REVIEW ARTICLE

NMDA receptors: Biological properties and their roles in neuropsychiatric disorders

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Abstract

Proper signal transmission is the fundamental process of the brain activity. Changes and adaption of neuroplasticity based on the strength of synaptic transmission are essential for the information propagation in the central nervous system, which contribute to cognition, learning, and memory. Being the major excitatory neurotransmitter in the central nervous system, glutamate acts primarily through binding to the glutamate receptors, the glutamate-gated ion channels localized on post-synaptic membrane. The ionotropic glutamate receptors, pharmacologically grouped into α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, N-methyl-D-aspartic acid (NMDA) receptors, and kainate receptors, have been shown to play distinct roles in excitatory neurotransmission and synaptic plasticity. Due to their high permeability to Ca2+, the NMDA receptors have very unique function in neurotransmission and particular importance in the induction of long-term synaptic plasticity. Dysfunction of NMDA receptors causes impairment in synaptic plasticity and learning and memory. In recent years, with the development of genome-wide association studies and next-generation sequencing technology, mutations of NMDA receptor subunits have been in a variety of neuropsychiatric disorders, such as cognitive impairment, schizophrenia, autism or epilepsy. In clinical practice, NMDA receptors are known as the targets for the treatment of many neuropsychiatric disorders. In current review, we summarize current knowledge of NMDA receptors with different subunit compositions in the context of expression pattern, channel properties, protein trafficking, and synaptic plasticity as well as their roles in neuropsychiatric disorders.

Keywords: NMDA receptor; Ion channel; Protein trafficking; Synaptic plasticity; Neuropsychiatric disorders

1. Introduction

The ionotropic glutamate receptors play essential roles in excitatory neurotransmission. When action potential propagates through the axons, glutamate released from the vesicles at the presynaptic terminals enters the synaptic cleft, the tiny, and highly organized extracellular space, where the neurotransmission occurs. The glutamate binds to ionotropic glutamate receptors on the post-synaptic membrane and triggers the ion channel function, which gives rise to neuronal signal transfer between neurons.
Pharmacologically, the ionotropic glutamate receptors are grouped into three types\(^1\): α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (AMPARs), kainate receptors, and N-methyl-D-aspartic acid (NMDA) receptors (NMDARs). AMPARs are composed of homomeric or heteromeric assembly of four subunits: GluA1-4. Kainite receptors are homomeric GluK1-3 (GluR5-7 in old nomenclature), or heteromeric assembly of GluK1/2/3 with GluK4/5 (used to be KA1/2). NMDARs are heterotetramers composed of two subunits of GluN1, the obligatory subunits, and GluN2A-D or GluN3A-B. Virtually, glutamate receptors play essential roles in probably every physiological function in the brain; dysregulation of these receptors causes a variety of neuropsychiatric disorders.

Neuropsychiatric disorders, including neurodegenerative and neurodevelopmental disorders, such as Alzheimer’s disease (AD) and Autism spectrum disorders (ASD), are severely impair the self-cognition and social communication of individuals and may also genetically affect their descendants\(^2-5\). As the growing and aging population, researching on the neuropsychiatric disorders is of particular interest to scientists and clinicians. Due to the complexity of these diseases, it is still very challenging for researchers to understand the underlying mechanisms of these diseases\(^6-9\). The rapid development of genetic and molecular biotechnology provides an avenue for us to explore the pathogenesis of neuropsychiatric disorders\(^10\). With the support from genome-wide association studies and next-generation sequencing technology, the potential genetic architecture of human psychiatric diseases could be directly investigated\(^11\). In combination with genetic modified mouse, the disease-associated risk genes could be further confirmed in different psychiatric disorders, such as SHANK gene that is associated with autistic-like behavior\(^15\) and GRIA3 gene that are associated with aggressive behavior\(^16\). As numerous genetic variants have been identified in psychiatric patients, potential molecular mechanism underlying these diseases could be gradually elucidated.

Many gene variants, which may act as the causal factors for these neuropsychiatric disorders, have been uncovered to affect the neuroplasticity\(^17\). In the central nervous system (CNS), precise signal transmission is the cornerstone of human physiological processes, and the proper protein structure and function are required to maintain the fine-tune neuronal communication\(^19\). Therefore, numerous efforts have focused on identifying new gene variants in neuropsychiatric disorders and investigating the related mechanism. Understanding of the physiological and pathogenic function of these genes is essential to guide the treatments of the neuropsychiatric disorders.

In this review, we discuss the molecular properties of the NMDA receptors and their roles in neuropsychiatric disorders. We also extend our discussion to the potential therapeutic effects of NMDAR; specifically, it is possible to reverse the improper synaptic transmission and to further mitigate the clinical symptoms of neuropsychiatric disorders by targeting NMDARs.

2. Molecular properties of NMDA receptors

2.1. NMDARs subunit structure and expression pattern

NMDARs are composed of seven distinct subunits, including GluN1 subunit, four distinct GluN2 subunits (GluN2A, GluN2B, GluN2C, and GluN2D), and two GluN3 subunits (GluN3A and GluN3B)\(^11,21\). All NMDARs are heterotetramers, each composed of two GluN1 subunits and two identical or different subunits of GluN2s or GluN3s\(^11,21,22\). The different combination of GluN2/GluN3 subunits also leads to the diversity of receptor compositions in the CNS.

The GluN1 subunit is encoded by a single gene, but due to alternative splicing, it has eight different isoforms (GluN1-1a-4a and GluN1-1b-4b). Compared to GluN1-a isoforms, GluN1-b isoforms contain exon 5, leading to additional extracellular 21 amino acid extensions (called N1 cassette) that influence the NMDA affinity and pharmacological properties\(^11,24\). GluN1-1 to -4 were derived from the difference of alternative splicing in exon 21 and exon 22, which alter the C-terminal domain (CTD) length and trafficking capacity\(^25\).

All ionotropic glutamate receptor subunits consist of four domains\(^1,12,26\). A long N-terminal domain (NTD) in the extracellular domain is mainly involved in subunit assembly and allosteric regulation. A ligand-binding domain (LBD) consisting of two discontinuous fragments (S1 and S2) is the domain for binding of glycine (or D-serine) in GluN1 or GluN3 and of glutamate in the GluN2 subunit. The transmembrane domain (TMD) of NMDAR is composed of three transmembrane regions (M1, M3, and M4) and a reentrant loop (M2), which form the channel pore for the influx of ions. The final structure is the intracellular CTD, the length of which varies a lot and determines the length difference among NMDAR subunits\(^1\). CTD is involved in receptor trafficking, post-synaptic protein anchoring and protein-protein interactions, as well as many signaling pathways\(^12,28,29\).

The NTD of NMDARs plays a critical role in the assembly of NMDARs. The NTD, formed by 1–350 amino
acids that associate as back-to-side heterodimers between GluN1 and GluN2 subunits, adopts a bilobed structure. Upper R2 lobes of GluN1 and GluN2 subunits interact to form a protein-protein interface, while lower R1 lobes connect to the LBD, thus forming a unique dimer-of-dimer arrangement\[30-33\]. Moreover, there are binding sites for allosteric modulators in NTD, including the sites for extracellular Zn\(^{2+}\) and ifenprodil, the GluN2B-selective antagonist\[34,36\]; therefore, the NTD also plays a role in regulating NMDAR gating and function.

The LBD is formed by the S1 and S2 segments, which forms kidney-shaped bilobed structures consisting of an upper lobe and a lower lobe with the agonist binding sites in the gap located between the two lobes\[37\]. Besides, there are three independent contact regions in the LBD heterodimer crystal structures of GluN1 and GluN2A (referred to as sites I, II, and III). Hydrophobic residues of GluN1 and GluN2 form sites I and III, and non-polar interactions between these residues mediate agonist binding domain (ABD) heterodimerization\[37\]. The site II of the ABD contains the binding sites of positive and negative allosteric modulators, which are highly selective for GluN2A\[38-40\].

The TMD is formed by M1, M3, and M4 and a reentrant loop (M2). The M2 is in the intracellular of the ion channel pore, and the M3 forms the extracellular region of the channel pore. The residues of pore region are highly conserved, which indicates the importance of the region. Normally, M3 forms the helical bundle and blocks the pore of channel so that ions cannot pass through the channel when the M3 helical changes its position\[41-43\]. The agonist binding to the LBD is the first step leading to M3 rearrangement\[30,31,34,35,44\], followed by multiple short-lived, intermediate conformations, and eventually channel opening\[45\]. NMDARs are widely distributed throughout the CNS, though the expression of NMDAR subunits varies in different brain regions and developmental stages. Consistent with a broad CNS distribution, the expression of GluN1 subunits generally begins from embryonic E14 and continues into adulthood\[46-48\]. Among the GluN1 splicing isoforms, GluN1-2 is widely distributed. The GluN1-1 and GluN1-4 expression distribution is complementary; the former is distributed in more rostral regions (including cerebral cortex and hippocampus). GluN1-a and GluN1-b subtypes have largely overlapped expression patterns, but their relative abundance varies from region to region. It is noteworthy that GluN1-a is expressed in all principal neurons in the hippocampus, while GluN1-b is mainly confined to the CA3 layer\[49\].

Expression of the GluN2 subunit varies in different brain regions during development. In rodents, the GluN2B and GluN2D subunits are highly expressed in the embryonic brain\[47,48,50\]. GluN2B expression remains high in the postnatal period, but only in forebrain regions. GluN2D expression is significantly reduced in adults; remaining GluN2D is mainly expressed in midbrain structures, including diencephalon and midbrain. The expression of GluN2A starts from birth and gradually increases over time, eventually becoming abundant throughout the CNS. Thus, NMDAR composition of GluN2B changes to predominantly GluN2A during development in the cerebral cortex and hippocampus\[51\]. The expression of GluN2C begins in the 2\(^{nd}\) week after birth, but is limited to the cerebellum and olfactory bulb. The shift from GluN2B to GluN2C occurs in cerebellar granulosa cells during development, resulting in a sharp decrease in the GluN2B expression in adulthood\[48\].

GluN3A and GluN3B subunits also show different expression patterns\[52,53\]. GluN3A expression is the highest in the early postnatal period and then begins to decline gradually. In contrast, GluN3B expression is increased during development, with high levels of expression in motor neurons in adulthood. GluN2B, GluN2D, and GluN3A subunits are highly expressed in the early development, suggesting that these subunits play important roles in synaptic maturation and synaptogenesis\[52,53\]. GluN2A and GluN2B are major subunits in the CNS of adult, especially in hippocampus and cortex, suggesting that they play a role in synaptic function and plasticity\[46-49\].

2.2. Dynamic characteristics of NMDAR

2.2.1. Activation of NMDAR

Glycine and glutamate are required for activation of NMDA receptors consisting of GluN1/GluN2 subunits\[54-58\]. The activation of NMDAR containing of GluN1/GluN3 requires only glycine\[53,56\]. In the nervous system, glycine is naturally present in the extracellular environment (4.2 ± 1.6 μM of glycine in cerebrospinal fluid)\[60\]. Other molecules can also activate GluN1/GluN2 receptors as coagonists, such as D-Serine, L-Serine, D-alanine, and L-alanine. In recent years, D-Serine has been proposed as the main coagonist of synaptic NMDARs, while glycine is the main coagonist of NMDARs at extrasynapse\[60\]. Glutamate, the excitatory neurotransmitter in the CNS, is the native agonist of GluN1/GluN2 NMDARs. Glutamate (L-glutamic acid or D-glutamic acid) can activate NMDARs by binding to the LBD of GluN2 subunit. NMDA, N-methyl-L-aspartic acid, D-aspartic acid, and L-aspartic acid are also the agonists of NMDARs\[60\].

Unlike the conventional NMDARs, glycine binding to the GluN1/GluN3 receptor only produces a small excitatory current. Indeed, glycine binding to GluN3 activates GluN1/GluN3 receptors, but binding to GluN1
inhibits the channel\(^{[99,63-67]}\). The physiological function of GluN3 NMDARs remains largely unknown.

### 2.2.2. Gating function of NMDAR

NMDARs composed of different subunits have different channel characteristics. The GluN2A and GluN2B-containing NMDARs have higher conductance, higher Ca\(^{2+}\) permeability, and higher Mg\(^{2+}\) sensitivity compared to GluN2C and GluN2D-containing NMDARs, which are regulated by the Ser632 in GluN2A and S633 in GluN2B site in M3 region\(^{[68]}\). Besides, the channel gating properties are different among NMDARs, including the open probability, deactivation kinetics, and agonist potency. The open probability of GluN2A-containing NMDARs is higher than that of other GluN2-containing NMDARs, and the deactivation of GluN2A-NMDAR is faster too\(^{[69,70]}\). Therefore, the channel of GluN2A closes earlier after activation by glutamate, leading to a fast decay time. Interestingly, GluN1 splicing isoforms also affect NMDAR gating kinetics, that is, the NMDARs with GluN1-a deactivates slower than those with GluN1-b\(^{[23,24]}\).

For the major NMDAR components in the cortex of adult, the GluN1/GluN2A receptors have the faster decay time, while the GluN1/GluN2B receptors have higher Ca\(^{2+}\) permeability and charge transfer\(^{[71]}\).

### 2.3. NMDARs trafficking

NMDAR trafficking is mainly mediated by intracellular CTD. The difference in CTD sequences of NMDAR subunits leads to subunit-specific regulations on receptor transport, localization and signal transduction\(^{[72-74]}\). The synaptic transmission and escape from the endoplasmic reticulum (ER) of NMDARs are regulated by the C-terminal splicing of GluN1\(^{[85]}\), a process that appears to be driven by neuronal activity\(^{[75]}\). The different motives in the CTDs of GluN2 and GluN3 diversify the trafficking procedures of NMDARs\(^{[76]}\).

#### 2.3.1. Receptor biogenesis

Typically, NMDARs are first assembled in ER and matured by glycosylation in the Golgi apparatus before being transported to the plasma membrane through vesicles. Cells have strict mechanisms to prevent unassembled or misfolded NMDARs from being transported to the cell surface\(^{[77]}\). The previous studies indicated that only in the form of GluN1/GluN2, NMDAR could escape from the ER\(^{[78]}\). Grin1 gene deletion causes the retention of GluN2 subunit in the ER of hippocampus\(^{[79]}\). Both GluN1 and GluN2 subunits contain ER retention signals, which can be masked by the co-assembly of GluN1 and GluN2 subunit\(^{[80]}\). For example, the CTD of the GluN1 subunit contains positively charged ER retention signals, including lysine-lysine-lysine (KKK), and arginine-arginine-arginine (RRR)\(^{[23,81,82]}\). The overexpression of GluN2A and GluN2B in cerebellar granular neurons leads to a significant increase in the number of NMDARs and synaptic targeting, probably through the co-assembly with extra GluN1\(^{[83]}\). An ER retention sequence (HLFY) has been proposed in the CTD of GluN2B subunit\(^{[84]}\). However, subsequent studies showed that HLFY motif was required in the CTD-oriented structure of GluN2B, but its might not serve as an ER retention signal\(^{[85]}\). In a recent study, the KKK879-881 of GluN2A was proven to be an ER retention signal\(^{[17]}\), regulating the surface expression of GluN2A-NMDAR.

GluN2 subunits interact with the proteins of membrane-associated guanylate kinases (MAGUK) family, such as synaptic associated proteins-102 kDa (SAP102) and synaptic associated proteins-97 kDa (SAP97), which is necessary for NMDAR secretion\(^{[66,87]}\). SAP102 is highly expressed in the hippocampus on the 2nd day after birth, and its PDZ region interaction with GluN2A and GluN2B subunits of NMDARs makes a difference\(^{[88,89]}\). Moreover, SAP102 is also widely present in the cytoplasm and ER\(^{[84]}\). In addition, SAP102 interacts with mPins through its Src-homology 3 (SH3)/guanylate kinase domain to stabilize the SAP102-exocyst-NMDAR complex in ER. This process plays an important role in promoting NMDAR trafficking and membrane targeting\(^{[86,87]}\).

NMDARs also have a trafficking pattern that bypasses the traditional somatic Golgi network. In this pattern, these receptors mix directly within the dendrite Golgi\(^{[90]}\). This strategy can promote more efficient insertion of NMDARs at the post-synaptic density (PSD). Because they contain large protein complexes including scaffold molecules, vesicles produced by this pathway are highly mobile (0.76 μm/s). Mlin7 binds GluN2B with the motor protein KIF17, which promote the long-distance transport of NMDAR-containing vesicles on microtubules along dendrites\(^{[90-93]}\). Studies have shown that KIF17-mediated NMDARs trafficking is critical in long-term potentiation (LTP), long-term depression (LTD), learning, and memory\(^{[93]}\). Deletion of kif17 leads to NMDAR degradation due to enhanced ubiquitination, resulting in partial synaptic GluN2A and GluN2B receptors loss. It is interesting that the interaction of CASK leads SAP97 to preferentially bind NMDARs\(^{[94]}\). Meanwhile, SAP97 is phosphorylated by Ca\(^{2+}\)/calmodulin-dependent protein kinase II (CaMKII) at two key sites, Ser-39 (in the L27 domain) and Ser-232 (in the PDZ1 domain)\(^{[95,96]}\). Phosphorylation of SAP97 at Ser-39 leads to translocation of SAP97 from the ER to the post-synaptic compartment, while phosphorylation at Ser-232 disrupts binding of SAP97 to GluN2A. In
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2.3.3. Receptor lateral diffusion

Lateral diffusion of NMDAR on the membrane is along extrasynaptic and synapses. GluN2A NMDAR and GluN2B-NMDAR appear to be differentially located on the neuronal surface. GluN2A-NMDAR is preferentially expressed in the synapse, while the expression of GluN2B-NMDAR tends to be higher in extrasynapse during development phase. The underlying mechanism seems to be that the interaction between CTD of GluN2A with PDZ domain of post-synaptic density protein-95 (PSD-95) is relatively stabler. Furthermore, the peptides mimicking GluN2A or GluN2B PDZ binding motif only causes a decrease in synaptic GluN2A-NMDAR but not in synaptic GluN2B-NMDAR, indicating that the PDZ-domain dependent regulation is subunit-related.

2.3.4. Receptor endocytosis

The surface receptors are also regulated through receptor internalization. NMDAR endocytosis is dependent on development and neuronal activity; the rate of internalization decreases gradually as neurons mature. The CTD of GluN2A and GluN2B contains endocytosis motifs, but GluN2B subunits have relatively higher endocytosis rates in mature neurons. The phosphorylation of Y1472 by Fyn kinase induces GluN2B binding with MAGUKs, which stabilizes GluN2B in the synaptic membranes. Reduction in Y1472 phosphorylation induces the interaction between YEKL1472-1475 endocytic motif and adaptors protein-2 (AP-2), resulting in increased internalization of GluN2B. On the other hand, Ser-1480 phosphorylation by CK2 contributes to increased GluN2B internalization. Therefore, the phosphorylation/dephosphorylation plays an important role in receptor internalization. In GluN2A subunit, the endocytosis is mediated by the di-leucine LL1319-1320.

GluN1 subunit also affects the endocytosis of NMDARs containing GluN1/GluN2BΔCTD. Studies have shown that there are two motifs of internalization in the C0 cassette in GluN1: YKRH838-841 and VWRK858-861. Similar sequences have been found in GluN2A (YWKL841-844). On the other hand, Ser-1480 phosphorylation causes a decrease in synaptic GluN2B-NMDAR, indicating that the interaction between CTD of GluN2A and PDZ domain of post-synaptic density protein-95 (PSD-95) is relatively stabler. Furthermore, the peptides mimicking GluN2A or GluN2B PDZ binding motif only causes a decrease in synaptic GluN2A-NMDAR but not in synaptic GluN2B-NMDAR, indicating that the PDZ-domain dependent regulation is subunit-related.

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Thus, the NMDARs undergo various regulation of protein synthesis, trafficking, and internalization. These regulations also ensure the dynamic abundance and composition of NMDARs on the synaptic membrane, thereby allowing physiological functions regulated by neuronal activity and plasticity.

2.4. NMDARs in neuroplasticity

Synaptic plasticity refers to the long-lasting change in morphology and function of synapses caused by the neural activity induced by experience\(^{130}\). Two classic types of synaptic plasticity, LTP and LTD, have been studied at hippocampal excitatory synapses; both requires the activation of NMDARs\(^{131}\). LTP strengthens synapse function and is induced by high-frequency presynaptic stimulation, while LTD weakens synapse function and requires low presynaptic stimulation to induce. NMDAR-dependent synaptic plasticity is the basis of learning and memory in hippocampus. Blocking hippocampal NMDARs before training impairs rodent learning ability\(^{132,133}\), but memory is enhanced after hippocampal-dependent task training\(^{134,135}\).

In hippocampal synapses, AMPARs and NMDARs involve the forms of LTP and LTD. AMPARs and NMDARs are glutamate receptors that are permeable to Na\(^+\) and K\(^+\), while all NMDARs and part of AMPARs are also permeable to Ca\(^{2+}\). When the post-synaptic membrane is at resting potential, NMDARs cannot conduct currents because Mg\(^{2+}\) blocks the channel pore. When AMPAR current causes local membrane depolarization, Mg\(^{2+}\) is removed from the NMDAR channel, allowing Ca\(^{2+}\) flow into the cell. LTP and LTD require NMDARs-mediated influx of Ca\(^{2+}\); LTP requires a large elevation of Ca\(^{2+}\) in spine while that it is much less for LTD. When NMDARs mediate a large influx of Ca\(^{2+}\), protein kinases, especially CaMKII acting on receptor proteins, accessory receptors, or transcriptional regulators increase glutamate receptor activity and/or levels in the synapses, thus inducing the induction and maintenance of LTP\(^{136,137}\). When NMDAR-mediated Ca\(^{2+}\) elevation is modest, Ca\(^{2+}\)/calmodulin-dependent protein phosphatase, protein phosphatase 1, and calcineurin are phosphorylated and activated, thereby inducing the dephosphorylation of AMPAR that results in the internalization of AMPAR from the synapses and LTD\(^{138-140}\).

Synaptic plasticity requires Ca\(^{2+}\), and the composition of NMDARs has different permeability to Ca\(^{2+}\), which could couple with the phosphatase pathway and downstream signaling to regulate the plasticity\(^{140}\). However, how specific subunit composition determines synaptic plasticity remains unclear and controversial.

2.4.1. LTP

To investigate the possible specific role of GluN2 in synaptic plasticity, both genetic and pharmacological approaches have been applied.

NMDARs containing GluN2B showed a greater current\(^{140}\) and carried more Ca\(^{2+}\)\(^{71}\). Besides, GluN2B preferentially interacts with CaMKII\(^{141}\), and it is speculated that the GluN2B subtype is more likely to induce LTP than the GluN2A subtype. For example, ifenprodil, the GluN2B antagonist, blocks the pairing-induced LTP in hippocampal slices\(^{142}\) and in the barrel cortex\(^{143}\). Moreover, the GluN2B antagonist could block the pairing- and theta burst-induced LTP in the anterior cingulate cortex at 6–8-week-old mice\(^{144}\). The tetanus-induced LTP in hippocampal CA3 synapses was abolished in mice with conditional GluN2B knockout\(^{145}\). Lacking GluN2B in the Cornu ammonis 1 (CA1), the LTP is impaired\(^{146}\). Another study showed that LTP is deficient by pairing protocol of GluN2B knockout in the forebrain\(^{147}\). LTP is enhanced when GluN2B is overexpressed in hippocampal neurons of 4–6-month-old mice\(^{148}\). Disruption of the interaction between GluN2B and CaMKII by overexpressing the CTD of GluN2B eliminates the LTP of 3–4-month-old mice\(^{149}\). Genetic deletion of GluN2A has no effect on the LTP in P28 mice, indicating that GluN2B is essential for the LTP\(^{150-152}\). Other genetic methods that influence the level of GluN2B also impair the induction of LTP. For instance, knockout of the KIF17, a protein that transports GluN2B to the synapses, reduces synaptic GluN2B and abolishes LTP\(^{93}\). Besides, Cdk5 knockout mice show increased GluN2B and enhanced LTP\(^{153}\). Recently, it has been found that enhanced GluN2A surface and synaptic expression causes LTP impairment, likely through compensatory GluN2B decrease\(^{157}\). Hence, GluN2B-containing NMDARs play a role in the induction of LTP.

However, some studies have shown that GluN2A is important for LTP\(^{153,154}\). In pharmacological experiments, blocking of GluN2A by NVP-AAM077 could prevent tetanus- and pairing-induced LTP in 3–4-week-old rats, while the ifenprodil and Ro 25-6981, the antagonists of GluN2B, have no effect on LTP but could block the induction of LTD\(^{154}\). Another study that used the same antagonist concentration and rats of the same age found that NVP-AAM077 completely blocks LTP, and ifenprodil and Ro 25-6981 partially block LTD\(^{155}\). Low Zn\(^{2+}\) which selectively inhibited GluN2A impairs LTP\(^{72}\). GluN2A knockout mice\(^{156}\) and deletion CTD of GluN2A mice\(^{72}\) show impaired LTP in hippocampal synapses.

For LTP, a possibility is that both GluN2A and GluN2B subunits mediate Ca\(^{2+}\) influx, so both subunits are involved in the induction of LTP\(^{157,158}\). However, the exact extent of involvement of these two subunits in LTP remains unclear.
2.4.2. LTD

There are also many contradictory results on the LTD with the composition of NMDAR subunits. One study suggested that ifenprodil blocks LTD in hippocampus\[^{154}\] while the results of other research groups indicated that ifenprodil does not affect LTD\[^{159}\] or even enhances LTD\[^{160}\]. Disruption the interaction of GluN2B and PSD95 has no effect on LTD, although the level of synaptic GluN2B is reduced\[^{161}\]. Moreover, the overexpression of GluN2B does not affect the LTD\[^{162}\], while the LTD is deficient in GluN2B knockout mice and KIF17 knockout mice, due to the reduction of synaptic GluN2B\[^{93,146}\]. Thus, these conflicting findings point to the ambiguous function of the GluN2B subunit in LTD, and to the fact that the experimental conditions are important for the induction of LTD.

On the other hand, some studies found that NVP-AAM077 not only impaired LTP but also blocked LTD\[^{155,163}\]. By contrast, the NVP-AAM077 only affected LTP but did not impair LTD in slices\[^{154}\] or in vivo\[^{164}\]. Besides, overexpression GluN2A induced decreased LTD\[^{152}\] and GluN2A knockout mice displayed no impairment of LTD\[^{165}\]. However, the LTD could be induced by the 0.5 Hz stimulation in GluN2A knockout mice\[^{165}\].

More experiments are warranted to clarify the role of NMDAR subunits in the LTD.

2.5. NMDARs pharmacology

NMDARs play a role in the neuropsychiatric disorders. The dysfunction of NMDARs involved in many disease, such as AD, Parkinson’s disease (PD), epilepsy, and schizophrenia\[^{106}\]. Therefore, in the past decades, a great deal of money has been spent to develop NMDAR antagonists and agonists to cure the diseases associated with NMDAR. For example, the ketamine and rapastinel (GLYX-13) are used for the treatment of depression\[^{167-169}\]. Memantine, a NMDAR blocker, has been proven for use in treating AD and increasing cognitive behavior of AD patients\[^{170,171}\]. Unfortunately, due to the off-target or side effects of excessive inhibition of NMDAR, many drugs have failed in most clinical trials\[^{166,172}\].

Many positive and negative allosteric modulators (PAMs and NAMs, respectively) have been found recently. In addition to the antagonists and agonists of NMDAR, the allosteric modulators can positively and negatively regulate the NMDAR activity. Compared with antagonist or channel blocker, the allosteric modulators have many potential advantages in therapeutics development. The binding domain of allosteric modulators with NMDARs is not highly conserved ligand-binding site or channel pore. Therefore, allosteric agents have better subunit selectivity, which reduces side effects and off-target. Besides, the inhibition of NAMs is <100%, so partial function of NMDARs can be preserved, so as to avoid excessive blockade of receptors. This partial inhibition of NAMs has a better safety profile than competitive antagonists and channel blockers. In schizophrenia caused by NMDAR hypofunction, or other cognitive disorders, PAMs only enhanced the activity of weakly activated NMDAR-mediated signals to restore normal function. This is unlike the NMDAR agonists, which could activate all receptors and lead to side effects and excitotoxicity. Therefore, a better understanding of these allosteric modulators can improve their usage in clinical practice.

2.5.1. The antagonists of NMDARs

The previous studies have shown that most NMDAR antagonists basically interact with NMDARs by glutamate binding site, glycine binding sites, NTD binding sites, or ion channel pores. The glutamate is an activator of NMDARs. Agonists and antagonists that interact with glutamate binding sites were first identified\[^{166}\], such as D-α-amino adipic acid and D-AP5. Since glutamate binding affinity is the strongest in GluN2D followed by GluN2B/2C, and the lowest in GluN2A, the competitive antagonists generally have the strongest inhibition on GluN2A, then on GluN2B/2C. For example, CPP is more sensitive to GluN2A subunit than to other subunits\[^{173}\]. Quinoxalinedione derivative (1R,1’S)-PEAQX, a GluN2A competitive antagonist, has no effect on GluN2B\[^{174}\]. At present, the NVP-AAM077 ((1R,1’S)-stereoisomer) purified from (1R,1’S)-PEAQX is widely used to inhibit GluN2A-NMDARs.

Antagonists against the glycine binding site have been found\[^{175,176}\]. Glycine binds to GluN1 subunit of NMDARs, so these antagonists show no selectivity for the subunits. The antagonists that act through glycine site include HA-966\[^{177}\], 7-chloro-5-iodokynurenic acid\[^{176}\], L-701,324,\[^{178}\] and MDL 105,519\[^{178}\].

The channel sequence and structure of NMDARs are highly conserved, so the selectivity of channel blocker is little. The NMDAR blockers, such as ketamine and phencyclidine (PCP), act as the anesthetics that bind the ion channel pore\[^{179,180}\]. However, when the Mg\[^{2+}\] are present, the memantine appears to be more sensitive to GluN1/GluN2C and GluN1/GluN2D receptors. Besides, the MK-801 is also a NMDAR channel blocker, which binds to channel pore when the NMDARs are activated\[^{181}\].

2.5.2. NAMs

The binding sites of NMDAR subunits with NAMs are not a highly conserved ligand binding site or channel pore. Therefore, NAMs with different subunits can bind to the allosteric sites of NMDARs. Among them, the most well-studied is ifenprodil, which binds to channel pore when the NMDARs are activated. However, the LTD could be induced by the 0.5 Hz stimulation in GluN2A knockout mice\[^{165}\].
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2.5.3. PAMs

The function of PAMs is to enhance the NMDAR function. Endogenous PAMs include ATP [193], histamine [194], Mg\(^{2+}\), polyamines such as spermine [195], and pregnenolone sulfate (PS) [196]. The enhancement of histamine and ATP is both enhanced at high glutamate concentrations. The low concentrations of ATP can enhance the GluN2A-, GluN2B-, and GluN2C-containing NMDARs [193]. The effects of spermine on NMDARs are different; it can either increase the potency of glycine, or allosterically interact with GluN2B- and GluN1-lacked exon 5, that is, the glycine-independent [194, 195, 197]. PS potentiates GluN2A- and GluN2B-containing NMDARs at micromolar concentrations, while inhibits the GluN2C and GluN2D subunits [198]. The mechanism of the potentiation of PS is the increased open probability of NMDARs through phosphorylation [199, 200]. Similar results have been found by single channels analysis that the frequency of channel openings is enhanced by PS [201, 202]. Besides, the studies have proven that the S2 domain of GluN2A may be the interaction site of PS with GluN2A [200], while the S2 and M4 domain of GluN2B play an important role in the potentiation [203].

Other PAMs of NMDARs, such as phenanthrene, naphthalene, and coumarin derivatives, have been reported in many studies [204]. UBP512, a phenanthroic acid, enhanced the GluN2A-containing NMDAR, but not the GluN2B-containing NMDAR, and inhibited the GluN2C and GluN2D subunits. The UBP710 enhanced both GluN2A- and GluN2B-containing NMDARs, while inhibited the GluN2C and GluN2D subunits. The UBP551, a naphthoic acid NMDAR PAM, potentiated the GluN2D subunit, while had no effect on the other three GluN2 subunits [191]. Another naphthoic acid NMDAR PAM is the UBP684, which could enhance the effect on all GluN1/ GluN2 receptors by increasing the open probability and mean open time [205, 206]. The UBP714, a coumarin derivative, slightly potentiated the GluN2A, GluN2B and GluN2D [207]. The CIQ is a potentiator of GluN2C- or GluN2D-containing NMDAR [208, 209]. Studied indicated that the linker between NTD and LBD and T592 of GluN2D is the important sites of the GluN2D to activate the CIQ [208].

Recently, the GEN family has been reported as the PAMs of GluN2A. According to the analysis of the GluN2A binding with GEN-6901, we understand that the V783 of GluN2A is a necessary site for binding with GEN-6901 specifically [198]. The potentiation of GEN-8324, instead of GEN-6901, in GluN2A increased the potency of glutamate, but both of them had no effect on the sensitivity to glycine. Meanwhile, they also decreased the NMDAR deactivation [198]. However, there are differences between...
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the two potentiators. The GEN-8324 has an impact on the inhibitory neurons only, while the GEN-6901 plays a role in both inhibitory and excitatory neurons\(^\text{[30]}\); however, the underlying principle remaining to be explored. The GEN-0723 had been shown to enhance GluN2A not only in vitro but also in vivo\(^\text{[39]}\). The GEN-9278 potentiated not only the GluN2A-NMDARs but also the GluN2B-, GluN2C- and GluN2D-NMDARs\(^\text{[20]}\). The GEN-9278 increased the glutamate and glycine potency and reduced the deactivation of glutamate.

3. NMDAR in neuropsychiatric disorders

NMDARs play an important role in neuronal development. NMDARs dysfunction in subunits expression, localization, and trafficking may cause brain disorders. Therefore, both NMDAR antagonists and enhancers have the potential to be utilized as CNS treatment agents. In this section, we focus on some neuropsychiatric disorders with NMDAR dysfunction, with special emphasis on subunit specificity.

3.1. AD

AD is a dementia, which is characterized by increased beta-amyloid (A\(\beta\)) peptide and the intracellular tangles composed of tau protein in hyperphosphorylation. A\(\beta\) may aggregate to form soluble oligomers composed of multiple polypeptides or insoluble amyloid plaques. Hyperactivation of NMDAR is also associated with AD (Figure 1). Memantine, which is an NMDAR channel blocker, is currently used to treat patients with AD. Moreover, the antagonists of NMDAR, such as APV and ifenprodil, as well as the channel blocks, ketamine, and MK-801 can abolish the synaptic depression induced by A\(\beta\)\(^\text{[21]}\). Some studies, further, suggested that GluN2B is essential for the harmful effects of A\(\beta\). Synaptic loss\(^\text{[212]}\), impairment of LTP\(^\text{[213]-[214]}\), and increased LTD induced by A\(\beta\)\(^\text{[215]}\) can all be rescued by GluN2B antagonists. Some of these mechanisms may be the activation of extrasynaptic GluN2B receptors induced by changes in glutamate uptake\(^\text{[213]}\). Phosphorylation of the GluN2B by the tau and tyrosine protein kinase FYN trafficking to the dendritic spine enhances the interaction with PSD95, which leads to downstream excitatory toxicity\(^\text{[216]}\). Besides, the induction of A\(\beta\) is needed for the activation of extrasynaptic GluN2B-containing NMDARs\(^\text{[217]}\). A synthetic peptide that interferes with the interaction between GluN2B and PSD95 enhances memory and longevity in AD mouse models\(^\text{[216]}\). However, this peptide did not impair NMDAR-mediated synaptic currents, but reduced ischemic cell death in stroke model\(^\text{[216,218]}\). In addition, it should be noted that much of the evidence supporting the role of GluN2B in mediating A\(\beta\)-induced excitatory toxicity is obtained through synthetic A\(\beta\) preparations in vitro. Therefore, it remains to be clarified whether the GluN2B antagonists can prevent or reduce synapse loss and improve cognition in AD models.

3.2. PD

PD is a neurodegenerative disease, which is characterized by the degeneration of nigral dopaminergic neurons and the loss of dopamine in the striatum. Dopaminergic and glutaminergic signaling are involved in controlling motor function. Studies have shown that the NMDAR is impaired in the disorder (Figure 1). For example, in the PD model, the expression of GluN1 and GluN2B, but not GluN2A, was reduced, which can be rescued by L-DOPA\(^\text{[219]}\). In addition, after L-DOPA treatment in dyskinetic animals, GluN2B was transferred from the synaptic to the extrasynaptic region,
and GluN2A was increased in the synaptic region\textsuperscript{[220]} In addition, the expression of MAGUK protein was decreased, which is probably due to the impaired interaction between MAGUK with GluN2B in the PD models\textsuperscript{[220]}. However, the GluN2B selective antagonists have inconsistent effects on PD models and human PD patients\textsuperscript{[221,222]}. However, in the rat model of PD, specific interference of GluN2A in synaptic localization can reduce motor dysfunction\textsuperscript{[223]}.

Although these studies help us further understand the pathophysiology of PD, the disease involves many changes in organs and brain regions. Therefore, a complete cure for PD remains a major challenge.

3.3. Schizophrenia

Schizophrenia is psychiatric disorder with hallucinations and delusions (positive symptoms), aversion and anhedonia (negative symptoms), and cognitive dysfunction\textsuperscript{[234]}. Studies have shown that excessive release of dopamine in striatum is the reason of the positive symptoms\textsuperscript{[225]}, but the mechanism of negative symptoms and cognitive dysfunction remains elusive. Changes in glutamate signal may be a pathological basis for the schizophrenia\textsuperscript{[226]}, especially dysregulated NMDARs may induce the imbalance between excitation and inhibition in PV neuron (Figure 1).

Studies have indicated that reduction in NMDAR expression causes schizophrenia-like behavior in mice\textsuperscript{[227]} Impaired dopamine release is found in mice with GluN1 deletion in PV neurons\textsuperscript{[228]}. Recently, other studies in clinic proved the NMDAR hypofunction in schizophrenia. The noncompetitive NMDAR antagonists, PCP, and ketamine could induce schizophrenic phenotypes in people\textsuperscript{[229-231]}. Furthermore, the MK-801 also induced the PCP-like behavior in many species\textsuperscript{[232,233]}. The autoantibodies against NMDARs, which are found in patients with the anti-NMDAR encephalitis, cause NMDAR internalization. These patients show the symptoms similar to schizophrenia\textsuperscript{[234]}. These studies suggested that the NMDAR hypofunction may cause schizophrenia, providing new ideas for developing treatment of schizophrenia in the future.

3.4. Huntington’s disease (HD)

HD in human results from an inherited huntingtin (HTT) gene defect, which induces progressive degeneration of neurons in the brain and impairs movement, cognitive functions, and emotions. HD is defined by repeated CAG mutation in HTT gene\textsuperscript{[235]}. Some studies have indicated the NMDAR function is increased in HD mouse models\textsuperscript{[236]}, and the balance of synaptic and extrasynaptic NMDAR plays an important role in HD (Figure 1). The data found that the balance of synaptic and extrasynaptic NMDAR is disrupted in mice model of HD\textsuperscript{[237]}. The experiments also showed that in the HD model, caspase-6 cleavage, a process of the production of toxic mutation Htt fragments, increased extrasynaptic NMDA receptor-induced currents, and signaling pathways\textsuperscript{[237]}. In addition, the HD mice were treated with memantine, which only antagonized extrasynaptic NMDAR at low dose and rescued impaired learning as indicated by a test on rotarod motor\textsuperscript{[237]}. Another study also presented the similar results that the activation of synaptic NMDAR rendered Htt mutation-expressing cortical cells resistant to cell death, while the activation of extrasynaptic NMDAR rendered the cell more vulnerable to cell death\textsuperscript{[238]}. Clinical trials have shown that treating HD mice with low doses rather than high doses of memantine rescued adverse neuropathological and impaired behaviors\textsuperscript{[238]}. Binding of β-amyloid to synaptic NMDAR increases post-synaptic Ca\textsuperscript{2+} level, which impairs synaptic transmission and further affects LTD/LTP. The stimulation of extrasynaptic NMDAR could activate calpain which degrade tau protein to a toxic peptide and also phosphorylate p38-MAPK signaling pathways and leads to cell death. Moreover, tau protein is required to transport kinase Fyn to the post-synaptic localization, and to further promote the interaction with PSD95 and phosphorylation of NMDAR, which lead to the impaired LTD/LTD in AD. Dysregulated NMDAR could induce ER stress and DNA damage, probably through the overloading of Ca\textsuperscript{2+} ions and related signaling pathways. The impaired interaction between PSD95 and NMDAR may also affect the synaptic transmission and lead to dopaminergic neurons death in PD. Hypofunction of NMDAR affects the spinogenesis and also reduces the release of dopamine, resulting in an unbalance between excitatory and inhibitory transmission and schizophrenia. Increased level of extrasynaptic NMDAR attracts more Ca\textsuperscript{2+} ions, which induce mitochondrial dysfunction and further lead to neuron death. In addition, caspase 6 cleavage of HTT is essential to increase the extrasynaptic NMDAR current and subsequent excitotoxicity in HD.

3.5. Major depressive disorder (MDD)

MDD is currently one of the most common mental disorders in the world and frequently occurs as a complication in other diseases\textsuperscript{[239]} The efficacy of drug treatment for MDD patients usually lasts from weeks to even years. In addition to its severe effect on the social communication and cognitive functioning, the comorbid MDD and anxiety symptoms are also a challenge for pharmaceutical approaches\textsuperscript{[240,241]}. In 1960s, ketamine, a nonselective NMDAR antagonist, was originally developed as an anesthetic\textsuperscript{[242]}.
ketamine, which was tested in MDD patients, displayed potential clinical effectiveness [267]. Two enantiomers of ketamine, arketamine and esketamine, show antidepressant activity with different degree of affinity to NMDAR [240]. Recently, the treatment of esketamine for MDD has been approved by the USA and Europe FDA [244]. It has been suggested that the dysfunction of glutamatergic transmission may associated with MDD, and NMDAR attracts considerable attention with respect to its biological function in the CNS [245]. Studies with MDD patients showed significantly reduction of GluN2A and GluN2B subunits of NMDAR but did not change GluN1 protein level compared to the controls, along with reduced level of PSD-95 in prefrontal cortex, indicating an abnormal signaling in the synaptic transmission within MDD [246]. However, in the lateral amygdala and locus coeruleus of depressed subjects, increased levels of GluN2A and GluN2C expression have been detected [247, 248]. A recent research showed that α7nAChR-NMDAR complex may play a role in the MDD, and disruption of this complex with a peptide exhibits antidepressant effects [249]. Moreover, another study suggested that the antidepressant mechanism of ketamine is NMDAR-independent but related to AMPAR [250]. Taken together, these studies reveal a crucial role of NMDAR in MDD, underlining the significance of NMDAR in the development of next-generation antidepressants.

3.6. Stroke and traumatic brain injury (TBI)

In stroke and TBI, extracellular glutamate is continuously elevated, causing excitotoxicity and acute neuronal death [251]. The NMDAR-mediated excitotoxicity is a major cause of acute neuronal death after ischemia or injury. Studies have suggested that NMDAR antagonists could inhibit ischemic cell death [252, 253]. NMDAR antagonists protect neurons against ischemic cell death if they have been applied before [254-256], but not 30 min [254] or 3 h [255] after stroke in animal models. However, it has also been reported that GluN2B antagonists applied 2 h poststroke could reduce brain infarct volume [257]. Intriguingly, NMDAR-mediated excitotoxicity appears to be subunit-dependent: GluN2A antagonist aggravates but GluN2B antagonist blocks the ischemic cell death [255, 256]. Probably due to the intolerable side effects of NMDAR antagonists and the level of elevated extracellular glutamate that last less than an hour, the clinical trials concerning the application of NMDAR antagonists in stroke have so far been unsuccessful [258]. In addition to the direct inhibition of NMDAR activity, neuronal protection can be achieved by disrupting the interactions between NMDARs and their scaffold proteins, including PSD-95, phosphatase and tensin homolog, and associated signaling molecules in stroke animal models [258, 259] and in humans [260]. This could be a new strategy targeting NMDAR-associated signaling in stroke.

The clinical trials concerning NMDAR antagonists, including selective GluN2B antagonists, for use in the treatment of TBI were also unsuccessful [261]. Although overactivation of NMDARs is toxic, functional recovery after TBI requires physiological activation of NMDARs [262].

3.7. Epilepsy

Epilepsy is a very common neuropsychiatric disorder that causes abnormal brain activity, seizures, unusual behavior sensations, and sometimes, loss of consciousness. Glutamate-mediated excitability changes could be involved in the pathogenesis of epileptic discharge [263]. NMDAR may be involved in the seizure-induced excitotoxic cell death of hippocampal neuronal populations, as NMDAR antagonists provide protection against such damage [264]. Many animal models of epilepsy have been developed, including chemical induction models (such as kainic acid, pilocarpine, picrotoxin, or bicuculline), physical models (such as hyperthermia, or photic or auditory stimuli), genetic models (such as mutations, transgenes, or knockouts), electrical stimulation models, and spontaneous seizure models (such as post-kindling). Due to the differences in animal models, brain regions, and NMDAR subunits examined, the results of these studies vary. A study found that seizure enhances expression of GluN1 mRNA and protein in rat cerebral cortex [265]. Another study indicated that the mRNA of GluN1 is continuously increased in cortex of amygdaloid kindled rat [266]. However, application of picrotoxin (500 μM) caused a decrease in mRNA levels of GluN2A and GluN2B, while the mRNA level of GluN1 remained unchanged [267]. Besides, a study demonstrated that mRNA and protein levels of GluN2A and GluN2B were increased in spontaneous seizure, but not in kindled seizure [268]. Kainic acid-induced seizure reduces the mRNA level of GluN1 in CA1 and CA3 pyramidal cells, but not dentate gyrus [269].

NMDAR antagonists are proven to be anticonvulsant in several animal models of epilepsy. Felbamate (Felbatol®) is used in patients with intractable partial seizures, infantile spasms, or Lennox-Gastaut syndrome [270, 271]. Some studies reported that felbamate inhibits the NMDAR by binding to the glycine site [272-274], while others showed that felbamate binds with the site of channel pore [274]. Therefore, the binding site remains unsolved. Ifenprodil, a GluN2B-selective antagonist, has been reported to have effects on many animal models of seizure [275-277], except for seizure induced by imipenem or pefloxacin in DBA/2 mice [278]. Memantine, a blocker of NMDARs, exerts anticonvulsant effects in seizures [279-281] by blocking the NMDAR ion channel pore. However, many clinical trials have failed due to the side effects. In experimental models of epilepsy, the combination of conventional antiepileptic drugs with
low-dose NMDAR antagonists has shown significant efficacy but minimal side effects\textsuperscript{282}, although the potential advantage also requires further validation.

3.8. Neuropathic pain
Neuropathic pain is a type of chronic pain induced by the damage of neurons or nerves in the nervous system. During injury and inflammation, glutamate is released to activate NMDARs in the peripheral terminals of primary sensory afferents, leading to pain-related behaviors\textsuperscript{283}. During sensitization of the pain, GluN2B expression is increased in the nociceptive neurons in the dorsal horn of the spinal cord, a process that NMDARs activity appears to be involved\textsuperscript{283,284}. In animal models of peripheral nerve injury, NMDA-activated whole-cell current and calcium influx in spinal lamina II neurons appear to be increased in nerve-ligated rats\textsuperscript{285}. The phosphorylation of GluN1 subunit in the dorsal horn is increased in partial ligation of the sciatic nerve\textsuperscript{286}. However, the total protein levels of GluN1 and GluN2A-D subunits were unchanged in the spinal cord after nerve injury\textsuperscript{286,287}. Therefore, increased NMDAR phosphorylation may increase surface NMDAR function and is critical for central sensitization induced by nerve injury.

Blocking NMDARs could reduce the hypersensitivity of spinal dorsal horn neurons in neuropathic pain models. Memantine, ketamine, and MK-801, which are the NMDAR antagonists, attenuate evoked responses of dorsal horn neuron in spinal nerve-ligated rats\textsuperscript{288}. Besides, a study showed that ifenprodil, a GluN2B subunit-specific antagonist, reduces the amplitude of NMDAR currents in nerve-ligated mice\textsuperscript{289}. In clinic, intravenous infusion of ketamine can relieve pain in patients with refractory complex regional pain syndrome, but does not prevent chronic neuropathic pain caused by thoracotomy\textsuperscript{290,291}. Intravenous infusion of amantadine, another NMDAR antagonist, reduces persistent neuropathic pain in cancer patients after surgery, but often causes intolerable side effects\textsuperscript{293,294}. Therefore, there could be additional mechanisms underlying the enhanced NMDAR activity after nerve injury. Further studies along this direction may facilitate the development of neuropathic pain therapies.

3.9. Post-traumatic stress disorder (PTSD)
PTSD is a complex and chronic neuropsychiatric disorder characterized by recurrent appearance of unpleasant or even painful memories resulted from traumatic events, especially for the military members and also people who have recently been infected with COVID-19\textsuperscript{295-297}. The symptoms severely impair physical and mental health and lower the quality of life\textsuperscript{298}.

It has been suggested that over-response of fear function in the amygdala and a combination of weakened inhibitory effects of the projection from prefrontal cortex to amygdala may lead to PTSD\textsuperscript{299}. The functional brain circuits require the proper synaptic connectivity which can attribute to glutamate with its role in maintenance the neuronal activity\textsuperscript{300}. Ketamine plays a crucial role in repairing the synaptic network and also shows positive effects on the PTSD\textsuperscript{301,302}. The benefits of ketamine in PTSD may result from its anti-depressant and anti-inflammatory effects that improve the brain-derived neurotrophic factor levels and further re-establish the neuronal connectivity\textsuperscript{303}. High activity of NMDAR could impair formation of spontaneous intrusive memories that may contribute to the development of PTSD\textsuperscript{302}. A study on rat models of PTSD-induced by contextual fear showed that the level of brain-derived neurotrophic factor was strongly reduced, which could be reversed by ketamine treatment, and NMDAR inhibition interrupted the consolidation of fear conditioning related to hippocampus and hypothalamus-pituitary-adrenal axis\textsuperscript{303-305}. Taken altogether, the hyperactivity of NMDAR is tightly linked to PTSD and may lead to synaptic abnormalities and decreased expression of brain-derived neurotrophic factor especially under traumatic event. Ketamine is currently an effective pharmaceutical intervention for PTSD. In the future, the studies should focus on optimization of ketamine with appropriate therapeutic dose and duration, and on reducing the side effects.

3.10. NMDARs mutations in diseases
Mutations in NMDARs are related with neuropsychiatric diseases. Nowadays, the pathogenesis of and therapy development for brain diseases can be explored using genomics approaches following the emergence of whole-exome/genome sequencing and targeted therapy. Human genetics studies indicated that more than 500 variants of NMDARs subunit mutations have been found in patients with brain disorders, such as intellectual disability, hyperactivity disorder, ASD, schizophrenia, or epilepsy. These mutations are more prevalent in the GluN2A and GluN2B subunits of the amino terminal domain (ATD), ABD, TMD, and CTD regions. Discovering and analyzing the function of these mutations can help determine the role they play in these neuropsychiatric disorders. In addition, functional analysis of these mutations can advance the understanding in the etiology of the disease and facilitate the formulation of treatment plans in clinic.

3.10.1. The GluN1 mutations
GluN1 subunit is encode by GRIN1, which is located in human chromosome 9q34. Many mutations in GluN1 have
been found to be related to many diseases, including the ID, autism spectrum, and epilepsy; the function of some of the mutations has been studied, while others remain unclear. The function of mutations, including D227H, R306E, A349S, S549R, P557R, M641I, and N650K, has not been studied by biological techniques\(^\text{[106, 107]}\). The mutations of D552E, Q556*, S560dup, P557R, G620R, Y647S, G815R, F817L, and G827R are loss-of-functions. The S560 is located in pre-TM1 region, and the mutation of S560dup decreases the activity of NMDARs and changes the structure of the pore region\(^\text{[108]}\). The G815R and F817L mutations are adjacent to each other, thus their functions are similar, that is, they decreased sensitivity to glutamate and glycine\(^\text{[109]}\). However, the E662K, A645S, and R844C mutations did not change the function of NMDARs\(^\text{[109-112]}\). On the contrary, the mutations of Y647C, R659W, and R794Q enhanced the function of NMDARs\(^\text{[106]}\). The R659W and R794Q enhance the potency of glutamate and glycine, while the mutation of Y647C increases potency of glycine, but not glutamate.

### 3.10.2. The GluN2A mutations

GluN2A subunit is encoded by \textit{GRIN2A} in the human chromosome 16p13. More than 240 mutations have been found in \textit{GRIN2A}. Many patients had normal delivery at birth, with good appearance, facial expression, and vital signs scores. However, the patients at the 1 year after birth may begin to exhibit neurological abnormalities, such as abnormal electroencephalogram and myoclonic convulsions\(^\text{[113]}\), and then progress to epilepsy, which is possibly due to a gradual increase in GluN2A expression during development\(^\text{[117]}\). Some studies indicated that the patients carrying GluN2A mutations were more likely to show epilepsy, such as benign focal epilepsy with centrotemporal spikes and Landau-Kleffner syndrome\(^\text{[114-116]}\). Moreover, the mutations of GluN2A can produce different effects: gain-of-function and loss-of-function.

Some mutations are gain-of-function. The GluN2A_N447K is found in a male patient with Rolandic epilepsy and is located in the S1 domain of ABD. The GluN2A_N447K enhanced the current density of NMDAR by electrophysiological recording. The potency of glutamate was increased, while the inhibition of Mg\(^{2+}\) was decreased by GluN2A_N447K. Lamotrigine and valproate treatment could rescue the epilepsy in patient\(^\text{[117]}\). The patient is a child with impaired cognitive and epileptic encephalopathy. Another mutation, GluN2A_L812M, is located in the linker between S2 of ABD and M4 of TMD. Studies have shown that the GluN2A_L812M and M817V enhanced the open probability and potency with glutamate and glycine of NMDAR, and decreased the inhibition of Mg\(^{2+}\)\(^\text{[118, 119]}\). The patient with GluN2A_L812M was treated by memantine, which attenuated epilepsy\(^\text{[113]}\). The other mutation GluN2A_N615K is in the channel pore of M2 TMD domain. The patient was a 3-year-old female with abnormal electroencephalogram, developmental delay, and early-onset epileptic encephalopathy\(^\text{[120]}\). The GluN2A_N615K mutation changed the channel characteristics, including the decreased Ca\(^{2+}\) permeability and Mg\(^{2+}\) sensitivity\(^\text{[131-132]}\). The reduction of Mg\(^{2+}\) sensitivity to NMDARs increased the NMDAR current.

Meanwhile, the mutations of GluN2A are loss-of-function. The GluN2A_D731N was found in a child with developmental delay and epilepsy. The missense mutation is in the ABD of GluN2A. The results indicated that the mutation decreased the NMDAR current, glutamate sensitivity, and enhanced the potency of NAM\(^\text{[124]}\). The GluN2A_V685G is located in the S2 of ABD region and caused the developmental delay and epilepsy. The mutation caused a low glutamate potency with NMDAR and decreased NMDAR current with reduced surface expression\(^\text{[133]}\).

Besides, the mutations also lead to impairment in trafficking. The GluN2A_S1459G, which is located in the CTD-related to the protein trafficking of GluN2A, was found in the epilepsy patients\(^\text{[134]}\). The GluN2A_S1459G induced the impaired binding with SNX27 and PSD95, which led to deficits in NMDAR trafficking and spine density, and synaptic transmission in excitatory neurons\(^\text{[126]}\).

From the studies, we understand that the mutations may exist in any domains of GluN2A to cause the disorders. Since each mutation is specific, we need to better understand the pathogenesis and changes in function of the mutation so as to increase the efficacy of targeted therapy in the patients.

### 3.10.3. The GluN2B mutations

\textit{GRIN2B} gene encodes the GluN2B subunit and is in the human chromosome 12p13. Over 200 mutations have been found in \textit{GRIN2B} in the patients not only with epilepsy, epileptic encephalopathy\(^\text{[125, 127]}\), intellectual disability\(^\text{[120, 125, 127, 129]}\), and ASD\(^\text{[120, 125, 127]}\), but also with the AD\(^\text{[129]}\) and schizophrenia\(^\text{[130-133]}\). The mutations exist in all regions of GluN2B. Some of the mutations have been functionally analyzed.

Many GluN2B mutations are loss-of-function in patient with intellectual disability or ASD. The GluN2B_E413G is located in the ATD domain, which is adjacent to the glutamate-binding site. The E413G reduced the potency of glutamate and deactivation, resulting in the loss-of-function of NMDAR\(^\text{[134]}\). Another study reported the function of GluN2B_C456Y mutation. They constructed the heterozygous GluN2B_C456Y mutation mice and
found that the protein levels of GluN2B was decreased. Besides, the NMDAR current was reduced and the LTD was impaired, while the LTP was normal. The behavior data showed that the mice represented the anxious behavior with normal social interaction. In rescue experiments, the D-cycloserine had an effect on the NMDAR currents and LTP and recued the impaired behavior in adult mice. The mutation GluN2B_C461F is located in the S1 domain of ABD in patient with Lennox-Gastaut syndrome and autism. Functional analysis described the C461F mutation decreased the glutamate potency. In the same study, the P553L was found in the patient with intellectual disability. The mutation, which is located in the pre-MI domain, decreased the glutamate potency and NMDAR current in the neurons. Another study found the mutation, which, however, mutated to the threonine (P553T), at the same site. The mutation was found in a 5-year-old patient with Rett-like syndrome. The P553T reduced the potency of glutamate, NMDAR currents and spine density in the neurons. Furthermore, the D-serine could restore the deficits induced by GluN2B_P553T.

The mutations of N615I and V618G are gain-of-function and found in the patients with West syndrome and intellectual disability. The two mutations reduced the inhibition of Mg\(^2+\), although the glutamate potency was unchanged. Furthermore, the mutation of R540H increased the sensitivity to glutamate and Ca\(^{2+}\) permeability. The gain-of-function mutations may lead to neuronal hyperexcitability, resulting in the disorders. Therefore, we can treat the diseases by inhibiting NMDAR function in gain-of-function mutations.

### 3.11. The challenge and opportunity in treatment of diseases

In biological experiments, the addition of glycine, D-serine, and D-cycloserine can enhance the function of NMDAR, which can provide a new drug choice for clinical use as NMDAR potentiators. Besides, in some studies, patients carrying GluN2A and GluN2B mutations were treated with drugs, such as memantine and the blocker of NMDAR. Likewise, the other drugs, such as ketamine, magnesium, and TCN-201, have effects on the inhibition of NMDAR current in vitro. Since different patients respond differently to the drug, personalized treatment is needed for patients with NMDAR mutations.

However, due to the wide distribution and function of NMDARs, drugs targeting NMDARs may cause severe adverse effects limiting their clinical potential. The competitive NMDAR antagonists, which prevent glutamate-mediated neurotoxicity by inhibiting NMDAR function, could cause extensive inhibition of NMDAR function. Inhibition of NMDAR with non-competitive antagonists is the most attractive therapeutic intervention, because the effect of antagonists requires pre-activation of the NMDA receptor. However, NMDAR hypofunction has an influence on the brain function. Even low doses of NMDAR antagonists can cause decreased excitability of NMDAR, leading to memory dysfunction and learning disabilities. Besides, enhancing the function of NMDARs may cause NMDAR hyperexcitability due to the inability to distinguish between extrasynaptic and synaptic NMDARs. Comprehensive weighing of the benefits versus adverse effects need be carried out during the clinical development of drugs targeting NMDARs.

### 4. Summary

NMDAR plays an important role in many processes, including learning and memory, development, and neuroplasticity. Many functions of NMDAR depend primarily on the GluN2 subunit. GluN2 subunits are mainly expressed in the cortex and hippocampus, and they differ in expression patterns, protein trafficking, channel dynamics, synaptic plasticity, and neuropsychiatric disorders. This difference also determines the different functions of NMDAR. In addition, the composition of the NMDAR subunit is also regulated by neural activity, which, further, indicates that the composition of NMDARs is consistent with neural function. However, it is still difficult to distinguish the functions and effects of individual subunits, which also leads to the difficulty in clinical treatment of neuropsychiatric disorders. Therefore, in addition to using new drugs and genetic approaches to specifically target different subunits and related signaling pathways in the treatment of neuropsychiatric disorders, it would be also interesting to identify the auxiliary subunits of NMDAR, which is involved in the regulation of the ions accessibility, and how this interaction affects the downstream signaling pathways may contribute to the understanding of the cellular mechanism in different brain diseases. The double-sided function of NMDAR poses great challenges for clinical application, so we still need to make continuous efforts in the treatment of neuropsychiatric disorders targeting NMDARs.

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References
1. Traynelis SF, Wollmuth LP, McBain CJ, et al., 2010, Glutamate receptor ion channels: Structure, regulation, and function. Pharmacol Rev, 62(3): 405–496. https://doi.org/10.1124/pr.109.002451
2. Alzheimer's Association, 2022, 2022 Alzheimer's disease facts and figures. Alzheimers Dement, 18(4): 700–789. https://doi.org/10.1002/alz.12638
3. Avila J, Perry GA, 2021, Multilevel view of the development of Alzheimer's disease. Neuroscience, 457: 283–293. https://doi.org/10.1016/j.neuroscience.2020.11.015
4. Christensen DL, Baio J, Braun KV, et al., 2018, Prevalence and characteristics of autism spectrum disorder among children aged 8 year autism and developmental disabilities monitoring network, 11 sites, United States, 2012. Morb Mort Wkly Rep, 65: 1–23. https://doi.org/10.15585/mmwr.ss6513a1
5. Lord C, Brugha TS, Charman T, et al., 2020, Autism spectrum disorder. Nat Rev Dis Primers, 6(1): 5. https://doi.org/10.1038/s41572-019-0138-4
6. Anderson RM, Hadjichrysanthou C, Evans S, et al., 2017, Why do so many clinical trials of therapies for Alzheimer's disease fail? Lancet, 390: 2327–2329. https://doi.org/10.1016/S0140-6736(17)33299-1
7. Mitsumoto H, Brooks BR, Silani V, 2014, Clinical trials in amyotrophic lateral sclerosis: Why so many negative trials and how can trials be improved? Lancet Neurol, 13: 1127–1138. https://doi.org/10.1016/S1474-4422(14)70129-2
8. Henriquez F, Cabello V, Baez S, et al., 2021, Multidimensional clinical assessment in frontotemporal dementia and its spectrum in Latin America and the Caribbean: A narrative review and a glance at future challenges. Front Neurol, 12: 768591. https://doi.org/10.3389/fneur.2021.768591
9. Panza, F, Solfrizzi V, Seripa D, et al., 2015, Progresses in treating agitation: A major clinical challenge in Alzheimer’s disease. Expert Opin Pharmacother, 16: 2581–2588. https://doi.org/10.1517/14656566.2015.1092520
10. Song J, Patel RV, Sharif M, et al., 2022, Chemogenetics as a neuromodulatory approach to treating neuropsychiatric diseases and disorders. Mole Ther, 30: 990–1005. https://doi.org/10.1016/j.ycthe.2021.11.019
11. Thompson PM, Andreassen OA, Arias-Vasquez A, et al., 2017, ENIGMA and the individual: Predicting factors that affect the brain in 35 countries worldwide. NeuroImage, 145(Pt B): 389–408. https://doi.org/10.1016/j.neuroimage.2015.11.057
12. Schang AL, Saberan-Djoneidi D, Mezger V, 2018, The impact of epigenomic next-generation sequencing approaches on our understanding of neuropsychiatric disorders. Clin Genet, 93(3): 467–480. https://doi.org/10.1111/cge.13097
13. Dorado G, Galvez S, Rosales TE, et al., 2021, Analyzing modern biomolecules: The revolution of nucleic-acid sequencing review. Biomolecules, 11(8): 1111. https://doi.org/10.3390/biom11081111
14. Dehghan A, 2018, Genome-wide association studies. Methods Mol Biol, 1793: 37–49. https://doi.org/10.1007/978-1-4939-7868-7_4
15. Qin Y, Du Y, Chen L, et al., 2022, A recurrent SHANK1 mutation implicated in autism spectrum disorder causes autistic-like core behaviors in mice via downregulation of mGluR1-IP3R1-calcium signaling. Mole Psychiatry, 27(7): 2985–2998. https://doi.org/10.1038/s41380-022-01539-1
16. Peng SX, Pei J, Ge Y, et al., 2022, Dysfunction of AMPA receptor GluA3 is associated with aggressive behavior in human. Mol Psychiatry, Online ahead of print. https://doi.org/10.1038/s41380-022-01659-8
17. Li QQ, Chen J, Hu P, et al., 2022, Enhancing GluN2A-type NMDA receptors impairs long-term synaptic plasticity and learning and memory. Mol Psychiatry, Online ahead of print. https://doi.org/10.1038/s41380-022-01579-7
18. Teng XY, Hu P, Chen Y, et al., 2022, A novel Lgi1 mutation causes white matter abnormalities and impairs motor coordination in mice. FASER J, 36: e22212. https://doi.org/10.1096/fj.202101652R
19. Hall J, Bray NJ, 2022, Schizophrenia genomics: Convergence facts and on our understanding of neuropsychiatric disorders. Clin Genet, 65: 1–23. https://doi.org/10.1016/j.cgen.2021.10.018
20. Ding YD, Chen X, Guo WB, et al., 2022, Reduced nucleus accumbens functional connectivity in reward network and default mode network in patients with recurrent major depressive disorder. *Transl Psychiatry*, 12: 236. https://doi.org/10.1038/s41398-022-01995-x

21. Paoletti P, 2011, Molecular basis of NMDA receptor functional diversity. *Eur J Neurosci*, 33: 1351–1365. https://doi.org/10.1111/j.1460-9568.2011.07628.x

22. Cull-Candy SG, Leszkiewicz DN, 2004, Role of distinct NMDA receptor subtypes at central synapses. *Sci STKE*, 2004(255): re16. https://doi.org/10.1126/stke.2552004re16

23. Rumbaugh G, Prybylowski K, Wang JF, et al., 2000, Exon 5 and spermine regulate deactivation of NMDA receptor subtypes. *J Neurophysiol*, 83: 1300–1306. https://doi.org/10.1152/jn.2000.83.3.1300

24. Vance KM, Hansen KB, Traynelis SF, 2012, GluN1 splice variant control of GluN1/GluN2D NMDA receptors. *J Physiol*, 590(16): 3857–3875. https://doi.org/10.1113/jphysiol.2012.234062

25. Horak M, Wenthold RJ, 2009, Different roles of C-terminal casettes in the trafficking of full-length NR1 subunits to the cell surface. *J Biol Chem*, 284(15): 9683–9691. https://doi.org/10.1074/jbc.M807050200

26. Paoletti P, Bellone C, Zhou Q, 2013, NMDA receptor subunit diversity: Impact on receptor properties, synaptic plasticity and disease. *Nat Rev Neurosci*, 14: 383–400. https://doi.org/10.1038/nrn3504

27. Mayer ML, 2011, Emerging models of glutamate receptor ion channel structure and function. *Structure*, 19(10): 1370–1380. https://doi.org/10.1016/j.str.2011.08.009

28. Won S, Incontro S, Nicoll RA, et al., 2016, PSD-95 stabilizes NMDA receptors by inducing the degradation of STEP61. *Proc Natl Acad Sci U S A*, 113: E4736–E4744. https://doi.org/10.1073/pnas.1609702113

29. Incontro S, Díaz-Alonso J, Iafrati J, et al., 2019, The CaMKII/NMDA receptor complex controls hippocampal synaptic transmission by kinase-dependent and independent mechanisms. *Nat Commun*, 9(1): 2069. https://doi.org/10.1038/s41467-018-04439-7

30. Karakas E, Furukawa H, 2014, Crystal structure of a heterotetrameric NMDA receptor ion channel. *Science*, 344: 992–997. https://doi.org/10.1126/science.1251915

31. Lee CH, Lü W, Michel JC, et al., 2014, NMDA receptor structures reveal subunit arrangement and pore architecture. *Nature*, 511(7508): 191–197. https://doi.org/10.1038/nature13548

32. Meyerson JR, Kumar J, Chittorsi S, et al., 2014, Structural mechanism of glutamate receptor activation and desensitization. *Nature*, 514(7522): 328–334. https://doi.org/10.1038/nature13603

33. Sobolevsky AI, 2015, Structure and gating of tetrameric glutamate receptors. *J Physiol*, 593(1): 29–38. https://doi.org/10.1113/jphysiol.2013.264911

34. Tajima N, Karakas E, Grant T, et al., 2016, Activation of NMDA receptors and the mechanism of inhibition by ifenprodil. *Nature*, 534(7605): 63–68. https://doi.org/10.1038/nature17679

35. Zhu S, Stein RA, Yoshioka C, et al., 2016, Mechanism of NMDA receptor inhibition and activation. *Cell*, 165(3): 704–714. https://doi.org/10.1016/j.cell.2016.03.028

36. Romero-Hernandez A, Simorowski N, Karakas E, et al., 2016, Molecular basis for subtype specificity and high-affinity zinc inhibition in the GluN1-GluN2A NMDA receptor amino-terminal domain. *Neuron*, 92(6): 1324–1336. https://doi.org/10.1016/j.neuron.2016.11.006

37. Furukawa H, Singh SK, Mancuso R, et al., 2005, Subunit arrangement and function in NMDA receptors. *Nature*, 438(7065): 185–192. https://doi.org/10.1038/nature04089

38. Hackos DH, Lupardus PJ, Grand T, et al., 2016, Positive allosteric modulators of GluN2A-containing NMDARs with distinct modes of action and impacts on circuit function. *Neuron*, 89(5): 983–999. https://doi.org/10.1016/j.neuron.2016.01.016

39. Volgraf M, Sellers BD, Jiang Y, et al., 2016, Discovery of GluN2A-selective NMDA receptor positive allosteric modulators (PAMs): Tuning deactivation kinetics via structure-based design. *J Med Chem*, 59(6): 2760–2779. https://doi.org/10.1021/acs.jmedchem.5b02010

40. Yi F, Mou TC, Dorsett KN, et al., 2016, Structural basis for negative allosteric modulation of GluN2A-Containing NMDA receptors. *Neuron*, 91(6): 1316–1329. https://doi.org/10.1016/j.neuron.2016.08.014

41. Jones KS, Van Dongen HM, Van Dongen AM, 2002, The NMDA receptor M3 segment is a conserved transduction structural and functional control of N-methyl-D-aspartate receptor gating by transmembrane domain M3. *J Biol Chem*, 277(15): 13163–13169. https://doi.org/10.1016/S0021-9258(02)00747-8
Advanced Neurology

NMDA receptors in neuropsychiatric diseases

280(33): 29708–29716.
https://doi.org/10.1074/jbc.M414215200

43. Chang HB, Kuo CC, 2008, The activation gate and gating mechanism of the NMDA receptor. J Neurosci, 28(7): 1546–1556.
https://doi.org/10.1523/JNEUROSCI.3485-07.2008

44. Twomey EC, Sobolevsky AL, 2018, Structural mechanisms of gating in ionotropic glutamate receptors. Biochemistry, 57(3): 267–276.
https://doi.org/10.1021/acs.biochem.7b00891

45. Watanabe M, Inoue Y, Sakimura K, et al., 1992, Developmental changes in distribution of NMDA receptor subunit mRNA. Neuroreport, 3(12): 1138–1140.
https://doi.org/10.1097/00001756-199212000-00027

46. Akazawa C, Shigemoto R, Bessho Y, et al., 1994, Differential expression of five N-methyl-D-aspartate receptor subunit mRNAs in the cerebellum of developing and adult rats. J Comp Neurol, 347(1): 150–160.
https://doi.org/10.1002/cne.903470112

47. Monyer H, Burnashev N, Laurie DJ, et al., 1994, Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. Neuron, 12(3): 529–540.
https://doi.org/10.1016/0896-6273(94)90210-0

48. Laurie DJ, Seeburg PH, 1994, Regional and developmental heterogeneity in splicing of the rat brain NMDAR1 mRNA. J Neurosci, 14(5): 3180–3194.
https://doi.org/10.1523/JNEUROSCI.14-05-03180.1994

49. Ishii T, Moriyoshi K, Sugihara H, et al., 1993, Molecular characterization of the family of the N-methyl-D-aspartate receptor subunits. J Biol Chem, 268(4): 2836–2843.

50. Sheng M, Cummins J, Roldan LA, et al., 1994, Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. Nature, 368(6467): 144–147.
https://doi.org/10.1038/368144a0

51. Henson MA, Roberts AC, Perez-Otano I, et al., 2010, Influence of the NR3A subunit on NMDA receptor functions. Prog Neurobiol, 91: 23–37.
https://doi.org/10.1016/j.pneurobio.2010.01.004

52. Pachernegg S, Strutz-Seebohm N, Hofmann M, 2012, GluN3 subunit-containing NMDA receptors: Not just one-trick ponies. Trends Neurosci, 35(4): 240–249.
https://doi.org/10.1016/j.tins.2011.11.010

53. Johnson JW, Ascher P, 1987, Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature, 325(6104): 529–531.
https://doi.org/10.1038/325529a0

54. Watkins JC, Evans RH, 1981, Excitatory amino acid transmitters. Annu Rev Pharmacol Toxicol, 21: 165–204.
https://doi.org/10.1146/annurev.pa.21.040181.001121

55. Sheng M, Cummings J, Roldan LA, et al., 2002, Regional and developmental heterogeneity in splicing of the rat brain NMDAR1 mRNA. Neuron, 36(7): 529–540.
https://doi.org/10.1016/s0896-6273(02)00373-8

56. Erreger K, Geballe MT, Kristensen A, et al., 2007, Subunit-specific agonist activity at NR2A, NR2B, NR2C, and NR2D-containing N-methyl-D-aspartate glutamate receptors. J Biol Chem, 282(48): 34261–34272.
https://doi.org/10.1016/j.jbc.2007.06.029

57. Madry C, Betz H, Geiger JR, et al., 2010, Potentiation of glycine-gated NMDA receptors relieves ca-dependent outward rectification. Front Mol Neurosci, 3: 6.
https://doi.org/10.3389/fnmol.2010.00006

58. Ulbrich MH, Isacoff EY, 2007, Subunit counting in membrane-bound proteins. Nat Methods, 4(4): 319–321.
https://doi.org/10.1038/nmeth0124

59. Ulbrich MH, Isacoff EY, 2008, Rules of engagement for NMDA receptor subunits. Proc Natl Acad Sci U S A, 105(37): 14163–14168.
66. Awobuluuy M, Yang J, Ye Y, et al., 2007, Subunit-specific roles of glycine-binding domains in activation of NR1/NR3 N-methyl-D-aspartate receptors. Mol Pharmacol, 71(1): 112–122. https://doi.org/10.1124/mol.106.030700

67. Madry C, Mesci I, Nicke A, et al., 2007, Principal role of NR3 subunits in NR1/NR3 excitatory glycine receptor function. Biochem Biophys Res Commun, 354(1): 102–108. https://doi.org/10.1016/j.bbrc.2006.12.153

68. Retchless S, Gao B, Johnson J W, 2012, A single GluN2 subunit residue controls NMDA receptor channel properties via intersubunit interaction. Nat Neurosci, 15: 406–413, S401–S402. https://doi.org/10.1038/nn.3025

69. Chen N, Luo T, Raymond LA, 1999, Subtype-dependence of NMDA receptor channel open probability. J Neurosci, 19(16): 6844–6854. https://doi.org/10.1523/JNEUROSCI.1221-05.2005

70. Errege K, Dravid SM, Banke TG, et al., 2005, PDZ and synaptic removal of NR3A-containing NMDA receptors. J Physiol, 563(Pt 2): 345–358. https://doi.org/10.1113/jphysiol.2004.080028

71. Sobczyk A, Scheuss V, Svoboda K, 2005, NMDA receptor subunit-dependent [Ca2+]i signaling in individual hippocampal dendritic spines. J Neurosci, 25(26): 6037–6046. https://doi.org/10.1523/JNEUROSCI.1221-05.2005

72. Sprengel R, Suchanek B, Amico C, et al., 1998, Importance of the intracellular domain of NR2 subunits for NMDA receptor function in vivo. Cell, 92(2): 279–289. https://doi.org/10.1002/s0892-8674(00)80921-6

73. Martel MA, Ryan TJ, Bell KE, et al., 2012, The subtype of GluN2 C-terminal domain determines the response to excitotoxic insults. Neuron, 74(3): 543–556. https://doi.org/10.1016/j.neuron.2012.03.021

74. Sanz-Clemente A, Nicoll RA, Roche KW, 2013, Diversity in NMDA receptor composition: Many regulators, many consequences. Neuroscientist, 19(1): 62–79. https://doi.org/10.1177/1073858411435121

75. Mu Y, Otsuka T, Horton AC, et al., 2003, Activity-dependent mRNA splicing controls ER export and synaptic delivery of NMDA receptors. Neuron, 40(3): 581–594. https://doi.org/10.1016/s0896-6273(03)00676-7

76. Perez-Otano I, Luján R, Tavalin SJ, et al., 2006, Endocytosis and synaptic removal of NR3A-containing NMDA receptors by PACSIN1/syndapin1. Nat Neurosci, 9(5): 611–621. https://doi.org/10.1038/nn1680

77. Horak M, Petralia RS, Kaniakova M, et al., 2014, ER to synapse trafficking of NMDA receptors. Front Cell Neurosci, 8: 394. https://doi.org/10.3389/fncel.2014.00394

78. McIlhinney RA, Le Bourdellès B, Molnár E, et al., 1998, Assembly intracellular targeting and cell surface expression of the human N-methyl-D-aspartate receptor subunits NR1a and NR2A in transfected cells. Neuropharmacology, 37(10–11): 1355–1367. https://doi.org/10.1016/s0028-3908(98)00121-x

79. Fukaya M, Kato A, Lovett C, et al., 2003, Retention of NMDA receptor NR2 subunits in the lumen of endoplasmic reticulum in targeted NR1 knockout mice. Proc Natl Acad Sci U S A, 100(8): 4855–4860. https://doi.org/10.1073/pnas.0830996100

80. Horak M, Chang K, Wenthold RJ, 2008, Masking of the endoplasmic reticulum retention signals during assembly of the NMDA receptor. J Neurosci, 28(13): 3500–3509. https://doi.org/10.1523/JNEUROSCI.5239-07.2008

81. Standley S, Roche KW, McCallum J, et al., 2000, PDZ domain suppression of an ER retention signal in NMDA receptor NR1 splice variants. Neuron, 28(3): 887–898. https://doi.org/10.1016/s0896-6273(00)00161-6

82. Scott DB, Blanpied TA, Swanson GT, et al., 2001, An NMDA receptor ER retention signal regulated by phosphorylation and alternative splicing. J Neurosci, 21(3): 3063–3072. https://doi.org/10.1523/JNEUROSCI.21-09-03063.2001

83. Prybylowski K, Fu Z, Losi G, et al., 2002, Relationship between availability of NMDA receptor subunits and their expression at the synapse. J Neurosci, 22(20): 8902–8910. https://doi.org/10.1523/JNEUROSCI.22-20-08902.2002

84. Hawkins LM, Prybylowski K, Chang K, et al., 2004, Export from the endoplasmic reticulum of assembled N-methyl-D-aspartic acid receptors is controlled by a motif in the c terminus of the NR2 subunit. J Biol Chem, 279(28): 28903–28910. https://doi.org/10.1074/jbc.M402599200

85. Yang W, Zheng C, Song Q, et al., 2007, A three amino acid tail following the TM4 region of the N-methyl-D-aspartate receptor (NR) 2 subunits is sufficient to overcome endoplasmic reticulum retention of NR1-a subunit. J Biol Chem, 282(1): 9269–9278. https://doi.org/10.1074/jbc.M70050200

86. Sans N, Prybylowski K, Petralia RS, et al., 2003, NMDA receptor trafficking through an interaction between PDZ proteins and the exocyst complex. Nat Cell Biol, 5(6): 520–530. https://doi.org/10.1038/ncb990
NMDA receptors in neuropsychiatric diseases

87. Sans N, Wang PY, Du Q, et al., 2005, mPins modulates PSD-95 and SAP102 trafficking and influences NMDA receptor surface expression. Nat Cell Biol, 7(12): 1179–1190. https://doi.org/10.1038/ncb1325

88. Sans N, Petralia RS, Wang YX, et al., 2000, A developmental change in NMDA receptor-associated proteins at hippocampal synapses. J Neurosci, 20(3): 1260–1271. https://doi.org/10.1523/JNEUROSCI.20-03-01260.2000

89. Muller BM, Kistner U, Kindler S, et. al., 2001, Activation of LTP requires driving AMPA receptors. J Neurosci, 21(16): 6058–6068. https://doi.org/10.1523/JNEUROSCI.21-16-06058.2001

90. Jeyifous O, Waites CL, Specht CG, et al., 2009, SAP97 and CASK mediate sorting of NMDA receptors through a previously unknown secretory pathway. Nat Neurosci, 12(8): 1011-1019. https://doi.org/10.1038/nn.2362

91. Setou M, Nakagawa T, Seog DH, et al., 2007, Dual role of KIF17 in NMDA receptor-containing vesicle transport. Science, 318: 1796–1802. https://doi.org/10.1126/science.1161748

92. Guillaud L, Setou M, Hirokawa N, 2003, KIF17 dynamics and regulation of NR2B trafficking in hippocampal neurons. J Neurosci, 23(1): 131–140. https://doi.org/10.1523/JNEUROSCI.23-01-00131.2003

93. Yin X, Takei Y, Kido MA, et al., 2011, Molecular motor KIF17 is fundamental for memory and learning via differential support of synaptic NR2A/2B levels. Neuron, 70(2): 310–325. https://doi.org/10.1016/j.neuron.2011.02.049

94. Gardoni F, Mauceri D, Fiorentini C, et al., 2003, CaMKII-dependent phosphorylation regulates SAP97/NR2A interaction. J Biol Chem, 278(45): 44745–44752. https://doi.org/10.1074/jbc.M303576200

95. Mauceri D, Gardoni F, Marcello E, et al., 2007, Dual role of CaMKII-dependent SAP97 phosphorylation in mediating trafficking and insertion of NMDA receptor subunit NR2A. J Neurochem, 100(4): 1032–1046. https://doi.org/10.1111/j.1471-4159.2006.04267.x

96. Wang YX, Takei Y, et al., 2012, Regulation of NMDA receptor transport: A KIF17-cargo binding/releasing underlies synaptic plasticity and memory in vivo. J Neurosci, 32: 5486–5499. https://doi.org/10.1523/JNEUROSCI.0718-12.2012

97. Thomas GM, Huganir RL, 2013, Palmitoylation-dependent regulation of glutamate receptors and their PDZ domain-containing partners. Biochem Soc Trans, 41: 72–78. https://doi.org/10.1042/BST20120223

98. Washbourne P, Liu XB, Jones EG, et al., 2004, Cycling of...
NMDA receptors in neuropsychiatric diseases

https://doi.org/10.1038/jneurosci.2555-04.2004

110. Suh YH, Terashima A, Petralia RS, et al., 2010, A neuronal role for SNAP-23 in postsynaptic glutamate receptor trafficking. Nat Neurosci, 13(3): 338–343.
https://doi.org/10.1038/nn.2488

111. Tovar KR, Westbrook GL, 2002, Mobile NMDA receptors at hippocampal synapses. Neuron, 34(2): 255–264.
https://doi.org/10.1016/s0896-6273(02)00658-x

112. Groc L, Heine M, Cousins SL, et al., 2006, NMDA receptor surface mobility depends on NR2A-2B subunits. Proc Natl Acad Sci U S A, 103(49): 18769–18774.
https://doi.org/10.1073/pnas.0605238103

113. Dupuis JP, Ladépêche L, Seth H, et al., 2014, Surface dynamics of GluN2B-NMDA receptors controls plasticity of maturing glutamate synapses. EMBO J, 33(8): 842–861.
https://doi.org/10.1002/embj.201386356

114. Ferreira JS, Papouin T, Ladépêche L, et al., 2017, Co-agonists differentially tune GluN2B-NMDA receptor trafficking at hippocampal synapses. Elife 6: e25492.
https://doi.org/10.7554/eLife.25492

115. Sun YJ, Xu YG, Chen XK, et al., 2018, The differences between GluN2A and GluN2B signaling in the brain. J Neuro Res, 96: 1430–1443.
https://doi.org/10.1002/jnr.24251

116. Kellermayer B, Ferreira JS, Dupuis J, et al., 2018, Differential nanoscale topography and functional role of GluN2-NMDA receptor subtypes at glutamatergic synapses. Neuron, 100(1): 106–119. e107.
https://doi.org/10.1016/j.neuron.2018.09.012

117. Bard L, Sainlos M, Bouchet D, et al., 2010, Dynamic and specific interaction between synaptic NR2-NMDA receptor and PDZ proteins. Proc Natl Acad Sci U S A, 107(45): 19561–19566.
https://doi.org/10.1073/pnas.1002690107

118. Chung HJ, Huang YH, Lau LF, et al., 2004, Regulation of the NMDA receptor complex and trafficking by activity-dependent phosphorylation of the NR2B subunit PDZ ligand. J Neurosci, 24: 10248–10259.
https://doi.org/10.1523/JNEUROSCI.0546-04.2004

119. Chiu AM, Wang J, Fiske MP, et al., 2019, NMDAR-Activated PP1 Dephosphorylates GluN2B to Modulate NMDAR Synaptic Content. Cell Rep, 28(2): 332–341 e335.
https://doi.org/10.1016/j.celrep.2019.06.030

120. Les sept F, Chevillée A, Jezequel J, et al., 2016, Tissue-type plasminogen activator controls neuronal death by raising surface dynamics of extrasynaptic NMDA receptors. Cell Death Dis, 7(11): e2466.
https://doi.org/10.1038/cddis.2016.279

121. Michaluk P, Gloc L, Mikasova L, et al., 2009, Matrix metalloproteinase-9 controls NMDA receptor surface diffusion through integrin beta1 signaling. J Neurosci, 29(18): 6007–6012.
https://doi.org/10.1523/JNEUROSCI.5346-08.2009

122. Mikasova L, Xiong H, Kerckhofs A, et al., 2017, Stress hormone rapidly tunes synaptic NMDA receptor through membrane dynamics and mineralocorticoid signalling. Sci Rep, 7: 8053.
https://doi.org/10.1038/s41598-017-08695-3

123. Potier M, Georges F, Brayda-Bruno L, et al., 2016, Temporal memory and its enhancement by estradiol requires surface dynamics of hippocampal CA1 N-methyl-D-aspartate receptors. Biol Psychiatry, 79: 735–745.
https://doi.org/10.1016/j.biopsych.2015.07.017

124. Roche KW, Standley S, McCallum J, et al., 2001, Molecular determinants of NMDA receptor internalization. Nature Neurosci, 4: 794–802.
https://doi.org/10.1038/90498

125. Lavezzari G, McCallum J, Dewey CM, et al., 2004, Subunit-specific regulation of NMDA receptor endocytosis. J Neurosci, 24: 6383–6391.
https://doi.org/10.1523/JNEUROSCI.1890-04.2004

126. Blanpied TA, Scott DB, Ehlers MD, 2002, Dynamics and regulation of clathrin coats at specialized endocytic zones of dendrites and spines. Neuron, 36: 435–449.
https://doi.org/10.1016/s0896-6273(02)00979-0

127. Przybylowski K, Chang K, Sans N, et al., 2005, The synaptic localization of NR2B-containing NMDA receptors is controlled by interactions with PDZ proteins and AP-2. Neuron, 47: 845–857.
https://doi.org/10.1016/j.neuron.2005.08.016

128. Lavezzari G, McCallum J, Lee R, et al., 2003, Differential binding of the AP-2 adaptor complex and PSD-95 to the C-terminus of the NMDA receptor subunit NR2B regulates surface expression. Neuropsychopharmacology, 45: 729–737.
https://doi.org/10.1016/s0028-3908(03)00308-3

129. Scott DB, Michailidis I, Mu Y, et al., 2004, Endocytosis and degradative sorting of NMDA receptors by conserved membrane-proximal signals. J Neurosci, 24: 7096–7109.
https://doi.org/10.1523/JNEUROSCI.0780-04.2004

130. Bliss TV, Lomo T, 1973, Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit hippocampal slice. J Physiol, 232: 331–356.
113. Collingridge GL, Kehl SJ, McLennan H, 1983, The antagonism of amino acid-induced excitations of rat hippocampal CA1 neurones in vitro. J Physiol, 334: 19–31. https://doi.org/10.1113/jphysiol.1973.sp010273

114. Lu HC, Gonzalez E, Crair MC, 2001, Barrel cortex critical period plasticity is independent of changes in NMDA receptor subunit composition. Neuron, 32: 619–634. https://doi.org/10.1016/s0896-6273(01)00501-3

115. Villarreal DM, Do V, Haddad E, et al., 2007, Interactions between NMDA receptor subunits control synaptic plasticity by regulating receptor GluN2B (GluR epsilon 2/NR2B) subunit is crucial for channel function, postsynaptic macromolecular organization, and actin cytoskeleton at hippocampal CA3 synapses. J Neurosci, 29: 10869–10882. https://doi.org/10.1523/JNEUROSCI.5531-08.2009

116. Brigman JL, Wright T, Talani G, et al., 2010, Loss of GluN2B-containing NMDA receptors in CA1 hippocampus and cortex impairs long-term depression, reduces dendritic spine density, and disrupts learning. J Neurosci, 30: 4590–4600. https://doi.org/10.1523/JNEUROSCI.0640-10.2010

117. Malenka RC, 2002, AMPA receptor trafficking and synaptic plasticity. Annu Rev Neurosci, 25: 103–126. https://doi.org/10.1146/annurev.neuro.25.112701.142758

118. Citri A, Malenka RC, 2008, Synaptic plasticity: multiple forms, functions, and mechanisms. Neureropsychopharmacology, 33: 18–41. https://doi.org/10.1038/jn.2008.776

119. Tang YP, Shimizu E, Dube GR, et al., 1999, Genetic enhancement of learning and memory in mice. Nature, 401: 63–69. https://doi.org/10.1038/43432

120. Zhou Y, Takahashi E, Li W, et al., 2007, Interactions between the NR2B receptor and CaMKII modulate synaptic plasticity and spatial learning. J Neurosci, 27: 13843–13853. https://doi.org/10.1523/JNEUROSCI.4486-07.2007

121. Berberich S, Punnakkal P, Jensen V, et al., 2009, Lack of NMDA receptor subtype selectivity for hippocampal long-term potentiation. J Neurosci, 25: 6907–6910. https://doi.org/10.1523/JNEUROSCI.1905-05.2005

122. Weitlauf C, Honse Y, Auberson YP, et al., 2005, Activation of NR2A-containing NMDA receptors is not obligatory for NMDA receptor-dependent long-term potentiation. J Neurosci, 25: 8386–8390. https://doi.org/10.1523/JNEUROSCI.3888-05.2005

123. Cui Z, Feng R, Jacobs S, et al., 2005, Increased NR2A: NR2B ratio compresses long-term depression range and constrains long-term memory. Sci Rep, 3: 1036. https://doi.org/10.1038/srep01036

124. Hawasli AH, Benavides DR, Nguyen C, et al., 2007, Neurobiol Learn Mem, 9: 3040–3057. https://doi.org/10.1016/j.nlm.2006.11.007

125. Lu HC, Gonzalez E, Crair MC, 2001, Barrel cortex critical period plasticity is independent of changes in NMDA receptor subunit composition. Neuron, 32: 619–634. https://doi.org/10.1016/s0896-6273(01)00501-3

126. Graybiel AM, 1982, The basal nuclei: Possible functions of their cell types. Annu Rev Neurosci, 5: 481–497. https://doi.org/10.1146/annurev.neuro.05.090182.002343

127. Malinow R, Malenka RC, 2002, AMPA receptor trafficking and synaptic plasticity. Annu Rev Neurosci, 25: 103–126. https://doi.org/10.1146/annurev.neuro.25.112701.142758

128. Citri A, Malenka RC, 2008, Synaptic plasticity: multiple forms, functions, and mechanisms. Neureropsychopharmacology, 33: 18–41. https://doi.org/10.1038/jn.2008.776

129. Tang YP, Shimizu E, Dube GR, et al., 1999, Genetic enhancement of learning and memory in mice. Nature, 401: 63–69. https://doi.org/10.1038/43432

130. Zhou Y, Takahashi E, Li W, et al., 2007, Interactions between the NR2B receptor and CaMKII modulate synaptic plasticity and spatial learning. J Neurosci, 27: 13843–13853. https://doi.org/10.1523/JNEUROSCI.4486-07.2007

131. Berberich S, Punnakkal P, Jensen V, et al., 2009, Lack of NMDA receptor subtype selectivity for hippocampal long-term potentiation. J Neurosci, 25: 6907–6910. https://doi.org/10.1523/JNEUROSCI.1905-05.2005

132. Weitlauf C, Honse Y, Auberson YP, et al., 2005, Activation of NR2A-containing NMDA receptors is not obligatory for NMDA receptor-dependent long-term potentiation. J Neurosci, 25: 8386–8390. https://doi.org/10.1523/JNEUROSCI.3888-05.2005

133. Cui Z, Feng R, Jacobs S, et al., 2005, Increased NR2A: NR2B ratio compresses long-term depression range and constrains long-term memory. Sci Rep, 3: 1036. https://doi.org/10.1038/srep01036

134. Lu HC, Gonzalez E, Crair MC, 2001, Barrel cortex critical period plasticity is independent of changes in NMDA receptor subunit composition. Neuron, 32: 619–634. https://doi.org/10.1016/s0896-6273(01)00501-3

135. Villarreal DM, Do V, Haddad E, et al., 2007, Interactions between NMDA receptor subunits control synaptic plasticity by regulating receptor GluN2B (GluR epsilon 2/NR2B) subunit is crucial for channel function, postsynaptic macromolecular organization, and actin cytoskeleton at hippocampal CA3 synapses. J Neurosci, 29: 10869–10882. https://doi.org/10.1523/JNEUROSCI.5531-08.2009

136. Brigman JL, Wright T, Talani G, et al., 2010, Loss of GluN2B-containing NMDA receptors in CA1 hippocampus and cortex impairs long-term depression, reduces dendritic spine density, and disrupts learning. J Neurosci, 30: 4590–4600. https://doi.org/10.1523/JNEUROSCI.0640-10.2010

137. Malinow R, Malenka RC, 2002, AMPA receptor trafficking and synaptic plasticity. Annu Rev Neurosci, 25: 103–126. https://doi.org/10.1146/annurev.neuro.25.112701.142758

138. Citri A, Malenka RC, 2008, Synaptic plasticity: multiple forms, functions, and mechanisms. Neurepsychopharmacology, 33: 18–41. https://doi.org/10.1038/jn.2008.776

139. Tang YP, Shimizu E, Dube GR, et al., 1999, Genetic enhancement of learning and memory in mice. Nature, 401: 63–69. https://doi.org/10.1038/43432

140. Zhou Y, Takahashi E, Li W, et al., 2007, Interactions between the NR2B receptor and CaMKII modulate synaptic plasticity and spatial learning. J Neurosci, 27: 13843–13853. https://doi.org/10.1523/JNEUROSCI.4486-07.2007

141. Strack S, Colbran RJ, 1998, Autophosphorylation-dependent targeting of calcium/calmodulin-dependent protein kinase II by the NR2B subunit of the N-methyl-D-aspartate receptor. J Biol Chem, 273: 20689–20692. https://doi.org/10.1074/jbc.273.33.20689

142. Barria A, Malinow R, 2005, NMDA receptor subunit composition controls synaptic plasticity by regulating binding to CaMKII. Neuron, 48: 289–301. https://doi.org/10.1016/j.neuron.2005.08.034
154. Liu L, Wong TP, Pozza MF, et al., 2004, Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. Science, 304: 1021–1024.
https://doi.org/10.1126/science.1096615

155. Li R, Huang FS, Abbas AK, et al., 2007, Role of NMDA receptor subtypes in different forms of NMDA-dependent synaptic plasticity. BMC Neurosci, 8: 55.
https://doi.org/10.1186/1471-2202-8-55

156. Sakimura K, Kutsuwada T, Ito I, et al., 1995, Reduced hippocampal LTP and spatial learning in mice lacking NMDA receptor epsilon 1 subunit. Nature, 373: 151–155.
https://doi.org/10.1038/373151a0

157. Foster KA, McLaughlin N, Edbauer D, et al., 2010, Distinct roles of NR2A and NR2B cytoplasmic tails in long-term potentiation. J Neurosci, 30: 2676–2685.
https://doi.org/10.1523/JNEUROSCI.1052-09.2010

158. Delaney AJ, Sedlak PL, Autuori E, et al., 2000, Activation of NR2A at CA1 synapses is obligatory for the susceptibility of hippocampal plasticity to sleep loss. J Neurosci., 29: 9026–9041.
https://doi.org/10.1523/JNEUROSCI.1215-09.2009

159. Morishita W, Lu W, Smith GB, et al., 2007, Activation of NR2B-containing NMDA receptors is not required for NMDA receptor-dependent long-term depression. Neuropharmacology, 52: 71–76.
https://doi.org/10.1016/j.neuropharm.2006.07.005

160. Hendrison AW, Miao CL, Lippmann MJ, et al., 2002, Ifenprodil and ethanol enhance NMDA receptor-dependent long-term depression. J Pharmacol Exp Ther, 301: 938–944.
https://doi.org/10.1124/jpet.301.3.938

161. Gardoni F, Mauceri D, Malinverno M, et al., 2009, Decreased NR2B subunit synaptic levels cause impaired long-term potentiation but not long-term depression. J Neurosci, 29: 669–677.
https://doi.org/10.1523/JNEUROSCI.3921-08.2009

162. Wang D, Cui Z, Zeng Q, et al., 2009, Genetic enhancement of memory and long-term potentiation but not CA1 long-term depression in NR2B transgenic rats. PLoS One, 4: e7486.
https://doi.org/10.1371/journal.pone.0007486

163. Bartlett TE, Bannister NJ, Collett VJ, et al., 2007, Differential roles of NR2A and NR2B-containing NMDA receptors in LTP and LTD in the CA1 region of two-week old rat hippocampus. Neuropharmacology, 52: 60–70.
https://doi.org/10.1016/j.neuropharm.2006.07.013

164. Ge Y, Dong Z, Bagot RC, et al., 2010, Hippocampal long-term depression is required for the consolidation of spatial memory. Proc Natl Acad Sci U S A, 107: 16697–16702.
https://doi.org/10.1073/pnas.1008200107

165. Longordo F, Kopp C, Mishina M, et al., 2009, NR2A at CA1 synapses is obligatory for the susceptibility of hippocampal synaptic plasticity. Science, 324: 9026–9041.
https://doi.org/10.1523/JNEUROSCI.1215-09.2009

166. Kalia IV, Kalia SK, Salter MW, 2008, NMDA receptors in clinical neurology: excitatory times ahead. Lancet Neurol, 7: 742–755.
https://doi.org/10.1016/S1474-4420(08)70165-0

167. Berman RM, Cappiello A, Anand A, et al., 2000, Antidepressant effects of ketamine in depressed patients. Biol Psychiatry, 47: 351–354.
https://doi.org/10.1016/S0006-3223(99)00230-9

168. Murrough JW, Perez AM, Pillemer S, et al., 2013, Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry, 74: 250–256.
https://doi.org/10.1016/j.biopsych.2012.06.022

169. Preskorn S, Macaluso M, Mehra DO, et al., 2015, Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder unresponsive to a previous antidepressant agent. J Psychiatric Pract, 21: 140–149.
https://doi.org/10.1097/01.pra.0000462606.17725.93

170. Jiang J, Jiang H, 2015, Efficacy and adverse effects of memantine treatment for Alzheimer’s disease from randomized controlled trials. Neurol Sci, 36: 1633–1641.
https://doi.org/10.1007/s10072-015-2221-2

171. Knapp M, King D, Romeo R, et al., 2017, Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer’s disease (the DOMINO-AD trial). Int J Geriatr Psychiatry, 32: 1205–1216.
https://doi.org/10.1002/gps.4583

172. O’Collins VE, Macleod MR, Donnan GA, et al., 2006, 1,026 experimental treatments in acute stroke. Ann Neurol, 59: 467–477.
https://doi.org/1002/ana.20741

173. Feng B, Morley RM, Jane DE, et al., 2011, Antidepressant effects of ketamine in major depressive disorder: randomised controlled trials. Lancet, 376: 742–755.
https://doi.org/1097/01.pra.0000462606.17725.93

174. Auberson YP, Allgeier H, Bischoff S, et al., 2017, Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. J Psychiatric Pract, 21: 140–149.
https://doi.org/10.1097/01.pra.0000462606.17725.93

175. Berman RM, Cappiello A, Anand A, et al., 2000, Antidepressant effects of ketamine in depressed patients. Biol Psychiatry, 47: 351–354.
https://doi.org/10.1016/S0006-3223(99)00230-9

176. Murrough JW, Perez AM, Pillemer S, et al., 2013, Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry, 74: 250–256.
https://doi.org/10.1016/j.biopsych.2012.06.022

177. Preskorn S, Macaluso M, Mehra DO, et al., 2015, Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder unresponsive to a previous antidepressant agent. J Psychiatric Pract, 21: 140–149.
https://doi.org/10.1097/01.pra.0000462606.17725.93

178. Jiang J, Jiang H, 2015, Efficacy and adverse effects of memantine treatment for Alzheimer’s disease from randomized controlled trials. Neurol Sci, 36: 1633–1641.
https://doi.org/10.1007/s10072-015-2221-2

179. Knapp M, King D, Romeo R, et al., 2017, Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer’s disease (the DOMINO-AD trial). Int J Geriatr Psychiatry, 32: 1205–1216.
https://doi.org/10.1002/gps.4583

180. O’Collins VE, Macleod MR, Donnan GA, et al., 2006, 1,026 experimental treatments in acute stroke. Ann Neurol, 59: 467–477.
https://doi.org/1002/ana.20741

181. Feng B, Morley RM, Jane DE, et al., 2011, Antidepressant effects of ketamine in major depressive disorder: randomised controlled trials. Lancet, 376: 742–755.
https://doi.org/1097/01.pra.0000462606.17725.93
NMDA receptors in neuropsychiatric diseases

175. Kemp JA, Foster AC, Leeson PD, et al., 1988, 7-Chlorokynurenine acid is a selective antagonist at the glycine modulatory site of the N-methyl-D-aspartate receptor complex. *Proc Natl Acad Sci U S A*, 85: 6547–6550. https://doi.org/10.1073/pnas.85.17.6547

177. Davies J, Watkins JC, 1972, Is 1-hydroxy-3-amino-4-pyrrrolidone-2 (HA-966) a selective excitatory amino-acid antagonist? *Nat New Biol*, 238: 61–63. https://doi.org/10.1038/newbio238061a0

184. Chenard BL, Bordner J, Butler TW, et al., 1995, (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol: A potent new neuroprotectant which blocks N-methyl-D-aspartate responses. *J Med Chem*, 38: 3138–3145. https://doi.org/10.1021/jm00016a017

185. Fischer G, et al., 1997, Ro 25-6981, a highly potent and selective blocker of N-methyl-D-aspartate receptors containing the NR2B subunit. Characterization in vitro. *J Pharmacol Exp Ther*, 283: 1285–1292.

186. Bettini E, Sava A, Griffante C, et al., 2010, Identification and characterization of novel NMDA receptor antagonists selective for NR2A over NR2B-containing receptors. *J Pharmacol Exp Ther*, 335: 636–644. https://doi.org/10.1124/jpet.110.172544

187. Hansen KB, Ogden KK, Traynelis SF, 2012, Subunit-selective allosteric inhibition of glycine binding to NMDA receptors. *J Neurosci*, 32: 6197–6208. https://doi.org/10.1523/JNEUROSCI.5757-11.2012

188. Edman S, McKay S, MacDonald LJ, et al., 2012, TCN 201 selectively blocks GluN2A-containing NMDARs in a GluN1 co-agonist dependent but non-competitive manner. *Neuropharmacology*, 63: 441–449. https://doi.org/10.1016/j.neuropharm.2012.04.001

189. Mosley CA, Acker TM, Hansen KB, et al., 2010, Quinazolin-4-one derivatives: A novel class of noncompetitive NR2C/D subunit-selective N-methyl-D-aspartate receptor antagonists. *J Med Chem*, 53: 5476–5490. https://doi.org/10.1021/jm100027p

190. Hansen KB, Traynelis SF, 2011, Structural and mechanistic determinants of a novel site for noncompetitive inhibition of GluN2D-containing NMDA receptors. *J Neurosci*, 31: 3650–3661. https://doi.org/10.1523/JNEUROSCI.5665-10.2011

191. Costa BM, Irvine MW, Fang G, et al., 2010, A novel family of negative and positive allosteric modulators of NMDA receptors. *J Pharmacol Exp Ther*, 335: 614–621. https://doi.org/10.1124/jpet.110.174144

192. Costa BM, Irvine MW, Fang G, et al., 2012, Structure-activity relationships for allosteric NMDA receptor inhibitors based on 2-naphthoic acid. *Neuropharmacology*, 62: 1730–1736. https://doi.org/10.1016/j.neuropharm.2011.11.019

193. Kloa A, Clements JD, Lewis RJ, et al., 2004, Adenosine triphosphate acts as both a competitive antagonist and a positive allosteric modulator at recombinant N-methyl-D-aspartate receptors. *Mol Pharmacol*, 65: 1386–1396. https://doi.org/10.1124/mol.65.6.1386

194. Williams K, 1994, Subunit-specific potentiation of recombinant N-methyl-D-aspartate receptors by histamine. *Mol Pharmacol*, 46: 531–541.

195. Williams K, Zappia AM, Pritchett DB, et al., 1994, Sensitivity of the N-methyl-D-aspartate receptor to polyamines is controlled by NR2 subunits. *Mol Pharmacol*, 45: 803–809.

196. Sedlacek M, Konek M, Petrovic M, et al., 2008, Neurosteroid...
modulation of ionotropic glutamate receptors and excitatory synaptic transmission. *Physiol Res*, 57(Suppl 3): S49–S57.  
https://doi.org/10.36922/an.v1i2.148

197. Paolletti P, Neyton J, Ascher P, 1995, Glycine-independent and subunit-specific potentiation of NMDA responses by extracellular Mg2+. *Neuron*, 15: 1109–1120.  
https://doi.org/10.1016/0896-6273(95)90099-3

198. Malayev A, Gibbs TT, Farb DH, 2002, Inhibition of the NMDA response by pregnenolone sulphate reveals subtype selective modulation of NMDA receptors by sulphated steroids. *Br J Pharmacol*, 135: 901–909.  
https://doi.org/10.1038/sj.bjp.0704543

199. Petrovic M, Sedlacek M, Cais O, *et al.*, 2009, Pregnenolone sulfate modulation of N-methyl-D-aspartate receptors is phosphorylation dependent. *Neuroscience*, 160: 616–628.  
https://doi.org/1016/j.neuroscience.2009.02.052

200. Horak M, Vlcek K, Petrovic M, *et al.*, 2004, Molecular mechanism of pregnenolone sulfate action at NR1/NR2B receptors. *J Neurosci*, 24: 10318–10325.  
https://doi.org/101523/JNEUROSCI.0929-2004

201. Bowlby MR, 1993, Pregnenolone sulfate potentiation of N-methyl-D-aspartate receptor channels in hippocampal neurons. *Mol Pharmacol*, 43: 813–819.

202. Wong M, Moss RL, 1994, Patch-clamp analysis of direct steroid modulation of glutamate receptor-channels. *J Neuroendocrinol*, 6: 347–355.  
https://doi.org/10.1111/j.1365-2826.1994.tb00592.x

203. Jang MK, Mierke D, Russeki S, *et al.*, 2004, A steroid modulatory domain on NR2B controls N-methyl-D-aspartate receptor proton sensitivity. *Proc Natl Acad Sci U S A*, 101: 8198–8203.  
https://doi.org/10173/pnas.0401838101

204. Monaghan DT, Irvine MW, Costa BM, *et al.*, 2012, Pharmacological modulation of NMDA receptor activity and the advent of negative and positive allosteric modulators. *Neurochem Int*, 61: 581–592.  
https://doi.org/1016/j.neuint.2012.01.004

205. Sapkota K, Irvine MW, Fang G, *et al.*, 2017, Mechanism and properties of positive allosteric modulation of N-methyl-D-aspartate receptors by 6-alkyl 2-naphthoic acid derivatives. *Neuropharmacology*, 125: 64–79.  
https://doi.org/1016/j.neuropharm.2017.07.007

206. Chopra DA, Sapkota K, Irvine MW, *et al.*, 2017, A single-channel mechanism for pharmacological potentiation of GluN1/GluN2A NMDA receptors. *Sci Rep*, 7: 6933.  
https://doi.org/10138/s41598-017-07292-8

207. Irvine MW, Costa BM, Dlaboga D, *et al.*, 2012, Piperazine-2,3-dicarboxylic acid derivatives as dual antagonists of NMDA and GluK1-containing kainate receptors. *J Med Chem*, 55: 327–341.  
https://doi.org/1021/jm201230z

208. Mullasseril P, Hansen KB, Vance KM, *et al.*, 2010, A subunit-selective potentiator of NR2C- and NR2D-containing NMDA receptors. *Nat Commun*, 1: 90.  
https://doi.org/10138/ncomms1085

209. Zhang X, Feng ZJ, Chergui K, 2014, Allosteric modulation of GluN2C/GluN2D-containing NMDA receptors bidirectionally modulates dopamine release: implication for Parkinson's disease. *Br J Pharmacol*, 171: 3938–3945.  
https://doi.org/1111/bph.12758

210. Wang TM, Brown BM, Deng L, *et al.*, 2017, A novel NMDA receptor positive allosteric modulator that acts via the transmembrane domain. *Neuropharmacology*, 121: 204–218.  
https://doi.org/1016/j.neuropharm.2017.04.041

211. Kessler HW, Nabavi S, Malinow R, 2013, Metabotropic NMDA receptor function is required for beta-amyloid-induced synaptic depression. *Proc Natl Acad Sci U S A*, 110: 4033–4038.  
https://doi.org/10.1073/pnas.1219605110

212. Ronicke R, Mikhaylova M, Rönicle S, *et al.*, 2011, Early neuronal dysfunction by amyloid beta oligomers depends on activation of NR2B-containing NMDA receptors. *Neurobiol Aging*, 32: 2219–2228.  
https://doi.org/1016/j.neurobiolaging.2010.01.011

213. Li S, Jin M, Koeglsperger T, *et al.*, 2011, Soluble Abeta oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. *J Neurosci*, 31: 6627–6638.  
https://doi.org/101523/JNEUROSCI.0203-11.2011

214. Hu NW, Klyubin I, Anwyl R, *et al.*, 2009, GluN2B subunit-containing NMDA receptor antagonists prevent Abeta-mediated synaptic plasticity disruption in vivo. *Proc Natl Acad Sci U S A*, 106: 20504–20509.  
https://doi.org/10173/pnas.0908038106

215. Li S, Hong S, Shepardson NE, *et al.*, 2009, Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron*, 62: 788–801.  
https://doi.org/1016/j.neuron.2009.05.012

216. Ittner LM, Ke YD, Delerue F, *et al.*, 2010, Dendritic function of tau mediates amyloid-beta toxicity in Alzheimer’s disease mouse models. *Cell*, 142: 387–397.  
https://doi.org/1016/j.cell.2010.06.036

217. Bordj K, Becerril-Ortega J, Nicole O, *et al.*, 2010, Activation of extrasynaptic, but not synaptic, NMDA receptors modifies
NMDA receptors in neuropsychiatric diseases

amloid precursor protein expression pattern and increases amyloid-ss production. *J Neurosci*, 30: 15927–15942.
https://doi.org/10.1523/JNEUROSCI.3021-10.2010

1. Lai TW, Shyu WC, Wang YT, 2011, Stroke intervention pathways: NMDA receptors and beyond. *Trends Mol Med*, 17: 266–275.
https://doi.org/10.1016/j.molmed.2010.12.008

2. Dunah AW, Wang Y, Yasuda RP, et al., 2000, Alterations in subunit expression, composition, and phosphorylation of striatal N-methyl-D-aspartate glumamate receptors in a rat 6-hydroxydopamine model of Parkinson's disease. *Mol Pharmacol*, 57: 342–352.

3. Gardoni F, Picconi B, Ghiglieri V, et al., 2006, A critical interaction between NR2B and MAGUK in L-DOPA induced dyskinesia. *J Neurosci*, 26: 2914–2922.
https://doi.org/10.1523/JNEUROSCI.5326-05.2006

4. Gardoni F, Picconi B, Ghiglieri V, et al., 2009, Allosteric modulators of NR2B-containing NMDA receptors: Molecular mechanisms and therapeutic potential. *Br J Pharmacol*, 157: 1301–1317.
https://doi.org/10.1111/j.1476-5381.2009.00304.x

5. Sgambato-Faure V, Cenci MA, 2012, Glutamatergic mechanisms in the dyskinesias induced by pharmacological dopamine replacement and deep brain stimulation for the treatment of Parkinson's disease. *Prog Neurobiol*, 96: 69–86.
https://doi.org/10.1016/j.pneurobio.2011.10.005

6. Mony L, Kew JN, Gunthorpe MJ, et al., 2009, Allosteric modulators of NR2B-containing NMDA receptors reduces L-DOPA-induced dyskinesias. *Neurobiol Aging*, 33: 2138–2144.
https://doi.org/10.1016/j.neurobiolaging.2011.06.019

7. Nakazawa K, Sapkota K, 2020, The origin of NMDA receptor hypofunction in schizophrenia. *Pharmacol Ther*, 205: 107426.
https://doi.org/10.1016/j.pharmacother.2019.107426

8. Howes OD, Kapur S, 2009, The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull*, 35: 549–562.
https://doi.org/10.1093/ schbul/sbp006

9. Moghadam B, Javitt D, 2012, From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology*, 37: 4–15.
https://doi.org/10.1038/npp.2011.181

10. Mohn AR, Gainetdinov RR, Caron MG, et al., 1999, Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. *Cell*, 98: 427–436.
https://doi.org/10.1016/S0092-8674(99)81972-8

11. Nakao K, Jeevakumar V, Jiang SZ, et al., 2019, Schizophrenia-like dopamine release abnormalities in a mouse model of NMDA receptor hypofunction. *Schizophr Bull*, 45: 138–147.
https://doi.org/10.1093/schbul/sby003

12. Coyle JT, Tsai G, Goff D, 2003, Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. *Ann N Y Acad Sci*, 1003: 318–327.
https://doi.org/10.1196/annals.1300.020

13. Javitt DC, Zukin SR, 1991, Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry*, 148: 1301–1308.
https://doi.org/10.1176/ajp.148.10.1301

14. Krystal JH, Karper LP, Seibyl JP, et al., 1994, Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. *Psychotomimetic, perceptual, cognitive, and neuroendocrine responses*. *Arch Gen Psychiatry*, 51: 199–214.
https://doi.org/10.1001/archpsyc.1994.03950030035004

15. Koek W, Woods JH, Winger GD, 1988, MK–801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. *J Pharmacol Exp Ther*, 245: 969–974.

16. Kovacic P, Somnanthan R, 2010, Clinical physiology and mechanism of dizocilpine (MK–801): Electron transfer, radicals, redox metabolites and bioactivity. *Oxid Med Cell Longev*, 3: 13–22.
https://doi.org/10.4161/oxim.3.1.10028

17. Dalmau J, Lancaster E, Martinez-Hernandez E, et al., 2011, Clinical effects and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*, 10: 63–74.
https://doi.org/10.1016/S1474-4422(10)70253-2

18. 1993, A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's disease Collaborative Research Group. *Cell*, 72: 971–983.
https://doi.org/10.1016/S0092-8674(93)90585-e

19. Fan MM, Raymond LA, 2007, N-methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. *Prog Neurobiol*, 81: 272–293.
https://doi.org/10.1016/j.pneurobio.2006.11.003

20. Milnerwood AJ, Gladding CM, Pouladi MA, et al., 2010, Early increase in extrasynaptic NMDA receptor signaling and expression contributes to phenotype onset in Huntington's disease mice. *Ann N Y Acad Sci*, 1196: 1301–1308.
https://doi.org/10.1196/annals.1300.020

21. Okamoto S, Pouladi MA, Talantova M, et al., 2009, Balance between synaptic versus extrasynaptic NMDA receptor activity influences inclusions and neurotoxicity of mutant
243. Pittenger C, Sanacora G, Krystal JH, 2007, The NMDA receptor as a therapeutic target in major depressive disorder. *J Neuropsychopharmacol*, 6: 22–31.
https://doi.org/1093/jnp/pyaa068

244. Tiller JW, 2013, Depression and anxiety. *Med J Aust*, 199: S28–S31.
https://doi.org/10.36922/an.v1i2.148

245. Fukuimoto K, Toki H, Iijima M, et al., 2017, Antidepressant potential of (R)-ketamine in rodent models: Comparison with (S)-ketamine. *J Pharmacol Exp Ther*, 361: 9–16.
https://doi.org/10.1124/jpet.116.239228

246. Ionescu DF, Fu DJ, Qiu X, et al., 2021, Esketamine nasal spray for rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicide ideation with intent: results of a phase 3, double-blind, randomized study (ASPIRE II). *Int J Neuropsychopharmacol*, 24: 22–31.
https://doi.org/1017/S1461145708008985

247. Feyissa AM, Chandran A, Stockmeier CA, et al., 2009, Reduced levels of NR2A and NR2B subunits of NMDA receptor and PSD-95 in the prefrontal cortex in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*, 33: 70–75.
https://doi.org/1017/S1461145708008985

248. Karolewicz B, Stockmeier CA, Ordway GA, 2009, Elevated levels of NR2A and PSD-95 in the lateral amygdala in depression. *Int J Neuropsychopharmacol*, 12: 143–153.
https://doi.org/10.1017/S1461145708008985

249. Jiang A, Su P, Li S, et al., 2021, Disrupting the alpha7nAChR-NR2A protein complex exerts antidepressant-like effects. *Mol Brain*, 14: 107.
https://doi.org/10186/s13041-021-00817-3

250. Zanos P, Moaddel R, Morris PJ, et al., 2016, NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature*, 533: 481–486.
https://doi.org/10.1013/nature17998

251. Bullock R, Zauner A, Woodward JJ, et al., 1998, Factors affecting excitatory amino acid release following severe human head injury. *J Neurosurg*, 89: 507–518.
https://doi.org/10.3727/0000510007780363267

252. Simon RP, Swan JH, Griffiths T, et al., 1984, Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science*, 226: 850–852.
https://doi.org/10.1126/science.6093256

253. Chen MH, Bullock R, Graham DI, et al., 1991, Ischemic neuronal damage after acute subdural hematoma in the rat: effects of pretreatment with a glutamate antagonist. *J Neurosurg*, 74: 944–950.
https://doi.org/10.1126/science.1072873

254. Margaill I, Parmentier S, Callebert J, et al., 1996, Short therapeutic window for MK-801 in transient focal cerebral ischemia in normotensive rats. *J Cerebral Blood Flow Metab*, 16: 107–113.
https://doi.org/1002/ddr.21347

255. Liu Y, Wong TP, Aarts M, et al., 2007, NMDA receptor subunits have differential roles in mediating excitotoxic neuronal death both in vitro and in vivo. *J Neurosci*, 27: 2846–2857.
https://doi.org/10.1126/science.1072873

256. Jiang A, Su P, Li S, et al., 2021, Disrupting the alpha7nAChR-NR2A protein complex exerts antidepressant-like effects. *Mol Brain*, 14: 107.
https://doi.org/10.1038/s1461145708008985

257. Yang Y, Li Q, Yang T, et al., 2003, Reduced brain infarct volume and improved neurological outcome by inhibition of the NR2B subunit of NMDA receptors by using CP101,606-27 alone and in combination with rt-PA in a thromboembolic stroke model in rats. *J Neurosurg*, 98: 397–403.
https://doi.org/10.1161/STROKEAHA.108.521898

258. Aarts M, Liu Y, Liu L, et al., 2002, Treatment of ischemic brain damage by perturbing NMDA receptor- PSD-95 protein interactions. *Science*, 298: 846–850.
https://doi.org/10.1126/science.1072873

259. Cook DJ, Teves L, Tymianski M, 2012, A translational
paradigm for the preclinical evaluation of the stroke neuroprotectant Tat-NR2B9c in gyrencephalic nonhuman primates. Sci Transl Med, 4: 154ra133. https://doi.org/10.1126/scitranslmed.3003824

260. Hill MD, Martin RH, Muklis D, et al., 2012, Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): A phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol, 11: 942–950. https://doi.org/10.1016/S1474-4422(12)70225-9

261. Beuchamp K, Mutlak H, Smith WR, et al., 2008, Pharmacology of traumatic brain injury: Where is the “golden bullet”? Mol Med, 14: 731–740. https://doi.org/10.1203/00001756-200809000-00003

262. Biegon A, Fry PA, Paden CM, et al., 2004, Dynamic changes in N-methyl-D-aspartate receptors after closed head injury in mice: Implications for treatment of neurological and cognitive deficits. Proc Natl Acad Sci U S A, 101: 5117–5122. https://doi.org/10.1073/pnas.0305741101

263. Carter DS, Deshpande LS, Rafiq A, et al., 2011, Characterization of spontaneous recurrent epileptiform discharges in hippocampal-entorhinal cortical slices prepared from chronic epileptic animals. Seizure, 20: 218–224. https://doi.org/10.1016/j.seizure.2010.11.022

264. Meldrum BS, 1993, Excitotoxicity and selective neuronal loss in epilepsy. Brain Pathol, 3: 405–412. https://doi.org/10.1111/j.1528-1147.1993.tb00768.x

265. Jensen PJ, Millan N, Mack KJ, 1997, Cortical NMDAR-1 gene expression is rapidly upregulated after seizure. Brain Res Mol Brain Res, 44: 157–162. https://doi.org/10.1016/s0169-328x(96)00262-8

266. Kikuchi S, Iwasa H, Sato T, 2000, Lasting changes in hippocampal-entorhinal cortical slices prepared from chronic epileptic animals. Seizure, 20: 218–224. https://doi.org/10.1016/j.seizure.2010.11.022

267. Gerfin-Moser A, Grogg F, Rietzschl L, et al., 1995, Alterations in glutamate but not GABAA receptor subunit expression as a consequence of epileptiform activity in vitro. Neuroscience, 67: 849–865. https://doi.org/10.1016/0034-958X(95)00130-0

268. Mathern GW, Pretorius JK, Leite JP, et al., 1998, Hippocampal AMPA and NMDA mRNA levels and subunit immunoreactivity in human temporal lobe epilepsy patients and a rodent model of chronic mesial limbic epilepsy. Epilepsy Res, 32: 154–171. https://doi.org/10.1016/s0920-1211(98)00048-5

269. Lason W, Turchan J, Przewlocki R, et al., 1997, Effects of pilocarpine and kainate-induced seizures on N-methyl-D-aspartate receptor gene expression in the rat hippocampus. Neuroscience, 78: 997–1004. https://doi.org/10.1016/s0306-4522(96)00635-5

270. Hosain S, Nagarajan L, Carson D, et al., 1997, Felbamate for refractory infantile spasms. J Child Neurol, 12: 466–468. https://doi.org/10.1177/088303789701200711

271. Zupanc ML, Werner RR, Schwabe MS, et al., 2010, Efficacy of felbamate in the treatment of intractable pediatric epilepsy. Pediatr Neurol, 42: 396–403. https://doi.org/10.1016/j.pediatrneurol.2010.02.013

272. McCabe RT, Wasterlain CG, Kucharczyk N, et al., 1993, Evidence for anticonvulsant and neuroprotectant action of felbamate mediated by strychnine-insensitive glycine receptors. J Pharmacol Exp Ther, 264: 1248–1252.

273. White HS, Harmsworth WL, Sofia RD, et al., 1995, Felbamate modulates the strychnine-insensitive glycine receptor. Epilepsy Res, 20: 41–48. https://doi.org/10.1016/j.eplepsyres.2004.03.004

274. Rho JM, Donevan SD, Rogawski MA, 1994, Mechanism of action of the anticonvulsant felbamate: opposing effects on N-methyl-D-aspartate and gamma-aminobutyric acidA receptors. Ann Neurol, 35: 229–234. https://doi.org/10.1002/ana.410350216

275. Singh L, Oles RJ, Vass CA, et al., 1991, A slow intravenous infusion of N-methyl-DL-aspartate as a seizure model in the mouse. J Neurosci Methods, 37: 227–232. https://doi.org/10.1016/0165-0270(91)90028-x

276. Baloso S, Maroso M, Sanchez-Alavez M, et al., 2008, A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta. Brain, 131: 3256–3265. https://doi.org/10.1093/brainawn271

277. Yen W, Williamson J, Bertram EH, et al., 2004, A comparison of three NMDA receptor antagonists in the treatment of prolonged status epilepticus. Epilepsy Res, 59: 43–50. https://doi.org/10.1016/j.eplepsyres.2004.03.004

278. Kleinrok Z, Turski WA, Czuczwar SJ, 1995, Excitatory amino acid antagonists and the anticonvulsant activity of conventional antiepileptic drugs. Polish J Pharmacol, 47: 247–252.

279. Brackett RL, Pouw B, Blyden JF, et al., 2000, Prevention of cocaine-induced convulsions and lethality in mice: Effectiveness of targeting different sites on the NMDA receptor complex. Neuropharmacology, 39: 407–418. https://doi.org/10.1002/ana.410350216

280. Vataev SI, Zhabko EP, Lukomskaia N, et al., 2009, Effects of memantine on convulsive reactions and sleep-waking cycle
in Krushinskii-Molodkina strain rats with the inherited predisposition to audiogenic convulsions. *Ross Fiziol Zh Im I M Sechenova*, 55: 802–812.

281. Frey HH, Voits M, 1991, Effect of psychotropic agents on a model of absence epilepsy in rats. *Neuropharmacology*, 30: 651–656.

https://doi.org/10.1016/0028-3908(91)90086-Q

282. Czuczwar SJ, Turski WA, Kleinrok Z, 1996, Interactions of excitatory amino acid antagonists with conventional antiepileptic drugs. *Metab Brain Dis*, 11: 143–152.

https://doi.org/10.1007/BF02069501

283. Wu LJ, Zhuo M, 2009, Targeting the NMDA receptor subunit NR2B for the treatment of neuropathic pain. *Neurotherapeutics*, 6: 693–702.

https://doi.org/10.1016/j.nurt.2009.07.008

284. Woolf CJ, Salter MW, Neuronal plasticity: increasing the gain in pain. *Science*, 288: 1765–1769.

https://doi.org/10.1126/science.288.5472.1765

285. Isaev D, Gerber G, Park SK, et al., 2000, Facilitation of NMDA-induced currents and Ca2+ transients in the rat substantia gelatinosa neurons after ligation of L5-L6 spinal nerves. *Neuroreport*, 11: 4055–4061.

https://doi.org/10.1097/00001756-200101180-00030

286. Ultenius C, Linderoth B, Meyerson BA, et al., 2006, Spinal NMDA receptor phosphorylation correlates with the presence of neuropathic signs following peripheral nerve injury in the rat. *Neurosci Lett*, 399: 85–90.

https://doi.org/10.1016/j.neulet.2006.01.018

287. Gao X, Kim HK, Chung JM, et al., 2005, Enhancement of NMDA receptor phosphorylation of the spinal dorsal horn and nucleus gracilis neurons in neuropathic rats. *Pain*, 116: 62–72.

https://doi.org/10.1016/j.pain.2005.03.045

288. Suzuki R, Matthews EA, Dickenson AH, 2001, Comparison of the effects of MK-801, ketamine and memantine on responses of spinal dorsal horn neurones in a rat model of mononeuropathy. *Pain*, 91: 101–109.

https://doi.org/10.1016/s0304-3959(00)00423-1

289. Iwata H, Takasusuki T, Yamaguchi S, et al., 2007, NMDA receptor 2B subunit-mediated synaptic transmission in the superficial dorsal horn of peripheral nerve-injured neuropathic mice. *Brain Res*, 1135: 92–101.

https://doi.org/10.1016/j.brainres.2006.12.014

290. Correll GE, Maleki J, Gracey EJ, et al., 2004, Subanesthetic ketamine infusion therapy: A retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med*, 5: 263–275.

https://doi.org/10.1111/j.1526-4637.2004.04043.x

291. Kiefer RT, Rohr P, Ploppa A, et al., 2008, Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: An open-label phase II study. *Pain Med*, 9: 1173–1201.

https://doi.org/10.1111/j.1526-4637.2007.00402.x

292. Duale C, Sibaud F, Guastella V, et al., 2009, Perioperative ketamine does not prevent chronic pain after thoracotomy. *Eur J Pain*, 13: 497–505.

https://doi.org/10.1016/j.ejpain.2008.06.013

293. Pud D, Eisenberg E, Spitzer A, et al., 1998, The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: A double blind, randomized, placebo controlled trial. *Pain*, 75: 349–354.

https://doi.org/10.1016/s0304-3959(98)00014-1

294. Fukui S, Komoda Y, Nosaka S, 2001, Clinical application of amantadine, an NMDA antagonist, for neuropathic pain. *J Anesth*, 15: 179–181.

https://doi.org/10.1007/s005400170025

295. Lancaster CL, Teeters JB, Gros DF, et al., 2016, Posttraumatic stress disorder: Overview of evidence-based assessment and treatment. *J Clin Med*, 5: 105.

https://doi.org/10.3390/jcm5110105

296. Gates MA, Holowka DW, Vasterling JJ, et al., 2012, Posttraumatic stress disorder in veterans and military personnel: Epidemiology, screening, and case recognition. *Psychol Serv*, 9: 361–382.

https://doi.org/10.1037/a0027649

297. Yuan K, Gong YM, Liu L, et al., 2016, Prevalence of posttraumatic stress disorder after infectious disease pandemics in the twenty-first century, including COVID-19: A meta-analysis and systematic review. *Mol Psychiatry*, 26: 4982–4998.

https://doi.org/10.1038/s41380-021-01036-x

298. Sofuoglu M, Rosenheck R, Petrakis I, 2014, Pharmacological treatment of comorbid PTSD and substance use disorder: Recent progress. *Addict Behav*, 39: 426–433.

https://doi.org/10.1016/j.addbeh.2013.08.014

299. Bestha D, Soliman L, Blankenship K, et al., 2018, The walking wounded: Emerging treatments for PTSD. *Curr Psychiatry Rep*, 20: 94.

https://doi.org/10.1007/s11920-018-0941-8

300. Krystal JH, Abdallah CG, Averill LA, et al., 2017, Synaptic loss and the pathophysiology of PTSD: Implications for ketamine as a prototype novel therapeutic. *Curr Psychiatry Rep*, 19: 74.

https://doi.org/10.1007/s11920-017-0829-z

301. Feder A, Parides MK, Murrough JW, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial.
302. McGhee LL, Maani CV, Garza TH, et al., 2008, The correlation between ketamine and posttraumatic stress disorder in burned service members. J Trauma, 64: S195–8; discussion S197–8.
https://doi.org/1097/TA.0b013e318160ba1d

303. Zhang LM, Zhou WW, Ji YJ, et al., 2015, Anxiolytic effects of ketamine in animal models of posttraumatic stress disorder. Psychopharmacology, 232: 663–672.
https://doi.org/1007/s00213-014-3697-9

304. Zimmerman JM, Maren S, 2010, NMDA receptor antagonism in the basolateral but not central amygdala blocks the extinction of Pavlovian fear conditioning in rats. Eur J Neurosci, 31: 1664–1670.
https://doi.org/1111/j.1460-9568.2010.07223.x

305. Liu JL, Li M, Dang XR, et al., 2009, A NMDA receptor antagonist, MK-801 impairs consolidating extinction of auditory conditioned fear responses in a Pavlovian model. PLoS One, 4: e7548.
https://doi.org/1371/journal.pone.0007548

306. Fry AE, Fawcett KA, Zelnik N, et al., 2018, De novo mutations in GRIN1 cause extensive bilateral polymicrogyria. Brain, 141: 698–712.
https://doi.org/1093/brain/awx3358

307. Yuan H, Low CM, Moody OA, et al., 2015, Ionotropic GABA and glutamate receptor mutations and human neurologic diseases. Mol Pharmacol, 88: 203–217.
https://doi.org/1124/mol.115.097998

308. Hamdan FF, Gauthier J, Araki Y, et al., 2011, Excess of de novo deleterious mutations in genes associated with glutamatergic systems in nonsyndromic intellectual disability. Am J Hum Genet, 88: 306–316.
https://doi.org/1016/j.ajhg.2011.02.001

309. Lemke JR, Geider K, Helbig KL, et al., 2016, Delineating the GRIN1 phenotypic spectrum: A distinct genetic NMDA receptor encephalopathy. Neurology, 86: 2171–2178.
https://doi.org/10122/WNL.0000000000002740

310. Chen W, Shieh C, Swanger SA, et al., 2017, GRIN1 mutation associated with intellectual disability alters NMDA receptor trafficking and function. J Hum Genet, 62: 589–597.
https://doi.org/1038/jhg.2017.19

311. Xu XX, Luo JH, 2018, Mutations of N-methyl-D-aspartate receptor subunits in epilepsy. Neurosci Bull, 34: 549–565.
https://doi.org/1007/s12264-017-0191-5

312. Ohba C, Shiina M, Tohyama J, et al., 2015, GRIN1 mutations cause encephalopathy with infantile-onset epilepsy, and hyperkinetic and stereotyped movement disorders. Epilepsia, 56: 841–848.
https://doi.org/1111/epi.12987

313. Pierson TM, Yuan H, Marsh ED, et al., 2014, GRIN2A mutation and early-onset epileptic encephalopathy: Personalized therapy with memantine. Ann Clin Transl Neurol, 1: 190–198.
https://doi.org/1002/acn3.39

314. Carvill GL, Regan BM, Yendle SC, et al., 2013, GRIN2A mutations cause epilepsy-aphasia spectrum disorders. Nat Genet, 45: 1073–1076.
https://doi.org/1038/ng.2727

315. Lemke JR, Lal D, Reinhalter EM, et al., 2013, Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. Nat Genet, 45: 1067–1072.
https://doi.org/1038/ng.2728

316. Lesca G, Rudolf G, Bruneau N, et al., 2013, GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet, 45: 1061–1066.
https://doi.org/1038/ng.2726

317. Xu XX, Liu XR, Fan CY, et al., 2018, Functional investigation of a GRIN2A variant associated with rolandic epilepsy. Neurosci Bull, 34: 237–246.
https://doi.org/1007/s12264-017-0182-6

318. Yuan H, Tano Y, Burger PB, et al., 2014, Functional analysis of a de novo GRIN2A missense mutation associated with early-onset epileptic encephalopathy. Nat Commun, 5: 3251.
https://doi.org/1038/ncomms4251

319. Chen W, et al., 2017, Functional evaluation of a de novo GRIN2A mutation identified in a patient with profound global developmental delay and refractory epilepsy. Mol Pharmacol, 91: 317–330.
https://doi.org/1124/mol.116.106781

320. Endele S, Rosenberger G, Geider K, et al., 2010, Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet, 42: 1021–1026.
https://doi.org/1038/ng.677

321. Hansen KB, Yi F, Perszyk RE, et al., 2018, Structure, function, and allosteric modulation of NMDA receptors. Nat Rev Neurosci, 19: 1–17.
https://doi.org/1002/acn3.39

322. Wollmuth LP, Kuner T, Sakmann B, 1998, Adjacent asparagines in the NR2-subunit of the NMDA receptor channel control the voltage-dependent block by extracellular Mg2+. J Physiol, 506(Pt 1): 13–32.
323. Mayer ML, 2006, Glutamate receptors at atomic resolution. Nature, 440: 456–462.  
https://doi.org/10.1038/nature04709

324. Gao K, Tankovic A, Zhang Y, et al., 2017, A de novo loss-of-function GRIN2A mutation associated with childhood focal epilepsy and acquired epileptic aphasia. PLoS One, 12: e0170818.  
https://doi.org/10.1371/journal.pone.0170818

325. Swanger SA, Chen W, Wells G, et al., 2016, Mechanistic insight into nmda receptor dysregulation by rare variants in the GluN2A and GluN2B agonist binding domains. Am J Hum Genet, 99: 1261–1280.  
https://doi.org/10.1016/j.ajhg.2016.10.002

326. Vieira MM, Nguyen TA, Wu K, et al., 2020, An epilepsy-associated GRIN2A rare variant disrupts CaMKIIalpha phosphorylation of GluN2A and NMDA receptor trafficking. Cell Rep, 32: 108104.  
https://doi.org/10.1016/j.celrep.2020.108104

327. Fedele L, Newcombe J, Topf M, et al., 2018, Disease-associated missense mutations in GluN2B subunit alter NMDA receptor ligand binding and ion channel properties. Nat Commun, 9: 957.  
https://doi.org/10.1038/s41467-018-02927-4

328. Glasgow NG, Retchless BS, Johnson JW, 2015, Molecular bases of NMDA receptor subtype-dependent properties. J Physiol, 593: 83–95.  
https://doi.org/10.1113/jphysiol.2014.273763

329. Andreoli V, De Marco EV, Trecroci F, et al., 2014, Potential involvement of GRIN2B encoding the NMDA receptor subunit NR2B in the spectrum of Alzheimer’s disease. J Neural Transm, 121: 533–542.  
https://doi.org/10.1007/s00702-013-1125-7

330. Myers RA, Casals F, Gauthier J, et al., 2011, A population genetic approach to mapping neurological disorder genes using deep resequencing. PLoS Genet, 7: e1001318.  
https://doi.org/10.1371/journal.pgen.1001318

331. Hu C, Chen W, Myers SJ, et al., 2016, Human GRIN2B variants in neurodevelopmental disorders. J Pharmacol Sci, 132: 115–121.  
https://doi.org/10.1016/j.j.phs.2016.10.002

332. Tarabeux J, Kebir O, Gauthier J, et al., 2011, Rare mutations in N-methyl-D-aspartate glutamate receptors in autism spectrum disorders and schizophrenia. Transl Psychiatry, 1: e55.  
https://doi.org/10.1038/tp.2011.52

333. Retterer K, Juusola J, Cho MT, et al., 2016, Clinical application of whole-exome sequencing across clinical indications. Genet Med, 18: 696–704.  
https://doi.org/10.1038/gim.2015.148

334. Wells G, Yuan H, McDaniel MJ, et al., 2018, The GluN2B-Glu413Gly NMDA receptor variant arising from a de novo GRIN2B mutation promotes ligand-unbinding and domain opening. Proteins, 86: 1265–1276.  
https://doi.org/10.1002/prot.25595

335. Shin W, Kim K, Serraz B, et al., 2020, Early correction of synaptic long-term depression improves abnormal anxiety-like behavior in adult GluN2B-C456Y-mutant mice. PLoS Biol, 18: e3000717.  
https://doi.org/10.1371/journal.pbio.3000717

336. Soto D, Olivella M, Grau C, et al., 2019, L-Serine dietary supplementation is associated with clinical improvement of loss-of-function GRIN2B-related pediatric encephalopathy. Sci Signal, 12: eaaw0936.  
https://doi.org/10.1126/scisignal.aaw0936

337. Lemke JR, Hendrickx R, Geider K, et al., 2014, GRIN2B mutations in West syndrome and intellectual disability with focal epilepsy. Ann Neurol, 75: 147–154.  
https://doi.org/10.1002/ana.24073

338. Mullier B, Wolff C, Sands ZA, et al., 2017, GRIN2B gain of function mutations are sensitive to radiprodil, a negative allosteric modulator of GluN2B-containing NMDA receptors. Neuropharmacology, 123: 322–331.  
https://doi.org/10.1016/j.neuropharm.2017.05.017

339. Li D, Yuan H, Ortiz-Gonzalez XR, et al., 2016, GRIN2D recurrent de novo dominant mutation causes a severe epileptic encephalopathy treatable with NMDA receptor channel blockers. Am J Human Genet, 99: 802–816.  
https://doi.org/10.1016/j.ajhg.2016.07.013

340. Chen HS, Lipton SA, 2006, The chemical biology of clinically tolerated NMDA receptor antagonists. J Neurochem, 97: 1611–1626.  
https://doi.org/10.1111/j.1471-4159.2006.03991.x