Neurosci Bull April 1, 2015, 31(2): 191–197. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1504-6

·Review·

Contribution of NMDA receptors to dorsolateral prefrontal cortical networks in primates

Min Wang, Amy F T Arnsten
Department of Neurobiology, Yale Medical School, New Haven, CT 06510, USA
Corresponding author: Min Wang. E-mail: Min.wang@yale.edu

Cognitive disorders such as schizophrenia and Alzheimer's disease are associated with dysfunction of the highly evolved dorsolateral prefrontal cortex (dlPFC), and with changes in glutamatergic N-methyl-*D*-aspartate receptors (NMDARs). Recent research on the primate dlPFC discovered that the pyramidal cell circuits that generate the persistent firing underlying spatial working memory communicate through synapses on spines containing NMDARs with NR2B subunits (GluN2B) in the post-synaptic density. This contrasts with synapses in the hippocampus and primary visual cortex, where GluN2B receptors are both synaptic and extrasynaptic. Blockade of GluN2B in the dlPFC markedly reduces the persistent firing of the Delay cells needed for neuronal representations of visual space. Cholinergic stimulation of nicotinic α7 receptors within the glutamate synapse is necessary for NMDAR actions. In contrast, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors have only subtle effects on the persistent firing of Delay cells, but contribute substantially to the firing of Cue and Response cells. Systemic administration of the NMDAR antagonist ketamine reduces the persistent firing of Delay cells, but increases the firing of some Response cells. The reduction in persistent firing produced by ketamine may explain why this drug can mimic or worsen the cognitive symptoms of schizophrenia. Similar actions in the medial PFC circuits representing the emotional aspects of pain may contribute to the rapid analgesic and anti-depressant actions of ketamine.

Keywords: glutamate; Alzheimer's disease; schizophrenia; depression; ketamine

Introduction

Glutamate acts at a variety of ionotropic receptors, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), kainate receptors, and N-methyl-*D*-aspartate receptors (NMDARs)[1]. NMDARs have been of particular interest due to their unique properties: they require depolarization to relieve their Mg^{++} block, and are permeable to Ca^{++} that can initiate second-messenger signaling events, such as mediating neuroplasticity or negative feedback through Ca^{++}-sensitive K^{+} channels. NMDARs contain an NR1 subunit and a mixture of NR2A–D subunits that alter the functional properties of the receptor, e.g. NMDARs with NR2A subunits (GluN2A) are more sensitive and have faster kinetics, while those with NR2B subunits (GluN2B) have slower kinetics and can produce increased levels of calcium influx[2]. As NMDARs are altered in cognitive disorders such as schizophrenia and Alzheimer's disease, there has been increasing research on these receptors[3, 4]. The highly-evolved dorsolateral prefrontal cortex (dlPFC) is only found in primates[5] and subserves higher cognitive functions, especially those affected in these mental disorders[6, 7]. The following review briefly summarizes new data demonstrating the key role of GluN2B receptors in the primate dlPFC, and how their actions in the dlPFC appear to differ from classical findings in the sensory cortex and hippocampus.

NMDAR and AMPAR Actions in Visual Cortex and Hippocampus

There have been extensive studies on the glutamate

NMDAR and AMPAR mechanisms underlying long-term synaptic plasticity in the primary visual cortex and in CA1 neurons of the hippocampus[8-10]. Long-term plasticity is powerfully regulated by the levels of AMPAR expression: the number of AMPARs inserted into the post-synaptic density can mediate the degree of spine depolarization and thus the NMDAR opening. AMPAR membrane insertion leads to structural synaptic changes such as enlarging the spine head and shortening/thickening of the spine neck[11, 12] to create a stable, mushroom-shaped spine and enduring strengthening of a synaptic connection[13], and/or the addition of new spines and synapses[11]. Synaptic plasticity in the mature visual cortex appears to be governed by GluN2A subunits, which have faster kinetics than GluN2B. GluN2B receptors are expressed in synapses early in development, but many move to extra-synaptic locations in the mature visual cortex and hippocampus[14]. In the hippocampus, there is some evidence that long-term potentiation (LTP) is mediated by synaptic GluN2A, while long-term depression is mediated by extrasynaptic GluN2B receptors[8]. However, this finding is controversial. For example, there is increasing evidence that GluN2B receptors are also important for LTP in hippocampal neurons[15-17]. In the mature visual cortex, long-term plastic changes in synapses appear to rely heavily on GluN2A, e.g. a selective GluN2A antagonist inhibits LTP induction, while neither a GluN2B antagonist[18] nor the over-expression of GluN2B[19] alters LTP in the visual cortex. The faster kinetics of GluN2A is well-suited to the rapid processing of continuous visual inputs and more faithful neuronal firing to sensory stimulation. Thus, it is appropriate that GluN2A actions predominate in visual cortical synapses.

NMDARs in Primate Dorsolateral Prefrontal Cortex

In contrast to sensory cortex, the dlPFC generates mental representations in the absence of sensory stimulation and these are the foundation of abstract thought. The dlPFC subserves working memory: the ability to keep information in mind and use these representations to provide top-down guidance of behavior, thought, and emotion. Working memory is active and relevant only for a short period of time, usually on the scale of seconds. This capability is a basic building block for more complex dlPFC cognitive operations. Working memory contrasts with long-term memory consolidation: it is a momentary, ever-changing pattern of recurrent activation of relatively stable architectural networks, while long-term memory consolidation retains events as structural changes in synapses. It is not surprising that the circuitry and modulation of working memory differ from those of long-term memory consolidation.

The visuo-spatial working memory operations of the dlPFC in monkeys are among the best understood. Much of the data arose from studies using a spatial working memory task termed the oculomotor delayed response (ODR) (Fig. 1). In this task, the monkey fixates on a center spot, while a cue appears briefly in one of eight possible locations. The monkey must remember the cue location over a delay period of several seconds. At the end of the delay period, the monkey makes an eye movement to the remembered location to receive a juice reward. The location of the cue randomly changes from trial to trial, thus requiring constant updating of the contents of working memory. The dlPFC is needed to perform this working memory task, and even small lesions in this area can produce permanent deficits in performance[20]. Neuronal recordings from the dlPFC in monkeys performing a spatial working memory task have found neurons that fire to the Cue and/or to the Response, but also neurons that are able to maintain spatially-tuned, persistent activity across the delay period[21]. This delay-related persistent activity has been considered to be the neuronal mechanism of working memory due to the following features[22]: first, this neuronal activity persists during the time period when a representation needs to be remembered; second, sustained neuronal activity ceases when a memory-guided response has been generated and the representation is no longer needed; third, when activity does not persist throughout the delay period, behavioral performance is compromised; and fourth, the persistent activity is direction-selective. The pioneering work of Goldman-Rakic revealed that this persistent memory-related activity is generated by the recurrent excitation of pyramidal cells interconnecting on dendritic spines in deep layer III of the dlPFC[23]. Computational models have predicted that this persistent memory-related activity requires stimulation of NMDARs rather than AMPARs[24], and that the slow kinetics of GluN2B receptors is particularly well-suited to persistent dlPFC network firing in the absence of sensory stimulation[25]. In

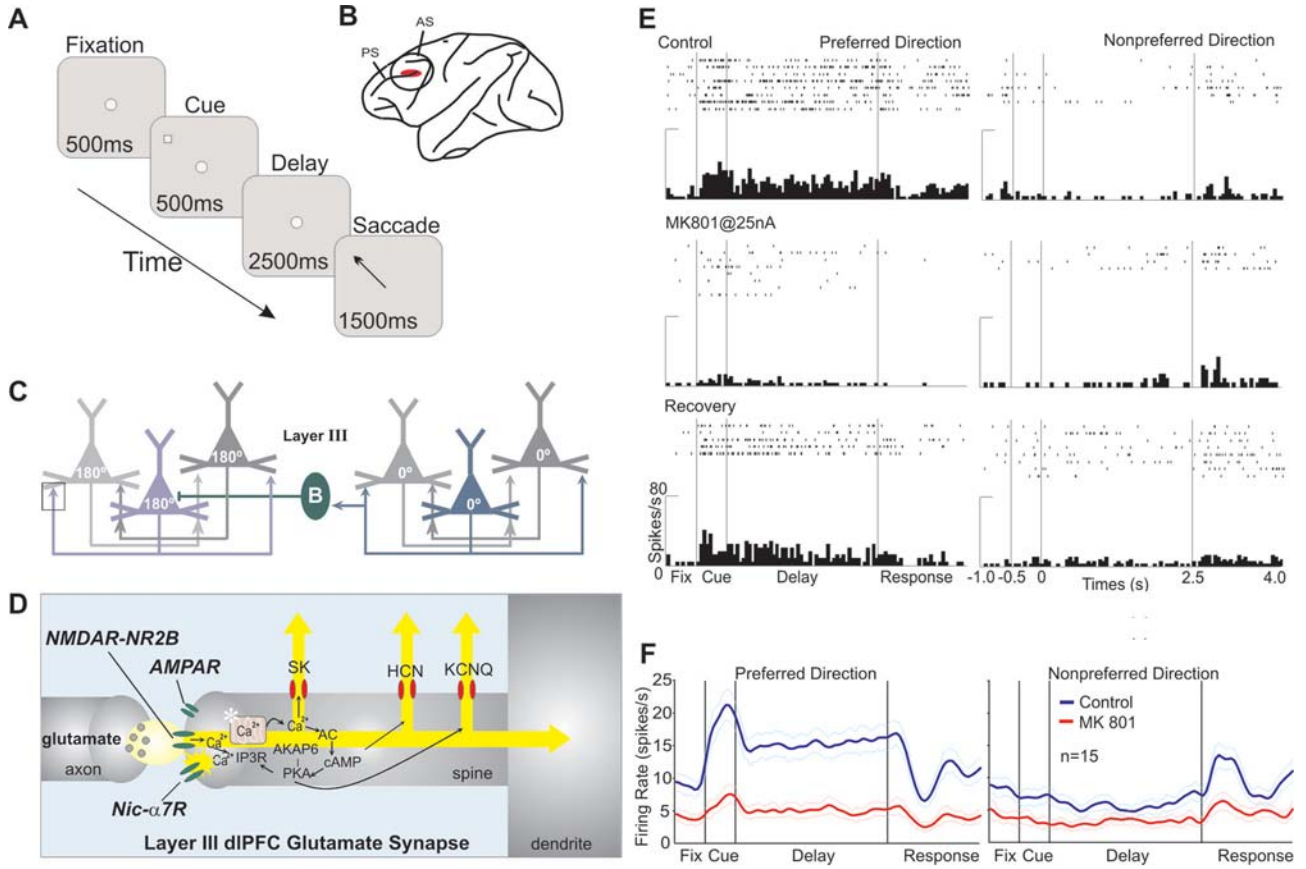

Fig. 1. The actions of NMDARs on the dlPFC neuronal circuitry underlying spatial working memory in primates. A. The spatial oculomotor delayed response (ODR) task. Trials begin when the monkey fixates on a central point for 0.5 s. A cue is presented in 1 of 8 possible locations for 0.5 s, followed by a 2.5-s delay period. When the fixation point is extinguished, the monkey makes a saccade to the location of the remembered cue. The position of the cue changes on each trial in a quasi-random manner, thus requiring the constant updating of working memory stores. B. The region of monkey dlPFC where recordings were made. PS, principal sulcus; AS, arcuate sulcus. C. The deep layer III microcircuits subserving spatially-tuned, persistent firing during the delay period. B, GABAergic basket cell. D. Working model of a glutamate synapse on a spine in layer III of the dlPFC. Glutamate stimulates NMDAR-NR2B receptors in the post-synaptic density, while AMPARs have only subtle actions. Permissive, depolarizing effects for NMDAR actions appear to be mediated by cholinergic stimulation of nicotinic (nic)-α7Rs, which are also localized in the synapse. Ca^{++} entry through NMDAR-NR2B may provide negative feedback by facilitating internal Ca^{++} release from the spine apparatus (asterisk); feedforward Ca^{++}-cAMP signaling opens nearby K^{+} channels to weaken synaptic efficacy and reduce firing. E. An example of an individual dlPFC Delay cell under control conditions and following iontophoresis of the NMDAR antagonist MK801 (25 nA). The rasters and histograms show firing patterns of the neuron's preferred direction and the non-preferred direction opposite to it. Iontophoresis of MK801 markedly reduced task-related firing, which returned towards control levels when delivery of MK801 was stopped (Recovery; *P* <0.05). F. Average responses showing the mean + SEM firing patterns of 15 dlPFC Delay cells for their preferred *versus* non-preferred directions under control conditions (blue) and following iontophoresis of MK801 (red). MK801 markedly suppressed task-related firing, especially for the neurons' preferred direction.

contrast, the faster kinetics of AMPARs leads to dynamic instability and network collapse[24]. Consistent with computational predictions, both *in vitro* and *in vivo* studies have found a prominent role of GluN2B neuronal firing in the PFC. Recordings from rat brain slices have shown more extensive expression of GluN2B in the medial PFC than in the primary visual cortex[26]. A more recent study of the primate dlPFC revealed GluN2B in synapses and that the GluN2B receptor mediates the persistent firing of dlPFC networks in monkeys performing a spatial working

memory task[27]. Immunoelectron microscopy demonstrated that GluN2B is localized exclusively within the postsynaptic densities of layer III dlPFC excitatory synapses on spines, with no evidence of extra-synaptic labeling. Single-unit recordings coupled with iontophoresis in monkeys performing the ODR task showed that the persistent activity of dlPFC neurons is highly dependent on NMDARs, including GluN2B. Iontophoretic blockade of all NMDARs using the antagonist MK801 completely suppresses task-related neuronal firing (Fig. 1). Similarly, blocking GluN2B receptors by iontophoresis of Ro25-6981 produces a marked loss of persistent neuronal firing, and blockade of GluN2A receptors also reduces firing. In contrast, blockade of AMPARs with CNQX/NBQX has only subtle effects on memory-related firing, reducing persistent firing in a small portion of the delay period. AMPAR blockade does alter the firing of sensory neurons in the dlPFC, i.e. it reduces the firing of Cue cells and Post-saccadic Response "feedback" cells. However, the neurons that generate representations of visual space are much more affected by NMDAR than by AMPAR blockade. Interestingly, systemic administration of the NMDAR antagonist ketamine reduces the firing of Delay cells, but increases the firing of Post-saccadic Response neurons (ibid). These results are consistent with the reliance of Delay cells on NMDARs, while the Post-saccadic Response cells have a large AMPAR influence.

If AMPARs have little effect on dlPFC Delay neurons, what depolarizes the membrane and relieves the Mg^{++} block in NMDARs? In the primate dlPFC, these permissive actions appear to be mediated by cholinergic stimulation of nicotinic α7 receptors (nic-α7Rs), rather than AMPARs. Nic-α7Rs are localized in and next to the postsynaptic density in glutamate synapses on spines, and blockade of nic-α7Rs prevents the excitatory actions of NMDA[28]. As acetylcholine is released during wakefulness but not deep sleep, nic-α7R stimulation may permit conscious thought in the waking state. Thus, in the dlPFC, neuronal networks communicate based on arousal state, while in sensory cortex and the hippocampus, NMDAR actions are based on levels of circuit activity, i.e. glutamate release onto AMPARs. Thus, deficits in either NMDAR or nic-α7R signaling weaken dlPFC function.

Finally, Ca^{++} entry through activated NMDARs may contribute to negative feedback to prevent seizures in recurrent excitatory networks. As schematically illustrated in Figure 1, many spines in layer III of the dlPFC contain a spine apparatus, the Ca^{++}-storing endoplasmic reticulum extended into the spine that is elaborated near the synapse. Accumulating evidence indicates that feedforward Ca^{++}-cAMP signaling opens nearby K^{+} channels on dendritic spines to decrease synaptic efficacy and reduce neuronal firing (reviewed in [29]). Future research is needed to determine whether high levels of Ca^{++} entry through GluN2B receptors activate these intracellular pathways.

Relevance to Mental Illness

A variety of cognitive disorders are associated with altered NMDAR signaling. For example, NMDARs are internalized by β-amyloid oligomers in Alzheimer's disease, and this effect occurs in association with nic-α7Rs[30]. Schizophrenia is also linked to genetic insults that weaken NMDAR[31, 32] and nic-α7R[33] signaling. Post-mortem studies have indicated altered GluN2B expression and trafficking[3, 34], including links between allelic changes in GluN2B and impaired reasoning in patients with schizophrenia[35]. There is also accumulating evidence that genetic insults to NMDAR and NMDAR-related synaptic proteins are associated with an increased risk of schizophrenia[32, 36, 37]. The NMDAR antagonist ketamine has been used to model the cognitive deficits of schizophrenia, reducing the blood oxygenation level-dependent response during the delay period of a working memory task in healthy human individuals[38, 39] similar to that seen in patients with schizophrenia[40]. In contrast, the hyperglutamate theories of schizophrenia based on rodent models[41] likely relate to the increased Post-saccadic Response "feedback" cell firing induced by the systemic administration of NMDA antagonists.

In contrast to schizophrenia, where ketamine worsens the symptoms[42], acute ketamine treatment rapidly ameliorates the symptoms in some patients with treatment-resistant depression[43-46], bringing relief within minutes following intra-nasal application[47, 48]. The positive response to ketamine in severely depressed patients has been related to their anterior cingulate response to fearful faces before treatment[49]. Neurons in the anterior cingulate of monkeys have been shown to represent negative emotions

such as symbolic punishment[50], as well as loss of expected rewards[51]. Thus, it is possible that ketamine treatment is helpful in treating depressive symptoms by reducing the firing of NMDAR-dependent, recurrent excitatory circuits in the anterior cingulate and/or in other ventromedial PFC circuits (e.g. Brodmann's area 25[52]) that represent negative emotions and instigate mental suffering. Interrupting the activity of these circuits might underlie the immediate beneficial effects of ketamine in some patients, prior to the regrowth of dendritic spines[53] that may underlie more prolonged beneficial actions. Decreased firing of neurons in the anterior cingulate and area 25 may also underlie the rapid relief of pain by intranasal ketamine (within 5–25 min)[54], as these medial PFC areas are part of the circuits that process the emotional response to painful events[55, 56]. Since intra-nasal ketamine relieves physical pain within minutes[54, 57, 58], it thus may relieve "psychic pain" as well. More research is needed to determine whether NMDARs mediate medial PFC circuits in primates similar to their actions in the dlPFC circuits representing visual space.

Conclusion

New research on the primate dlPFC indicates that GluN2B receptors play a prominent role in the generation of mental representations needed for abstract thought. The data suggest that cholinergic actions at nic-α7Rs are permissive for NMDA synaptic activity, and for the dlPFC network representation of visual space. These data underscore why changes in NMDAR or nic-α7R signaling in diseases such as schizophrenia and Alzheimer's disease have such devastating effects on higher cognition. The unique properties of these dlPFC circuits must be considered in order to design effective treatments for cognitive disorders.

ACKNOWLEDGEMENTS

This review was supported by the National Institutes of Health, USA (R01 MH 09335401 and PO1 AG030004), and a New Investigator Research Grant from the Alzheimer's Association.

Received date: 2014-06-07; Accepted date: 2014-09-20

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