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Synaptic plasticity of NMDA receptors: mechanisms and functional implications

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Abstract

Beyond their well-established role as triggers for LTP and LTD of fast synaptic transmission mediated by AMPA receptors, an expanding body of evidence indicates that NMDA receptors (NMDARs) themselves are also dynamically regulated and subject to activity-dependent long-term plasticity. NMDARs can significantly contribute to information transfer at synapses particularly during periods of repetitive activity. It is also increasingly recognized that NMDARs participate in dendritic synaptic integration and are critical for generating persistent activity of neural assemblies. Here we review recent advances on the mechanisms and functional consequences of NMDAR plasticity. Given the unique biophysical properties of NMDARs, synaptic plasticity of NMDAR-mediated transmission emerges as a particularly powerful mechanism for the fine tuning of information encoding and storage throughout the brain.

Keywords

LTP; LTD; metaplasticity; glutamate; metabotropic receptor; GluN2A; GluN2B; subunit switch; calcium signaling; receptor trafficking; receptor lateral mobility; bursting; burst firing; integrative functions

INTRODUCTION

A central task in contemporary neuroscience is to identify the cellular and molecular mechanisms underlying cognitive brain functions, and how alterations of these mechanisms can lead to neuropsychiatric disease states. Several decades of intense research indicate that activity-dependent changes in excitatory synaptic efficacy such as long-term potentiation (LTP) and long-term depression (LTD) likely are cellular correlates to learning and memory [1–4]. In the vertebrate central nervous system the predominant mode of excitatory transmission is mediated by the neurotransmitter glutamate and the ionotropic glutamate receptors [5]. While α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) support fast excitatory transmission at most synapses, *N*-methyl-D-aspartate receptors (NMDARs) have classically been thought of as coincidence detectors (i.e. coincidence of glutamate release and postsynaptic depolarization) for the induction of long-

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term plasticity expressed as changes in AMPAR-mediated transmission [6]. According to this view, changes in NMDAR function or expression can effectively modify the induction threshold for AMPAR-mediated plasticity, a phenomenon commonly known as metaplasticity [7]. While classical NMDAR-dependent LTP/LTD of AMPAR-mediated transmission and NMDAR-dependent metaplasticity are important, when considered alone, these dynamic actions of NMDARs constrain their functional capacity to that of simply regulating the induction of AMPAR-mediated plasticity. However, NMDARs can play a much broader functional role in basal synaptic transmission [8], particularly under certain physiological conditions (such as during bursting activity) [9], as well as contribute to the integrative properties of neurons [10]. The integrative functions of synaptic NMDARs stem from the unique nonlinear amplification properties endowed by the Mg^{2+} block of NMDARs at resting potential, their high permeability to Ca^{2+} , and the slow kinetics of NMDAR-EPSPs, which allow for temporal summation (Fig. 1) [5,11–13].

Extensive work, mainly using heterologous expression systems or cultured neurons, has been dedicated to elucidating the molecular mechanisms underlying modulation of NMDAR function and trafficking (for reviews see [14–18]). These studies have shown that a vast array of kinases, phosphatases, receptor-coupled signaling molecules, and intracellular signals can regulate NMDARs under various experimental conditions. However, what modes of regulation are engaged in more intact preparations under more physiological conditions remain a matter of active research. While originally thought to be less dynamic than their AMPAR counterparts [17], increasing evidence demonstrates that NMDARs themselves can be regulated in an activity-dependent manner, and both LTP and LTD of NMDAR-mediated transmission have been reported in several brain areas [15,19] (Table 1). In this review we will focus on recent work in which activity-dependent, long-term plasticity of NMDAR-mediated transmission has been identified and characterized mainly using acute brain slices. We will discuss the properties and molecular mechanisms underlying NMDAR-LTP/LTD throughout the brain (Fig. 2), and where appropriate, attempt to place these forms of plasticity in a physiological context.

LONG-TERM PLASTICITY OF NMDAR-MEDIATED TRANSMISSION

Long-term potentiation

The question of whether NMDAR-mediated transmission could undergo both LTP and LTD has been addressed by numerous studies spanning nearly three decades of research. Early studies using hippocampal brain slices showed that similar induction protocols that trigger AMPAR-LTP also induce NMDAR-LTP at the Schaffer collateral to CA1 pyramidal cell synapse (Sch-CA1) [20–27], and at the perforant path to dentate granule cell synapse (PP-DGC) [28–30]. However, the presence of NMDAR-LTP was not confirmed by others [31–34]. While this discrepancy could be due to different experimental conditions, it was suggested that a stronger induction protocol is required to elicit NMDAR-LTP vs AMPAR-LTP, at least at the Sch-CA1 synapse [22,25]. Following these initial descriptions of NMDAR-LTP in CA1 and dentate gyrus, the topic of both NMDAR-mediated transmission and NMDAR plasticity were immediately eclipsed by a massive number of studies on LTP and LTD of AMPAR-mediated transmission. Perhaps this shift in focus was based on the prevailing view in the field that AMPAR-LTP can occur independently of changes in NMDAR-mediated transmission, at least in the CA1 area [31–34]. It was also suggested that NMDARs could be relatively less dynamic at the synapse. Contrary to this notion, a growing body of evidence has demonstrated that NMDAR-mediated transmission can be dynamically regulated independently as well as concomitantly with AMPAR-mediated transmission.

Several groups have noted that NMDAR-LTP can develop over a longer timescale relative to AMPAR-LTP. At unitary connections between layer 5 pyramidal neurons in visual cortical slices, early LTP of the AMPAR-mediated component is followed by a delayed NMDAR-LTP, which seems to restore the AMPAR-to-NMDAR ratio [35]. Delayed NMDAR-LTP has been observed at other synapses as well [25–26,36]. The induction mechanism of this delayed NMDAR-LTP, the reason for delayed potentiation, and whether it requires previous AMPAR-LTP, all remain to be elucidated. Remarkably, *in vivo* induction of LTP in rat DG increased the surface expression of NMDARs in a delayed and protein synthesis-dependent manner [37], although it is uncertain whether such increase is associated with a measurable increase in synaptic NMDAR transmission (i.e., NMDAR-LTP).

Recent studies have shown that NMDAR-plasticity can occur independently of AMPAR-plasticity. For example, brief bursts of synaptic activity elicit NMDAR-LTP at mossy fiber to CA3 pyramidal cell synapses (MF-CA3) [38–39] and glutamatergic synapses onto dopaminergic neurons in the midbrain (e.g. substantia nigra and ventral tegmental area, or VTA) [40]. NMDAR-LTP at these synapses share several properties, including a postsynaptic mechanism of expression, and the requirement of NMDAR and mGluR5 co-activation for induction. The requirement of mGluR5 activation in NMDAR-LTP has also been reported at other hippocampal synapses [36,41–42], and is consistent with previous observations in cultured neurons and expression systems [14–15,43]. Notably, several studies indicate a direct physical interaction between the NMDAR and mGluRs complexes via PDZ domain-containing proteins in the postsynaptic density [44]. In addition to mGluR5, type 2 adenosine receptors are also required for the induction of NMDAR-LTP at the MF-CA3 synapse [39]. Another commonality between NMDAR-LTP in CA3 pyramidal and dopaminergic midbrain neurons is that induction requires a rise in postsynaptic $[Ca^{2+}]$, which can occur as a result of Ca^{2+} influx via NMDARs, as well as Ca^{2+} release from internal stores. The precise Ca^{2+} sensors involved in detecting these postsynaptic Ca^{2+} signals that lead to plasticity remain unclear. A point of divergence between these forms of NMDAR-LTP is the requirement of differential kinase activity, where PKC [38] and Src kinases [39] are required for plasticity in CA3 neurons, in agreement with NMDAR-LTP at other synapses [30,45–46], while PKA is required in dopaminergic neurons of the midbrain [40].

Diverse modes of expression have been identified for NMDAR-LTP. At MF-CA3 synapses, NMDAR-LTP appears to be expressed by exocytosis of NMDARs [38] as intracellular loading of a SNAP-25 interfering peptide blocks plasticity. An increase in NMDAR surface expression has also been implicated in NMDAR-LTP at Sch-CA1 synapses [45]. In the dentate gyrus, NMDAR-LTP can be expressed by recruitment of NMDARs from extrasynaptic to synaptic sites [47], in accordance with previous studies in neuronal cultures showing that NMDARs can move laterally between synaptic and extrasynaptic pools [48–49]. Beyond these few examples, the mechanisms of expression of NMDAR-LTP remain largely unexplored.

Long-term depression

Long-term depression of NMDAR-mediated transmission has also been reported at several synapses (Table 1). Similar to the case where AMPA and NMDAR plasticity can be co-induced, induction protocols used to trigger AMPAR-LTD (e.g. low frequency stimulation) can also induce NMDAR-LTD at hippocampal CA1 synapses [26,34,36,50–54], associative/commissural CA3 synapses [55–56], and PP-DGC synapses [42]. “Chemical” NMDAR-LTD at Sch-CA1 synapses can be induced by transient (10 min) perfusion of the group I mGluR agonist DHPG [57], or muscarinic cholinergic receptor (mAChRs) agonists [54]. Intriguingly, brief activation of mAChRs by acetylcholine (e.g., puff application or

endogenous release by theta-burst stimulation of the alveus) can cause a long-lasting increase in NMDAR-mediated transmission [58], raising the possibility that the duration, localization or magnitude of mAChR activation could determine the direction of NMDAR plasticity. NMDAR-LTD in midbrain dopaminergic neurons is elicited by a pairing (pre and postsynaptic) bursting protocol; however, little is known about the mechanisms of induction or expression of this form of plasticity [40].

Typically, NMDAR-LTD requires an intracellular $[Ca^{2+}]$ rise for induction and, at least in the dentate gyrus, the direction of NMDAR plasticity (e.g., LTP or LTD) appears to depend on the free Ca^{2+} concentration triggered by the induction protocol [42]. The precise mechanism by which Ca^{2+} elicits NMDAR LTD is unclear. However, hippocalcin has recently been identified as a Ca^{2+} sensor mediating cholinergic induction of NMDAR-LTD at Sch-CA1 synapses [54]. It remains to be determined how this protein can mediate Ca^{2+} sensing for both AMPAR-LTD [59] and NMDAR-LTD at the same synapse. These results may suggest that exquisite sensitivity to Ca^{2+} microdomains by spatially delimited signaling machinery may allow for AMPAR or NMDAR plasticity. Furthermore, it seems that the induction protocol can dictate the necessity for downstream phosphatase activity, where induction that requires NMDAR activation also requires PP1/PP2A activity [52], whereas induction via mAChRs does not [54].

Different forms of NMDAR-LTD can exhibit diverse mechanisms of expression. At Sch-CA1 synapses, there is evidence that NMDAR-LTD can be mediated by Ca^{2+} -dependent actin depolymerization, which promotes destabilization of the underlying cytoskeletal framework and lateral diffusion of NMDARs away from synaptic sites [36,52]. A similar mechanism can also underlie DHPG-induced NMDAR-LTD at these synapses [57]. However, when NMDARs are antagonized during induction, paired-pulse low frequency stimulation of Schaffer collaterals induces a form of NMDAR-LTD that requires mAChR activation and is expressed by a dynamin-dependent internalization of NMDARs [54]. At recurrent synapses between CA3 pyramidal cell pairs in organotypic slice cultures, NMDAR-LTD is also expressed by dynamin-dependent endocytosis [55–56].

Recent work has provided evidence for reversibility of NMDAR plasticity. NMDAR-LTP in midbrain dopaminergic neurons can be reversed by a burst of presynaptic stimulation [40], but the mechanism of this de-potentialization has yet to be elucidated. Likewise, de-depression of NMDAR-LTD at Sch-CA1 synapses has been reported, and appears to rely on NMDAR activation and mitogen activated protein kinase activity [51]. While the vast majority of reports focus solely on either LTP or LTD of NMDAR-mediated transmission, reports of bidirectional NMDAR plasticity are sparse (see Table 1).

Beyond the magnitude of NMDAR-mediated synaptic responses

While most forms of NMDAR plasticity discussed so far are expressed as a modification in the amplitude of NMDAR-mediated synaptic responses, several studies indicate that changes in NMDAR function can accompany, or occur irrespective to alterations in response amplitude. In hippocampal CA1 pyramidal neurons, low frequency trains of glutamate uncaging lead to a long-term depression of NMDAR-mediated transmission and, an even stronger depression of Ca^{2+} signals (i.e. depression of the NMDAR fractional Ca^{2+} current) at individual dendritic spines in an all-or-none manner [60]. While direct evidence of synaptic activity-dependent changes in NMDAR-mediated Ca^{2+} signaling without changes in response amplitude is scarce, there is experimental evidence suggesting how this regulation could occur. For instance, in CA1 pyramidal neurons, PKA activity upregulates NMDAR Ca^{2+} permeability without affecting NMDAR-EPSP amplitude [61]. In agreement with this observation, activation of metabotropic receptors signaling via PKA, such as type 2 dopamine receptors and type 2 adenosine receptors in dorsal striatum [62], and GABA_B

receptors in prefrontal cortex [63], modulate NMDAR-mediated calcium signals in dendritic spines. Dynamic NMDAR-mediated Ca^{2+} influx has the potential to influence the induction of NMDAR-dependent AMPAR-LTP/LTD, as well as NMDAR Ca^{2+} -coupled conductances (e.g., BK-type Ca^{2+} -activated K^{+} channels), the latter of which will impact neuronal excitability [64].

NMDARs are hetero-tetramers typically composed of GluN1 and GluN2 subunits, where the precise subunit composition determines the functional properties of NMDARs [5,65–66]. Notably, the subunit composition can be regulated in response to neural activity [53,67–69], and by sensory experience early in life [70–71]. An acute, activity-driven NMDAR switch in subunit composition was identified at neonatal Sch-CA1 synapses [53], and was later shown to require NMDAR and mGluR5 co-activation, PLC activity, Ca^{2+} release from IP3R-dependent stores, and PKC activity [67]. It therefore appears that this form of plasticity is mechanistically similar to NMDAR-LTP described at more mature synapses, including MF-CA3, PP-DG and Sch-CA1 synapses (see Table 1). Additional work at mature synapses in the DG and CA1 regions of the hippocampus indicates that expression of NMDAR plasticity can also be accompanied by a shift in subunit composition [36,47], a mechanism that does not appear to be associated with NMDAR-LTP in dopaminergic midbrain neurons [40]. In any case, activity-dependent changes in NMDAR subunit composition will have important implications for NMDAR function, including changes in Ca^{2+} influx through NMDARs and postsynaptic Ca^{2+} dynamics, which in turn can regulate the magnitude and sign of NMDAR-dependent forms of synaptic plasticity [70].

FUNCTIONAL SIGNIFICANCE OF NMDAR PLASTICITY

Metaplasticity

An expected consequence of NMDAR plasticity is the potential for a long-term change in the inducibility of NMDAR-dependent forms of plasticity, such as LTP and LTD of AMPAR-mediated transmission. Such a shift in the induction threshold of synaptic plasticity is one form of metaplasticity [72]. This higher order form of synaptic regulation is commonly regarded as a homeostatic mechanism to buffer the extent of synaptic modification against saturation, thereby ensuring the fidelity of synaptically encoded information within a given network [7]. Despite the key role of NMDARs in the induction of conventional LTP/LTD of AMPAR-mediated transmission, there is surprisingly little direct evidence in support of long-term NMDAR plasticity as a mechanism of metaplasticity. This is presumably due to the fact that NMDAR plasticity and the potentially associated metaplasticity are in several cases induced simultaneously, making the analysis of metaplasticity problematic. At hippocampal mossy fiber synapses, where NMDAR-LTP can occur in the absence of AMPAR-LTP [38–39], it has recently been reported that NMDAR-LTP could be a prerequisite for the induction of NMDAR-dependent AMPAR-LTP [73]. This observation is intriguing given previous evidence that the postsynaptic machinery commonly involved in AMPAR-LTP at most synapses is likely missing at the MF-CA3 synapse [74]. As mentioned above, NMDAR plasticity can include a shift in NMDAR subunit composition, and the associated change in receptor function could have an important impact on the magnitude and sign of AMPAR-plasticity [70]. In this context, new research using cultured hippocampal neurons has elegantly shown that prolonged suppression of spontaneous glutamate release up-regulates GluN2B-containing NMDARs and augments Ca^{2+} influx at single dendritic spines, thus facilitating the induction for AMPAR-LTP [68]. Whether this kind of metaplasticity occurs in more intact preparations awaits confirmation.

Recent studies have shown that *in-vivo* exposure to ethanol [75] or amphetamine [76] enhances NMDAR-LTP in the rat VTA. This enhancement seems to be due to increased Ca^{2+} release from internal stores as a result of PKA-dependent sensitization of IP3

receptors. Metaplasticity commonly refers to changes in AMPAR plasticity, but it may include other forms of plasticities as well. Under this more inclusive definition, these studies represent progress towards understanding the mechanisms underlying metaplasticity of NMDAR plasticity.

Bursting activity and integrative functions

NMDAR-mediated currents are minimal at membrane potentials more negative than -70 mV. However, given the region of negative slope conductance from approximately -70 to -35 mV [12–13] (Fig. 1A), current definitely flows through the channel and can be amplified in neurons that are usually depolarized by incoming excitatory activity, a condition commonly found *in vivo*. Due to the slow decay kinetics of NMDAR-EPSPs temporal summation of these responses can produce a sustained level of excitation, driving neuronal firing upon repetitive synaptic activity (Fig. 1B,C). NMDARs also carry a substantial fraction of the total synaptic charge [13] and may be important for recurrent excitation in cortical networks [77–78]. Thus, in addition to their well-known role as coincidence-detectors in the induction of AMPAR-LTP/LTD [6], NMDARs play an important role in basal synaptic transmission [8–9]. As a result, NMDARs can contribute significantly to the integrative properties of neurons [10], and in generating persistent activity of neural assemblies [79].

Neuronal bursting activity has been described in numerous neuronal subtypes across multiple model organisms [80], and is thought to represent particularly salient information, allowing for selective communication across anatomical brain regions [81–82]. Consistent with this notion, several reports spanning the past decade have indicated that coincident NMDAR activation across multiple synapses can generate non-linear signals in dendrites, such as “NMDA spikes” or “NMDA plateau potentials” (for recent reviews, see [10,83]) (Fig. 3A). This NMDAR-mediated nonlinearity has been shown to be critical in recognizing and subsequently generating bursts of action potentials [84], which likely occur as a result of a strict correlation between the generation of the dendritic NMDA plateau potential, and a prolonged depolarization of the somatic membrane potential. Moreover, NMDARs have been shown to control normal bursting activity as well as the epileptic discharge of granule cells of the DG [85], and play an important role in the transition from tonic firing mode to bursting mode in dopaminergic midbrain neurons [86] (Fig. 3B). As growing evidence indicates that NMDARs in VTA neurons are involved in addictive behaviors [70,75,87–88], it is likely that NMDAR plasticity in the VTA, by regulating bursting activity, may play a pivotal role in the encoding of reward and ultimately, in the development of addictive behaviors. Building on the biophysical properties of NMDARs, it has been shown that synaptic NMDARs contribute to overcoming the electrotonic disadvantage imposed by distal dendritic locations [89], in addition to a role in the spatio-temporal discrimination of synaptic inputs along dendrites [83]. Furthermore, NMDARs have been implicated in the generation of plateau potentials that mediate pathway interactions between different inputs across cortical layers [90]. While significantly more work will be needed to demonstrate directly the impact of NMDAR plasticity on bursting activity and the integrative functions of neurons and neural circuits, the available evidence indicates that synaptic NMDARs, and therefore NMDAR plasticity can be a major factor governing these important neural properties.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent work on NMDAR-mediated transmission has bolstered the notion that synaptic NMDARs, as with their AMPAR counterparts, are dynamically regulated and can undergo activity-dependent plasticity throughout the brain. In some cases, NMDAR plasticity occurs in the absence of AMPAR plasticity. When both components are potentiated or depressed,

the signaling cascades involved are not necessarily identical. In addition, some synapses seem to be more susceptible to NMDAR plasticity than others. The unique functional properties of the NMDAR, including high Ca^{2+} permeability, negative slope conductance (a property that enables signal amplification), and slow NMDAR-EPSP kinetics, makes NMDAR plasticity a particularly powerful mechanism for the fine tuning of information encoding and storage (Fig. 3C). Just considering the role of Ca^{2+} as a second messenger, NMDAR plasticity would be expected to have far reaching implications beyond amplitude changes of NMDAR-mediated synaptic responses. In addition to triggering AMPAR-LTP/LTD, NMDARs play an important role in other forms of synaptic plasticity, including inhibitory synaptic plasticity [91], thereby expanding the functional impact of activity-dependent NMDAR plasticity not only to excitatory but also inhibitory synapses. Despite extensive information regarding the regulation of NMDAR function and trafficking in cultured neurons and expression systems [14–18,92], much remains to be learned about the molecular basis of activity-dependent NMDAR plasticity in more intact preparations. Thus far, most work has examined NMDAR plasticity *in vitro* under rather unphysiological experimental conditions. An important future challenge is to determine the precise contribution of NMDAR-LTP/LTD *in vivo*, and its relationship to experience-driven changes in NMDAR-mediated transmission [71,93].

Some commonalities have emerged regarding the induction mechanism of NMDAR plasticity across synapses, most notably, the need for NMDAR and mGluR5 activation, as well as the role of postsynaptic Ca^{2+} , protein kinases and phosphatases (Fig. 2). A more divergent picture emerges for expression mechanisms since changes in NMDAR function, number and subunit composition have all been implicated. Changes in NMDAR expression can occur via exo/endocytosis or lateral mobilization in and out of the synapse. It is unclear whether these mechanisms of expression coexist at a given synapse type. Unlike AMPARs, which have been shown to have a vast array of auxiliary subunits modulating trafficking and/or function with significant relevance to AMPAR plasticity [94], the identity and function of auxiliary subunits of NMDARs remains relatively unexplored.

While the vast majority of studies support a postsynaptic locus of NMDARs, the existence and functional role of NMDARs localized to the presynapse has recently received greater appreciation (for a review, see [95]). There is evidence for presynaptic NMDARs acting as coincidence-detectors and playing an essential role for some forms of spike timing-dependent plasticity [96–97]. Whether these receptors themselves can undergo plastic changes remains untested. However, the recent observation that the subunit composition of presynaptic NMDARs can be developmentally regulated, thereby modulating the inducibility of spike-timing dependent plasticity [98], raises the possibility that presynaptic NMDARs could undergo some form of plasticity, which remains to be determined. Although we have focused primarily on the mechanisms and implications of rapid, synapse specific NMDAR plasticity, mounting evidence indicates that NMDARs can participate in homeostatic plasticity [92]. Homeostatic mechanisms of NMDAR plasticity act over relatively longer timescales and can underlie metaplasticity [68]. Further investigation of the link between NMDAR homeostatic plasticity and the molecular mechanisms governing NMDAR trafficking may serve to bridge the gap in our understanding of how these processes integrate activity over multiple timescales to support various cognitive functions. Finally, NMDAR dysregulation has been implicated in a variety of neurological and psychiatric disorders, including ischemia/stroke, epilepsy, schizophrenia, drug addiction, chronic pain, and several neurodegenerative diseases [15,99]. While emerging evidence suggests that activity-dependent regulation of NMDARs could play an important role in addictive behaviors, further studies are warranted to directly test the potential involvement of NMDAR plasticity to other neuropsychiatric conditions.

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- NMDARs exhibit diverse functional role based on their unique biophysical properties
- We review current work describing activity-dependent plasticity of NMDAR plasticity
- NMDARs can be dynamically regulated by numerous induction and expression mechanisms
- NMDAR plasticity is a powerful means by which information can be encoded and stored

Figure 1. Unique biophysical properties of NMDARs and the resultant functional impact on temporal summation and firing output

A) *Top*, current-voltage relationship comparison between AMPARs and NMDARs. NMDARs exhibit a characteristic region of negative slope from approximately -70 to -35 mV, a property that enables positive feedback, and allows for signal amplification. *Bottom*, Dual (AMPA and NMDAR) component EPSPs elicited at -70 and -40 mV membrane potential, highlighting the enhancement of the slow NMDAR component at -40 mV, whereas the fast AMPAR component is diminished. **B)** *Left*, Representation of temporal summation of dual (gray) and pharmacologically isolated AMPAR (black) and NMDAR (red) EPSPs elicited by a train of subthreshold synaptic stimulation (vertical black arrows). The relative difference between the AMPAR and NMDAR-mediated responses likely reflects both voltage-dependent Mg^{2+} block and slow decay kinetics. *Right*, Suprathreshold repetitive stimulation illustrating the contribution of NMDARs (red) to spike output relative to AMPARs (black). The temporal summation afforded by NMDARs leads to more reliable spike output throughout the train. Modified with permission from Augustinaite & Heggelund, *J Physiol* 582: 297–315, 2007.

Figure 2. Common pathways of NMDAR plasticity

Left: Induction of NMDAR plasticity has been shown to be triggered by postsynaptic Ca^{2+} rise that can be achieved through NMDARs and voltage gated calcium channels (VGCCs). Metabotropic receptors, such as group I mGluR, mAChR, D₂R, A_{2A}R, can also contribute by releasing Ca^{2+} from internal stores (either via inositol triphosphate receptors, IP₃R or ryanodine receptors, RyRs). Postsynaptic calcium signals activate enzymatic activity required for plasticity, including PKC, PKA, Src, PP1/PP2A. Metabotropic receptors could also directly activate the enzymatic activity (gray dash arrow). *Right:* Diverse modes of expression have been identified for NMDAR plasticity that involve NMDAR exo/endocytosis as well as lateral mobility between synaptic and extrasynaptic pools. Expression of NMDAR plasticity can also involve changes in the magnitude of fractional Ca^{2+} current through NMDARs. Modes of expression can also be associated with a shift in NMDAR subunit composition (*).

Figure 3. Functional consequences of NMDAR plasticity

A) NMDAR plasticity can modify the threshold for the initiation of an NMDA spike or plateau potential, an important integrative property of cortical neurons. **B)** NMDARs have been shown to be critical for the transition between single spike and complex spike/bursting output modes in several cell types, enabling the regulation of information transfer. **C)** Schematic representing the effects of AMPAR (black) vs. NMDAR (red) plasticity in response to repetitive synaptic activation (e.g. bursts like those depicted in Fig. 1B) where AMPAR plasticity generally leads to linear changes in gain while NMDAR plasticity enables nonlinear shifts in output.

Table 1

Activity-dependent NMDAR-LTP/LTD in the brain*

Brain area (Synapse type)	Induction protocol	Requirements/Properties	References
LTP	20–25 stimuli, 100 Hz	NMDAR activation	[20]
	(100 stimuli, 100 Hz)x2	NMDAR activation	[21]
	10 stimuli, 50 Hz, 0.1 mM (Mg^{2+}); 10–20 stimuli, 50 Hz, x2 stim strength; 2.0 mM (Mg^{2+}) _e		[23]
	TBS (10 trains at 5Hz, each train consisting of 4 stimuli, 100Hz); 0.05–0.2 mM (Mg^{2+}) _e		[24–25]
	2 trains at 10 intervals, each train consisting of 100 stimuli at 100 Hz.	mGluR5 activation	[41]
	6 trains at 20 s intervals, each train consisting of 7 stimuli at 200 Hz; depolarization to –45 mV		[100]
	5 trains at 10 intervals, each train consisting of 20 stimuli at 100 Hz, repeated four times during a period of 10 min; or single train of 20 stimuli at 50 Hz; 0.1 mM (Mg^{2+}) _e		[26]
	2–5 trains at 20 s intervals, each train consisting of 30 stimuli at 30 Hz		[27]
	3 trains at 20 s intervals, each train consisting of 100 stimuli at 100Hz; 0.3 mM (Mg^{2+}) _e		[22]
	4 trains at 30 s intervals, each train consisting of 100 stimuli at 100 Hz;	PKC and Src	[45]
	Pairing-protocol, 2 Hz repetitive stimulation for 90 s delivered at 0 mV	Subunit switch	[53]
	Pairing-protocol, 1 Hz repetitive stimulation for 90 s delivered at 0 mV	NMDAR activation, postsynaptic Ca^{2+} rise, PKC and Src	[46]
	Pairing-protocol, 200 stimuli at 2Hz delivered at 0 mV with a 2.5-min depolarization to 0 mV prior to stimulation; 0.25 mM (Mg^{2+}) _e	Postsynaptic Ca^{2+} rise, NMDAR and mGluR5 co-activation, PKC, SNARE complex, actin stabilization, incorporation of GluN2A-containing receptors	[36]
	Single train of 25 stimuli at 25 Hz	Postsynaptic Ca^{2+} rise, mGluR5 and NMDAR co-activation, PKC, SNARE complex	[38]
Hippocampus (Mossy fiber-CA3)	Single train of 60 stimuli at 50 Hz	Postsynaptic Ca^{2+} rise, A2AR mGluR5, NMDAR activation, Src	[39]
Dentate Gyrus (PP-DGC)	4 trains at 5 s intervals, each train consisting of 20 stimuli at 10 or 50 Hz	Postsynaptic Ca^{2+} rise	[28]
	8 trains at 2 s intervals, each train consisting of 8 stimuli at 200 Hz	Postsynaptic Ca^{2+} rise, mGluR5 and NMDAR activation, PKC	[29–30] [42,47]

Brain area (Synapse type)	Induction protocol	Requirements/Properties	References
Amygdala (Glutamatergic inputs to basolateral amygdala)	2 trains at 20 s intervals, each train consisting of 100 stimuli at 100 Hz.	NMDAR activation	[101]
Visual cortex (L5-1.5 pyramidal neurons)	Pairing 200 ms pre- and postsynaptic current injections (current clamp mode) 30 times at 0.1–0.2 Hz; 0.5 mM (Mg^{2+}) _e ; pharmacological blockade of CB1 receptors.	Requires previous AMPAR-LTP (at least in visual cortical cultures).	[35]
Midbrain Dopamine Neurons (Glutamatergic inputs onto SNC and VTA neurons)	10 trains at 20 s intervals, each train consisting of 70 stimuli at 50 Hz and paired with a burst of five postsynaptic unclamped APs at 20 Hz, pre → post, 0.1 mM (Mg^{2+}) _e	Postsynaptic Ca^{2+} rise, Ca^{2+} release from internal stores, NMDAR activation, IP3 signaling, PKA,	[40]
LTD	Low-frequency stimulation (1 Hz, 5 min) paired with 500 ms depolarization steps and cell firing (2–6 action potentials)	NMDAR activation	[50]
	2–5 trains at 20 s intervals, each train consisting of 5 stimuli at 5 Hz	mGluR activation	[27]
	Low-frequency stimulation (2 Hz, 10 min); 0.1 mM (Mg^{2+}) _e		[26]
	Low-frequency stimulation (1 Hz, 5–7 min); 6 trains at 120 s intervals, each train consisting of 100 stimuli at 10 Hz.	Postsynaptic Ca^{2+} rise, NMDAR activation	[34]
	Single train of 900 stimuli at 5 Hz delivered at –40 mV	Postsynaptic Ca^{2+} rise, protein phosphatase 1, actin depolymerization	[51–52]
	Pairing-protocol, 600 stimuli at 1 Hz delivered at –40 mV.		[53]
	Paired-pulse low-frequency stimulation [PP-LFS, 200 paired-pulses (50-ms interval) at 1 Hz] delivered at –40 mV	mAChR activation, postsynaptic Ca^{2+} rise from IP3-sensitive intracellular stores, hippocampin, dynamin activity	[54]
	Single train of 900 stimuli at 5 Hz delivered at –40 mV	Postsynaptic Ca^{2+} rise, NMDAR and mGluR5 co-activation, actin destabilization, incorporation of GluN2B-containing receptors	[36]
	4 trains at 10 s intervals, each train consisting of 13 glutamate pulses (single dendritic spine 2 photon laser uncaging) at 3.3 Hz		[60]
	Low-frequency stimulation (1 Hz, 10 min) paired with depolarization to ~ –50mV	NMDAR activation, dynamin activity	[55–56]
Hippocampus (CA3-CA3)	Low-frequency stimulation (1 Hz, 15 min)	Postsynaptic Ca^{2+} rise, mGluR5 activation	[42]
Dentate Gyrus (PP-DGC)	4 trains at 5 s intervals, each train consisting of 20 stimuli at 10 Hz; hyperpolarization to –100 mV	Postsynaptic Ca^{2+} rise	[28]
Midbrain Dopamine Neurons (Glutamatergic inputs onto SNC and VTA neurons)	10 trains at 20 s intervals, each train consisting of 70 stimuli at 50 Hz and paired with a burst of five postsynaptic unclamped APs at 20 Hz, post → pre, 0.1 mM (Mg^{2+}) _e		[40]
Nucleus Accumbens (Glutamatergic inputs onto NAc neurons)	1–3 trains at 10 s intervals, each train consisting of 100 stimuli at 100 Hz; pairing-protocol 120 stimuli at 2 Hz delivered at ~ –40 mV.	Postsynaptic Ca^{2+} rise, GluN2A-containing NMDARs	[102–103]

* The table includes examples of NMDAR-LTP/LTD in acute brain slices from rodents (rat and mouse), except for one example using rabbit [42].

Abbreviations: TBS, theta-burst stimulation; $(Mg^{2+})_o$, extracellular magnesium concentration; PP, perforant path; DGC, dentate granule cell; STDp, spike timing-dependent plasticity; VGCC, voltage-gated calcium channel; mGluR, metabotropic glutamate receptor; mAChR, muscarinic acetylcholine receptor; NAc, Nucleus Accumbens; Sch, Schaffer Collateral; SNc, Substantia Nigra pars compacta; VTA, Ventral tegmental area.