009). Furthermore, Lau et al. show that BDNF-induced neuroprotection is mediated by synaptic NMDA-receptor-dependent nuclear calcium signals activating transcription of inhibin b-A (activin A). Activin A, in turn, reduces toxic extrasynaptic NMDAR-mediated calcium influx, shields neurons from mitochondrial dysfunction, and protects against stroke-induced brain damage (Lau et al., 2015). Therefore, NMDAR dysfunction could significantly impact BDNF levels that in turn could negatively impact other systems involved in the pathophysiology of SZ. For example, an interaction between BDNF and dopamine receptor type 3 is implicated in SZ (Gourion et al., 2005). A clearer link exists between BDNF and GABA deficits (Hashimoto et al., 2005; Lu et al., 2009), as well as BDNF and DA dysfunction (Krebs et al., 2000), but the

correlation between NMDAR hypofunction and BDNF, and whether NMDAR hypofunction can affect BDNF secretion in the brain, remain to be explored.

Targeting NMDAR dysfunction during early stage is a promising avenue for prevention and therapeutic intervention of cognitive and social deficits

Early NMDAR hypofunction is a promising proposed mechanism for the development of SZ. However, it is critical to progress from a better understanding of disease mechanisms to promising therapeutic interventions. Unfortunately, less information can be gathered from the developing human SZ brain. Diagnosis is often in late adolescence and early adulthood and patients have already developed neuropathophysiological deficits that underlie cognitive and social impairments before treatment begins. It is unknown if treatment could fully reverse alterations to neuronal network development. Intervention during PFC development in patients at-risk for SZ presents a therapeutic window that is currently unopened.

As reviewed above, mounting evidence indicates that NMDAR hypofunction occurs during the early stages of postnatal development and is proceeded by disruption of the dopaminergic systems. The current therapeutic approaches target this later dopaminergic dysfunction to minimize the symptoms of SZ (Yang and Tsai, 2017). Further, current antipsychotic medications demonstrate minimal therapeutic efficacy in treating cognitive and social deficits in SZ (Kim et al., 2017). However, therapeutic agents that have previously failed to demonstrate efficacy in clinical trials may be more effective when employed during the earlier stages of development, specifically during the initial stages of NMDAR hypofunction (Li et al., 2015b). Indeed, treatment during juvenile development (Li et al., 2017b; Xing et al., 2018) with a metabotropic glutamate receptors (mGluR)2 agonist/mGluR3 antagonist or mGluR2/3 agonist has demonstrated ameliorative effects on NMDAR-mediated neurotransmission, working memory function, and social behaviors, as well synaptic morphology in the mPFC in animal models.

The mGluR2/3 subtypes of glutamate receptors have long been linked with SZ, and mGluR2/3 agonism has been proposed to target the dysfunctional glutamatergic system, particularly NMDAR hypofunction (Li et al., 2015b; Maksymetz et al., 2017; Moghaddam, 2004; Walker and Conn, 2015). In a series of recent studies using the MAM SZ model, we found that targeting NMDAR hypofunction during the early stage of development is effective to prevent SZ-like cognitive and social phenotypes in adult. In juvenile MAM animals, synaptic GluN2B protein levels are significantly decreased resulting in reduced NMDA-excitatory postsynaptic currents. Further, this protein loss was correlated with an aberrant increase in the enrichment of the epigenetic transcriptional repressor REST and the repressive histone marker H3K27me3 at the *Grin2b* promoter, as assayed by ChIP-qPCR (Gulchina et al., 2017). In adulthood, MAM animals exhibited PFC-dependent learning and memory deficits. Excitingly, both prefrontal NMDAR hypofunction and cognitive deficits were prevented by treatment with either mGluR2/3 modulators mGluR2 agonist/mGluR3 antagonist LY395756 (Li et al., 2017a) and mGluR2/3 agonist LY379268 (Xing et al., 2018) in the juvenile, but not adult (Li et al., 2015a) rats. Both LY395756 LY379268 prevented NMDA dysfunction, learning deficits, and cognitive flexibility. We also found that the

preventive effects of LY379268 were mediated by improving GluN2B-NMDAR function via inhibiting GSK3β (Xing et al., 2018).

Our work confirmed that NMDAR hypofunction is a feature of early postnatal development, with epigenetic hyper-repression of the *Grin2b* promoter being a contributing factor. The selective loss of GluN2B protein and subsequent synaptic dysfunction weakens the PFC function during development and may underlie early cognitive impairments in SZ models and patients. The latter is supported by the efficacy of glutamatergic modulators to prevent both prefrontal NMDAR hypofunction and cognitive deficits, highlighting the importance of targeting glutamatergic dysfunction as a potential early intervention for SZ. Altogether, these findings emphasize the importance of developmental NMDAR function in the maturation of cognitive functions, a process which is disrupted and can be subsequently recovered in the MAM model for SZ by a brief pharmacological intervention during juvenile development.

Another avenue of therapeutic intervention is targeting HDACs. HDACs compact chromatin structure and repress gene transcription. Clinical studies have demonstrated that HDAC inhibitors are efficacious when given in combination with atypical antipsychotics in the treatment of SZ (Fischer et al., 2010; Kurita et al., 2012). Specifically, chronic atypical antipsychotics downregulated the transcription of mGluR2 by decreasing histone acetylation at its promoter in mouse and human frontal cortex. Conversely, HDAC inhibitors prevented the repressive histone modifications induced at the mGluR2 promoter by atypical antipsychotics and augmented their therapeutic-like effects, suggesting that HDAC2 is a promising new target to improve SZ treatment (Kurita et al., 2013a). Furthermore, it has been reported that HDAC2 regulates atypical antipsychotic responses through the modulation of mGluR2 promoter activity in adult mice (Kurita et al., 2012). Kurita et al also reported repressive epigenetic changes at the mGluR2 promoter in the frontal cortex of 5-HT2A knockout mice (Kurita et al., 2013b). Specifically, disruption of 5-HT2A receptor-dependent signaling in mice was associated with decreased acetylation of histone H3 (H3ac) and H4 (H4ac) and increased H3K27me3 enrichment at the mGlu2 promoter, suggesting transcriptional repression of mGluR2 expression and possible indirect regulation of NMDAR function. However, despite the importance of the therapeutic potential of HDAC inhibition, it remains unclear exactly if and how HDAC inhibitors, mGluR, and NMDARs are related. More research is needed.

One question raised by these studies is whether positive allosteric modulators of mGluR2 would work better for SZ treatment and if this is related to NMDAR regulation (Ellaithy et al., 2015). Allosteric signaling through a mGluR2 and 5-HT2A heteromeric receptor complex has shown its potential contribution to SZ (Moreno et al., 2016). Ibi et al reported that antipsychotic-induced *HDAC2* transcription via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) leads to synaptic and cognitive side effects (Ibi et al., 2017), suggesting a protective effect on cognition from antipsychotics. In addition, Mitchell et al found that MEF2C transcription factor is associated with genetic and epigenetic risk architectures of SZ and improves cognition in mice (Mitchell et al., 2018). However, whether these effects have anything to do with glutamatergic dysfunction is unknown. A recent study reported that vorinostat, a histone deacetylase inhibitor, facilitates fear

extinction and enhances expression of the hippocampal GluN2B-containing NMDA receptor gene (Fujita et al., 2012). In addition, it has been shown that basal, but not evoked, NMDAR activity regulates gene expression in part through HDAC4, and, that HDAC4 has neuroprotective functions under conditions of low NMDAR activity, at least in hippocampal neuronal cultures (Chen et al., 2014). However, whether HDAC inhibitors would have side effects in the juvenile brain by regulating NMDAR activity directly is another concern that is worth exploring.

Potential questions regarding the epigenetics of SZ and future directions for research

SZ is a polygenic condition whose exact etiology remains unknown. Recent research highlights NMDAR hypofunctioning as an attractive hypothesis of its molecular basis (Snyder and Gao, 2013); however, NMDAR hypofunction itself could not explain the other anatomical and clinical abnormalities such as GABAergic deficits (Gonzalez-Burgos and Lewis, 2008) and dopaminergic dysfunction (Howes and Kapur, 2009) found in SZ. Although SZ is a neurodevelopmental disorder, the visible onset traditionally appears in later adolescence and is preceded by a period of apparent abnormality. Understanding exactly when and how brain development moves off course is of critical importance. Most likely there is more than one molecular mechanism involved and they are all governed by common factors. Reelin, Nrg1, and BDNF have been linked to SZ and they have three common features: their involvement in the GABAergic interneuron migration, in the proper functioning of the NMDA receptors, and they are all subject to similar epigenetic control (Moreau and Kullmann, 2013). Considering all of these aspects for treatment and how they are intertwined should improve the chances of successful therapeutic intervention. Future directions for treatment include mGluR2 positive allosteric modulators (PAM), selective mGluR2 agonist and mGluR effects through regulation of epigenetic mechanism, and treatment in different animal models, especially genetic models during early stage and multiple behavioral evaluations (Ellaithy et al., 2015; Griebel et al., 2016; Maksymetz et al., 2017; Matrisciano et al., 2016).

Operating under the hypothesis that SZ is a disorder of synaptic dysfunction, one may believe a single treatment, or combination of therapeutic agents will be able to completely recover cognitive deficits in this disorder. However, we must not forget the overt structural damage to the SZ brain. Decreases in grey and white matter, as observed by fractional anisotropy, demonstrate reductions in myelination (Green et al., 2004). Therefore, we must consider cognitive impairments, and even positive and negative symptoms, can likely only recover to a certain degree if treatment begins in the later stages, given our current inability to treat these structural alterations (Green et al., 2004). Nonetheless, functional improvement for patients will lessen the economic burden of this debilitating illness as well as the psychosocial burden on family and caregivers. These steps to independence for SZ patients are the ultimate goal of our research endeavors.

There are many outstanding questions for epigenetic changes in the developing brain, particularly the effects on behaviors associated with cognitive function and sociability, as

recently pointed by Kenerne et al (Keverne et al., 2015) in the Sackler Colloquium. For example, what are the roles of DNA methylation, including CpG islands, in NMDAR hypofunction? How does DNA methylation affect NMDAR subunits change during development? What are the relations among different epigenetic marks with NMDAR subunit composition and function during development in both normal brain and animal models for SZ? What are the roles of long noncoding RNAs in the modification of neuronal nuclear architecture, especially on NMDAR hypofunction occurrence? A large body of behavioral epigenetic studies attempts to correlate epigenetic marker changes (e.g., acetyl-histone H3) at global levels and in mixed populations of cells with phenotypic changes. However, specific changes at gene and single cell levels correlating with behavioral changes remain largely unknown. This is particularly true for NMDAR function in GABAergic interneurons and glial cells. The role of glial in normal and disease conditions is rapidly expanding and cannot be ignored for SZ. What are the epigenetic mechanisms for NMDAR subunit changes during the early development that would eventually be triggered to initiate the onset of SZ symptoms, especially early cognitive and social deficits? Answering these questions will provide not only new insights into the understanding of neuropathophysiology but also eventual early interventions for SZ.

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Abbreviations

CREB-CBP	cAMP response element-binding protein (CREB)-CREB binding protein
DA	dopamine
DISC1	disrupted-in-schizophrenia 1
DNMT	DNA methyltransferase
DTNBP1	dystrobrevin binding protein 1
GABA	gamma-aminobutyric acid
GWAS	genome-wide association study
HAT	acetyltransferase
HDAC	histone deactelyases
DNA	methyl transferases
NRG1	neuregulin 1
MAM	methylazoxymethanol acetate
NMDA	N-methyl-D-aspartate

PFC	prefrontal cortex
REST	repressor element 1-silencing transcription factor
SZ	schizophrenia
VGCC	voltage-gated calcium channels

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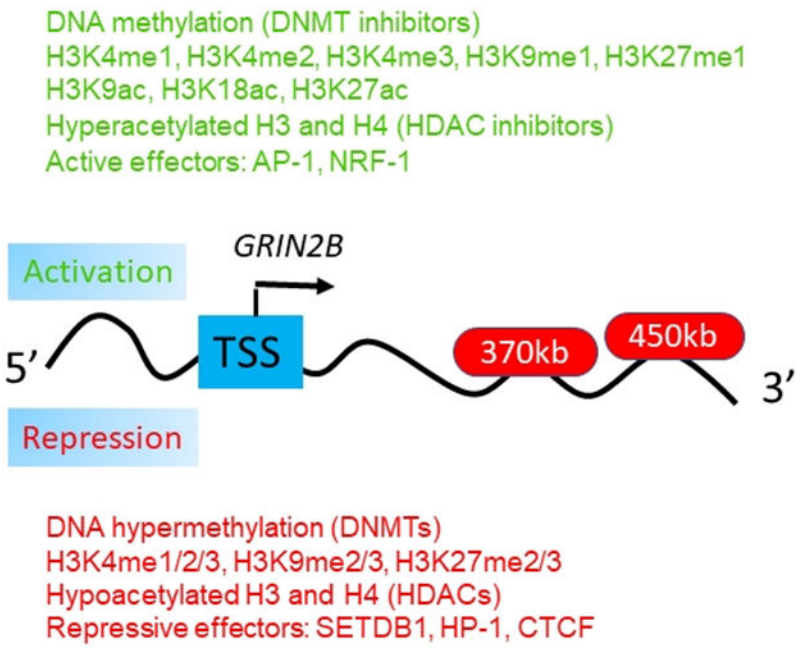

Figure 1.

Epigenetic markers and their functions in the regulation of NMDA receptors. Epigenetic markers that could potentially regulate the genes associated with NMDA receptor subunits, e.g., the *GRIN2B* gene locus (Bharadwaj et al., 2014). Multiple intronic and intergenic DNA sequences, up to 450kb downstream from the *GRIN2B/Grin2b* transcription start site (TSS), compete for access to the TSS. These sequences are loaded with multiple transcription factors and are in physical proximity to the *GRIN2B/Grin2b* transcription start site. It was proposed that transcriptional regulation at the *GRIN2B/Grin2b* locus involves a dynamic and competitive interplay of multiple effectors, each of which could engage with the *GRIN2B* promoter [Modified from Bharadwaj et al, 2014, Neuron (Bharadwaj et al., 2014). Copyright requested through the Copyright Clearance Center's RightsLink® service](Rajarajan et al., 2018).

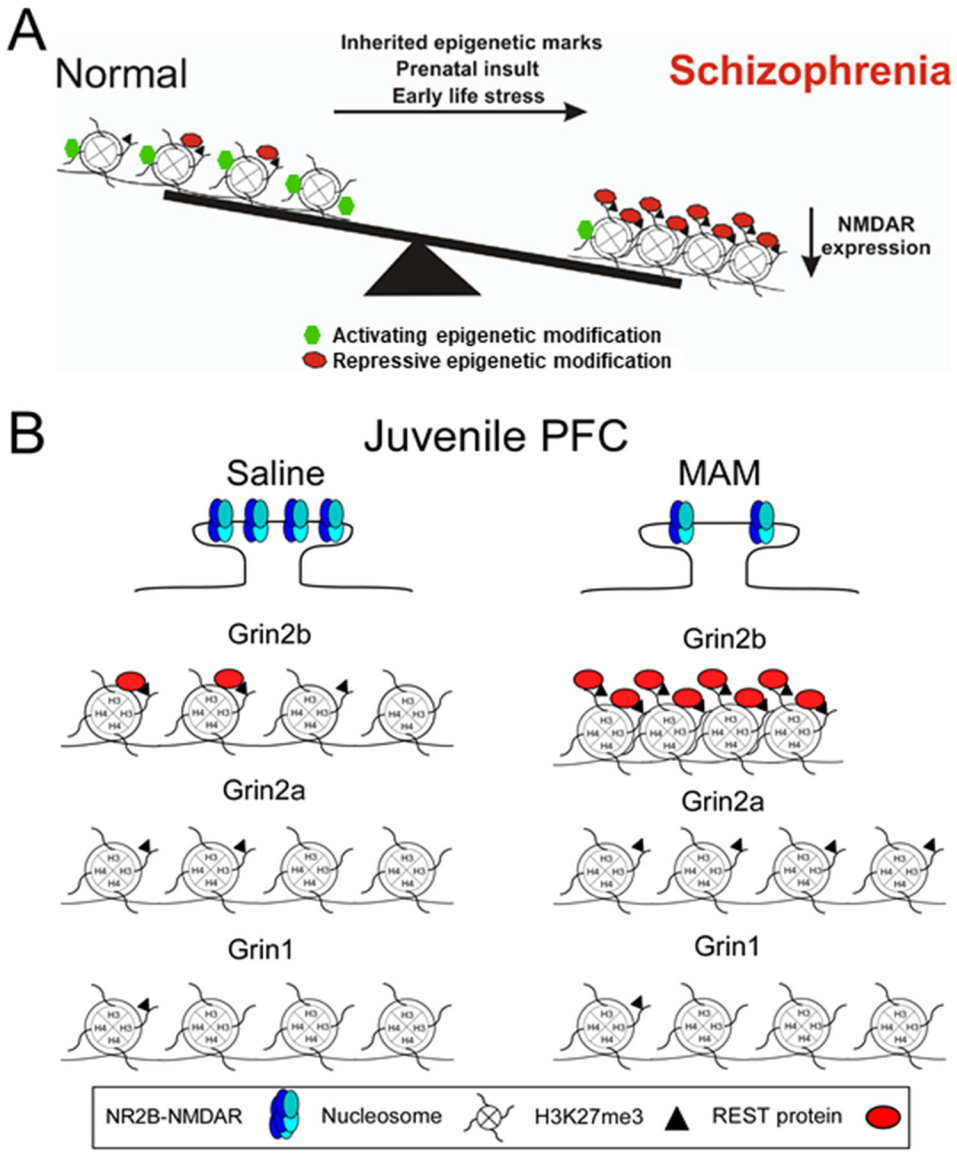

Figure 2.

A schematic representation of epigenetic changes to NMDARs on pyramidal neurons in Schizophrenia (SZ). **A**. Under normal conditions, NMDARs are subjected to both activating (green hexagons) and repressive epigenetic markers (red ovals). This balance allows for the proper expression of NMDARs. However prenatal insult, early life stress, or inherited epigenetic marks, switch the balance creating an over-abundance of repressive epigenetic markers. These modifications lead to a repression of NMDAR transcription and the NMDAR hypofunction found in SZ. **B**. Top panel, NR2B-NMDAR levels are persistently high in the developing mPFC and play a critical role in synaptic plasticity and PFC-dependent cognitive functions. However, in the MAM SZ model, animals are vulnerable to cognitive dysfunction due to the significant loss of synaptic NR2B-NMDARs in the critical juvenile period. Bottom panel, NR2B-NMDAR loss in juvenile MAM rat mPFC is due to epigenetic modifications within the promoter of Grin 2b. REST (red ovals) and H3K27me3

(black triangles) enrichment levels in saline mPFC are higher at the Grin2b response element (RE1) site compared to the Grin1 and Grin2a RE1 sites, demonstrating selective REST regulation of Grin2b is an endogenous repressor mechanism. In the MAM mPFC, REST and H3K27me3 enrichment levels are greatly elevated compared to the saline group, demonstrating the hyper-repression of the proximal promoter region of Grin2b (Modified from Gulchina et al, 2017, J. Neurochem. Copyright requested through Copyright Clearance Center's RightsLink® service).

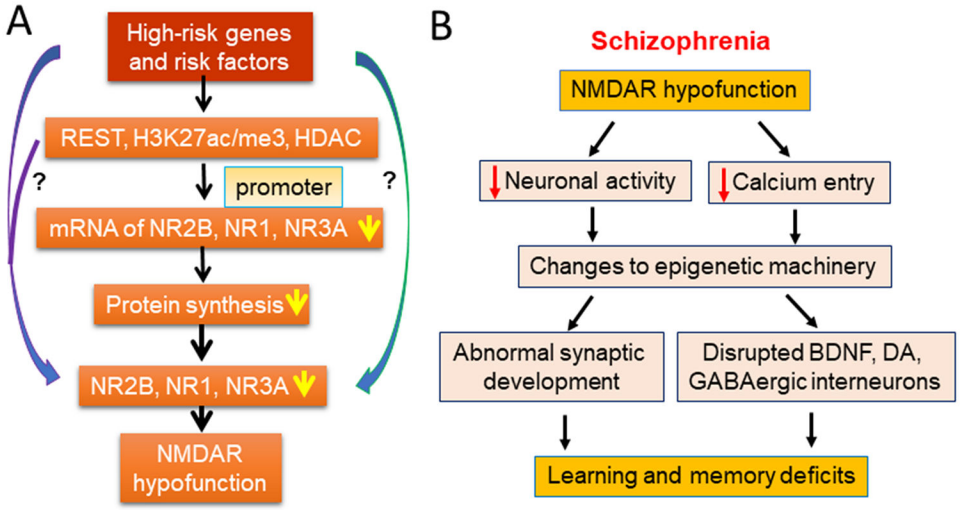

Figure 3.

Mechanism of NMDAR hypofunction and its consequences. A. Mechanisms of NMDA hypofunction in excitatory pyramidal neurons. Genetic and other risk factors lead to epigenetic alterations with the promoter regions of NMDARs. These, in turn, lead to reduced mRNA and protein expression with pyramidal neurons culminating in NMDAR hypofunction. B. NMDAR hypofunction within excitatory pyramidal neurons induces a cascade of downstream effects that alter synaptic development and sub-sequential GABAergic and dopaminergic dysfunction. Together these changes to neuronal network formation and function induce the learning, cognitive, and social deficit found in schizophrenia.

Table 1.

Epigenetic regulation of NMDA receptor subunits.

Treatment	NMDAR subunit expression	Epigenetic effect	Reference
Human brain development	H3K4me2 causes GRIN1, 2A and 2C increase in PFC, but no change in CB; H3K4me2 causes GRIN2B increase for 27 folds in CB; H3K27me3 induces no change in GRIN1, 2A-C in CB; GRIN2D not detectable; H3K4me2/3 is high at GRIN2B promotor in fetal/infant vs adult in CB.	Open: H3K4me2 and 3 Closed: H3K27me3 H4K20me3	(Stadler et al., 2005)

Treatment	Effector	NMDAR subunit expression	Epigenetic effect	Effect on gene expression	Gene altered	Reference
Chronic stress		GRIN1 increase	H3K27ac decrease	Gene expression	P300	(Nasca et al., 2015)
	MEF2C	GRIN1 increase	H3K4me3	Gene expression		(Mitchell et al., 2018)
	REST	GRIN1, GRIN2A	H3K9/14me, H3K9/14ac	Gene silencing	mSin3A,CoREST, HDACs-1/2, G9a, MeCP2	(Noh et al., 2012)
	HDAC2	GRIN2A decrease	H4K12ac	Gene silencing		(Graff et al., 2012); (Guan et al., 2009)
	HDAC2	GRIN2A decrease		Gene silencing		(Qin et al., 2018)
Glutamate in cultured hippocampal neurons		GRIN2A increase	H4ac, H3K4me3, H3K9me3, H3K27me3	Gene expression		(Kiese et al., 2017)
		GRIN2A increase	DNA hypermethylation	Gene expression	OTX2, LYNX1, GPR	(Kaut et al., 2015)
		GRIN2A increase	H3K27ac	Gene expression		(Sun et al., 2016)
	SETDB1	GRIN2B decrease	H3K9me2/3	Gene silencing	HP-1a	(Jiang et al., 2010)
	REST	GRIN2B decrease	H3K27me3 increase, H3K4me3 decrease	Gene silencing	G9a	(Rodenas-Ruano et al., 2012) (Tamminga and Zukin, 2015)
	REST	GRIN2B decrease	H3K27me3	Gene silencing	RE-1	(Gulchina et al., 2017)
	Kmt2a/ Mll1	GRIN2B decrease	H3K4me1/2/3	Gene silencing		(Bharadwaj et al., 2014)
	Kmt1e/ SETDB1	GRIN2B decrease	H3K9me3	Gene silencing	HP-1	(Bharadwaj et al., 2014)
		GRIN2B increase	H3K27ac	Gene expression	AP-1, NRF-1	(Bharadwaj et al., 2014)
Imipramine		GRIN2B increase	H3K9ac increase, H3K27ac increase, HDAC3 & 4 decrease	Gene expression		(Nghia et al., 2015)
Chronic ethanol (CIE) and TCA		GRIN2B increase	DNA methylation, H3K9ac	Gene expression	AP1, CRE	(Qiang et al., 2010), (Qiang et al., 2014)
	ERK	GRIN2B increase	H3K9me2 increase	Gene expression	H/Kmts-G9a, KDM-LSD1	(Gupta-Agarwal et al., 2014)
Prenatal Bisphenol A exposure		GRIN2B increase	DNA methylation	Gene expression		(Alavian-Ghavanini et al., 2018)

Treatment	Effector	NMDAR subunit expression	Epigenetic effect	Effect on gene expression	Gene altered	Reference
Vorinostat	HDAC	GRIN2B increase	HDAC inhibition	Gene expression	p-CREB	(Fujita et al., 2012)