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NMDARs in prefrontal cortex – regulation of synaptic transmission and plasticity

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Summary: In this review we consider the various roles played by N-methyl-D-aspartate receptors (NMDARs) located on pyramidal neurones in medial prefrontal cortex (mPFC). We focus on recent data from our lab that has investigated how NMDARs contribute to ongoing synaptic transmission in a frequency dependent manner, the plasticity of NMDARs and how this impacts their contribution to synaptic transmission, and finally consider how NMDARs contribute to plasticity induced by synchronous activation of two separate inputs to mPFC.

Introduction: NMDARs are best known for, and most associated, with their important roles in the induction of synaptic plasticity. Following the original observation that long-term potentiation (LTP) of glutamatergic EPSPs in CA1 of hippocampus was reversibly blocked by NMDAR antagonism (Collingridge et al 1983), there followed a series of other reports confirming this finding in hippocampus (Harris et al 1984, Wigstrom & Gustafsson 1984) and in other brain regions (Artola & Singer 1987). In addition, it was subsequently shown in hippocampus that long-term depression (LTD) of synaptic transmission was also dependent on activation of NMDARs (Dudek & Bear 1992).

It had been known since the work of Ault et al (1980) that Mg^{2+} ions block NMDAR responses and from the work of Ascher and others (Mayer et al 1984, Nowak et al 1984) that the voltage-dependence of NMDAR activation is a result of the depolarisation required to remove the Mg^{2+} block of the NMDAR channel. Once these necessary steps had occurred this would then allow the influx of Na^+ and Ca^{2+} ions into the postsynaptic cell – the influx of Ca^{2+} was considered the important cation since this was essential for triggering the cascade of events leading to induction of LTP (Lynch et al 1983) and LTD (Mulkey & Malenka 1992).

The strong association that was discovered between NMDAR activation and aspects of learning and memory (Doyere & Laroche 1992, Morris et al 1986, Morris et al 1990), development (Heynen et al 2003, Smith et al 2009), neurodegeneration (Liu et al 2019) and psychiatric disorders (Coyle & Tsai 2004, Frye et al 2007) led to a focus on understanding how NMDAR-dependent plasticity (LTP/LTD) could lead to these normal physiological as well as abnormal neurological processes.

NMDARs and hippocampal synaptic transmission: Over many years much of the focus on the role of NMDARs in neural function has remained on their capacity to induce synaptic plasticity. This was partly due to the assumption that synaptic plasticity was key for many normal and abnormal neural functions (as alluded to above) but also largely due to the various demonstrations that NMDARs played little or no role in basal synaptic transmission (Collingridge et al 1983) and therefore would only be important in specific instances, such as the conditions that lead to induction of LTP and LTD (Bliss & Collingridge 1993). However, studies showing NMDARs play no major role in synaptic transmission focussed largely on

CA1 of hippocampus (Collingridge et al 1988) and on study of EPSPs evoked by single stimuli. Based on such studies there emerged a simple but appealing mechanistic understanding of the role of NMDARs: these receptors are not functionally active during 'normal, basal' synaptic transmission and their role only becomes apparent during high frequency stimulation activity when there is sufficient depolarisation to alleviate Mg^{2+} block; the only important aspect of NMDARs in this context is that their activation leads to induction of synaptic plasticity (Bliss & Collingridge 1993).

NMDARs and synaptic transmission: However, this simple understanding of NMDARs was clearly not the whole story. In xenopus and lamprey spinal cord it had previously been shown that NMDARs contribute to synaptic transmission and to locomotion (Dale and Roberts 1984, 1985, Brodin et al 1985). In addition, in the context of cerebral cortex, it was demonstrated that NMDARs could contribute to varying degrees to 'basal transmission' in somatosensory and visual cortex (Artola & Singer 1987, Thomson 1986, Thomson et al 1985), which built on previous findings of non-linear voltage dependent currents in somatosensory pyramidal neurons, that are typical of NMDAR activation (Stafstrom et al 1982). Therefore, there was the early suggestion that NMDAR function at hippocampal synapse is not necessarily a model for other cortical synapses. In addition, another important regulator of NMDAR function is the timing and strength of inhibitory circuits within a region, and it is highly possible that the concerted feed-forward inhibition at CA3-CA1 synapses tightly controls depolarisation and NMDAR function more effectively than in other cortical regions. Furthermore, if one considers that synaptic transmission takes place in complex patterns of action potential bursts occurring at different frequencies, and if one mimics this experimentally (Herron et al 1986, Thomson 1986), this further uncovers major contributions of NMDARs to 'normal' synaptic transmission (Hunt & Castillo 2012). In addition, if we also consider the later discoveries that NMDARs themselves are subject to LTP (Bashir et al 1991, Berretta et al 1991) and LTD (Morishita et al 2005), then this uncovers a rich tapestry of what NMDARs can bring to the complex nature of synaptic function (Hunt et al 2013).

In this review we will focus on prefrontal cortex and consider how NMDARs contribute to synaptic transmission within mPFC, how NMDARs themselves are subject to plasticity and the consequences this has for synaptic transmission, and then finally also consider how the function of NMDARs is important for the induction of synaptic plasticity at synapses in mPFC.

Hippocampal to prefrontal cortex communication: The mPFC is an extensively interconnected region essential for many aspects of cognitive function including "executive" functions such as decision making, working memory and attentional control, adaptation of emotional responses as well as having a role in long-term memory (Dixon et al 2017, Euston et al 2012). An important region that provides input to prefrontal cortex is the hippocampal formation, particularly intermediate and ventral hippocampus (HPC) and ventral subiculum. HPC-mPFC interactions are known to be critical for a number of important roles, the most studied of which include spatial working and long-term memory (Barker et al 2017, Eichenbaum 2017, Hyman et al 2011, Sigurdsson & Duvarci 2015). During such learning tasks

there is synchronisation of hippocampal-mPFC activity (Benchenane et al 2010, Jones & Wilson 2005, Siapas et al 2005) and it has been shown that disruption of synchronisation between these 2 regions leads to cognitive deficits (Spellman et al 2015). One effective method that can lead to altered HPC-mPFC interactions is through the pharmacological antagonism of NMDARs (Gass et al 2014), suggesting important functions of NMDARs in HPC-mPFC coherence. In addition, dysfunction of NMDARs has long been associated with cognitive alterations, such as occur in schizophrenia and other psychiatric disorders (Javitt & Zukin 1991). Furthermore, NMDAR antagonism within mPFC also disrupts object in place associative memory (Barker & Warburton 2008). Therefore, there is clearly a role for NMDAR activity in normal mPFC function but what the role of NMDARs is specifically at HPC-mFPC synapses, and whether NMDAR contributions occur via induction of plasticity, contribution to normal mPFC synaptic transmission, or both is unclear.

NMDARs and HPC-mPFC communication: Parent et al (2010) described the anatomical course of ventral hippocampal projections to PFC and demonstrated that it is feasible in an acute slice preparation to preserve and electrically stimulate these hippocampal inputs to mPFC pyramidal cells. We took advantage of this approach and recorded EPSPs in layer V mPFC cells in response to stimulation of the HPC input (Fig 1A; Banks et al 2015). At resting membrane potential, we found little effect of the NMDAR antagonist AP5 on the peak amplitude of individual single EPSPs, however there was a large effect on the decay phase, demonstrating that at this synapse NMDARs contribute to the overall charge-transfer and depolarisation evoked by glutamatergic transmission (Fig 1B). This contribution of NMDARs to the decay phase of the EPSP is in keeping with the slower time course of NMDA versus AMPAR-mediated EPSPs (Collingridge et al 1988, Dale & Roberts 1985). In addition, GluN2B containing NMDARs are expressed at high levels in adult mPFC and appear not to decline significantly during development; this is in contrast to hippocampus and sensory cortices (Wang et al 2008). We find that in adult HPC-mPFC synapses there is also a substantial GluN2B contribution to pharmacologically isolated NMDAR EPSCs (Fig 1C). These NMDAR subtypes have slower kinetics than GluN2A containing NMDARs (Paoletti et al 2013) and therefore might explain the large effect of AP5 on single EPSPS at HPC-mPFC synapses, compared to the smaller effects of AP5 at other synapses, such as Schaffer collateral inputs to CA1 hippocampal pyramidal cells.

The above data would suggest that it is likely that the slow NMDAR-mediated component of transmission at HPC-mPFC synapses would allow for summation of depolarisation during repetitive high frequency stimulation and therefore NMDARs could provide substantial contribution to synaptic transmission. This hypothesis was tested (Fig 1D) and, under the conditions of our experiments, it was shown that AP5 produced major attenuation of the overall depolarisation and attenuation of action potential firing resulting from stimulation at 20Hz (but not at 50 or 100Hz). Individual place cells commonly show a peak in field firing rates of ~20Hz during spatial navigation (Huxter et al 2003) and so these results are likely to be physiologically relevant to transmission of spatial information from HPC to mPFC, amongst other functions. Therefore, these data demonstrate that NMDARs make a major contribution to synaptic transmission and to mPFC pyramidal cell spiking at frequencies that are within the normal range of HPC-PFC activity. These data are also in line with previous

reports showing that slow NMDAR kinetics contribute to temporal integration of glutamatergic transmission and subsequent generation of action potentials (Augustinaite & Heggelund 2007, Lisman 1997, Polsky et al 2009) and can coordinate spike firing dependent on the phase of oscillatory activity (Buzsaki 2002, Jensen & Lisman 1996).

Plasticity of NMDAR-transmission and its consequences for HPC-mPFC communication: It has been known for some decades that NMDAR-mediated synaptic transmission can undergo both LTP (Bashir et al 1991, Berretta et al 1991) and LTD (Morishita et al 2005). Since NMDARs are the trigger for LTP then this naturally leads to the conclusion that plasticity is not fixed but that the thresholds and magnitude of plasticity is dictated by LTP/LTD of NMDARs. This property has been termed 'metaplasticity' and arguments for how metaplasticity may control synaptic function have been made previously (Abraham 1999, Abraham 2008, Hunt & Castillo 2012). Metaplasticity is not simply a theoretical construct, having been demonstrated experimentally (Abraham et al 2001, Bhouri et al 2014, Hunt et al 2013, Mockett et al 2002, Rebola et al 2011).

However, the impact of plasticity of NMDARs on synaptic transmission has not been well studied. We were able to show at HPC-mPFC synapses that theta frequency stimulation (TFS; 300 stimuli at 5 Hz) results in LTD of NMDAR EPSCs and that this form of LTD was dependent on activation of dopamine D2Rs (Fig 2A) and was mimicked and occluded by pharmacological activation of D2Rs (Fig 2B; Banks et al 2015). Furthermore, plasticity induced by this induction protocol was specific to NMDA transmission, with no plasticity of AMPAR EPSCs observed. We then tested how this theta frequency induced, D2R-mediated LTD of NMDAR transmission impacted on synaptic activity at HPC-mPFC synapses. These data revealed that LTD of NMDAR transmission at HPC-mPFC synapses decreased the decay phase of single EPSPs and importantly during repetitive bursts of 20Hz activity there was a decrease in the summation of EPSPs (Fig 2C) and a subsequent decrease in action potential firing (Banks et al 2015). Blocking D2Rs during theta stimulation prevented the changes in EPSP decay, the decrease in summation (Fig 2D) and the decrease in action potential firing. This shows not just that NMDARs are important in normal ongoing synaptic function, but that plasticity of NMDARs induced by activation of dopamine receptors can sculpt synaptic communication between HPC and mPFC.

Together these data demonstrate how NMDARs contribute to normal synaptic transmission, postsynaptic depolarisation and action potential firing during bursts of HPC-mPFC activity. Activation of D2Rs can lead to LTD of NMDA transmission and therefore produce alterations in HPC-mPFC activity. At the present time it is not known whether the opposite phenomenon of LTP of NMDAR transmission occurs at this synapse and therefore whether bidirectional modulation of HPC-mPFC transmission can occur. If bidirectional plasticity of NMDARs occurs, that means this D2R mediated LTD process may represent one arm of normal ongoing control and modulation of cognitive function within mPFC. In addition, and if LTP of NMDARs in this circuit does not occur readily then, given the known roles of D2Rs and hypofunction of NMDARs in schizophrenia, it may be tempting to speculate that D2-dependent LTD of NMDARs may be associated with psychiatric conditions such as schizophrenia. A recent study has shown that ablation of GSK3β from D2R-containing

neurons in mPFC resulted in increased amplitude of NMDAR EPSCs, altered synaptic plasticity and a resistance to impairment of working memory (Li et al 2020). These data further enhance understanding of the D2-NMDAR interaction and their potential roles in cognitive function and impairment.

Plasticity in mPFC neurones by coactivation of HPC and reuniens/rhomboid nucleus inputs: mPFC is widely interconnected with cortical and subcortical brain regions and it is thought that the integration within mPFC of information from such diverse sources might be crucial in encoding and processing cognitive function and learning and memory. Recently ventral midline thalamic structures centred on the nucleus reuniens and rhomboid nucleus (ReRh) have emerged as critical regions for higher order cognitive functions, particularly those which require HPC-PFC interactions (Dolleman-van der Weel et al 2019). ReRh are involved in associative recognition memory and working memory and have strong reciprocal connections with both HPC and mPFC (Barker & Warburton 2018, Cassel et al 2013, Dolleman-van der Weel et al 2019, Hallock et al 2016) but little is known of how HPC and ReRh inputs converge onto cells in mPFC and how this regulates synaptic plasticity within mPFC (Viana Di Prisco & Vertes 2006). By using a combination of optogenetic stimulation of ReRh inputs and electrical stimulation of HPC inputs (Fig 3A) we were able to investigate in slices of mPFC whether HPC and NRe inputs converge at the single cell level, characterise receptor physiology at these synapses and determine whether interaction of these inputs results in synaptic plasticity which may allow encoding of information in mPFC (Banks et al 2020).

Stimulation of ReRh and HPC inputs resulted in a glutamatergic transmission in 68% of mPFC layer 5 pyramidal neurons, indicating the ReRh and HPC converge upon the same neurons in PFC and that these inputs target the majority of layer 5 pyramidal neurons. We found that the relative contribution of AMPA- and NMDA-receptor transmission at these two synapses was indistinguishable (Fig 3B), however that these inputs showed marked differences in their short-term plasticity, with ReRh synapses exhibiting substantial short-term depression at theta-range frequencies (5-10 Hz; Fig 3C), owing to a high initial release probability (Banks et al 2020).

We stimulated ReRh and HPC inputs converging onto a single mPFC pyramidal cell with a 10 ms interval between the two inputs; this was to mimic the synaptic delay between a direct monosynaptic projection from one region to mPFC and an indirect disynaptic projection to mPFC via the other region (Fig 3D). These paired stimuli with 10ms interval were repeated at 5Hz, based on the theta coherence that occurs across these regions (Hallock et al 2016). When these 5Hz stimulation patterns were carried out with the postsynaptic mPFC cell held at -50mV and HPC stimulated 10ms before ReRh this resulted in LTD at both HPC and NRe synaptic inputs to mPFC (Fig 3D). However, no plasticity was induced when the pairing was reversed (ReRh stimulated 10ms before HPC). LTD in both inputs following HPC-ReRh pairing was blocked by the NMDAR antagonist AP5 (Fig 3E). Therefore, ReRh and HPC inputs interact in a unidirectional manner at mPFC pyramidal cells to induce associative plasticity and this plasticity is via activation of NMDARs. NMDAR-dependence of this associative form of plasticity is somewhat novel in that LTD induction in PFC is not typically NMDAR-

dependent (Banks et al 2012, Caruana et al 2011, Huang & Hsu 2010, Otani et al 1998, Wang & Yuan 2009).

GluN2B subunit containing NMDARs exist at high levels in adult mPFC (Wang et al 2008) and their slower kinetics will result in increased charge transfer and increased Ca^{2+} influx; whilst this has not been tested explicitly, these properties of GluN2B-containing NMDARs could potentially be an important requirement for the induction of LTD. In addition, slow NMDAR transmission may facilitate interaction between spatially segregated HPC and ReRh synapses in order to bring about LTD at both inputs. Previous data have suggested elevated GluN2B expression in hippocampal inputs to PFC (Flores-Barrera et al 2014), and GluN2B expression in ReRh and HPC were not significantly different, which hints at high GluN2B prevalence in these pathways being conducive to induction of associative plasticity.

Summary

In this short review we have considered how NMDARs provide a rich orchestration of synaptic function within mPFC. Thus, NMDARs contribute to ongoing synaptic transmission and to neuronal firing at HPC-mPFC synapses. In addition, NMDARs as well as being crucial to synaptic plasticity at this synapse, are themselves also plastic. We demonstrate how in mPFC, D2R activation results in LTD of NMDARs and then show how this LTD disrupts normal HPC-mPFC synaptic transmission. Finally, we illustrate that co-activation of HPC and ReRh inputs to mPFC results in LTD that relies on the traditional role of NMDARs as inducers of synaptic plasticity. However, this LTD that occurs at both HPC and ReRh inputs to mPFC only occurs when NRe synapses are active following HPC synaptic activity, and not when activity occurs in the opposite direction. The mechanisms of and physiological function of this unidirectional induction of LTD is not understood and will require much more investigation.

It would also be interesting in future to determine what the effect of D2R-mediated LTD of NMDARs at HPC-mPFC would have on the pairing induced LTD at both ReRh-mPFC and HPC-mPFC synapses. Finally, whilst we know that NMDARs in mPFC are critical for various normal functions, such as object-in-place learning, it is not known whether this role of NMDARs in associative learning is due to NMDAR enhancement of depolarisation during bursts of activity, or due to the increased firing this brings about, or due to some form of plasticity at synaptic inputs that converge in mPFC.

The work described also raises the question of how generalisable these data might be. Clearly, NMDARs come in different types with differential distribution across cell types and brain regions and therefore there will be subtle or not so subtle differences in function and roles of NMDARs both within and across regions. This may mean that NMDARs are largely involved in induction of plasticity in some regions but contribute significantly to synaptic transmission and plasticity in other regions. Clearly therefore, NMDARs are not simple one dimensional initiators of synaptic plasticity but provide an important and critical multifaceted regulation of the rich tapestry of synaptic life.

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References

Abraham WC. 1999. Metaplasticity: Key Element in Memory and Learning? *News Physiol Sci* 14: 85

Abraham WC. 2008. Metaplasticity: tuning synapses and networks for plasticity. *Nat Rev Neurosci* 9: 387

Abraham WC, Mason-Parker SE, Bear MF, Webb S, Tate WP. 2001. Heterosynaptic metaplasticity in the hippocampus in vivo: a BCM-like modifiable threshold for LTP. *Proc Natl Acad Sci U S A* 98: 10924-9

Artola A, Singer W. 1987. Long-term potentiation and NMDA receptors in rat visual cortex. *Nature* 330: 649-52

Augustinaite S, Heggelund P. 2007. Changes in firing pattern of lateral geniculate neurons caused by membrane potential dependent modulation of retinal input through NMDA receptors. *The Journal of physiology* 582: 297-315

Ault B, Evans RH, Francis AA, Oakes DJ, Watkins JC. 1980. Selective depression of excitatory amino acid induced depolarizations by magnesium ions in isolated spinal cord preparations. *J Physiol* 307: 413-28

Banks PJ, Bashir ZI, Brown MW. 2012. Recognition memory and synaptic plasticity in the perirhinal and prefrontal cortices. *Hippocampus* 22: 2012-31

Banks PJ, Burroughs AC, Barker GR, Brown JT, Warburton EC, Bashir ZI. 2015. Disruption of hippocampal-prefrontal cortex activity by dopamine D2R-dependent LTD of NMDAR transmission. *Proc Natl Acad Sci U S A* 112: 11096-101

Banks PJ, Warburton EC, Bashir ZI. 2020. Plasticity in prefrontal cortex induced by coordinated nucleus reuniens and hippocampal synaptic transmission. *BioRxiv*

Barker GR, Banks PJ, Scott H, Ralph GS, Mitrophanous KA, et al. 2017. Separate elements of episodic memory subserved by distinct hippocampal-prefrontal connections. *Nat Neurosci* 20: 242-50

Barker GR, Warburton EC. 2008. NMDA receptor plasticity in the perirhinal and prefrontal cortices is crucial for the acquisition of long-term object-in-place associative memory. *J Neurosci* 28: 2837-44

Barker GRI, Warburton EC. 2018. A Critical Role for the Nucleus Reuniens in Long-Term, But Not Short-Term Associative Recognition Memory Formation. *J Neurosci* 38: 3208-17

Bashir ZI, Alford S, Davies SN, Randall AD, Collingridge GL. 1991. Long-term potentiation of NMDA receptor-mediated synaptic transmission in the hippocampus. *Nature* 349: 156-8

Benchenane K, Peyrache A, Khamassi M, Tierney PL, Gioanni Y, et al. 2010. Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. *Neuron* 66: 921-36

Berretta N, Berton F, Bianchi R, Brunelli M, Capogna M, Francesconi W. 1991. Long-term Potentiation of NMDA Receptor-mediated EPSP in Guinea-pig Hippocampal Slices. *The European journal of neuroscience* 3: 850-54

Bhouri M, Farrow PA, Motee A, Yan X, Battaglia G, et al. 2014. mGlu1 Receptor-Induced LTD of NMDA Receptor Transmission Selectively at Schaffer Collateral-CA1 Synapses Mediates Metaplasticity. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 34: 12223-9

Bliss TV, Collingridge GL. 1993. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361: 31-9

Brodin L, Grillner S, Rocainen CM 1985. N-Methyl-D-aspartate (NMDA), kainate and quisqualate receptors and the generatino of fictive locomotion in the lamprey spinal cord. Brain Res. 325: 302-306

Buzsaki G. 2002. Theta oscillations in the hippocampus. *Neuron* 33: 325-40

Caruana DA, Warburton EC, Bashir ZI. 2011. Induction of activity-dependent LTD requires muscarinic receptor activation in medial prefrontal cortex. *J Neurosci* 31: 18464-78

Cassel JC, Pereira de Vasconcelos A, Loureiro M, Cholvin T, Dalrymple-Alford JC, Vertes RP. 2013. The reuniens and rhomboid nuclei: neuroanatomy, electrophysiological characteristics and behavioral implications. *Prog Neurobiol* 111: 34-52

Collingridge GL, Herron CE, Lester RA. 1988. Synaptic activation of N-methyl-D-aspartate receptors in the Schaffer collateral-commissural pathway of rat hippocampus. *J Physiol* 399: 283-300

Collingridge GL, Kehl SJ, McLennan H. 1983. Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. *J Physiol* 334: 33-46

Coyle JT, Tsai G. 2004. NMDA receptor function, neuroplasticity, and the pathophysiology of schizophrenia. *Int Rev Neurobiol* 59: 491-515

N Dale, A Roberts. 1984. Excitatory amino acid receptors in Xenopus embryo spinal cord and their role in the activation of swimming. J Physiol. 348: 527–543.

Dale N, Roberts A. 1985. Dual-component amino-acid-mediated synaptic potentials: excitatory drive for swimming in Xenopus embryos. *J Physiol* 363: 35-59

Dixon ML, Thiruchselvam R, Todd R, Christoff K. 2017. Emotion and the prefrontal cortex: An integrative review. *Psychol Bull* 143: 1033-81

Dolleman-van der Weel MJ, Griffin AL, Ito HT, Shapiro ML, Witter MP, et al. 2019. The nucleus reuniens of the thalamus sits at the nexus of a hippocampus and medial prefrontal cortex circuit enabling memory and behavior. *Learn Mem* 26: 191-205

Doyere V, Laroche S. 1992. Linear relationship between the maintenance of hippocampal long-term potentiation and retention of an associative memory. *Hippocampus* 2: 39-48

Dudek SM, Bear MF. 1992. Homosynaptic Long-Term Depression in Area Ca1 of Hippocampus and Effects of N-Methyl-D-Aspartate Receptor Blockade. *Proceedings of the National Academy of Sciences of the United States of America* 89: 4363-67

Eichenbaum H. 2017. Prefrontal-hippocampal interactions in episodic memory. *Nat Rev Neurosci* 18: 547-58

Euston DR, Gruber AJ, McNaughton BL. 2012. The role of medial prefrontal cortex in memory and decision making. *Neuron* 76: 1057-70

Flores-Barrera E, Thomases DR, Heng LJ, Cass DK, Caballero A, Tseng KY. 2014. Late adolescent expression of GluN2B transmission in the prefrontal cortex is input-specific and requires postsynaptic protein kinase A and D1 dopamine receptor signaling. *Biol Psychiatry* 75: 508-16

Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM. 2007. Low cerebrospinal fluid glutamate and glycine in refractory affective disorder. *Biol Psychiatry* 61: 162-6

Gass N, Schwarz AJ, Sartorius A, Schenker E, Risterucci C, et al. 2014. Sub-anesthetic ketamine modulates intrinsic BOLD connectivity within the hippocampal-prefrontal circuit in the rat. *Neuropsychopharmacology* 39: 895-906

Hallock HL, Wang A, Griffin AL. 2016. Ventral Midline Thalamus Is Critical for Hippocampal-Prefrontal Synchrony and Spatial Working Memory. *J Neurosci* 36: 8372-89

Harris EW, Ganong AH, Cotman CW. 1984. Long-term potentiation in the hippocampus involves activation of N-methyl-D-aspartate receptors. *Brain Res* 323: 132-7

Herron, CE, Lester, RAJ, Coan, EJ, Collingridge GL 1986. Frequency-dependent involvement of NMDA receptors in the hippocampus: a novel synaptic mechanism. Nature 322, 265-268.

Heynen AJ, Yoon BJ, Liu CH, Chung HJ, Huganir RL, Bear MF. 2003. Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nat Neurosci* 6: 854-62

Huang CC, Hsu KS. 2010. Activation of muscarinic acetylcholine receptors induces a nitric oxide-dependent long-term depression in rat medial prefrontal cortex. *Cereb Cortex* 20: 982-96

Hunt DL, Castillo PE. 2012. Synaptic plasticity of NMDA receptors: mechanisms and functional implications. *Current opinion in neurobiology* 22: 496-508

Hunt DL, Puente N, Grandes P, Castillo PE. 2013. Bidirectional NMDA receptor plasticity controls CA3 output and heterosynaptic metaplasticity. *Nature neuroscience* 16: 1049-59

Huxter J, Burgess N, O'Keefe J. 2003. Independent rate and temporal coding in hippocampal pyramidal cells. *Nature* 425: 828-32

Hyman JM, Hasselmo ME, Seamans JK. 2011. What is the Functional Relevance of Prefrontal Cortex Entrainment to Hippocampal Theta Rhythms? *Front Neurosci* 5: 24

Javitt DC, Zukin SR. 1991. Recent advances in the phencyclidine model of schizophrenia. *The American journal of psychiatry* 148: 1301-8

Jensen O, Lisman JE. 1996. Theta/gamma networks with slow NMDA channels learn sequences and encode episodic memory: role of NMDA channels in recall. *Learning & memory* 3: 264-78

Jones MW, Wilson MA. 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol* 3: e402

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Lisman JE. 1997. Bursts as a unit of neural information: making unreliable synapses reliable. *Trends in neurosciences* 20: 38-43

Liu J, Chang L, Song Y, Li H, Wu Y. 2019. The Role of NMDA Receptors in Alzheimer's Disease. *Front Neurosci* 13: 43

Lynch G, Larson J, Kelso S, Barrionuevo G, Schottler F. 1983. Intracellular injections of EGTA block induction of hippocampal long-term potentiation. *Nature* 305: 719-21

Mayer ML, Westbrook GL, Guthrie PB. 1984. Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. *Nature* 309: 261-3

Mockett B, Coussens C, Abraham WC. 2002. NMDA receptor-mediated metaplasticity during the induction of long-term depression by low-frequency stimulation. *Eur J Neurosci* 15: 1819-26

Morishita W, Marie H, Malenka RC. 2005. Distinct triggering and expression mechanisms underlie LTD of AMPA and NMDA synaptic responses. *Nat Neurosci* 8: 1043-50

Morris RG, Anderson E, Lynch GS, Baudry M. 1986. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature* 319: 774-6

Morris RG, Davis S, Butcher SP. 1990. Hippocampal synaptic plasticity and NMDA receptors: a role in information storage? *Philos Trans R Soc Lond B Biol Sci* 329: 187-204

Mulkey RM, Malenka RC. 1992. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* 9: 967-75

Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. 1984. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* 307: 462-5

Otani S, Blond O, Desce JM, Crepel F. 1998. Dopamine facilitates long-term depression of glutamatergic transmission in rat prefrontal cortex. *Neuroscience* 85: 669-76

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

Parent MA, Wang L, Su J, Netoff T, Yuan LL. 2010. Identification of the hippocampal input to medial prefrontal cortex in vitro. *Cereb Cortex* 20: 393-403

Polsky A, Mel B, Schiller J. 2009. Encoding and decoding bursts by NMDA spikes in basal dendrites of layer 5 pyramidal neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 29: 11891-903

Rebola N, Carta M, Lanore F, Blanchet C, Mulle C. 2011. NMDA receptor-dependent metaplasticity at hippocampal mossy fiber synapses. *Nature neuroscience* 14: 691-3

Siapas AG, Lubenov EV, Wilson MA. 2005. Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46: 141-51

Sigurdsson T, Duvarci S. 2015. Hippocampal-Prefrontal Interactions in Cognition, Behavior and Psychiatric Disease. *Front Syst Neurosci* 9: 190

Smith GB, Heynen AJ, Bear MF. 2009. Bidirectional synaptic mechanisms of ocular dominance plasticity in visual cortex. *Philos Trans R Soc Lond B Biol Sci* 364: 357-67

Spellman T, Rigotti M, Ahmari SE, Fusi S, Gogos JA, Gordon JA. 2015. Hippocampal-prefrontal input supports spatial encoding in working memory. *Nature* 522: 309-14

Stafstrom CE, Schwindt PC, Crill WE. 1982. Negative slope conductance due to a persistent subthreshold sodium current in cat neocortical neurons in vitro. *Brain Res* 236: 221-6

Thomson AM. 1986. A magnesium-sensitive post-synaptic potential in rat cerebral cortex resembles neuronal responses to N-methylaspartate. *J Physiol* 370: 531-49

Thomson AM, West DC, Lodge D. 1985. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? *Nature* 313: 479-81

Viana Di Prisco G, Vertes RP. 2006. Excitatory actions of the ventral midline thalamus (rhomboid/reuniens) on the medial prefrontal cortex in the rat. *Synapse* 60: 45-55

Wang H, Stradtman GG, 3rd, Wang XJ, Gao WJ. 2008. A specialized NMDA receptor function in layer 5 recurrent microcircuitry of the adult rat prefrontal cortex. *Proc Natl Acad Sci U S A* 105: 16791-6

Wang L, Yuan LL. 2009. Activation of M2 muscarinic receptors leads to sustained suppression of hippocampal transmission in the medial prefrontal cortex. *J Physiol* 587: 5139-47

Wigstrom H, Gustafsson B. 1984. A possible correlate of the postsynaptic condition for long-lasting potentiation in the guinea pig hippocampus in vitro. *Neurosci Lett* 44: 327-32

Figure legends

Figure 1– NMDA receptors contribute to basal synaptic transmission in HPC-mPFC synapses

A – Experimental configuration showing electrical stimulation of HPC fibres to evoke EPSPs in prelimbic cortex (PrL) layer 5 pyramidal neurons

B- HPC-mPFC EPSPs show accelerated decay but little effect on amplitude following bath application of NMDAR antagonist AP5 (50 µM; magenta). Scale bars = 1 mV/100 ms.

C – Pharmacologically-isolated NMDA receptor-mediated EPSCs at HPC-mPFC synapses have considerable sensitivity to GluN2B-selective antagonist Ro 25-6981 (1 µM, shaded region).

D – Bursts of HPC-mPFC EPSPs delivered at 20 Hz are attenuated by NMDAR antagonism, resulting in reduced total charge transfer and reduced action potential firing.

Figure adapted with permission from: Banks et al 2015.

Figure 2 –D2R-dependent LTD of NMDARs in HPC-mPFC pathway attenuates temporal summation

A – Theta-frequency stimulation (TFS; 300 stimuli at 5 Hz) induces robust LTD of isolated $EPSC_{NMDA}$ in HPC-mPFC pathway (black), but is blocked by D2R-antagonist sulpiride (10 μM; cyan). Inset shows representative $EPSC_{NMDA}$ before (black) and after (red) delivery of TFS, scale bars = 20 pA/200 ms.

B – Bath application of D2R agonist quinpirole (10 μM; magenta) induces LTD of $EPSC_{NMDA}$ which occludes subsequent activity-dependent LTD by TFS.

C – TFS-induced LTD of NMDARs accelerates the decay kinetics of HPC-mPFC EPSPs as was observed under pharmacological NMDAR blockade (Fig 1B), leading to attenuated integration of 20 Hz stimuli. Scale bars: upper = 1 mV/100 ms, middle = 2 mV/200 ms.

D – D2R antagonist sulpiride prevents TFS-induced NMDAR plasticity such that EPSP kinetics and summation of 20 Hz activity is unaffected by TFS. Scale bars: upper: 0.5 mV/100 ms, middle = 1 mV/200 ms.

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Figure 3 – Pairing of HPC and ReRh inputs induces NMDAR-dependent associative plasticity

A – Following transduction of midline thalamic nuclei ReRh by AAV9-CaMKii-ChR2(E123T/T159C)-mCherry (left), HPC afferents were stimulated electrically and ReRh afferents stimulated optogenetically whilst recording from layer 5 pyramidal neurons; this resulted in glutamatergic EPSPs in both pathways.

B – HPC and ReRh inputs show similar NMDAR:AMPAR ratios.

C – ReRh synapses show marked short-term plasticity when stimulated at 5 and 10 Hz. This is in stark contrast to HPC inputs which display little short-term plasticity at these frequencies. Scale bars = 0.3 mV/200 ms.

D – Upper left: schematic of HPC-ReRh-mPFC circuitry. Oscillatory signals originating in HPC (green pathway) innervate mPFC directly (solid line) and disynaptically via ReRh (dashed lines); HPC EPSPs would therefore precede those of ReRh resulting in a negative lag (-10ms). Alternatively, a signal originating in ReRh (purple pathway) may project directly to PFC (solid line) and indirectly via HPC (dashed line), therefore resulting in the opposite temporal profile (+10 ms lag). 5Hz pairing of HPC and ReRh 100 times with -10 ms lag results in robust LTD in both pathways (upper right), whereas pairing with +10 ms does not induce plasticity (lower right). Lower left: summary plot of above experiments

E –NMDAR antagonism blocks induction of associative plasticity of HPC and ReRh inputs. Lower panel compares experiments in presence and absence of AP5.

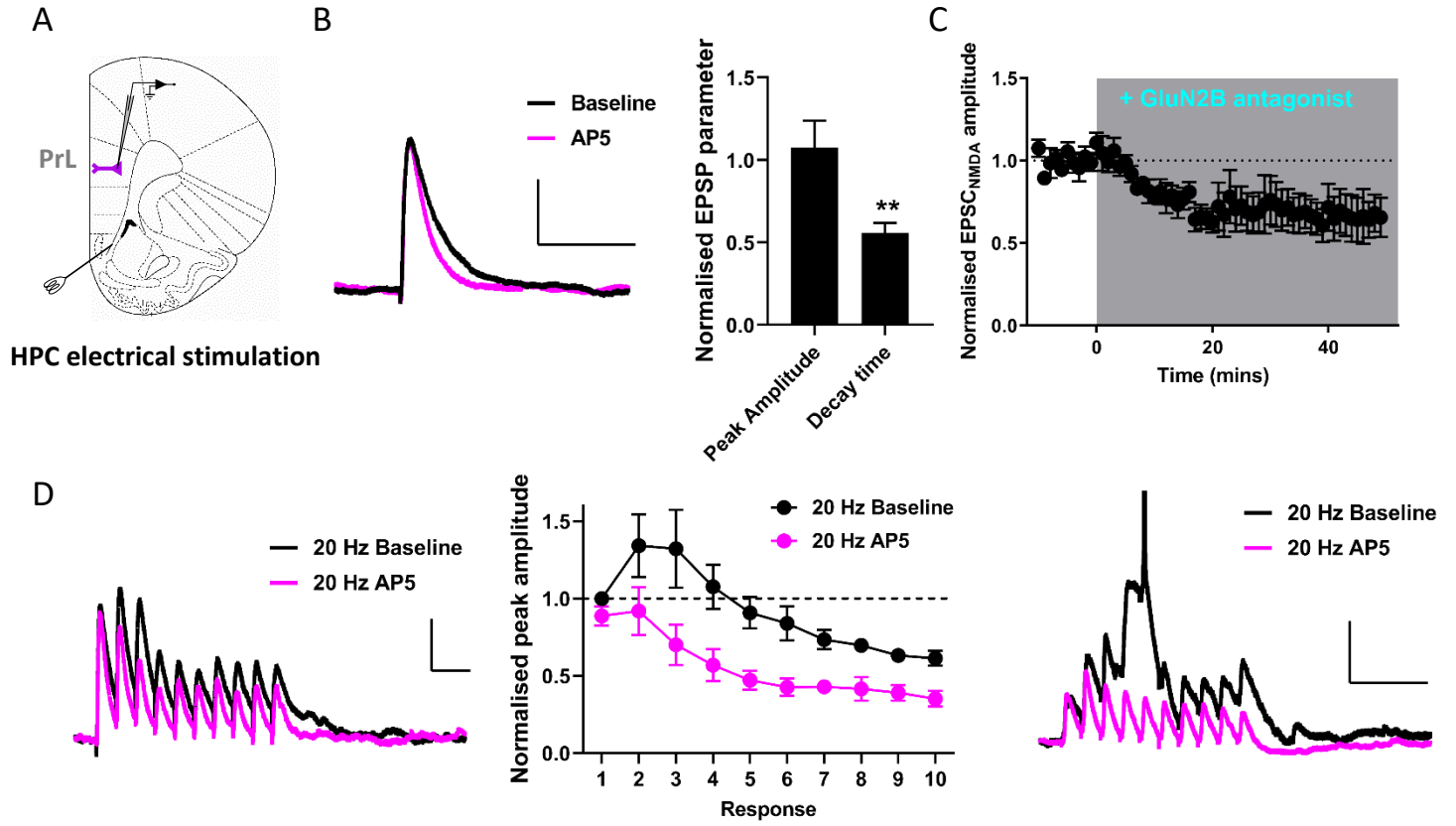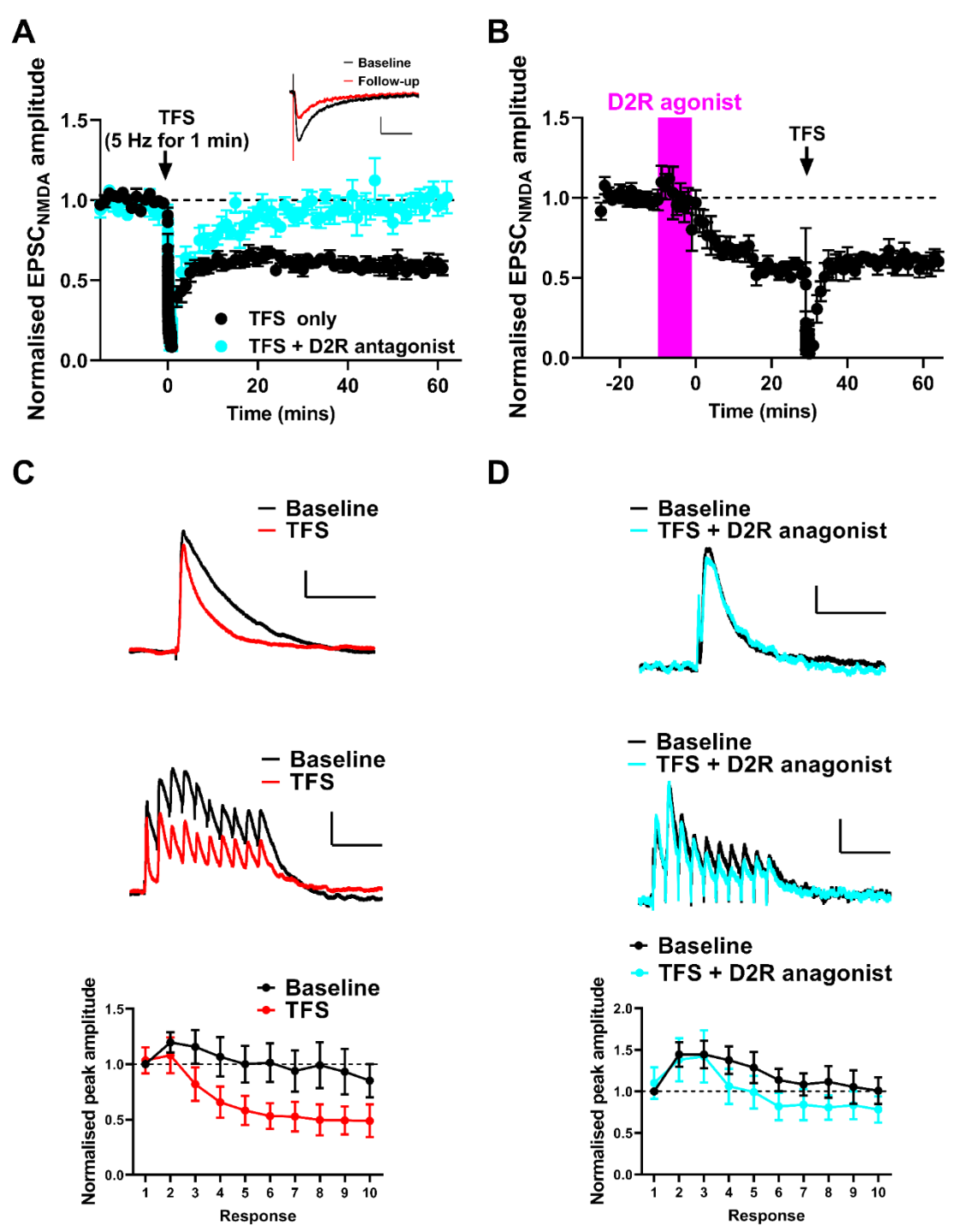Figure adapted with permission from Banks et al 2020.

FIGURE 1

A

PrL

HPC electrical stimulation

B

— Baseline
— AP5

Normalised EPSP parameter

1.5
1.0
0.5
0.0

Peak Amplitude   Decay time

**

C

Normalised EPSC$_{NMDA}$ amplitude

1.5
1.0
0.5
0.0

+ GluN2B antagonist

0   20   40

Time (mins)

D

— 20 Hz Baseline
— 20 Hz AP5

Normalised peak amplitude

1.5
1.0
0.5
0.0

1 2 3 4 5 6 7 8 9 10

Response

● 20 Hz Baseline
● 20 Hz AP5

— 20 Hz Baseline
— 20 Hz AP5

FIGURE 2

FIGURE 3