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The Opposing Roles of GluN2C and GluN2D NMDA Receptor Subunits in Modulating Neuronal Oscillations

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THE OPPOSING ROLES OF GluN2C AND GluN2D NMDA RECEPTOR SUBUNITS IN MODULATING NEURONAL OSCILLATIONS

by

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University of Nebraska, 2018

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Abstract

N-methyl-D-aspartate receptors (NMDARs) are ligand-gated ion channels consisting of two GluN1 subunits and two other subunits from among GluN2A-2D and GluN3A-3B subunits. NMDARs play critical roles in synaptic plasticity, learning and memory, and higher brain function such as cognition and perception. Dysfunction of NMDARs (hyper-function and hypo-function of NMDARs) are related to various diseases, including stroke, schizophrenia, Alzheimer's disease, and others. However, to date, NMDARs antagonists have mostly failed in clinical trials due to adverse effects.

NMDARs antagonists replicate the core symptoms of schizophrenia which may underlie its ability to alter neuronal oscillations in the neural circuitry of different brain regions. Recent evidence has shown that GluN2C subunits of NMDAR are expressed in astrocytes in the cortex, and that GluN2D NMDAR subunits are enriched in the parvalbumin-containing GABAergic inhibitory interneurons in the cortex and midbrain structures. Other studies have shown that both astrocytes and parvalbumin-containing interneurons play an essential role in generating and maintaining neuronal oscillations. These findings imply that GluN2C and GluN2D subunits may be involved in the distinct neural circuitry which regulates neuronal oscillations and thus influence the brain function and contribute to various diseases states. The initial aims of this dissertation are to determine if GluN2C and GluN2D subunits have a role in regulating neuronal oscillations. We also measured the auditory evoked responses in wildtype and GluN2C- and GluN2D-KO mice.

Lastly, we use ketamine as the tool drug to determine the role of NMDARs in neuronal oscillations in a CDKL5-KO mouse model.

We found that spontaneous basal neuronal oscillations were elevated in GluN2C- and GluN2D-KO mice compared to WT mice. NMDARs antagonists increased the power of neuronal oscillations in WT mice; we found drug-induced power increase is abolished in GluN2D-KO mice and is augmented in GluN2C-KO mice.

Furthermore, we also found GluN2D-KO mice displayed abnormal auditory evoked responses. Lastly, we test subunit-selective NMDARs drug and NMDARs allosteric modulators with distinct subunits selectivity developed by our lab, including PAMs and NAMs on these KO models.

List of Abbreviations

ABD	agonist binding domain
AD	Alzheimer's disease
AMPA	(S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid
ASD	autism spectral disorder
ASSR	auditory steady-state response
ATD	amino terminal domain
AVOVA	analysis of variance
Aβ	amyloid-β
CDKL5	cyclin-dependent kinase-like 5
CIQ	(3-Chlorophenyl)[3,4-dihydro-6,7-dimethoxy-1-[(4-methoxyphenoxy)methyl]-2 (1H)-isoquinolinyl]methanone
CP-101,606	Traxoprodil
CPP	3- ((R)-2-Carboxypiperazin-4-yl)-propyl-1-phosphonic acid
CTD	c-terminal domain
D-AP5	D-2-Amino-5-phosphonovaleric acid
DISC1	disrupted in schizophrenia 1
DN	dominant negative

ECoG	electrocorticography
EEG	electroencephalogram
EPSC	excitatory postsynaptic current
ERP	event-related potential
GABA	gamma-amino butyric acid
GluN2C-KO	GluN2D knockout
GluN2D-KO	GluN2D knockout
HD	Huntington's disease
HFOs	high-frequency oscillations
IC50	half-maximal inhibitory concentration
ID	intellectual disability
KA	kainic acid
LTD	long-tern depression
LTP	long-term potentiation
MEG	magnetoencephalography
MK-801	dizoclipine maleate
MMN	mismatch negativity
NAM	negative allosteric modulator
NMDAR	N-methyl-D-aspartate receptor
NVP-AAM077	[[[(1S)-1- (4-Bromophenyl)ethyl]amino] (1,2,3,4-tetrahydro-

	2,3-dioxo-5-quinoxalinyl)methyl] phosphonic acid tetrasodium hydrate
PAM	positive allosteric modulator
PCP	phencyclidine
PPI	pre-pulse inhibition
PSD	postsynaptic density
PV	parvalbumin
PTZ	Pentylenetetrazol
PYD-106	Methyl 4- (3-acetyl-4-hydroxy-1- (2- (2-methyl-1H-indol-3-yl)ethyl)-oxo-2,5-dihydro-1H-pyrrol-2-yl)benzoate
Ro25-6981	(αR,βS)-α- (4-Hydroxyphenyl)-β-methyl-4- (phenylmethyl)-1-piperidinepropanol maleate
SCZ	schizophrenia
TCN-201	3-Chloro-4-fluoro-N-[4-[[2- (phenylcarbonyl)hydrazino] Carbonyl-benzyl] benzenesulfonamide
TMD	transmembrane domain
UBP791	1- (7- (2-carboxyethyl)phenanthrene-2-carbonyl)piperazine-2,3-dicarboxylic acid
WT	wild type

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Chapter 1
Introduction

1.1 Glutamate neurotransmission/Glutamate receptors

Synaptic transmission is central to the ability of the nervous system to process and store information. There are electrical synapses and chemical synapses in the brain. Chemical synapses are specialized contacts between neurons, when a presynaptic neuron is activated, it releases neurotransmitters into the synaptic cleft which then bind to receptors on the membrane of the postsynaptic neuron. Excitatory synaptic transmission in the mammalian central nervous system is mainly mediated by glutamate. Glutamate can activate two different groups of receptors: ionotropic and metabotropic glutamate receptors. The first functional ionotropic glutamate receptor was cloned in 1989 (Hollmann, O'Shea-Greenfield, Rogers, & Heinemann, 1989). The ionotropic glutamate receptors can be subdivided into NMDA (N-methyl-D-aspartate) receptors (NMDARs), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and kainate (KA) receptors based on their specific agonists (Monaghan, Bridges, & Cotman, 1989; Traynelis et al., 2010). These subtypes of ionotropic glutamate receptors serve distinct roles at excitatory synapses and abnormality of them has been implicated in pathologies of various neurological and psychiatric diseases in the central nervous system (Bowie, 2008).

1.2 NMDA receptors

1.2.1 NMDA receptor activation

At resting membrane potential, NMDARs channel is blocked in a voltage-sensitive manner by extracellular Mg2+ (Mayer, Westbrook, & Guthrie, 1984). When the cell is depolarized, the extracellular Mg2+ block is removed and glutamate is then able to activate NMDARs by binding to the ligand binding domain of the GluN2 subunits, while the co-agonists, glycine/D-serine bind to GluN1 subunits (Anson, Chen, Wyllie, Colquhoun, & Schoepfer, 1998; Laube, Kuhse, & Betz, 1998). Activated NMDAR channels are permeable to Na^{+}, K^{+}, and Ca^{2+}. Calcium influx through NMDARs activates downstream cytoplasmic biochemical pathways that underlie synaptic plasticity under physiological conditions and neuronal death under pathological conditions.

Physiological levels of protons can suppress NMDARs activation, and extracellular Zn^{2+} and polyamines also act on NMDARs to modify its activity. In addition, NMDARs subunits interact with many different kinds of intracellular scaffolding, anchoring and signaling molecules.

1.2.2 NMDARs characters

Compared to other glutamate receptors, NMDARs display the following distinct characteristics: 1) require co-agonists (D-serine/glycine binding) plus glutamate for channel activation (Clements & Westbrook, 1991; J. W. Johnson & Ascher, 1987; Kleckner & Dingledine, 1988); 2) are voltage-dependent, simultaneous excitatory inputs are required to sufficiently depolarize the membrane to remove the Mg^{2+} block, which enables NMDARs to act as a coincident detectors that respond to both the presynaptic glutamate release and postsynaptic depolarization (Nevian & Sakmann, 2004; Seeburg et al., 1995).3) have higher Ca2+ permeability. 4) NMDARs also display remarkably slow activation and deactivation kinetics which enable NMDARs to have a physiologically-distinct impact on various physiological and pathological processes, such as higher functions including learning and memory.

1.2.3 NMDARs subunits composition and distribution

NMDARs are often thought to occur as a diheteromeric which consist of two GluN1 subunits and two identical subunits from GluN2A-2D, however, multiple lines of evidence have shown that triheteromeric NMDARs (two GluN1 subunits and two different GluN2 subunits) and tetrameric NMDARs consist of only GluN1 and GluN3 subunits are also exist in many brain regions and display different pharmacological properties compare to traditional diheteromeric NMDARs (Delaney, Sedlak, Autuori, Power, & Sah, 2013; Hansen, Ogden, Yuan, & Traynelis, 2014; Hatton & Paoletti, 2005; Huang & Gibb, 2014; Kvist, Greenwood, Hansen, Traynelis, & Brauner-Osborne, 2013; Lu, Du, Goehring, & Gouaux, 2017; Pachernegg, Strutz-Seebohm, & Hollmann, 2012; Perez-Otano, Larsen, & Wesseling, 2016; Rozeboom et al., 2015; Stroebel,

Casado, & Paoletti, 2018; Tovar, McGinley, & Westbrook, 2013; Wee, Tan, Cheong, Khanna, & Low, 2016; Yi, Traynelis, & Hansen, 2017). The distribution of NMDARs has been studied by detecting mRNA in the brain. The common NMDARs subunit, GluN1 is found throughout the brain. However, the four different GluN2 subunits are expressed in different brain regions in distinct patterns. They also have distinct physiological properties as well (Monyer, Burnashev, Laurie, Sakmann, & Seeburg, 1994; Wenzel, Fritschy, Mohler, & Benke, 1997). GluN2B and GluN2D appear prenatally, GluN2C and GluN2A are detected near birth. Both GluN2A and GluN2B are expressed in the telencephalon, but there is a subunit switch from GluN2B to GluN2A before adulthood (Monyer et al., 1994; Yashiro & Philpot, 2008). GluN2C is mainly found in the cerebellum, GluN2D has low expression in adulthood and mainly expressed in midbrain structures (Wenzel et al., 1997; Wenzel, Villa, Mohler, & Benke, 1996). In addition, in the telencephalon, GluN2C and GluN2D subunits have been reported to be expressed in astrocytes and interneurons (Monyer et al., 1994). Furthermore, there is additional evidence showing that NMDARs is also expressed in various glial cells, such as astrocytes (Krebs, Fernandes, Sheldon, Raymond, & Baimbridge, 2003), oligodendrocytes (Karadottir, Cavelier, Bergersen, & Attwell, 2005; Salter & Fern, 2005), and microglia (H. Liu, Leak, & Hu, 2016; Pocock & Kettenmann, 2007). For reasons discussed below, it is likely that the regional and cellular diversity of GluN2 subunit expression in the brain confer to GluN2A/2B/2C/2D-containing NMDARs essential and distinct roles in neuronal oscillations and regulating network activity.

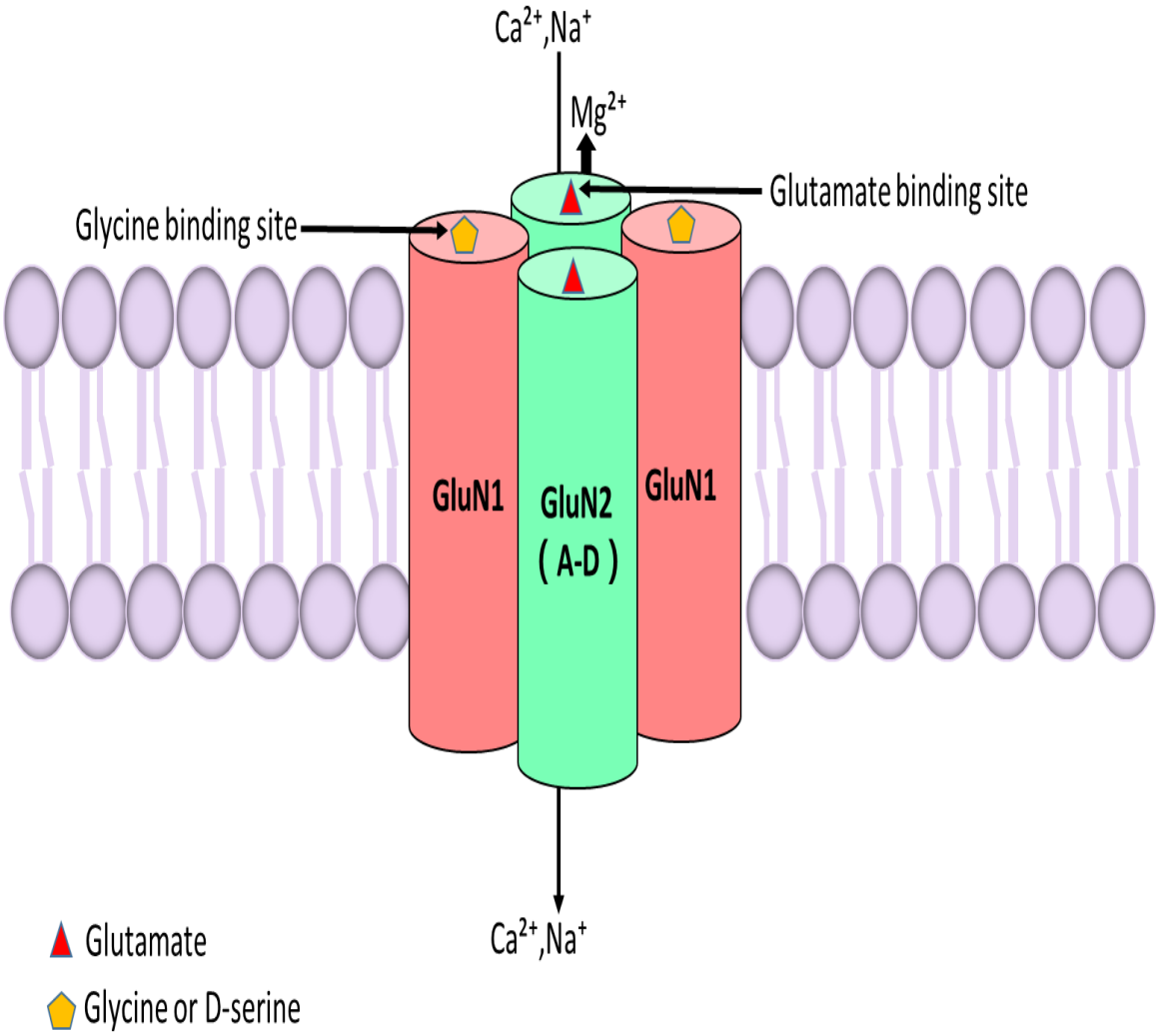


Figure 1. 1 Schematic diagram of NMDARs subunit composition

Diagram showing the NMDARs consist of two GluN1 and two GluN2 subunits with glycine binding sites and glutamate binding sites, respectively. NMDARs form a "dimer of dimers" structure, permeable to Ca^{2+}, Na^{+}, and Mg^{2+} block will be moved by the depolarization of the membrane.

1.2.4 NMDARs subunits properties

There are seven subunits of NMDARs have been identified so far: the ubiquitously expressed GluN1 subunit, and four distinct GluN2 subunits (GluN2A-2D), two GluN3 subunits (GluN3A and GluN3B). The GluN1 subunit is encoded by a single gene which has 22 exons. Exon 5, 21, 22 are spliced alternatively which generate 8 GluN1 splice variants (Hollmann et al., 1993; Nakanishi, Axel, & Shneider, 1992; Sugihara, Moriyoshi, Ishii, Masu, & Nakanishi, 1992a). On the other hand, GluN2 subunits are encoded by four different genes, and GluN3 subunits are encoded by two different genes.

Several properties of NMDARs that depend on GluN1 subunits: specifically, GluN1 subunits with residues encoded by exon 5 show reduced agonist potency (Traynelis, Burgess, Zheng, Lyuboslavsky, & Powers, 1998). Exons 21 and 22 splicing changes the amino acid composition of the CTD of GluN1 subunits (Traynelis et al., 2010), and it also affects the cellular distribution of NMDARs (Scott, Blanpied, & Ehlers, 2003; Scott, Blanpied, Swanson, Zhang, & Ehlers, 2001; Wenthold, Sans, Standley, Prybylowski, & Petralia, 2003). However, various evidence shows that most of the electrophysiological, biochemical and pharmacological properties of NMDARs function depend on its GluN2 subunits:1) GluN2 subunits affect the potency of glutamate (Buller et al., 1994; P. E. Chen et al., 2008; Hansen, Brauner-Osborne, & Egebjerg, 2008); 2) the time course of deactivation after removal of glutamate (Vicini et al., 1998b); 3) the potency of glycine and D-serine at GluN1 subunits also influenced by different GluN2 subunits (P. E. Chen et al., 2008; Dravid et al., 2010; Jessen et al., 2017; Sheinin, Shavit, & Benveniste, 2001); 4) NMDARs channel kinetic properties and the decay time of NMDAR-mediated excitatory postsynaptic currents (EPSCs) are strongly affected by GluN2 subunits. The sequence of deactivation time of NMDARs with different GluN2 subunits composition is GluN2A<2C=2B<<2D. Additionally, single-channel conductances and the Mg^{2+} block of NMDARs are also subunits dependent, GluN2A and GluN2B-containing NMDARs display higher

conductances openings, higher sensitivity to Mg2+ block and higher Ca2+ permeability compared to GluN2C and GluN2D-containing NMDARs (Kuner & Schoepfer, 1996; Qian, Buller, & Johnson, 2005). Furthermore, the channel open probability is also strongly affected by GluN2 subunits after all agonist-binding sites are fully occupied. For example, GluN2A and GluN2B-containing NMDARs display higher channel open probability than GluN2C and GluN2D-containing NMDARs. Lastly, the inhibition of NMDARs by endogenous protons or Zn^{2+} is also controlled by GluN2 subunits. GluN3 subunits do not form functional receptors alone, however, it can form functional receptors with GluN1 or GluN1/GluN2 subunits, the receptors formed by GluN1 and GluN3 subunits can only be activated by glycine; When GluN3 form NMDARs with GluN1 and GluN2A, it also generates low conductances channel openings (Das et al., 1998; Perez-Otano et al., 2001).NMDARs are thought to be essential for memory formation as the activation of postsynaptic NMDARs in most hippocampal pathways controls the forms of activity-dependent synaptic plasticity known as long-term potentiation (LTP) and long-term depression (LTD) (Canevari, Richter-Levin, & Bliss, 1994; Collingridge & Bliss, 1995; Kombian & Malenka, 1994), these processes have been postulated to underlie the brain's most important ability: storing and encoding information (Morris, 2013; M. Wang et al., 2013). Because of its role in synaptic plasticity, NMDARs are considered to be involved in higher cognitive functions such as learning and memory in the mammalian brain. NMDARs are also important for working memory and perception.

NMDAR subtype	Gating and Ligand-Binding Properties (GluN2 NTD-Dependent)					
	Maximal P_{open}	**Agonist potency**	**Deactivation Kinetics**	**Zn^{2+} Sensitivity**	**Proton Sensitivity**	**Ifenprodil Sensitivity**
GluN1/2A	High	Low	Fast	High	Intermediate	Low
GluN1/2B	Intermediate	Low	Intermediate	Intermediate	High	High
GluN1/2C	Low	Intermediate	Intermediate	Low	Low	Low
GluN1/2D	Low	High	Slow	Low	High	Low

Table 1. 1 Summary of NMDAR subtype-dependent gating and lignad-binding properties.

Adapted from (Glasgow, Siegler Retchless, & Johnson, 2015)

NMDAR subtype	Channel Properties (GluN2 S/L Site-Dependent)		
	Mg^{2+} Sensitivity/voltage dependence	**Ca^{2+} Permeability**	**Single-channel Conductance**
GluN1/2A	High	High	High
GluN1/2B	High	High	High
GluN1/2C	Low	Intermediate	Intermediate
GluN1/2D	Low	Intermediate	Intermediate

Table 1. 2 Summary of NMDAR subtype-dependent channel properties.

Adapted from (Glasgow et al., 2015)

1.2.5 NMDARs structure

Each subunit of a functional NMDAR has an extracellular amino-terminal domain (ATD), which links to an extracellular agonist binding domain (ABD), which, in turn, is connected to a transmembrane domain (TMD) forming the ion channel. The transmembrane helices communicate with an intracellular carboxy-terminal domain (CTD) (Traynelis et al., 2010). The ATD formed a bi-lobed structure by first ~350 amino acid which plays an essential role in the assembly and strongly modulates NMDARs function (Atlason, Garside, Meddows, Whiting, & McIlhinney, 2007; Farina et al., 2011; Yuan, Hansen, Vance, Ogden, & Traynelis, 2009). A distinctive feature of NMDARs compares to AMPA and Kainate receptors is that ion channel gating of NMDARs is significantly regulated by the ATD. For example, the ATD controls the open probability and speed of deactivation of NMDARs. Additionally, the structure of ATD creates binding sites for allosteric modulators, for example, extracellular Zn2+ and various GluN2B subunits selective antagonists (e.g., ifenprodil) have been shown to bind ATD(Karakas, Simorowski, & Furukawa, 2009, 2011; Tajima et al., 2016).

The ABD is formed by S1 and S2 segments of the polypeptide chain where M1, M2, M3 segments are in the middle of S1 and S2 segments. The ABD form bi-lobed structures that create the agonist binding site in the cleft between these two lobes. Binding of neurotransmitter agonists to the ABD produces a large conformational change involving the closure of the bi-lobed structure that is required for channel gating in all iGluRs (Armstrong, Sun, Chen, & Gouaux, 1998; Furukawa, Singh, Mancusso, & Gouaux, 2005; Mayer, 2005; Tajima et al., 2016). The glycine binding pocket in GluN1 subunits is considerably smaller and more hydrophobic than the glutamate binding pocket in GluN2 subunits (Furukawa & Gouaux, 2003; Furukawa et al., 2005; Inanobe, Furukawa, & Gouaux, 2005). One reason for ligands that show poor selectivity between different GluN2 subunits is the residues that make atomic contact with agonists and competitive antagonists within glutamate binding pocket are mostly conserved in GluN2 subunits. The residues at the heterodimer interface

between GluN1 and GluN2 ABDs also strongly modulate NMDARs function (Hansen et al., 2018). For example, (Borschel, Cummings, Tindell, & Popescu, 2015; Furukawa et al., 2005) have shown that the heterodimer interface can influence factors controlling deactivation, such as agonist dissociation or channel open time. In addition, a pair of conserved cysteine residues within GluN1 subunits interact as a disulfide bond in the GluN1 and GluN2A ABD heterodimer interface, and reduction of this conformational constraint only in GluN1 will enhance NMDARs function (Talukder, Kazi, & Wollmuth, 2011). Binding of both glutamate and co-agonist (glycine or D-serine) to GluN2 and GluN1 subunits trigger ABD closure and cause a series of conformational changes and ultimately open the NMDARs ion channel pore. However, binding of competitive antagonists, such as D-AP5, stabilizes the open cleft conformation of ABD which is incapable of triggering channel gating (Hansen et al., 2018). Interestingly, ABD can go through state changes between open and closed cleft conformations even without agonists present (Cooper et al., 2015; Dai & Zhou, 2015; Dolino, Rezaei Adariani, Shaikh, Jayaraman, & Sanabria, 2016; Yao, Belcher, Berger, Mayer, & Lau, 2013).

The TMD that contributes to the formation of the core of the ion channel is formed by three transmembrane helices (M1, M3, M4) and a reentrant loop (M2) (Hansen et al., 2018). Variations of amino acid residues in the TMD confer to the distinct pore properties of each type of ionotropic glutamate receptors (Traynelis et al., 2010). The M2 loop of NMDARs has sequence and structural homology to the P-loop of potassium (Kuner, Seeburg, & Guy, 2003; Wo & Oswald, 1995).QRN site resides at the apex of the reentrant M2 loop is critical for controlling the ion permeation properties of NMDARs. The high Ca^{2+} permeability of NMDARs is attributed to DRPEER motif in GluN1 subunit, which serves as a binding site for Ca2+ and is located in the extracellular vestibule near C-terminal to the M3 helix (J. Watanabe, Beck, Kuner, Premkumar, & Wollmuth, 2002). The M4 helix is known to play an important role in assembly and trafficking of NMDARs (Kaniakova, Lichnerova, Vyklicky, & Horak, 2012; Schorge & Colquhoun, 2003). The TMD of

the GluN1/GluN2B NMDA receptor forms a heterotetrameric ion channel with pseudo-four-fold symmetry (Karakas & Furukawa, 2014). They also observed that the tetrameric crossing of the M3 helices occludes the ion penetration pathway. This crossing of the M3 helices occurs around the highly conserved SYTANLAAF motifs in iGluRs, mutations of which are known to modify gating properties (Zuo et al., 1997). In addition, the aspargine at the tip of M2-loop is important for Ca^{2+} permeability and Mg^{2+} block of NMDARs (Kuner, Wollmuth, Karlin, Seeburg, & Sakmann, 1996; Wollmuth, Kuner, & Sakmann, 1998a, 1998b). The binding site for PCP, Mk-801, and ketamine also resides in TMD. Amino acids residues at or near QRN site and around the permeation pathway are shown to be critical for the block by these channel blockers (Chang & Kuo, 2008; Kashiwagi et al., 2002; Limapichat, Yu, Branigan, Lester, & Dougherty, 2013; Lipton & Chen, 2005; Mori, Masaki, Yamakura, & Mishina, 1992).

The CTD domain is the most diverse domain in terms of amino acid sequence composition and length. To date, only part of the GluN1 CTD binding with Ca2+/calmodulin structural details are known (Ataman, Gakhar, Sorensen, Hell, & Shea, 2007). The CTD is known to encode short docking motifs for intracellular binding proteins, and the CTD is thought to influence membrane targeting, stabilization, post-translational modifications, and targeting for degradation (Traynelis et al., 2010). Deletion of CTD domain on GluN1 and GluN2A subunits does not abolish their function but does alter its regulation (Ehlers, Fung, O'Brien, & Huganir, 1998; Kohr & Seeburg, 1996; J. J. Krupp, B. Vissel, S. F. Heinemann, & G. L. Westbrook, 1998; Vissel, Krupp, Heinemann, & Westbrook, 2001), because CTD domains contain different phosphorylation sites and binding sites for various intracellular proteins which are important for membrane trafficking and receptors function. The CTD domain of NMDARs binds to various classes of intracellular proteins, including cytoskeletal, scaffolding, adaptors, anchoring, structural, and signaling proteins (Fang et al., 2011; Gardoni et al., 1999; Logan, Rivera, & Leonard, 1999; Mori, Yamakura, Masaki, & Mishina, 1993; Tingley, Roche, Thompson, & Huganir, 1993). The interactions between the CTD domain and

intracellular proteins allow local signaling to proceed, providing the possibility of spatial and temporal specificity to receptor regulation (Traynelis et al., 2010). In addition, NMDARs are embedded into a rich complex of signaling molecules that are localized by a myriad of adaptor and scaffolding proteins (Husi, Ward, Choudhary, Blackstock, & Grant, 2000). Further enhancing the complexity among different subunits, for example, alternative RNA splicing of GluN1 subunits of NMDARs causes variation in the CTD that also affect binding sites for intracellular proteins.

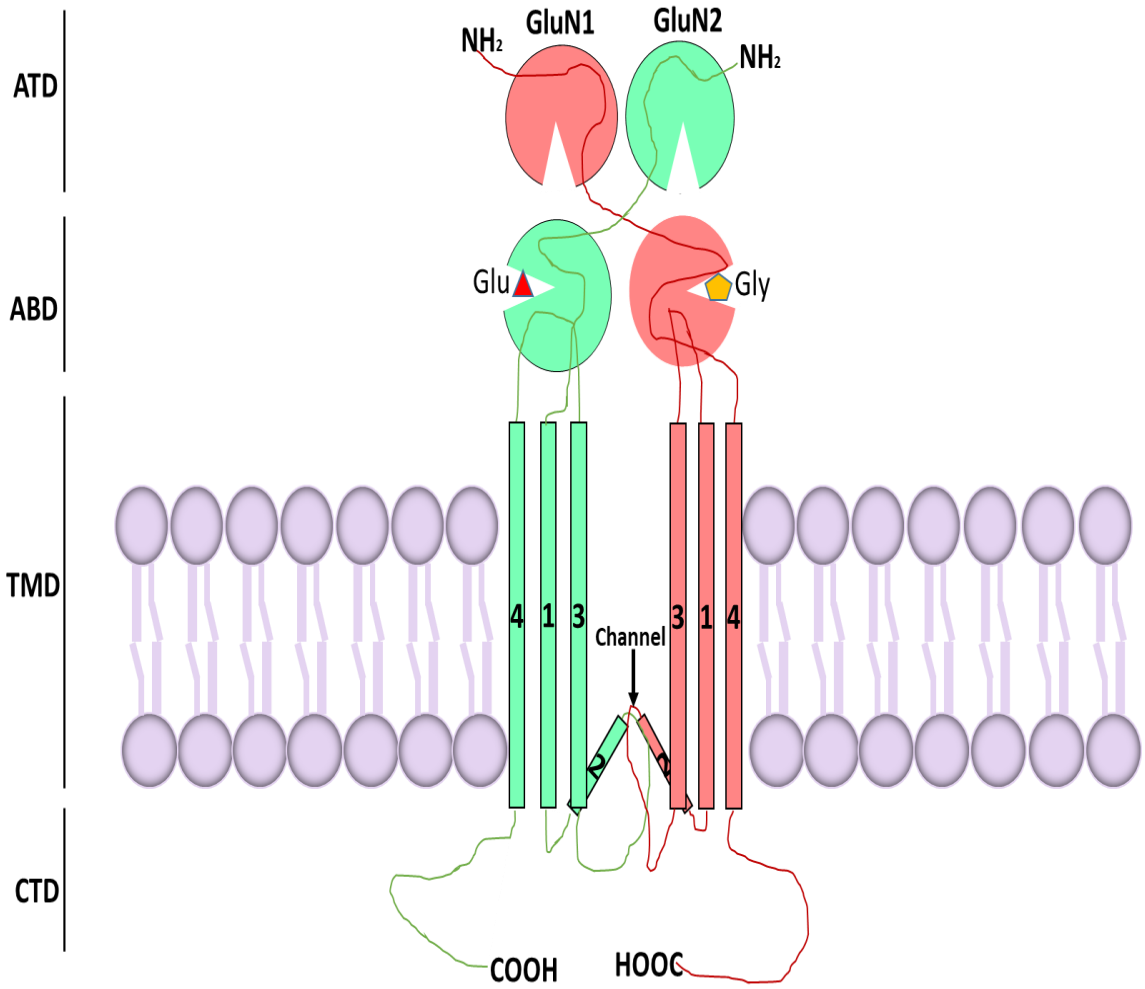


Figure 1. 2 NMDARs structure

NMDARs consist of four distinct domians: A-teminal domian (ATD), Agonist-binding domian (ABD), Transmembrane domian (TMD), and a C-teminal domain (CTD). The transmembrane domain have four segments (M1,M3,M4, and a re-entrant loop M2) which forming the channel pore.

1.3 Synaptic and extrasynaptic NMDAR signaling

Activation of NMDARs can be either toxic to neurons or promote their survival and plasticity. For example, (Tymianski, Charlton, Carlen, & Tator, 1993) found that Ca2+ entry through NMDARs was the most efficient way to kill neurons compared to entry through other channels. In contrast, others have shown that NMDAR activity and function is important for the survival of several types of neurons (Hardingham, 2006; Hetman & Kharebava, 2006; Ikonomidou & Turski, 2002). In addition, (Adams, de Rivero Vaccari, & Corriveau, 2004; Gould, Cameron, & McEwen, 1994; Ikonomidou et al., 1999; Monti & Contestabile, 2000; Pohl et al., 1999) demonstrated that elimination of NMDAR activity *in vivo* leads to apoptosis and enhances trauma-induced injury in developing neurons. Thus, NMDAR activation has been linked to the specific pathophysiological mechanisms of certain neurodegenerative diseases such as stroke and Huntington's disease (Choi, 1988; Lipton & Rosenberg, 1994; Rothman & Olney, 1986), and yet NMDAR activation could also be neuroprotective and may represent promising therapeutic targets. It has been proposed that it is the location of the NMDARs that influences whether it is coupled to pro-death or pro-survival signals and synaptic NMDARs are neuroprotective, whereas extrasynaptic NMDARs mainly contribute to neurotoxicity and cell death (Hardingham, Fukunaga, & Bading, 2002). According to this hypothesis, it is not the Ca2+ influx itself that leads to neurotoxicity, but the Ca2+ influx through NMDARs located outside of the synapses that are particularly harmful to neurons. In immature hippocampal neurons, around ¾ of all NMDARs are extrasynaptic (Tovar & Westbrook, 1999), and there is an extrasynaptic NMDARs switch to synaptic NMDARs during development, but extrasynaptic NMDARs still represent a large number of NMDARs until adulthood (Cottrell, Dube, Egles, & Liu, 2000; Petralia et al., 2010; Rosenmund, Feltz, & Westbrook, 1995; Tovar & Westbrook, 1999). This distribution may explain observations that some effects of extrasynaptic NMDARs signaling are dominant over the effects of synaptic NMDARs signaling (Hardingham & Bading, 2003; Ivanov et al., 2006; Papadia et al., 2008; S. J.

Zhang et al., 2007). There are three possibilities that might explain the differences between the synaptic and extrasynaptic NMDARs signaling: 1) the NMDARs signaling complexes have a different composition at synaptic locations and extrasynaptic locations; 2) NMDAR subunit composition is different in synaptic NMDARs and extrasynaptic NMDARs; 3) the manner by which synaptic NMDARs and extrasynaptic NMDARs are activated may be distinct. For hypothesis #2), it has been shown that GluN2A subunits are enriched in synaptic NMDARs (Steigerwald et al., 2000) and GluN2B subunits are more abundant at extrasynaptic locations (Groc et al., 2006; Martel, Soriano, et al., 2009). However, studies also demonstrated that both GluN2A and GluN2B subunits express at some extrasynaptic locations (Petralia et al., 2010). GluN2B and GluN2A-containing NMDARs has been linked to neuronal death and neuronal survival, respectively (Y. Liu et al., 2007). Conversely, both GluN2A and GluN2B-containing NMDARs can promote neuronal death as well as neuronal survival (Martel, Wyllie, & Hardingham, 2009; Papadia et al., 2008; von Engelhardt et al., 2007). Interestingly, GluN2C-containing NMDARs suppression also has been shown to benefit the ischemic stroke (Chung et al., 2016; Holmes, Zhou, Donahue, Balsara, & Castellino, 2018; Kadotani, Namura, Katsuura, Terashima, & Kikuchi, 1998). Because of the lack of a compound that could efficiently differentiate these subunits and the existence of the tri-heteromeric NMDARs that contain both GluN2A, GluN2B, and GluN2C subunits, it is difficult to prove this hypothesis.

1.4 The role of NMDARs in diseases

Both NMDAR hyper-function and hypo-function have been shown to be related to disease states. Various studies have shown that NMDARs contribute to a variety of diseases in the brain, including schizophrenia (Balu, 2016; J. T. Coyle, G. Tsai, & D. Goff, 2003; Gilmour et al., 2012; J. T. Kantrowitz & D. C. Javitt, 2010; J. W. Olney, J. W. Newcomer, & N. B. Farber, 1999), stroke (Hoyte, Barber, Buchan, & Hill, 2004; Ikonomidou & Turski, 2002; Lai, Shyu, & Wang, 2011; Lees, 1997; Q. J. Wu & Tymianski, 2018), Huntington’s disease (Cepeda et al., 2001; Dau,

Gladding, Sepers, & Raymond, 2014; Hansson et al., 2001; Heng, Detloff, Wang, Tsien, & Albin, 2009; L. Li et al., 2003; Saft et al., 2011), Alzheimer's disease (Cain, Ighanian, & Boon, 2000; Hu et al., 2017; Makhaeva et al., 2015; Schmitt, 2005; Shankar et al., 2007), neuropathic pain (Chizh & Headley, 2005; Niesters & Dahan, 2012; Planells-Cases, Perez-Paya, Messeguer, Carreno, & Ferrer-Montiel, 2003; Sang, 2000; L. J. Wu & Zhuo, 2009), depression (Burgdorf, Colechio, Stanton, & Panksepp, 2017; Deutschenbaur et al., 2016; Duman & Li, 2012; D. J. Newport et al., 2015; Reus et al., 2016; Skolnick et al., 1996; Szewczyk, Palucha-Poniewiera, Poleszak, Pilc, & Nowak, 2012; N. R. Williams & Schatzberg, 2016), autism spectrum disorder (Burgdorf, Moskal, Brudzynski, & Panksepp, 2013; Kiani et al., 2015; E. J. Lee, Choi, & Kim, 2015; Moskal, Burgdorf, Kroes, Brudzynski, & Panksepp, 2011), and intellectual disability (W. Chen et al., 2017; Kiani et al., 2015; Marwick, Skehel, Hardingham, & Wyllie, 2015; Metzler, 2011).

1.4.1 NMDA and stroke

NMDAR-dependent excitotoxicity appears to be a primary cause of neuronal death which occurs acutely after ischemia or traumatic brain injury (Ikonomidou & Turski, 2002; Lai et al., 2011; Q. J. Wu & Tymianski, 2018). Loss of cerebral blood flow rapidly triggers energy deficits and neuronal depolarization that cause a large amount of glutamate to be released to the extracellular space. Overactivated NMDARs then lead to ion imbalance within the neurons, particularly calcium. Calcium overload then is thought to be highly effective in producing cell death (Besancon, Guo, Lok, Tymianski, & Lo, 2008). NMDAR antagonists, especially GluN2B selective antagonists have been shown to have neuroprotective effects against ischemia and injury-induced cell death (Cho, Park, Chung, & Gwag, 2010; Diener et al., 2002; Krivonos, Amosova, & Smolentseva, 2010; Lapchak, 2006; Yu, Wu, & Wang, 2015). On the other hand, even though inhibition of excessive NMDAR activity in the initial period of ischemia and TBI have been shown neuroprotective in animal models, more than two decades of neuroprotection research has not yielded any clinical therapies (Besancon et al., 2008; Q. J. Wu & Tymianski, 2018). Reasons behind

this failure might be: 1) the synaptic NMDAR signal might be neuroprotective while extrasynaptic NMDAR signal could lead to cell death. NMDARs antagonists disrupt both of these signals thus limiting the beneficial effects of NMDAR blockade (Hardingham & Bading, 2003; Hetman & Kharebava, 2006); 2) not only do neurons play an important role in glutamate signal, astrocytes and oligodendrocytes also play crucial roles in glutamate signaling. To develop better clinical therapies for stroke based on NMDARs, NMDAR subunit distribution at both synaptic and extrasynaptic sites in neurons and glia should be more well defined. For example, if specific NMDARs subunits are expressed in specific cellular sites (e.g., GluN2B mainly in extrasynaptic sites, GluN2A mainly in synaptic sites, GluN2C in astrocytes), then targeting those specific NMDARs subunits should reduce the side effects and achieve more satisfactory outcomes.

1.4.2 NMDARs and neurodegenerative diseases

Excessive activation of NMDARs is also involved in the pathogenesis of some neurodegenerative diseases such as Huntington's disease (HD) and Alzheimer's disease (AD). NMDARs are highly expressed in striatal medium spiny neurons which is also the major neuronal population that degenerates in the striatum in Huntington's disease (Albin et al., 1990; Reiner et al., 1988). In addition, NMDARs agonists could replicate the behavioral and neuropathological features of HD. For example, injection of quinolinic acid into the striatum of rodents or primates induces selective loss of striatal neurons but sparing of interneurons (Fan & Raymond, 2007; Ferrante, Kowall, Cipolloni, Storey, & Beal, 1993; Hantraye, Riche, Maziere, & Isacson, 1990; Schwarcz, Brush, Foster, & French, 1984; Schwarcz, Foster, French, Whetsell, & Kohler, 1984). Various studies have demonstrated that both human and rodent striatum are enriched in GluN2B subunits of NMDARs while other subunits also exist (Kuppenbender et al., 2000; Peter, Panova, Christie, & Taylor, 2000; Rigby et al., 1996; Standaert, Friberg, Landwehrmeyer, Young, & Penney, 1999). In different HD animal models, GluN2A and GluN2B subunits levels have been found

reduced, with GluN1 subunits unchanged (Ali & Levine, 2006; Carter, Hunt, & Morton, 2000; Cha et al., 1999; Jarabek, Yasuda, & Wolfe, 2004).

There are two main hallmarks of Alzheimer's disease (AD), amyloid-β and tau protein (V. E. Johnson, Stewart, & Smith, 2010; Spires-Jones & Hyman, 2014). It is widely accepted that Aβ-induced changes in the availability of glutamate and the function of NMDARs are related to the neurotoxicity and neurodegeneration observed in the AD (R. Wang & Reddy, 2017). For example, GluN2B antagonists reverse Aβ-induced impairment of LTP, loss of synapses and synaptic proteins, etc. (Hanson et al., 2014; Hanson, Pare, Deng, Smith, & Zhou, 2015; Rammes et al., 2017; Zhou, 2014). The non-selective NMDAR antagonists such as memantine (clinically approved drug for the AD) can also block Aβ-induced spine loss, which indicates that activation of additional NMDARs subunits, not only GluN2B, may be required for Aβ-induced synaptic dysfunction (Danysz & Parsons, 2012; Olivares et al., 2012). Additionally, tau protein has been shown to enhance NMDAR association with PSD-95 and coupling to downstream effects. Blocking the interaction between NMDARs and PSD-95 by a synthetic peptide improved memory function and reduced premature death seen in AD mouse models (Amadoro et al., 2006; Chohan & Iqbal, 2006; De Montigny, Elhiri, Allyson, Cyr, & Massicotte, 2013; S. Kobayashi, Tanaka, Soeda, Almeida, & Takashima, 2017; Warmus et al., 2014).

1.4.3 NMDARs and neuropathic pain

NMDARs are also known to be present in neurons of the nociceptive pathway (Aiyer, Mehta, Gungor, & Gulati, 2018; Lefevre et al., 2015). NMDARs appear to play a critical role in neuropathic pain since non-selective NMDARs antagonists and GluN2B-selective antagonists have been reported to reduce neuropathic pain in animal studies (Y. Kim, Cho, Ahn, Kim, & Yoon, 2012; Pud et al., 1998; Takahashi, Miyazaki, Nanbu, Yanagida, & Morita, 1998; Wei & Pertovaara, 1999). However, the precise role of different NMDARs subunits in the development and maintenance of neuropathic pain is still unknown.

1.4.4 NMDARs and other neurological disorders

The implication of NMDARs in depression arises from the observation that the non-selective NMDAR antagonist ketamine can exert a rapid and sustained antidepressant effect on human patients with treatment-resistant depression (Berman et al., 2000; Murrough et al., 2013; N. R. Williams & Schatzberg, 2016; Zarate et al., 2006). Blocking NMDARs in GABAergic interneurons can lead to disinhibition of pyramidal excitatory neurons and thus enhancing neural activity and causing the antidepressant effects (Kavalali & Monteggia, 2012; Miller et al., 2014; D Jeffrey Newport et al., 2015).

Converging evidence from genetic and pharmacological studies also indicate that NMDARs have an important role in autism spectrum disorder (ASD) (Ghanizadeh, 2011; Moskal et al., 2011; Saunders, Gandal, Roberts, & Siegel, 2012). Genetic analysis of ASD patients and their families have identified disease-associated mutations for multiple NMDA receptor genes (Barnby et al., 2005; O'Roak, Vives, Fu, et al., 2012; O'Roak, Vives, Girirajan, et al., 2012; Tarabeux et al., 2011; Yoo, Cho, Park, Yang, & Kim, 2012). Of *de novo* mutations in genes associated with sporadic autism, the gene for the NMDAR subunit GluN2B was the most frequently affected (O'Roak, Vives, Girirajan, et al., 2012). In addition, NMDARs are also known to directly interact with other identified ASD-associated genes, such as neuroligin-4 and SHANK and appear to be part of a hub of ASD-associated genes (Arons et al., 2012; Barrow et al., 2009; Blundell et al., 2010). Together, these findings are consistent with observations that NMDAR antagonists can mimic the symptoms of ASD. For example, low doses of the NMDAR blockers MK-801 and ketamine can impair social interactions, decrease social vocalizations, and promote restricted, repetitive behaviors (Burket, Cannon, Jacome, & Deutsch, 2010; Moy et al., 2013; Saunders et al., 2012; Zou et al., 2008). At higher doses, NMDAR antagonists mimic schizophrenia (including the negative symptoms of schizophrenia which overlap with ASD and have comorbidity with ASD (Gadow, 2013)).

NMDARs are essential for most forms of synaptic plasticity and learning. Thus it is not surprising that NMDARs are involved in different forms of Intellectual Disability (ID). More than 50 NMDAR mutations have been identified for ID as well as 36 for schizophrenia and 24 for ASD (Yuan, Low, Moody, Jenkins, & Traynelis, 2015). For example, in patients with epilepsy aphasia spectrum (EAS), mutations in the GluN2A subunit are found in up to 20% of the population and were the first identified monogenic cause of the disorder (Turner, Morgan, Perez, & Scheffer, 2015). ID conditions other than those involving NMDAR mutations are also known to affect NMDAR activity. In fragile X, for example, the disrupted FMRP protein is known to bind to the G quadruplex structure of RNA for synaptic proteins, including GluN2B (Stefanovic et al., 2015).

1.5 NMDARs pharmacology

Even though many different compounds that target NMDARs have shown promising therapeutic effects in preclinical studies, most of these compounds are unable to be translated into effective drugs for human clinical therapy. Reasons behind this failure might be that those compounds have poor subunit-selectivity and/or unsuitable affinity to the target which might not be able to reverse the abnormal NMDARs activity. If only the NMDARs subgroups that are undergoing pathological changes can be modulated properly, then more efficient therapeutics with fewer side effects should emerge.

NMDA receptor activity can be modulated both positively and negatively. Antagonists can be sorted according to their place of action: at the agonist binding site (competitive), within the ion channel pore (channel blockers), or at specific modulation sites (noncompetitive).

A large number of compounds inhibit NMDARs by occupying its ion channel pore (channel blockers), such as some dissociative anesthetics (e.g., ketamine and phencyclidine), and dizocilpine maleate (MK-801) (N. Anis et al., 1990; Lodge & Johnson, 1990; Wong et al., 1986). Because of the side effects caused by these channel blockers, their clinical application has been limited (Finiels-Marlier, Marini, Williams, & Paul, 1993; Jevtovic-Todorovic, Wozniak, Powell,

Nardi, & Olney, 1998; Journey & Bentley, 2018; Luckenbaugh et al., 2014; Nicholi, 1984; Popke et al., 2002; Short, Fong, Galvez, Shelker, & Loo, 2018). A special case is memantine, the clinically approved drug for Alzheimer's Disease, probably due to its fast dissociation out of the channel upon receptor inactivation, resulting in minimal interference with the normal synaptic transmission (Glasgow, Povysheva, Azofeifa, & Johnson, 2017; J. W. Johnson & Kotermanski, 2006; Y. N. Wu & Johnson, 2015). Since the ion channel is highly conserved between different NMDAR subunits, most channel blockers, including those mentioned above, poorly discriminate between different NMDAR subtypes (Dravid et al., 2007). Blockade of the ion channel is voltage- and use-dependent, which means that the blockade requires channel opening so that channel blockers can occupy the channel afterwards. Because of this, the inhibition effect by channel blockers is slow in onset stage and increases with the probability of channel opening. The inhibition by channel blockers could also be impacted by Mg^{2+}, for example, studies have shown (Kotermanski, Wood, & Johnson, 2009) that physiological levels of Mg^{2+} preferentially decreases memantine inhibition of GluN2A or GluN2B-containing NMDARs compared to GluN2C/2D-containing receptors, which makes memantine weakly selective for GluN2C and GluN2D-containing NMDARs. Other NMDARs channel blockers (polyamine derivatives, e.g., argiotoxin-636) display higher selectivity (more than 50 fold) at receptors with GluN2A or GluN2B subunits compared to receptors with GluN2C or GluN2D subunits. This large group of NMDARs channel blockers can be used as pharmacological tool drugs to differentiate GluN2A- and GluN2B- versus GluN2C- and GluN2D-containing NMDARs.

Competitive antagonists compete with the agonist for binding but do not activate the receptor. For example, D-AP5, among the first competitive antagonist discovered, binds to the glutamate binding site and displays high selectivity for NMDA receptors over AMPA and kainate receptors (Watkins & Evans, 1981). However, due to the high homology of the LBDs between different GluN2 subunits, the GluN2 subunits selectivity for competitive antagonists is difficult to

achieve(Kinarsky et al., 2005). For example, D-AP5 displayed a low selectivity (less than 10-fold) for different GluN2 subunits (Feng, Morley, Jane, & Monaghan, 2005). Adding a bulky hydrophobic group resulting in a compound weakly preferring GluN2C/2D-containing receptor. Further improvement in selectivity are seen in (2R*,3S*)-1 (phenanthrene-3-carbonyl) piperazine-2,3-dicarboxylic acid (UBP141) or (2R*,3S*)-1- (9-bromophenanthrene-3-carbonyl)piperazine-2,3-dicarboxylic acid (UBP145) which show improved selectivity for receptors containing GluN2D subunits (Costa et al., 2009). Other compounds that display specific subunit selectivity includes Ro25-6981, NVP-AAM 077, and CPP. These compounds display unique pharmacodynamic and pharmacokinetics profiles which show various affinities (Table 1.3 and 1.4) to each subunit and are useful pharmacological tools for sorting out the distinct function of each NMDAR subtype. GluN2 subunit-selective NMDAR antagonists are likely to have novel therapeutic/adverse effect profiles because these subunits differ significantly in their anatomical and physiological properties (J. H. Li et al., 1998; Masu et al., 1993; Monyer et al., 1994). For example, an NR2D-selective antagonist would be expected to be effective in some cases of neuropathic pain (Minami et al., 2001), and NR2C-selective antagonists may be useful in ischemic stroke (Holmes et al., 2018).

NMDARs channel blockers: IC_{50} (μM) value

Agents	GluN2A	GluN2B	GluN2C	GluN2D	Subunit selectivity
Ketamine	0.7	0.5	0.5	0.7	2A≈2B≈2C≈2D
(+)MK-801	0.01	0.01	0.1	0.1	2A≈2B>2C≈2D
Memantine	0.9	0.8	N/A	0.5	2A≈2B≈2D
PCP	0.1	0.1	0.2	0.2	2A≈2B≈2C≈2D

Table 1. 3 IC_{50} value of NMDARs channel blockers on each subunits and their relative subunits selectivity.

Adapted from (Paoletti & Neyton, 2007)

NMDARs Non-competitive antagonist: IC_{50} (μM) value

Agents	GluN2A	GluN2B	GluN2C	GluN2D	Subunit selectivity
Zn^{2+}	0.02	2.0	20	10	2A>>2B>2C≈2D
Ro 25-6981	>30	0.009	N/A	N/A	2B>>2A≈2C≈2D (>3000-fold)
Ifenprodil	>30	0.15	>30	>30	2B>>2A≈2C≈2D (>200-fold)
NVP-AAM077	0.006	0.06	0.01	0.04	2A≈2C>2B≈2D
(R)-CPP	0.04	0.3	0.6	2.0	2A>2B≈2C>2D

Table 1. 4 IC_{50} value of NMDARs non-competitive antagonists on each subunits and their relative subunits selectivity.

Adapted from (Paoletti & Neyton, 2007)

1.6 NMDARs allosteric modulators

NMDARs allosteric modulators are compounds that act at subunit-specific allosteric sites of NMDARs subunits which and promising candidates for NMDAR-related drug development as they should display fewer side effects compared to NMDARs channel blockers and competitive antagonists (Monaghan, Irvine, Costa, Fang, & Jane, 2012). Positive allosteric modulators (PAMs) are compounds that bind to an allosteric site and enhance the activity of NMDARs. Inhibitory modulators that bind to sites other than orthosteric sites or in the channel are named NMDARs negative allosteric modulators (NAMs).

Many PAMs has been identified and developed in recent years. For example, the pyrrolidone derivative PYD-106 displays a higher selectivity for GluN2C-containing receptors, this compound binds to the ATD/ABD interface of GluN2C subunits (Khatri et al., 2014). The substituted tetrahydroisoquinoline CIQ is a NMDARs potentiator which displays selectivity for GluN2C and GluN2D-containing NMDARs over GluN2A and GluN2B-containing NMDARs. The actions of CIQ depend on a single residue in the M1 region (GluN2D Thr592) and the linker between the n-terminal domain and agonist binding domain (Mullasseril et al., 2010). The helical segment before M1 in GluN2D subunits of NMDARs is also critical for the action of CIQ (Ogden & Traynelis, 2013). By replacing chlorine with the bromine on CIQ, CIQ displayed higher selectivity on GluN2C-containing over GluN2D-containing NMDARs (Santangelo Freel et al., 2013). Additionally, our group has identified a series of PAMs. For example, phenanthrene derivatives with a carboxylic acid group at the 3-position which enhance NMDAR current. UBP512 selectively potentiates receptors containing GluN2A subunits but inhibits GluN2C and GluN2D subunits. Similarly, UBP710 potentiates receptors with GluN2A and GluN2B subunits whereas it inhibits GluN2C and GluN2D-containing NMDARs. Naphthalene derivatives with a 2-position carboxyl group also display PAMs activities. UBP551 selectively potentiates GluN2D subunits whereas it inhibits other NMDAR subtypes (Costa et al., 2010). Other PAMs includes UBP608

which inhibits GluN2A-containing receptors 23 times more potently compared to GluN2D-containing NMDARs (Costa et al., 2010).

Ifenprodil was the first subunit-specific NMDA receptor antagonist discovered, it is known for its allosteric inhibitory activity at NMDARs. Ifenprodil is a non-competitive, voltage- and use-independent inhibitor of NMDARs (Legendre & Westbrook, 1991). Ifenprodil binds to the interface between ATDs of GluN1/GluN2B heterodimers (Tajima et al., 2016) and displays inhibition of GluN1/GluN2B receptors with a 200- to 400-fold higher affinity than any other combination of GluN1/GluN2 subunits (K. Williams, 1993). Protons such as Zn^{2+} also display NMDAR NAM activity (Traynelis & Cull-Candy, 1990; Traynelis, Hartley, & Heinemann, 1995). Zn^{2+} inhibits only GluN2A-containing NMDARs at low concentrations but displays inhibitory activity at both GluN2A and GluN2B-containing NMDARs at high concentrations (Paoletti et al., 2000; Rachline, Perin-Dureau, Le Goff, Neyton, & Paoletti, 2005). Many novel noncompetitive antagonists with distinctive GluN2 subunit selectivity have been described in recent years. For example, TCN-201 shows high selectivity for GluN2A-containing receptors (Bettini et al., 2010). TCN-201 acts as a negative allosteric modulator which modulates glycine binding, and the binding site of TCN-201 is located at the interface between ABDs of GluN1 and GluN2A subunits (Hansen, Ogden, & Traynelis, 2012). UBP791 act as a competitive negative allosteric modulator that preferentially blocks receptors with GluN2C and GluN2D subunits. Our group also identified that UBP618 and UBP552 act as general NMDARs NAMs with high potency (Costa et al., 2012; Irvine et al., 2012; Irvine et al., 2015).

1.7 The role of NMDARs in neuronal oscillations

Neuronal oscillations reflect coordination of neuronal activity- groups of cells firing at the same time. It is thought to be generated, in part, by inhibitory GABAergic interneuron firing that synchronizes nearby pyramidal excitatory neurons in a certain frequency range (Buzsaki & Draguhn, 2004; Gray, 1994; Traub, Bibbig, LeBeau, Buhl, & Whittington, 2004). This is necessary

for cognition and perception and is disrupted in schizophrenia (McNally & McCarley, 2016; McNally, McCarley, & Brown, 2013). NMDAR antagonists have been shown to augment neuronal oscillations, and this is thought to underlie the schizophrenia-like symptoms induced by NMDAR antagonists (Caixeta, Cornelio, Scheffer-Teixeira, Ribeiro, & Tort, 2013; Gu et al., 2013; Molina, Skelin, & Gruber, 2014; Neymotin et al., 2011; Olszewski, Dolowa, Matulewicz, Kasicki, & Hunt, 2013). Evidence show that in the cortex, pyramidal cells express GluN2A and GluN2B subunits (Q. Chen & Reiner, 1996; Petralia, Wang, & Wenthold, 1994; Siegel et al., 1994) and interneurons specifically PV+ interneurons express GluN2D subunits of NMDARs (Standaert et al., 1999; Standaert, Landwehrmeyer, Kerner, Penney, & Young, 1996). This expression pattern places NMDARs in a critical position for both generating and regulating neuronal oscillations. NMDARs antagonists like ketamine and MK-801 can increase the power of spontaneous neuronal oscillations in rodents (Ehrlichman et al., 2009; Gonzalez-Burgos & Lewis, 2012). In a human subject study, ketamine increased the amplitude of the 40-Hz auditory steady state response (Plourde, Baribeau, & Bonhomme, 1997) and impaired the activity of neurons in connected brain regions to synchronize their firing (Krystal et al., 1994; Uhlhaas et al., 2006; Uhlhaas & Singer, 2006).

In the reticular nucleus of the thalamus, GluN2C has been proposed to be the critical subunit mediating NMDAR control of delta oscillations (1-4 Hz) directed to the hippocampus (Y. Zhang, Buonanno, Vertes, Hoover, & Lisman, 2012; Y. Zhang, Llinas, & Lisman, 2009; Y. Zhang, Yoshida, Katz, & Lisman, 2012). Studies (Middleton et al., 2008) have shown that NMDAR antagonists can alter the interactions between high gamma and low gamma oscillations in the hippocampus. In addition, NMDAR antagonists generate high-frequency oscillations (80-200 Hz) in the nucleus accumbens which can be recorded from cortex and hippocampus (Goda et al., 2015; Hunt, Falinska, Leski, Wojcik, & Kasicki, 2011; Hunt, Olszewski, Piasecka, Whittington, & Kasicki, 2015; Olszewski, Dolowa, et al., 2013). The medial prefrontal cortex-hippocampus-nucleus reuniens of thalamus circuits loop is critical for cognitive and memory deficits in SCZ

(Cassel & Pereira de Vasconcelos, 2015). Thus, this loop is probably critical for synchronizing neuronal oscillations in these regions. GluN2D subunits are highly expressed in the nucleus reuniens, GluN2D could potentially influence the function of this loop.

1.8 Schizophrenia and its hypothesis

1.8.1 Dopamine hyper-function hypothesis of schizophrenia

Schizophrenia is a deleterious psychiatric disease affecting almost 1% of the population globally. The symptoms of SCZ can be categorized into positive symptoms (hallucinations, delusions); negative symptoms (anhedonia, social withdraw); and cognitive deficits (deficits in attention, learning, and working memory) (Messias, Chen, & Eaton, 2007). The negative and cognitive deficits of most schizophrenics cannot be treated properly under current medications. These treated SCZ patient have a diminished ability to live independently and gain meaningful employment in society, causing large social and financial burden for both their families and society (Rossler, Salize, van Os, & Riecher-Rossler, 2005). The total cost of schizophrenia in the United States is estimated to be around $156 billion in 2013 (Cloutier et al., 2016).

Traditionally, the dopamine hyperfunction hypothesis was the dominating theory in the field which was based on studies showing that administration of amphetamine and other compounds which increase extracellular concentrations of dopamine can induce similar psychotic symptoms seen in schizophrenic patients (Grace, 2016; O. D. Howes & S. Kapur, 2009; Kesby, Eyles, McGrath, & Scott, 2018; Seeman, 2006; Thompson, Pogue-Geile, & Grace, 2004). Conversely, drugs, such as reserpine and alpha-methyl-para-tyrosine which can reduce dopamine levels, displayed the ability to alleviate psychotic symptoms (Brodie, Murphy, Goodwin, & Bunney Jr, 1971; Gershon, Hekimian, Floyd, & Hollister, 1967; Nur & Adams, 2016; Pozuelo, 1979). In addition, post-mortem studies provide various evidence linking dopamine and SCZ. For example, an increase in striatal dopamine levels and an increase in D2 receptor density has been found as

neuropathological changes in schizophrenia (Davis & Kahn, 1991; Mackay et al., 1982). Various post-mortem studies also showed that the presynaptic D2 autoreceptor was upregulated, while the predominantly post-synaptic D2 receptors were downregulated in the dorsolateral prefrontal cortex compared with healthy controls (Arinami, Gao, Hamaguchi, & Toru, 1997; Cross, Crow, & Owen, 1981; Mackay et al., 1982). Research has also shown that environmental risk factors might contribute to the impaired dopamine function, which fits with a recent finding that stress and other risk factors can impact a vulnerable dopamine system to dysregulate it and lead to psychosis (Oliver D Howes & Shitij Kapur, 2009; Swanson et al., 2007; van Os, Kenis, & Rutten, 2010). This evidence suggests that there is a presynaptic hyperdopaminergic abnormality in schizophrenia and antipsychotics can treat psychotic symptoms by blocking D2 receptors. However, these findings do not explain how a biochemical abnormality can account for the phenomenology and specific symptoms of the SCZ (Kebabian & Calne, 1979). In addition, One-third of individuals with schizophrenia, especially those with negative and cognitive symptoms, do not respond to typical antipsychotics (dopamine receptor antagonists) despite high levels of D2 occupancy (Crow, 1980; Javitt & Zukin, 1991). Furthermore, they do not respond to manipulations that deplete presynaptic dopamine either (Perrault, Depoortere, Morel, Sanger, & Scatton, 1997). These evidence suggest that the pathophysiological basis of a large number of SCZ patients' symptoms involves more than dopaminergic excess, or may be unrelated to dopaminergic dysfunction (Carlsson & Carlsson, 1990; Davis & Kahn, 1991; Oliver D Howes & Shitij Kapur, 2009; Laruelle, Kegeles, & ABI‐DARGHAM, 2003). This implies that other pathways, such as glutamate pathways, may contribute to SCZ, especially for the negative symptoms and cognitive dysfunction (Coyle, 2006; Javitt, 2007).

1.8.2 NMDAR hypofunction hypothesis of schizophrenia

One of the earliest observations suggesting glutamate involvement in schizophrenia is the finding that schizophrenic patients show reduced cerebrospinal fluid glutamate levels (Tsai et al., 1995). Since then, a growing body of evidence supports the theory of abnormal glutamatergic

neurotransmission in schizophrenia (Mouri, Noda, Enomoto, & Nabeshima, 2007; John W Olney, John W Newcomer, & Nuri B Farber, 1999). Although many glutamate receptors have been implicated in SCZ, the current prevailing hypothesis is the NMDAR hypofunction of SCZ (J. T. Coyle et al., 2003; Gilmour et al., 2012; Gonzalez-Burgos & Lewis, 2012; J. W. Olney et al., 1999). The NMDAR hypofunction hypothesis of SCZ originated from the discovery that dissociative anesthetics phencyclidine (PCP) and ketamine can reproduce the full spectrum of the SZ-like symptoms in healthy human subjects and exacerbate symptoms in people with SCZ (Jentsch & Roth, 1999; John W Olney et al., 1999). In addition, many SCZ risk genes have been identified that can directly or indirectly affect NMDAR function (Akbarian et al., 1996; Gainetdinov, Mohn, & Caron, 2001; Hahn et al., 2006; John E Lisman et al., 2008; Mohn, Gainetdinov, Caron, & Koller, 1999). In postmortem studies, downregulation of NMDAR and reduced levels of D-serine had been found in schizophrenic brain (Bendikov et al., 2007; Kornhuber et al., 1989). In a clinical trial, an agent that activates through the glycine site of NMDAR improves the negative symptoms and cognitive deficits of SCZ patients, and in some cases, it improves the medication outcomes in patients with positive symptoms (Buchanan et al., 2007; D'Souza, Charney, & Krystal, 1995). In vivo imaging studies also provide evidence that SCZ patients, as well as high-risk psychosis individuals have abnormal glutamate levels in their brains (Bressan & Pilowsky, 2000; Shenton et al., 1992).

In conclusion, the major dopaminergic abnormality in SCZ appears to be presynaptic, it is present at the onset of SCZ and is related to the onset of psychosis. However, this hypothesis has many limitations, in particular, how can dopamine changes account for negative and cognitive symptoms. On the other hand, there are several converging lines of evidence supporting the NMDAR hypofunction hypothesis of SCZ (J. T. Coyle et al., 2003). These two hypotheses should not be considered mutually exclusive; they might be interconnected by a specific mechanism. For example, positive symptoms account for presynaptic dopamine hyperfunction, and negative and

cognitive symptoms account for NMDAR hypofunction. Moreover, reduced NMDARs function has been found to increase dopamine release (Mohn et al., 1999), and allosteric modulation of GluN2C/2D-containing NMDARs has been shown to bidirectionally modulates dopamine release (X. Zhang, Feng, & Chergui, 2014). Taken all together, it is plausible that both dopamine and glutamate are involved in schizophrenia and can be integrated into one hypothesis.

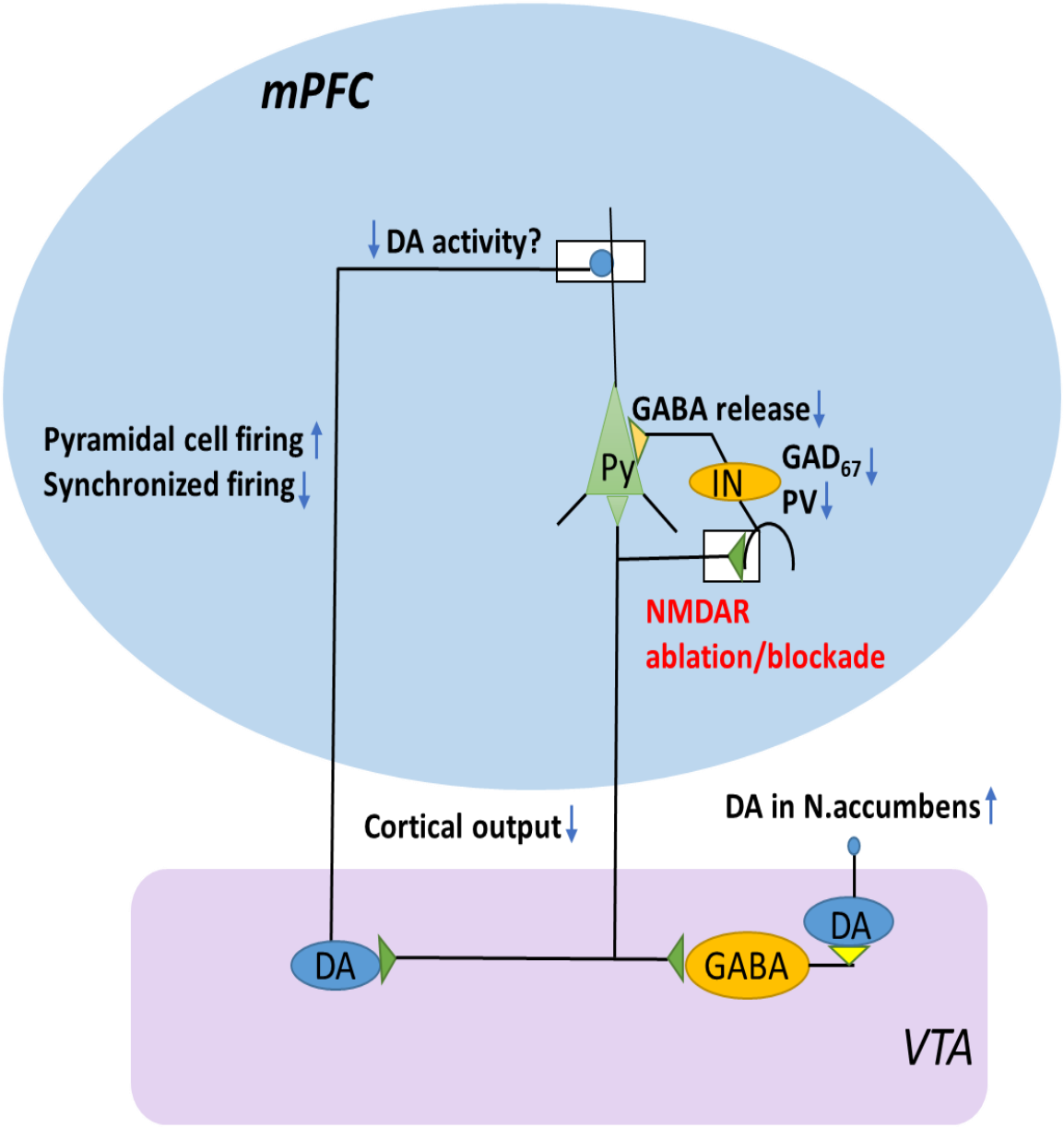


Figure 1. 3 Mechanism of NMDAR deletion/blockade in cortical parvalbumin (PV) inhibitory interneurons altering cortical activity, leading to the emergence of subcortical dopamine hyperactivity in mice.

NMDAR knockout or blockade in cortical PV GABAergic inhibitory interneurons down-regulates their GABA synthesis and release, which not only results in cortical disinhibition but also impairs the synchronized activity of principal neurons in the cortex. This may reduce the cortical output to VTA and thus increases dopamine activity in the nucleus accumbens. Adapted from (Nakazawa et al., 2012)

1.9 Neuronal oscillations and schizophrenia

Neuronal oscillations are electrical activities arising from a group of neurons that fire together at the same time in a rhythmic manner (Buzsáki & Draguhn, 2004). It facilitates different brain regions to communicate with each other and exchange information in order to achieve higher brain functions (Singer, 1993). Neuronal oscillations are essential components for normal brain function, for example, learning and memory, attention and perception (Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001). Neuronal oscillations can be divided into different subcategories based on their specific frequency ranges, for example, alpha (8-12 Hz), theta (4-7 Hz), delta (1-3 Hz), beta (13-30Hz) and gamma (30-200Hz) (Başar et al., 2001; Buzsáki & Draguhn, 2004). Neuronal oscillations can be measured by the electroencephalogram (EEG) (on the scalp), electrocorticography (ECoG) (epidural) and magnetoencephalography (MEG), etc. (Buzsáki, Anastassiou, & Koch, 2012; Pfurtscheller & Da Silva, 1999). To define the role of neuronal oscillations in neurological diseases, besides the basal/drug-induced power changes, we can measure basal neuronal oscillations; drug-induced neuronal oscillations; auditory steady-state evoked potentials; auditory-evoked potentials; mismatch negativity; as different measurements.

Schizophrenia and many psychiatric disorders, such as autism spectrum disorder and intellectual disability had been shown to display abnormal neuronal oscillations in many of specific frequencies (Uhlhaas & Singer, 2010). Several studies have shown that schizophrenic patients show reduced amplitude of the evoked beta and gamma response (Hoptman et al., 2010; Shin, O'Donnell, Youn, & Kwon, 2011; Woo, Spencer, & McCarley, 2010). Schizophrenic patients also demonstrated abnormalities in amplitude and synchronization of self-generated induced oscillations when they are in cognitive tasks such as executive and working memory tasks (C. M. Chen et al., 2014; Hong, Summerfelt, McMahon, Thaker, & Buchanan, 2004; McNally, McCarley, McKenna, Yanagawa, & Brown, 2011). Moreover, patients with schizophrenia display a reduced amplitude of gamma and theta oscillations in working memory tasks in their frontal lobes (Basar-

Eroglu et al., 2007; Howard et al., 2003). Schizophrenic patients have also been characterized by abnormal neuronal oscillations at resting state with increased activity in low-frequency range and reduced activity in the high-frequency range (Hoptman et al., 2010; Van Den Heuvel & Pol, 2010).

Many neurobiological abnormalities underlie the abnormal neuronal oscillations in schizophrenia. Anatomically, schizophrenia has been shown to have a reduced volume of gray matter which is thought to cause reduced synaptic connectivity (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Suddath, Christison, Torrey, Casanova, & Weinberger, 1990). This reduction of synaptic connectivity might be the reason that schizophrenics show reduced evoked neuronal oscillations. A study has shown a relationship between grey matter reduction and the ERP amplitudes reduction (B. O'donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004). Evidence also indicated that white matter volume and integrity are changed in schizophrenic patients, as well as reduced organization of connections between different brain regions (Davis et al., 2003; Lim et al., 1999; Pol et al., 2004). Because of the disrupted connections in a certain brain region or between different brain regions, patients with schizophrenia show impaired synchronization of oscillatory activity in the cortex in different frequency ranges (Hipp, Engel, & Siegel, 2011; Spencer et al., 2004; Uhlhaas, Haenschel, Nikolić, & Singer, 2008). On the other hand, the disruption in different brain regions can cause deficits in long-range synchronization (Mulert, Kirsch, Pascual-Marqui, McCarley, & Spencer, 2011).

To summarize, impairments and deficits in neuronal oscillations may be considered as an endophenotype of schizophrenia, each subcategory of the schizophrenia symptoms might be related to specific deficits found in amplitude (power) changes in the spontaneous and/or drug-induced neuronal oscillations, auditory-evoked response, etc.

1.10 NMDAR involvement in mismatch negativity deficits in schizophrenia

In the normal condition, humans or rodents respond to an unexpected stimulus (deviant stimulus) more strongly than to expected stimulus (standard stimulus) among a series of stimuli

consisting of both standard and deviant stimuli which are presented randomly (oddball paradigm) (Näätänen, Pakarinen, Rinne, & Takegata, 2004; Segalowitz & Barnes, 1993). Mostly the amplitude of the response to the deviant stimuli will be larger in both positive and negative direction. Mismatch negativity (MMN) is an auditory event-related potential component that is calculated based on the amplitude difference in response to unexpected stimuli (deviant) and standard stimuli (Näätänen, 1995; Näätänen, Paavilainen, Rinne, & Alho, 2007). This difference was first shown to be reduced in patients with schizophrenia 27 years ago (Shelley, Ward, Michie, et al., 1991). There are two main features of the reduced MMN seen in SCZ: 1) the size of deviant response is reduced with unchanged standard response; 2) the MMN increased with the higher deviance, but this increase reach a ceiling sooner in SCZ patients (Lavoie et al., 2008; P. Michie et al., 2000). The aspects that differentiate the deviant stimuli from the standard one can be frequency, latency, amplitude, etc. In humans, there are few evident peaks that show up in oddball paradigm response waveform, according to their specific latency in milliseconds after the onset of the stimuli, they have been named as P100, P200, P400 (P1, P2 and P4) (Shelley, Ward, Catts, et al., 1991). Even though hundreds of studies have reported detectable MMN in humans, detecting MMN in animal models was not well-established until recently (L. Harms, Michie, & Naatanen, 2016). Several studies have now proved that rodents can recapitulate the MMN seen in humans and at least in part meet the most important criteria in human MMN- adaptation independence (Connolly et al., 2004; Nelken & Ulanovsky, 2007; Umbricht, Vyssotki, Latanov, Nitsch, & Lipp, 2005).

In both the NMDAR hypofunction and neurodevelopmental animal models of schizophrenia, reduced MMN have been reported (Robert E Featherstone et al., 2015; L. Harms, 2016). Among the NMDAR hypofunction models, uncompetitive NMDAR antagonists and GluN2B-selective blockers have been shown to cause reduced MMN (Daniel C Javitt, Mitchell Steinschneider, Charles E Schroeder, & Joseph C Arezzo, 1996; Korostenskaja, Nikulin, Kičić, Nikulina, & Kähkönen, 2007). However, ketamine increased the standard response while the

GluN2B blocker CP-101,606 reduced the deviant response similar to patients with schizophrenia instead (Digavalli V Sivarao et al., 2014), which suggest that ketamine might only affect the adaptation of MMN and NR2B subunits specifically might play a critical role in the MMN reduction seen in human schizophrenics. The observation that SCZ patients cannot establish deviance detection in the oddball paradigm is consistent with an essential role of NMDARs in short-term memory (Juanita Todd et al., 2008; Walker & Davis, 2000). This might be because they did not form intended short-term memory due to NMDAR dysfunction for those standard stimuli so that their brain cannot differentiate the deviant stimulus properly. On the other hand, developmental models of schizophrenia such as the neonatal ventral hippocampal lesion model and the social isolation model also demonstrated reduced oddball mismatch response (L. Harms, 2016). Since these studies did not consider the adaptation effect and lack controls for that, it is not clear whether this deficit represents adaptation or deviance detection has been affected in these models (L. Harms et al., 2016; L. R. Harms & Michie, 2013).

1.11 NMDAR involvement in auditory steady-state response deficit in schizophrenia

Sensory cortical neurons can be entrained to a stimulus at a specific frequency through the duration of the presented stimulus. Auditory steady-state response (ASSR) is an auditory-evoked potential that is generated in the brain when a large group of neurons synchronize together to a train of click stimuli between 1-200 Hz or by periodic modulation of amplitude and/or frequency of a continuous tone, and can be measured by methods like EEG (Korczak, Smart, Delgado, M Strobel, & Bradford, 2012; Picton, John, Dimitrijevic, & Purcell, 2003). ASSR have been extensively used in investigating the electrophysiological response to sensory stimulation in both children and adults (Roß, Borgmann, Draganova, Roberts, & Pantev, 2000; Swanepoel, Hugo, & Roode, 2004). ASSR can be obtained non-invasively with minor task demand from patients and healthy controls which allow the ASSR to be used to test the ability of neural circuits to support oscillatory activity.

Although different frequency of stimuli can induce ASSR, ASSR to 40 Hz stimuli has been shown repeatedly to be prominent deficient in patients with schizophrenia by various studies while the ASSR to other frequency stimuli outside the gamma range seems to be less affected (Brenner et al., 2009; Jordan P Hamm, Casey S Gilmore, & Brett A Clementz, 2012; Krishnan et al., 2009; Kwon et al., 1999; Spencer, 2012). The brain region that generates ASSR is believed to be the primary auditory cortex and neurons in superficial layers, which suggests that the ASSR entrainment deficit at gamma frequency range seen in SCZ patients might due to the dysfunction of excitatory and/or inhibitory neurotransmission in their brain (Gutschalk et al., 1999; Herdman et al., 2002; Ross, Herdman, & Pantev, 2005). It is postulated that this deficit is secondary to the dysregulation of GABAergic neurons or NMDAR function (Jordan P Hamm et al., 2012; Kwon et al., 1999).

However, several animal studies have examined the effects of NMDAR antagonists on the rat's ASSR (B. F. O'Donnell et al., 2013; Jenifer L Vohs, Chambers, O'Donnell, Krishnan, & Morzorati, 2012) and found that ASSR power and phase synchronization was increased near auditory cortex at 20, 30, 40 Hz stimuli after ketamine administration (J. L. Vohs et al., 2010). Moreover, acute MK-801 administration has also been shown to increase ASSR synchronization at 20 and 40 Hz (Sivarao, 2015; Sivarao et al., 2016; Sivarao et al., 2013). In a human study, SCZ patients displayed augmented ASSR compared to healthy controls (J. P. Hamm, C. S. Gilmore, & B. A. Clementz, 2012).

Thus, while most studies report a deficit in entrainment, several studies have reported increased signal power in ASSR. The inconsistency might be due to the usage of different tone and set up as stimuli such as the length of the click trains, the inter-stimulus intervals can affect the result of the ASSR (J. P. Hamm et al., 2012), the symptoms of the patients and different measurements seem to contribute to this controversial results as well (Sivarao, 2015).

1.12 Disrupted in the schizophrenia (DISC1) gene in schizophrenia

Schizophrenia is a devastating psychiatric disorder that is thought to be caused by the interaction of genetic and environmental risk factors (Allardyce & Boydell, 2006; Van Os, Rutten, & Poulton, 2008). Many genes have been identified as risk genes of schizophrenia (Harrison & Weinberger, 2005; Jia, Sun, Guo, & Zhao, 2010). Compelling evidence for DISC1 gene involvement in schizophrenia is originally from a large Scottish family many of whom have a disrupted DISC1 gene and suffered from various mental illness, including SCZ (F. Zhang et al., 2006). Many gene association studies have been conducted after this report. There is a consensus now that DISC1 is a major genetic risk factor for many mental disorders, e.g., SCZ and mood disorder (Hodgkinson et al., 2004; Koko Ishizuka, Matt Paek, Atsushi Kamiya, & Akira Sawa, 2006). Clinical studies have demonstrated that mutations of DISC1 can cause abnormal brain function and anatomy (Callicott et al., 2005; Jaaro-Peled et al., 2009). In addition, the role of DISC1 protein at the cellular level has been extensively studied as well. It is believed that DISC1 protein is a critical anchoring molecule that regulates its interacting proteins in different subcellular compartments (Atkin & Kittler, 2012; Brandon, 2007; Dahoun, Trossbach, Brandon, Korth, & Howes, 2017; Hattori et al., 2007; K. Ishizuka, M. Paek, A. Kamiya, & A. Sawa, 2006; James et al., 2004). The expression level of DISC1 is high in the developing brain, especially in the developing cortex where the DISC1 protein has been shown to be essential in various cellular processes, including progenitor cell proliferation, radial neuronal migration, dendritic arborization, and outgrowth, etc. In the adult brain, DISC1 is highly expressed in the dentate gyrus of hippocampus, which might suggest its possible role in neurogenesis in the mature brain (Dranovsky & Hen, 2007; J. Y. Kim et al., 2012; H. Lee et al., 2015; Q. Wu, Li, & Xiao, 2013; Ye et al., 2017). To summarize, DISC1 protein is critical for neurodevelopment which fits with SCZ that is being a neurodevelopmental disorder. There are animal studies showing that DISC1-mutated mice display various behavioral abnormalities and biochemistry changes that parallel to symptoms of SCZ

(Hikida et al., 2007; Niwa et al., 2010; Pletnikov et al., 2008). Chapter 4 is meant to obtain MMN and ASSR in DN-DISC1 transgene mice as the endophenotypes of SCZ to examine the relationship between DISC1 and SCZ.

1.13 NMDAR and CDKL5 deficiency disorder

Mutations in cyclin-dependent kinase-like 5 (CDKL5) gene reduce the amount of functional CDKL5 protein and/or alter its activity in neurons. It has been reported that deficiency of CDKL5 or impairment of its function leads to disrupted brain development (Charlotte Kilstrup-Nielsen et al., 2012; Rusconi et al., 2008), yet it is not clear that how these molecular changes cause specific features of the diseases. Studies demonstrated that the CDKL5 gene provides instructions for making proteins that are critical for normal brain development and function. It is involved in the formation, growth, and migration of neurons in the brain (Bertani et al., 2006; Fehr et al., 2013; Lin, Franco, & Rosner, 2005). Clinically, CDKL5 deficiency shares symptoms with Rett syndrome，e.g. seizures, intellectual disability and other developmental impairments (Mari et al., 2005). Specifically, CDKL5 deficiency disorder is featured with seizures initiated from infancy, usually occurred as early as the first three months of life. Other characteristics of CDKL5 deficiency disorder include impaired motor skills, delayed language acquisition, and other deficits (Bahi-Buisson & Bienvenu, 2011). In addition, CDKL5 deficiency disorder is an X-linked mutation disorder that has been reported more in females probably due to more severe consequences than in males (Mangatt et al., 2016).

In the animal models where CDKL5 gene function has been selectively knockout from excitatory and inhibitory neurons in forebrain, various biological and behavioral abnormalities have been reported, including abnormal EEG responses to convulsant agent, reduced visual-evoked responses, reduced dendritic arborization of cortical neurons, hypoactivity, and limb clasping (Amendola et al., 2014). Relationships between NMDAR and CDKL5 have been reported by several studies. For example, a cellular study of CDKL5 revealed that both CDKL5 subcellular

localization and expression were regulated by extrasynaptic NMDARs (Rusconi, Kilstrup-Nielsen, & Landsberger, 2011); On the other hand, another recent study uncovered that post-synaptic localization of GluN2B-containing NMDAR in the hippocampus was controlled by the CDKL5 (Kosuke Okuda et al., 2017).

Chapter 2

The role of GluN2C containing NMDA receptors in NMDA receptor antagonist-induced neuronal oscillations

2.1 Abstract

NMDA receptor (NMDAR) antagonists such as ketamine and phencyclidine (PCP), can reproduce many of the symptoms of schizophrenia, including deficits in perception, cognition ,and working memory. A reliable indicator of NMDAR antagonist action *in vivo* is the augmentation of neuronal oscillation power. Since the coordinated and rhythmic activation of neuronal assemblies (oscillations) is necessary for perception, cognition and working memory, their disruption both in psychiatric conditions and with NMDAR antagonists may reflect the underlying defects causing schizophrenia symptoms. Using four well-characterized NMDAR antagonists (ketamine, MK-801, PCP, and memantine) and knockout (KO) mice, we evaluated the role of GluN2C NMDAR subunits in generating NMDAR antagonist-induced oscillations. We find that basal oscillatory power was elevated in the low gamma frequencies in GluN2C-KO mice. Compared to wildtype (WT) mice, all NMDAR antagonists increased oscillatory power more in GluN2C-KO mice, however, memantine was less effective than other antagonists in enhancing low gamma oscillations in the GluN2C-KO. Moreover, classic oddball response (the highly-sensitive measures for the endophenotype of schizophrenia) has been measured from GluN2C-KO mouse, KO mouse displayed impaired oddball response with lower amplitude peaks and shifted peaks latency. We propose a model wherein NMDARs containing GluN2C in astrocytes serve to detect local cortical excitatory synaptic activity and provide excitatory feedback to postsynaptic excitatory neurons. In this manner, local excitatory activity modulates the postsynaptic potential and, in turn, oscillatory power.

2.2 Introduction

The rhythmic and coordinated activation of groups of neurons results in neuronal oscillations which are thought to be necessary for cognition, perception and working memory (Uhlhaas, Haenschel, Nikolic, & Singer, 2008; Uhlhaas & Singer, 2012). Thus, in patients with schizophrenia, the increase in basal oscillatory power and a decrease, or aberrant augmentation, in the synchrony of oscillations between regions may be responsible for the symptoms of the disease (S. H. Lee et al., 2006; Spencer et al., 2003; Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009). The ability of the NMDAR antagonists ketamine, MK-801 and PCP to mimic the spectrum of symptoms seen in SZ initiated the NMDAR hypofunction hypothesis of schizophrenia. This hypothesis is now supported by a variety of pharmacological and genetic studies in both humans and rodents (J. T. Coyle et al., 2003; J. W. Olney et al., 1999; Snyder & Gao, 2013). Consistent with this hypothesis, NMDAR blockade causes a well-described and robust augmentation of neuronal oscillations and a deficit in neural synchrony (Dzirasa et al., 2009; Hakami et al., 2009; Korotkova, Fuchs, Ponomarenko, von Engelhardt, & Monyer, 2010; Pinault, 2008). Thus, NMDAR blockade may be disrupting cognition and perception by increasing the noise of oscillations, thus decreasing the signal to noise ratio, or by decreasing appropriate synchrony or increasing aberrant synchrony between brain regions. Presently, it is not clear how different NMDAR subtypes participate in the oscillatory generators.

NMDAR complexes are composed of subunits from seven genes - GluN1, GluN2A-GluN2D, and GluN3A-GluN3B (Masu et al., 1993; Mishina et al., 1993; Monyer et al., 1994; M. Watanabe, Inoue, Sakimura, & Mishina, 1993b). These subunits assemble into hetero-tetrameric complexes in various combinations resulting in functionally-distinct NMDARs. Many NMDARs are thought to be composed of two GluN1 subunits and two GluN2 subunits. The different alternatively spliced GluN1 isoforms have largely similar pharmacological and physiological properties whereas the GluN2 subunits confer distinct physiological, biochemical, and

pharmacological properties to the NMDAR complex (Buller et al., 1994; Hollmann et al., 1993; Ikeda et al., 1992; Monyer et al., 1994; Sugihara, Moriyoshi, Ishii, Masu, & Nakanishi, 1992b; Vicini et al., 1998a). NMDAR containing GluN2C or GluN2D subunits have distinct physiological properties compared to most forebrain NMDARs. They display a reduced voltage-dependency due to a weaker Mg^{2+} block, do not desensitize, have relatively high affinity for L-glutamate, and have long-lasting current responses (Glasgow et al., 2015; Monyer et al., 1994; Paoletti, Bellone, & Zhou, 2013). These properties, combined with their varied developmental profiles and anatomical distributions (M. Watanabe, Inoue, Sakimura, & Mishina, 1992, 1993a), imply that NMDAR containing these subunits may have a function in the CNS that is markedly distinct from the major GluN2A- and GluN2B-containing receptors.

In recent studies, we have found that the potent non-selective NMDAR antagonist MK-801 augmented gamma oscillations in GluN2C-KO mice more than in wildtype mice (Gupta et al., 2016). In contrast, in the GluN2D-KO mouse, ketamine-induced oscillations were greatly diminished (Sapkota et al., 2016). Since ketamine and MK-801 each have additional off-target activities (Briggs & McKenna, 1996; Clarke & Reuben, 1995; Sleigh, Harvey, Voss, & Denny, 2014), we sought in the present study to directly compare 4 non-selective NMDAR antagonists in GluN2C-KO and mice to determine if these NMDAR antagonists effects on GluN2C-KO mice are a general feature of NMDAR antagonists. Furthermore, since memantine has a potency, selectivity, and mechanism of action very similar to ketamine, but has less association with psychotomimetic effects, we were also interested to determine if memantine displays different effects on neuronal oscillations than other general NMDAR antagonists.

We find that NMDAR antagonists, in general, have a significantly larger effect on neuronal oscillations in the GluN2C-KO mouse than in wildtype (WT) mice. Interestingly, while GluN2C-KO mice were associated with increased oscillatory power induced by all NMDAR antagonists, ketamine, MK-801 and PCP augmented oscillatory power in the low gamma

frequency range (30-60 Hz) while memantine and MK-801 augmented high gamma (60-90 Hz), thus potentially accounting for their differential ability to produce psychosis. Additionally, mismatch negativity is a reliable marker that is reduced in schizophrenia and it is considered to be a highly-sensitive measure for SCZ. To determine if GluN2C-containing NMDARs knockout will cause the phenotypes of SCZ, such as reduced MMN, we measure the classic oddball responses from WT and KO mouse and find that MMN is impaired in GluN2C-KO mouse.

2.3 Materials and methods

2.3.1 Animal husbandry

We used the GluN2C knockout/nβ-galactosidase knockin mouse (Karavanova, Vasudevan, Cheng, & Buonanno, 2007) which were backcrossed on to C57BL/6 background (95% and remaining 129 Sv/Ev). Experimental procedures were performed on male GluN2C wildtype (WT), heterozygous (HET), and knockout (KO) littermate mice. Mice (8-16 weeks old) were age matched (within one week of age) for ECoG recordings. Unless specified otherwise, animals were group-housed on a 12:12 light/dark cycle with ad libitum access to food and water. At least 3 or more litters formed the subjects of each of the experimental groups and experiments were conducted in at least 2 or more batches and assimilated.

2.3.2 Surgery

All procedures were approved by the University of Nebraska Medical Center's Institutional Animal Care and Use Committee (IACUC) in compliance with the National Institutes of Health guidelines. 12-16 weeks old WT, GluN2C-KO and GluN2D-KO mice were surgically implanted with tripolar electrodes (MS333/2; Plastics One, Roanoke, VA) under xylazine/ketamine/acepromazine anesthesia as required by IACUC regulations. Two holes were made in the skull 3mm posterior to bregma at 1mm and 2.5mm lateral. Two electrodes were placed in the medial hole onto the dura surface near the retrosplenial cortex, and the third electrode was placed in the lateral hole for ground. The electrodes were secured to the skull as described elsewhere (Jeffrey et al., 2013). After 7 days of recovery, electroencephalographic (ECoG) recordings were made with a DP-311 differential amplifier (Warner Instruments, Hamden, CT) with high-pass/low-pass filters set at 0.1 and 300 Hz and digitized/recorded at 2000 Hz sampling rate (Digidata 1400, pClamp 10; Molecular Devices, Sunnyvale, CA).

2.3.3 Drugs

We used the general NMDAR antagonists: ketamine (30mg/kg, Par Pharmaceutical, Spring Valley, New York or Hospira, Inc., Lake Forrest, IL), MK-801 (0.2mg/kg, kindly provided by Merck & Co.), memantine (20mg/kg), and PCP (3mg/kg, Sigma-Aldrich, St. Louis, MO). All drugs are dissolved in the saline. The dosage of each drug was determined by prior experiments and literature values (M. J. Hunt, B. Raynaud, & R. Garcia, 2006).

2.3.4 ECoG Recordings

At least one-week after electrode implant surgery, animals in their home cage were placed inside a surrounding Faraday cage, the electrode assembly was connected to a commutator by a cable and the animals were allowed to acclimate for 10 minutes. After 30 minutes of baseline recordings, the animals were injected i.p. with NMDA antagonists or saline and recorded for additional 60-90 minutes.

2.3.5 Oddball response recordings design

Mice were tested for one half-hour session each day, for three days. The awake mouse recovered after 7 days from the surgery was placed in the experimental chamber for 15 min before each session to acclimatize. Each session consisted of an ascending and a descending oddball sequence separated by a 3 min break. The order of the two sequences alternated for each mouse across test sessions. Two sequences were presented in the experiment. These were oddball sequences where the roles of the deviant and standard were reversed (flip-flop condition) resulting in either an ascending deviant sequence (low frequency standard and high frequency deviant) or a descending deviant sequence (high frequency standard and low frequency deviant). In the ascending and descending oddball sequences, 87.5% of the tones were standards and 12.5% deviants. For all sequences, tones had a 10 ms rise and fall time and a stimulus onset asynchrony (SOA) of 500 ms. Two tones of 100 ms duration were used: a low frequency tone of 9000 Hz and

a high frequency tone of 13000 Hz, Each of the sequences consisted of 1800 tones and ran for 20 minutes.

2.3.6 Data Analysis

A power spectrum analysis was performed with Clampfit (Molecular Devices) using a Hamming window with 50% overlap. Spectrogram analysis was performed by Neuroexplorer software. Data are expressed as mean of individual experiments along with the standard error of the mean. Statistical comparisons were made using one- or two-way ANOVA and multiple t-test. Graphpad Prism was used for statistical analysis and graphing the data.

2.4 Results

ECoG recording of awake WT, GluN2C-KO mice displayed typical ECoG traces before and after drug administration (Figure 2.1). Average baseline absolute power of the two mice genotypes are displayed in (Figure 2.2) and values normalized by the WT mice values are shown in (Figure 2.3). Relative to WT mice, GluN2C-KO mice displayed higher basal oscillatory power at frequencies above 10 Hz, especially within the beta and low gamma range of 20 to 60 Hz.

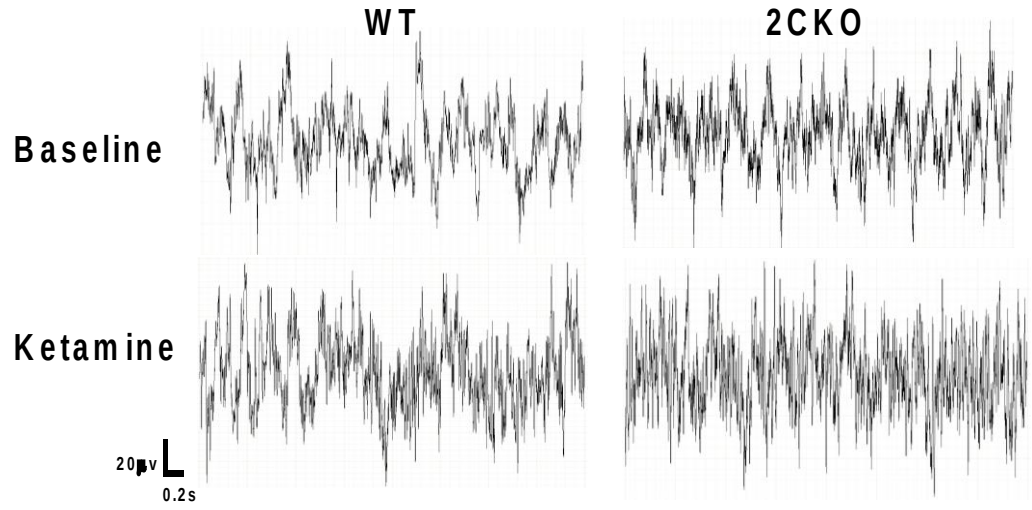


Figure 2. 1 Sample traces of ECoG recordings of wildtype and GluN2C-KO mice before (baseline) and after ketamine administration.

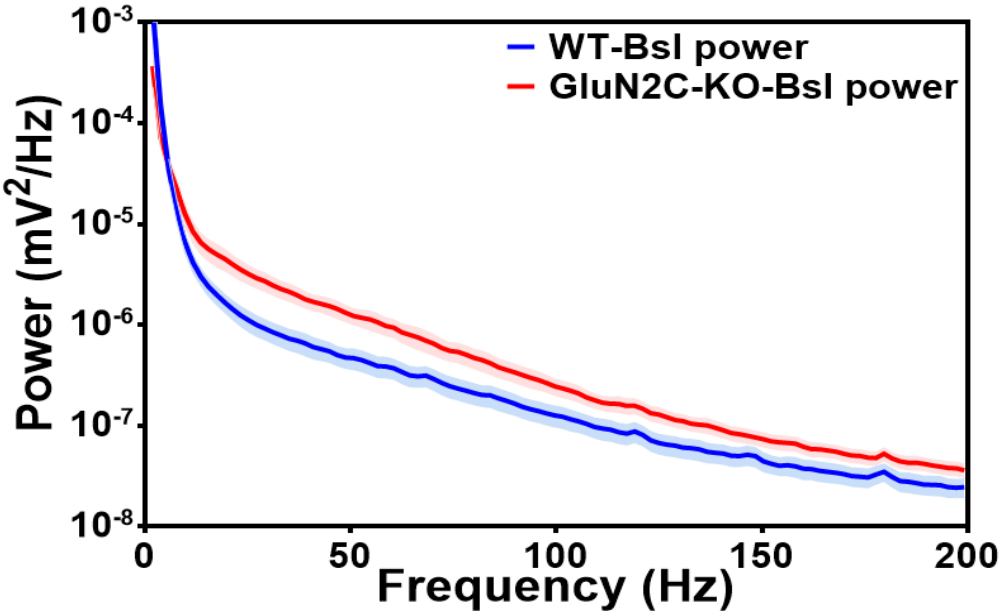


Figure 2. 2 Baseline power spectrum of WT and GluN2C-KO animals.

GluN2C-KO mice (n = 15) display higher spontaneous oscillatory power than wildtype mice (n = 22), especially in low-gamma frequency range (20-60 Hz). SEMs are shown by light shading.

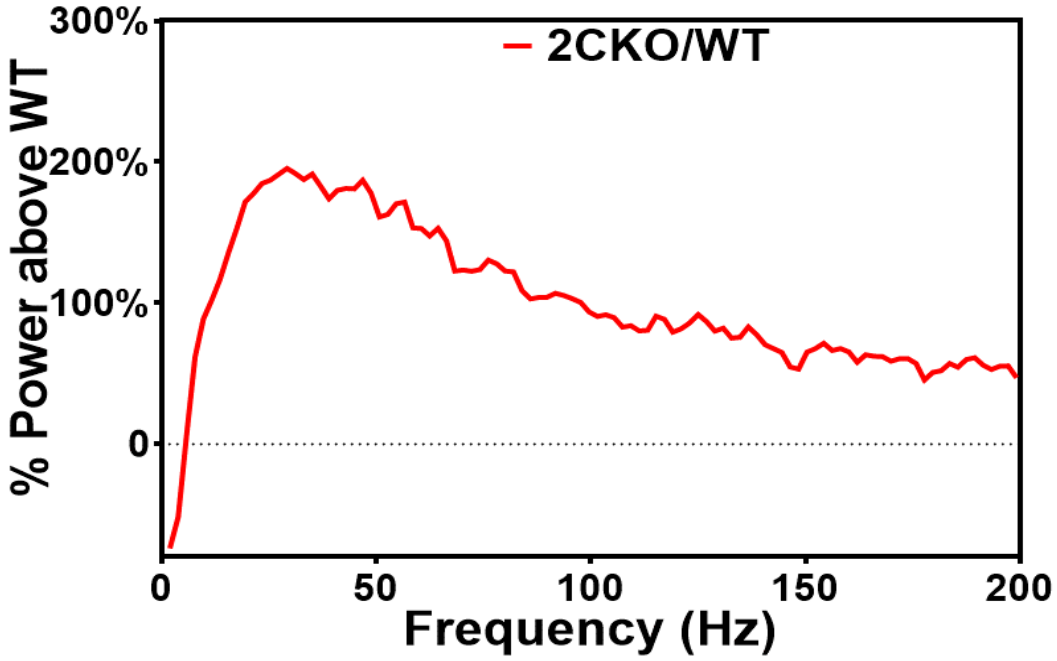


Figure 2. 3 % Power of oscillations in GluN2C-KO normalized by WT mice values.

GluN2C-KO mice display higher oscillatory power than WT mice, the largest difference occur in the beta and low-gamma frequency range, which is distinct from the comparison of GluN2D-KO in chapter 3.

Ketamine administration is followed by increased cortical neuronal oscillations in rodents, as we (Sapkota et al., 2016) and others (Hunt & Kasicki, 2013) have reported. The ketamine response in WT and GluN2C KO mice is rapid (~1-2 minutes) and decays with a half-life of 15-20 minutes, consistent with the known half-life for ketamine in mice (Sato et al., 2004) (Figure 2.4). This suggests that these actions are mediated by ketamine and not an active metabolite of ketamine. The ketamine-induced increase in oscillatory power was greater in GluN2C-KO mice than in WT mice at all frequencies between 5 and 200 Hz (Figure 2.5). The differences between WT and GluN2C-KO mice were most prominent between 30 and 60 Hz; all frequencies in this range showed p values < 0.05 by both multiple t-test (Figure 2.5) and two-way ANOVA.

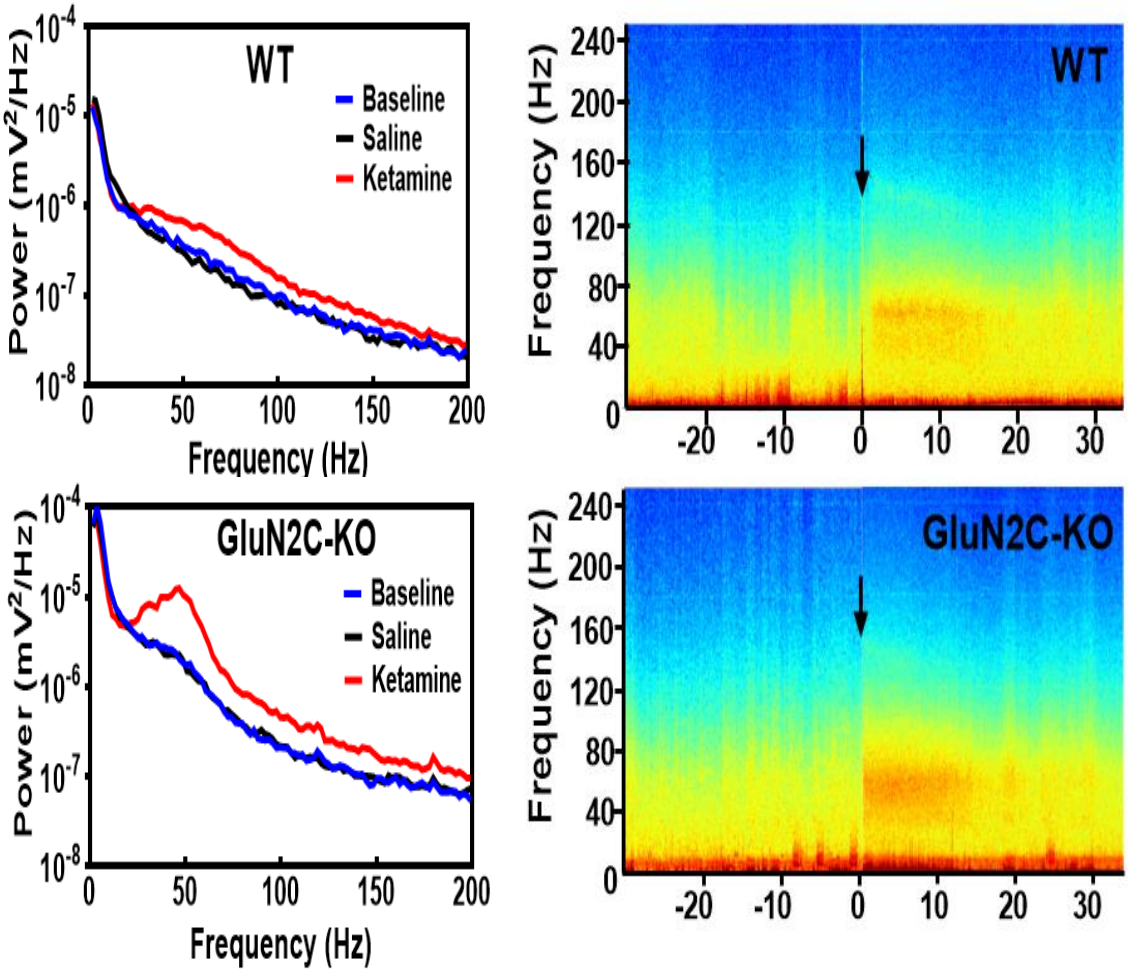


Figure 2. 4 Ketamine-induced gamma oscillations increase is augmented in GluN2C-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2C-KO mice before and after ketamine administration. Ketamine was injected at time = 0 (minute) (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

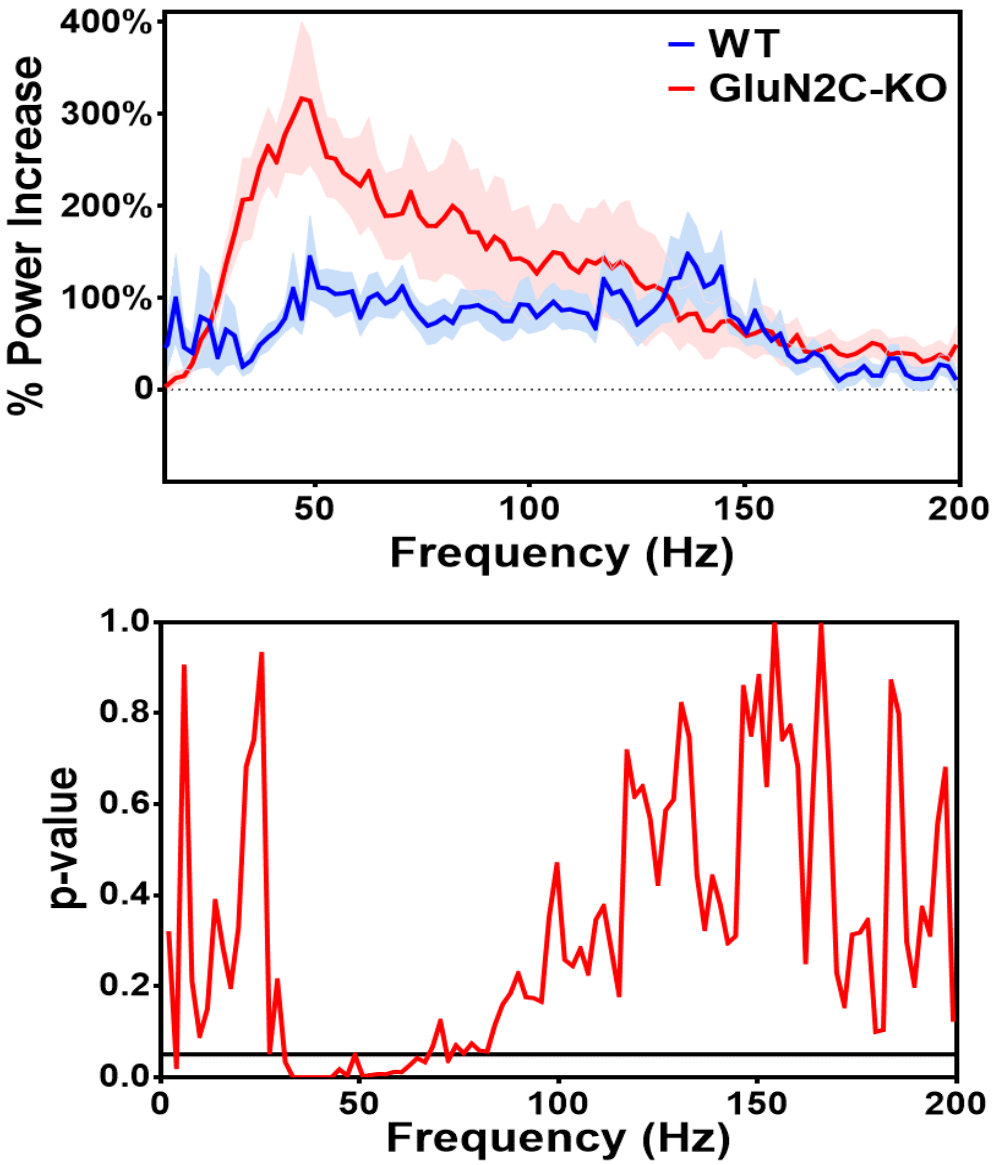


Figure 2. 5 The average % oscillatory power increase of WT and GluN2C-KO mice after ketamine administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. Ketamine induced a maximal increase of 300% at ~50 Hz in the GluN2C=KO (red line, n = 6) while ketamine produced only a 100% in power increase over a broad range of frequencies in the WT (blue line, n = 10). The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

We next compared the ability of the potent NMDAR blocker MK-801 to induce oscillations in WT and GluN2C-KO mice. Typical baseline and MK-801-induced ECoG recording traces of WT, GluN2C heterozygous, and GluN2C-KO mice are displayed in Figure 2.6. MK-801-induced augmentation of oscillations is significantly greater in GluN2C-KO mice than in WT mice (Figure. 2.7). MK-801 induce similar power increase in GluN2C heterozygous mice and WT mice (Figure 2.8). Statistical analysis indicates that WT and GluN2C-KO were different with a $p < 0.05$ for all frequencies between 45 Hz and 160 Hz (Figure. 2.9). A possible difference between ketamine and MK-801 is that MK-801augmented oscillations in the GluN2C-KO mouse over a broader frequency range. These results include results from Gupta et al., 2016, adds additional animals, and excludes one GluN2C-KO animal which displayed a 26-fold greater increase in low frequency power than any other GluN2C-KO animal. Inclusion of this animal increases the difference between WT and GluN2C-KO mice and significantly distorts the averaged response below 30 Hz.

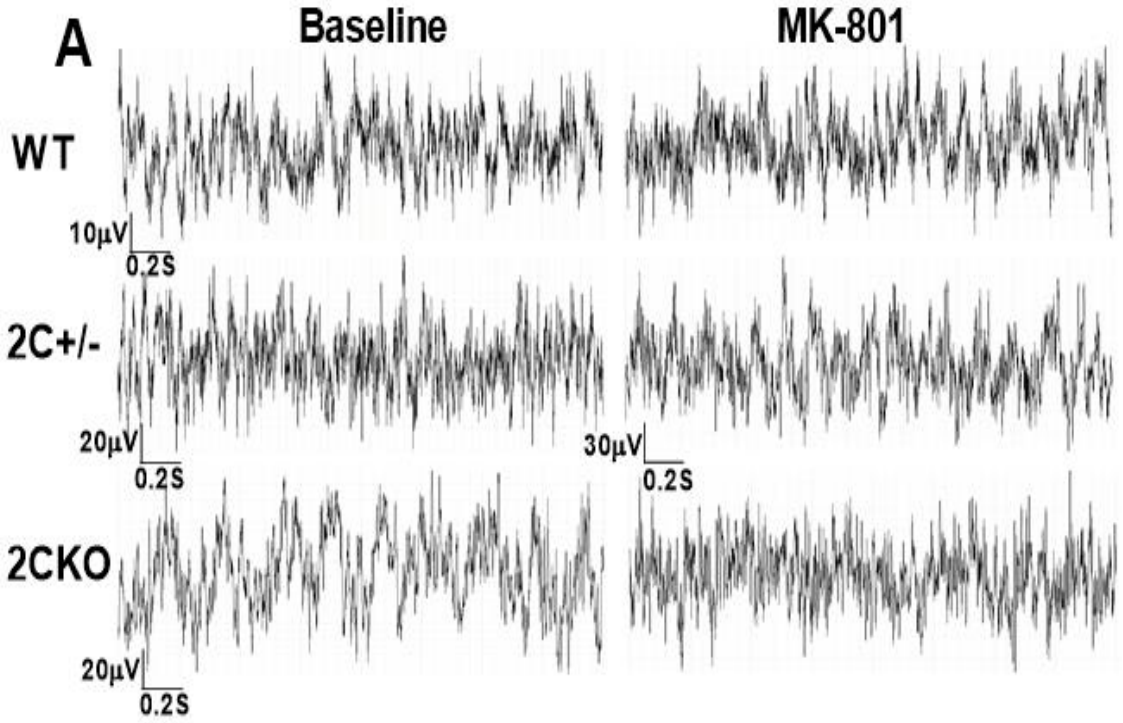


Figure 2. 6 Sample traces of ECoG recordings of wildtype, GluN2C heterozygous, and GluN2C-KO mice before (baseline) and after MK-801 administration.

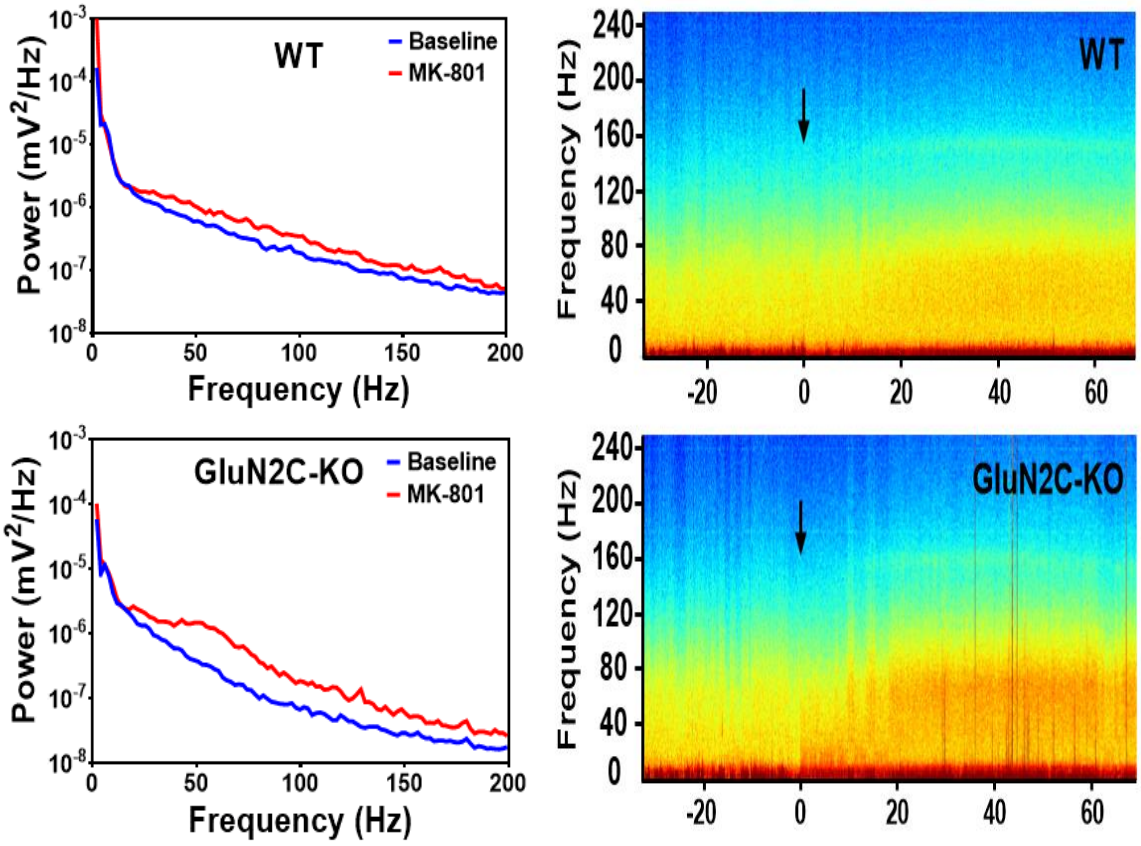


Figure 2. 7 MK-801-induced gamma oscillations increase is augmented in GluN2C-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2C-KO mice before and after MK-801 administration. MK-801 was injected at time = 0 (minute) (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

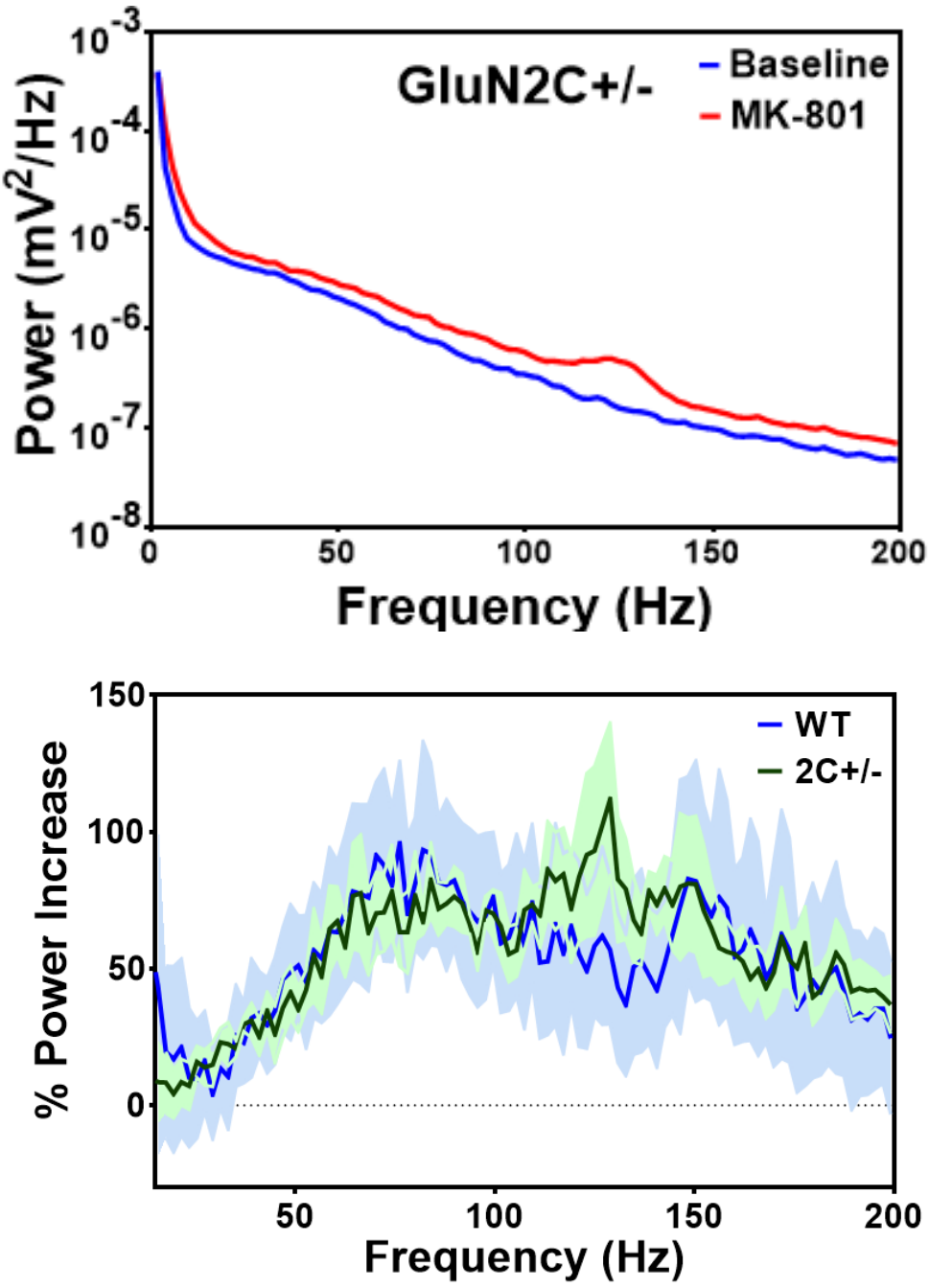


Figure 2. 8 MK-801 increase the power of gamma oscillations in GluN2C heterozygous mice.

Upper panel: Representative power spectrum of GluN2C heterozygous mice. Bottom panel: Average % power increase of WT (blue line, n = 6) and GluN2C+/- (green line, n = 4) mice after MK-801 administration. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading.

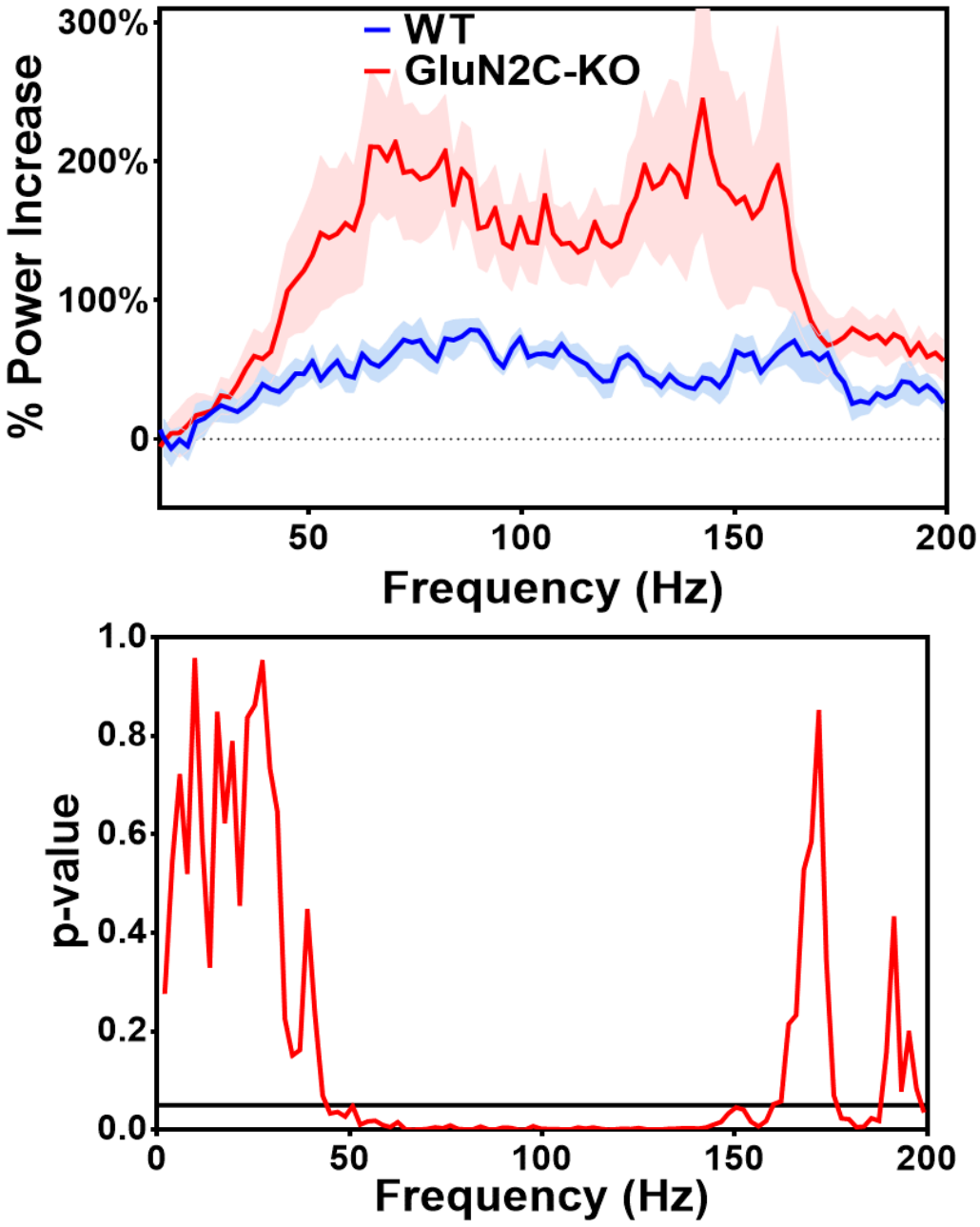


Figure 2. 9 The average % oscillatory power increase of WT and GluN2C-KO mice after MK-801 administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. MK-801 induced a maximal increase of 200% between 65 to 165 Hz in the GluN2C=KO (red line, n = 5) while MK-801 produced only an 80% increase in power over a broad range of frequencies in the WT (blue line, n = 12). The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

PCP-induced oscillations were also appeared greater in the GluN2C-KO than in WT mice (Figure 2.10). The average power of PCP induced oscillations was greater in GluN2C-KO mice especially in the range of 45 to 60 Hz. P-values obtained by two-way ANOVA followed by Fisher LSD were < 0.05 for all frequencies between 45 and 60 Hz. However, the SD appeared to be a function of frequency. P-values determined by multiple t-test, thus allowing SD values that may vary as a function of frequency, show a consistent band of low, but > 0.05, p-values between 40 and 70 Hz (Figure 2.11).

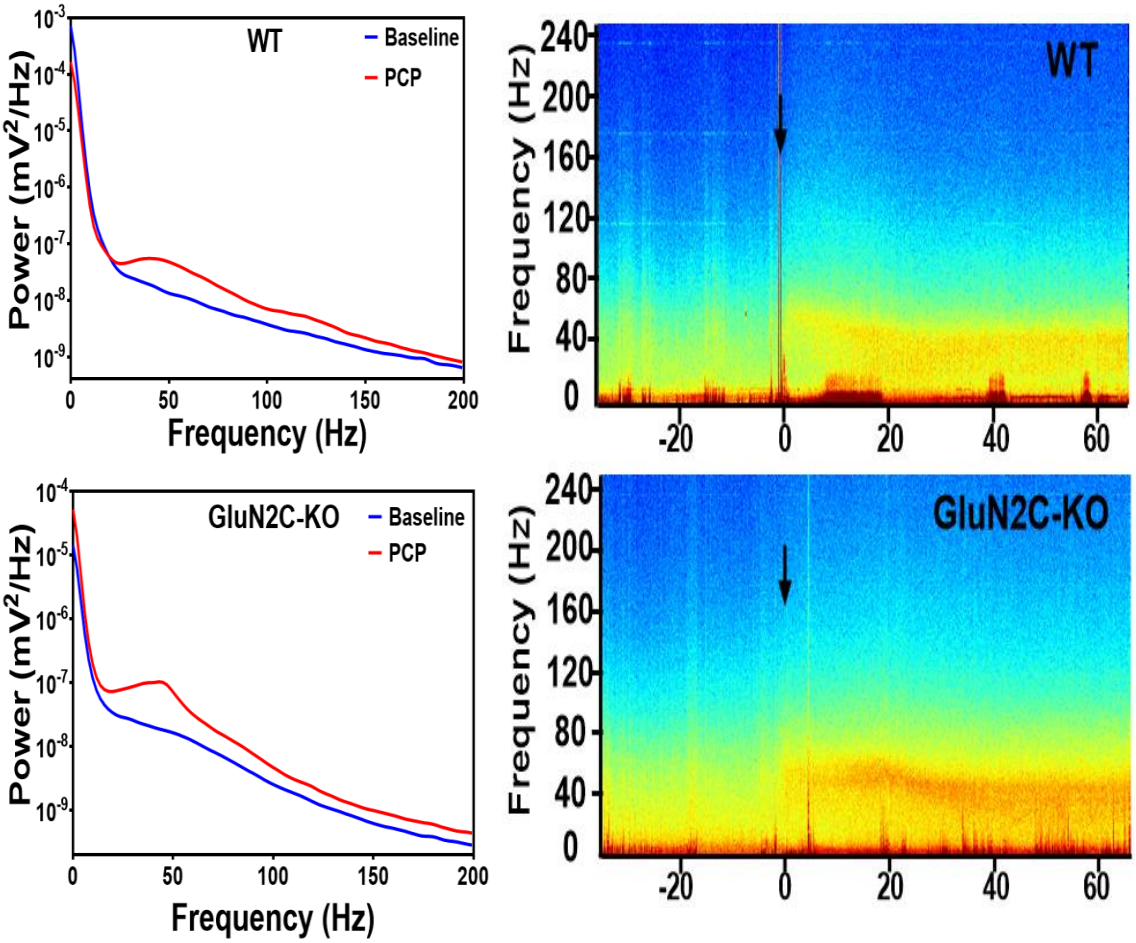


Figure 2. 10 PCP-induced gamma oscillations increase is augmented in GluN2C-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2C-KO mice before and after PCP administration. PCP was injected at time = 0 (minute) (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

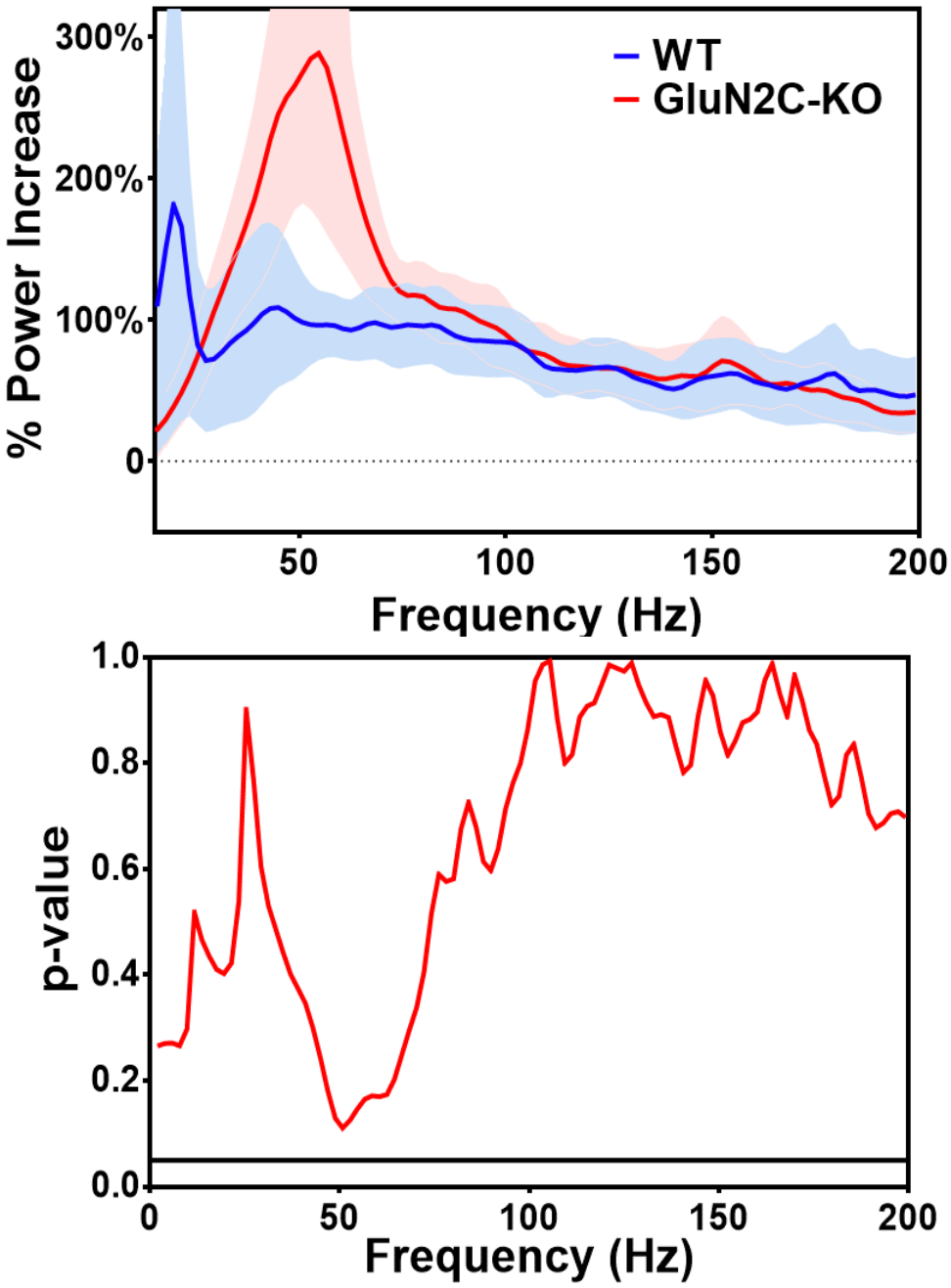


Figure 2. 11 The average % oscillatory power increase of WT and GluN2C-KO mice after PCP administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. PCP induced a maximal increase of 290% at 55 Hz in the GluN2C=KO (red line, n = 5) while PCP produced only a 90% increase in power over a broad range of frequencies in the WT (blue line, n = 5). The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

Memantine augmented neuronal oscillations to a similar extent as do other general NMDAR antagonists, an approximately 100% increase especially over the gamma frequency band. The average memantine-induced response in GluN2C-KO was larger than in WT mice. This augmentation above WT values was strongest between 70 and 90 Hz (Figure 2.12). Unlike ketamine, MK-801, and PCP, memantine did not appear to augment oscillations in GluN2C-KO mice to a greater extent than in WT mice in the low gamma range of 30 – 60 Hz (Figure 2.13). High frequency oscillations (~140 – 160 Hz) were variably present after ketamine and MK-801 administration, but not observed after PCP or memantine.

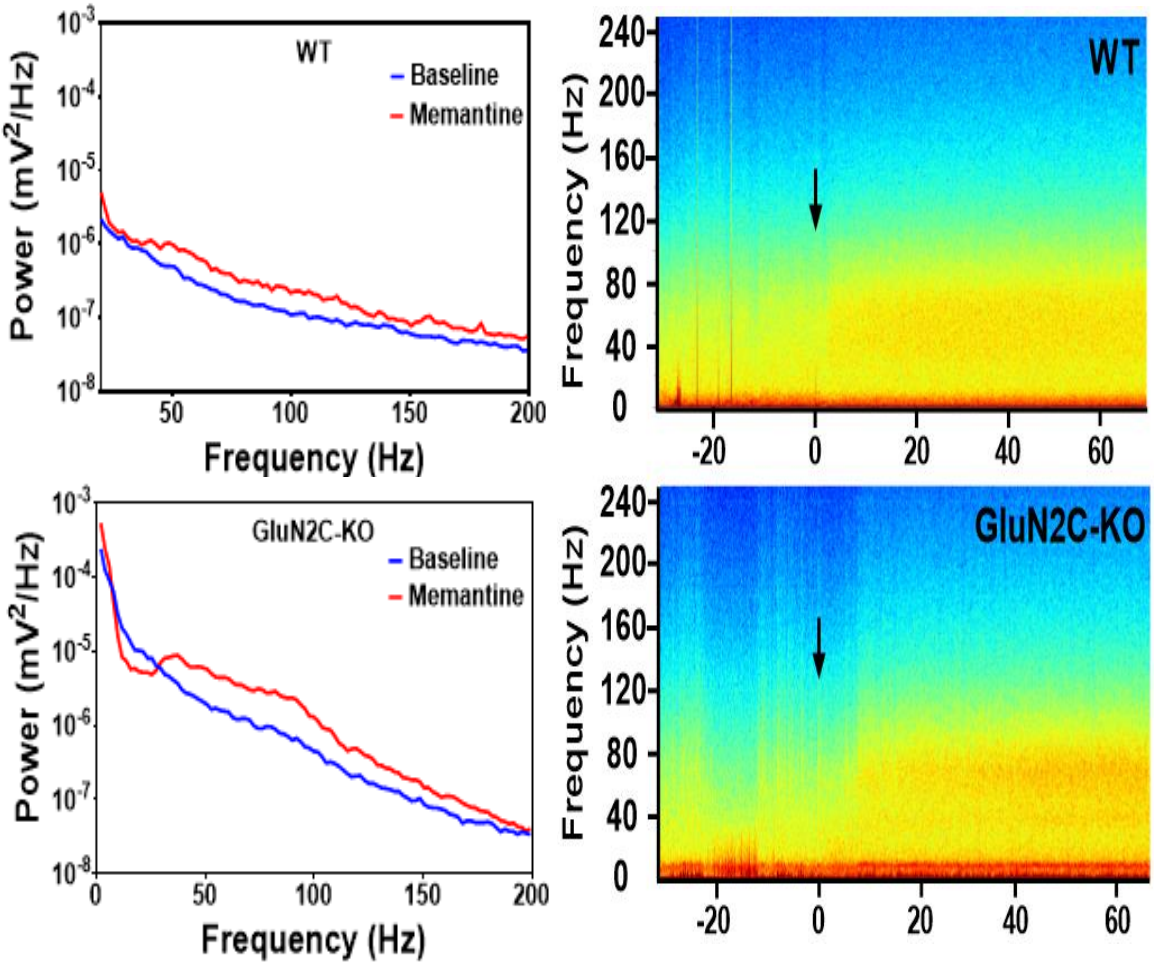


Figure 2. 12 Memantine-induced gamma oscillations increase is augmented in GluN2C-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2C-KO mice before and after memantine administration. Memantine was injected at time = 0 (minute) (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

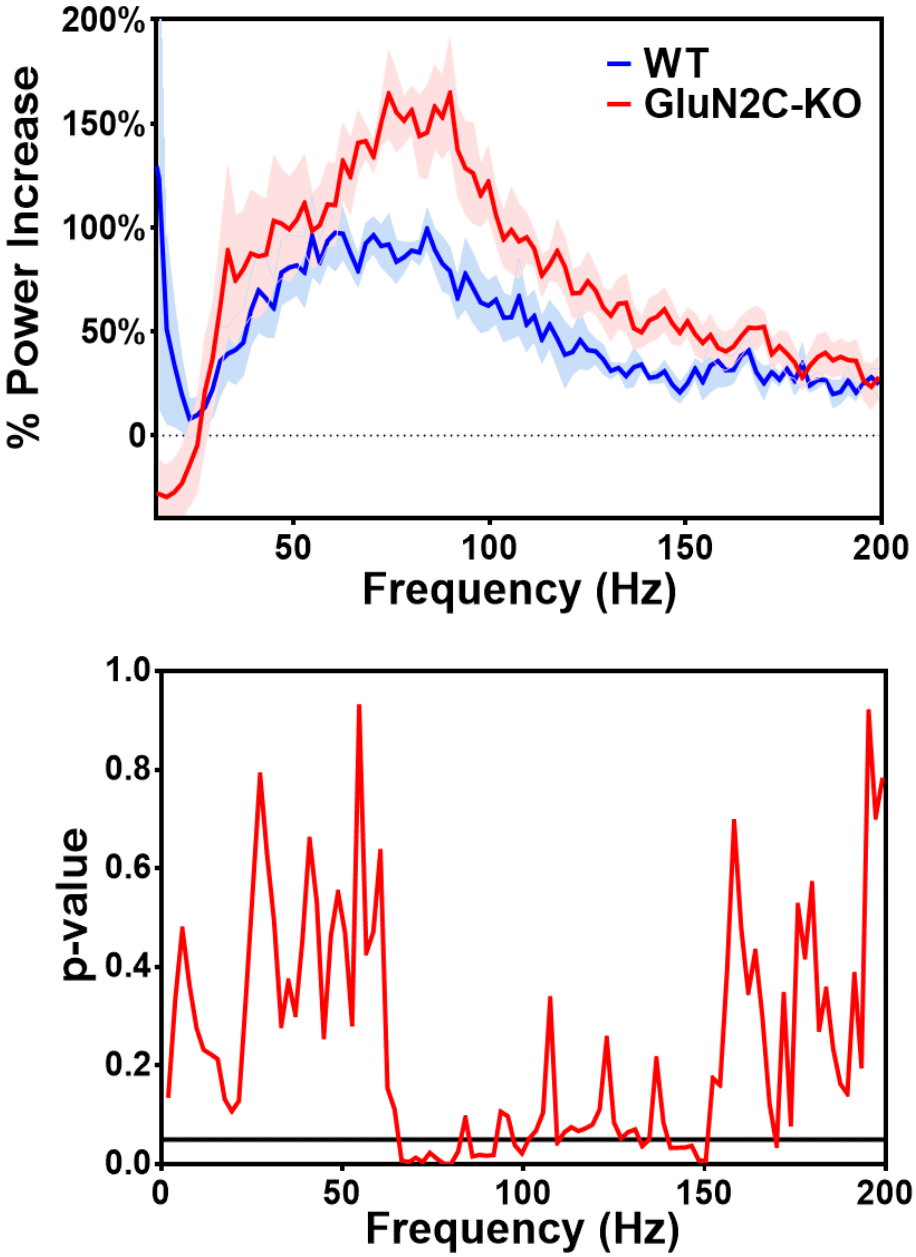


Figure 2. 13 The average % oscillatory power increase of WT and GluN2C-KO mice after memantine administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. Memantine induced a maximal increase of 160% from 70 to 90 Hz in the GluN2C=KO (red line, n = 5) while memantine produced only a 90% from 60 to 80 Hz in the WT (blue line, n = 5). The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

Compared to WT, GluN2C-KO displayed abnormal evoked and oddball responses. The WT mouse display classic oddball response (Figure 2.14) in which the deviant tone induced a larger peak response. The latency of each peak is: P1 ~ 18 ms, N1 ~ 37 ms, P2 ~ 70-120 ms. These peaks were shifted in GluN2C-KO mouse (Figure 2.15), and the deviant tone did not generate a larger response.

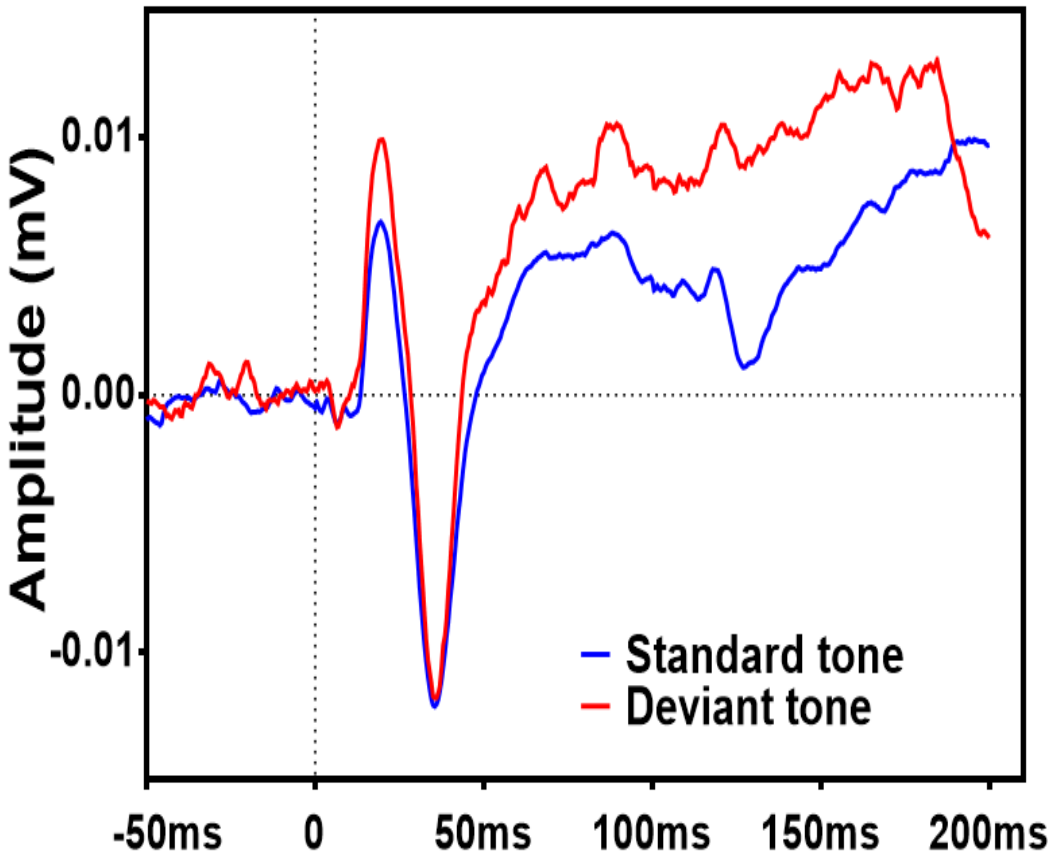


Figure 2. 14 WT Oddball auditory-evoked response.

In an ECoG recording from above the WT mouse cortex, the classic auditory evoked response is enhanced when an oddball tone is presented. The average of the 13K Hz responses is shown for when the tone is presented as a standard (8:1) or a deviant (1:8). The P1 wave is at ~18 ms, N1 ~37 ms and P2 ~ 70-120 ms. The greater amplitude of the P1/P2 waves is consistent with an oddball response. In some experiments, N2 was also enhanced.

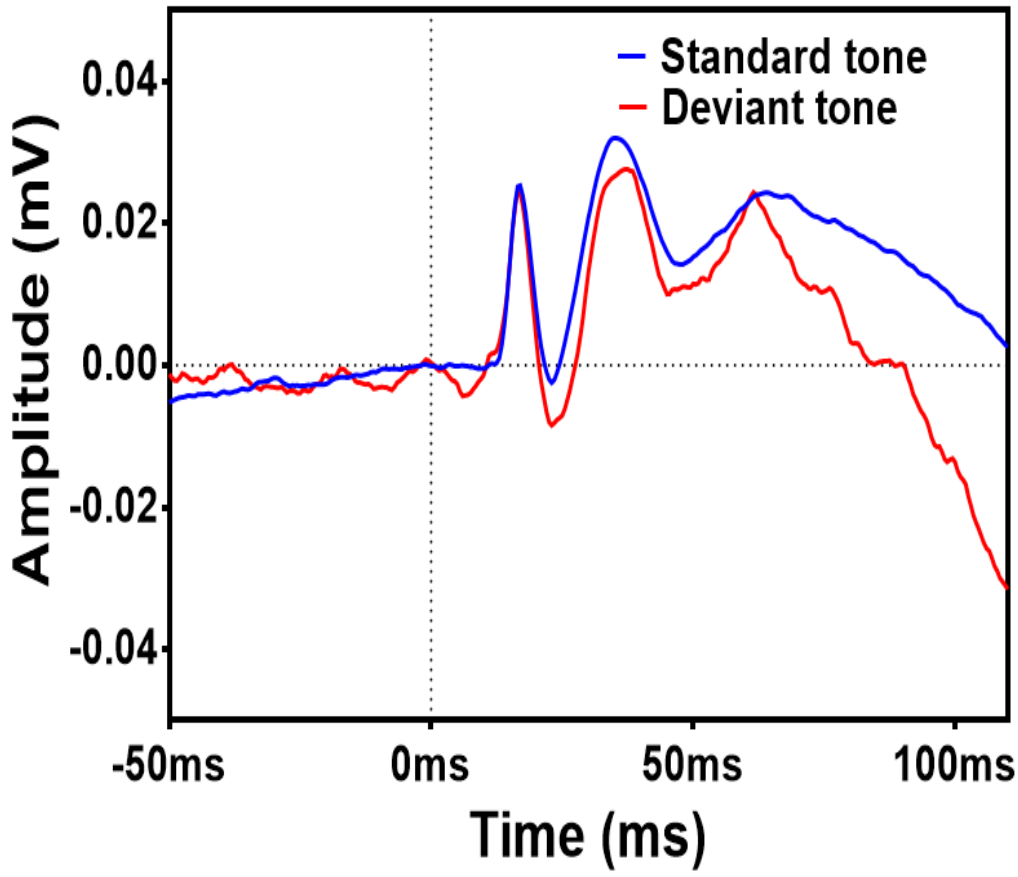


Figure 2. 15 GluN2C-KO Oddball auditory-evoked response.

In an ECoG recording from above the GluN2C-KO mouse cortex, the classic auditory evoked response is impaired when an oddball tone is presented. The average of the 13K Hz responses is shown for when the tone is presented as a standard (8:1) or a deviant (1:8). The latency of the peaks shifted compared to WT mouse, the P1 wave is at ~17 ms, N1 ~23 ms and P2 ~ 36 ms. The deviant tone did not generate a significantly greater response in the P1/P2 waves suggesting that MMN might be inhibited.

2.5 Discussion

Neuronal oscillations are critical for cognition and working memory. Thus, changes in NMDAR-modulated neuronal oscillations would have important implications for behavior and cognition. Blockade of NMDAR activity in vivo causes a well-documented increase in oscillations, especially in the gamma frequency band. In the GluN2C KO mouse, NMDAR blockade causes enhanced gamma oscillations relative to those in WT mice. The enhanced response to NMDAR antagonists in the GluN2C-KO may correspond to a loss of GluN2C subunits from astrocytes that provide feedback to neurons. Astrocytic processes near excitatory synapses can respond to L-glutamate spill-over during bursts of synaptic stimulation with an increase in intracellular calcium (for reviews see (Haydon, 2001; Verkhratsky, Orkand, & Kettenmann, 1998)). At least some of the astrocyte calcium response is thought to be due to NMDAR activation (Palygin, Lalo, Verkhratsky, & Pankratov, 2010). We have recently shown that in the telencephalon, GluN2C mRNA is commonly found in GFAP-positive glial cells and rarely found in neurons(Alsaad et al., 2018). This result is thus consistent with the original conclusions from in situ hybridization studies (M. Watanabe et al., 1993a) and with transcriptome databases (Mancarci et al., 2017; Y. Zhang et al., 2014). Pankratov and colleagues (Palygin, Lalo, & Pankratov, 2011) have shown that the GluN2C/D preferring NMDAR antagonist UBP141 (Costa et al., 2009) preferentially blocks NMDA-evoked currents in astrocytes. Since GluN2D mRNA is not found in glial cells in the cerebral cortex (Alsaad et al., 2018) these astrocyte currents are most likely to be mediated by GluN2C-containing NMDARs. This is consistent with the recent observation that agonist-evoked NMDAR currents in astrocytes are eliminated in the GluN2C-KO (Ravikrishnan et al., 2018). Thus, there are functional GluN2C-containing receptors in astrocytes that could be responding to bursts of synaptic excitation. In response to intracellular calcium elevations, astrocytes can exhibit calcium-dependent release of glial transmitters such as glutamate and ATP (Araque, Li, Doyle, & Haydon, 2000; Bezzi et al., 1998; Pasti, Zonta, Pozzan, Vicini, & Carmignoto, 2001). In turn, L-

glutamate released from astrocytes has been shown to activate GluN1/GluN2B NMDARs synchronously in multiple postsynaptic neurons (Fellin et al., 2004), thus providing a mechanism by which astrocytes can provide a synchronizing feedback signal to excitatory neurons in response to strong synaptic stimulation (Angulo, Kozlov, Charpak, & Audinat, 2004; Fellin & Carmignoto, 2004). This hypothesis is consistent with our finding that burst stimulation, but not single stimulation, of the CA3-CA1 excitatory pathway results in a long-lasting postsynaptic NMDAR current that is blocked by both GluN2B and GluN2C/D antagonists (N. A. Lozovaya et al., 2004).

GluN2C and astrocytes may be preferentially modulating low gamma oscillations. In the GluN2C-KO, basal oscillations displayed greater power in the low gamma frequencies. While NMDAR antagonists enhance oscillations over a broad range of frequencies in WT animals, in the GluN2C-KO, the antagonist ketamine, and sometimes PCP, selectively augmented low gamma oscillations. Thus, it is noteworthy that recent studies have shown that astrocytes contribute specifically to the modulation of beta/low gamma in the 20 – 40 Hz range. Transgenic animals that cannot release L-glutamate from astrocytes display a depressed oscillatory power at 20–40 Hz (H. S. Lee et al., 2014). Conversely, in an ex vivo preparation, selective optogenetic stimulation of astrocytes depresses 20-40 Hz kainate-induced gamma oscillations in a manner blocked by A1 adenosine receptor antagonists (Tan et al., 2017). Thus, astrocytes appear to be able to modulate 20-40 Hz oscillations in a bidirectional manner by releasing L-glutamate and ATP. If GluN2C-containing NMDARs regulate glial transmitter release, then their specific regulation of low gamma would be expected. The greater oscillatory power in the GluN2C-KO in response to NMDAR blockers suggests that in the WT, GluN2C blockade normally suppresses low gamma (while blocking other NMDARs enhance oscillations). Thus, in the WT, tonic activation of GluN2C-containing receptors may be enhancing low gamma. This hypothesis is thus a telencephalic, astrocyte variation of that proposed for GluN2C-containing receptors in interneurons of the

thalamic reticular nucleus where the tonic activation of NMDARs with GluN2C modulate delta oscillations (Y. Zhang et al., 2009).

Compared to GluN2A/B-containing NMDARs, GluN2C- and GluN2D-containing NMDARs have higher affinity for L-glutamate, show less voltage-dependency due to reduced Mg^{++} sensitivity, and they do not desensitize (Glasgow et al., 2015; Johannes J Krupp, Bryce Vissel, Stephen F Heinemann, & Gary L Westbrook, 1998; Traynelis et al., 2010; Wyllie, Livesey, & Hardingham, 2013). Thus these receptors are well suited for being activated by low concentrations of extracellular glutamate and they can retain their activity under tonic or fast-spiking activity. With GluN2C in astrocytes, these receptors can provide excitatory feedback to the local ensemble of excitatory neurons in response to excitatory drive. This subtype represents numerically minor NMDAR subtypes in the forebrain. Thus, their potential ability to differentially modulate neuronal oscillations, while minimally impacting the major populations of NMDARs that are involved in a variety of other processes, suggests that these receptors could be useful targets for therapeutic applications.

Chapter 3

The role of GluN2D containing NMDA receptors in NMDA receptor antagonist-induced neuronal oscillations

3.1 Abstract

Phencyclidine (PCP) and the dissociative anesthetic ketamine and elicit symptoms of schizophrenia at subanesthetic doses by blocking N-methyl-D-aspartate receptors (NMDARs). This property led to a variety of studies resulting in the now well-supported theory that hypofunction of NMDARs is responsible for many of the symptoms of schizophrenia. The ability of NMDAR antagonists to increase neuronal oscillations, and disrupt their synchrony between regions are thought to contribute to the pathophysiology of schizophrenia. However, the roles played by specific NMDAR subunits in modulating the neuronal oscillations and thus their contribution to different symptom components are still unknown. To evaluate the potential contribution of GluN2D NMDAR subunits to antagonist-induced neuronal oscillations, we determined the ability of ketamine, MK-801, memantine and PCP to alter gamma frequency band neuronal oscillations in wild-type (WT) and GluN2D-knockout (GluN2D-KO) mice. In the electrocorticographic analysis, four NMDA non-selective antagonists induced-gamma oscillations increase seen in wildtype mice was abolished in GluN2D-KO mice whereas the MMN response was intact in GluN2D-KO mouse. These results suggest a critical role of GluN2D-containing NMDARs in neuronal oscillations and ketamine and PCP's psychotomimetic, dissociative effects and hence suggests a critical role for GluN2D subunits in cognition and perception.

3.2 Introduction

The discovery that the N-methyl-D-aspartate receptor (NMDAR) antagonists ketamine and phencyclidine (NA Anis, Berry, Burton, & Lodge, 1983) can mimic the symptoms of schizophrenia prompted genetic, biochemical, and pharmacologic studies resulting in the NMDAR-hypofunction theory of schizophrenia (Joseph T Coyle, Guochuan Tsai, & Donald Goff, 2003; Joshua T Kantrowitz & Daniel C Javitt, 2010; John E Lisman et al., 2008). Pharmacologic blockade of NMDAR in healthy humans elicits a spectrum of schizophrenia symptoms, and NMDAR blockade in laboratory animals provides a model for schizophrenia (Joshua T Kantrowitz & Daniel C Javitt, 2010). Further support for the NMDAR hypofunction hypothesis comes from the identification of many schizophrenia candidate genes that impair NMDAR function (Darrick T Balu & Joseph T Coyle, 2011; Greenwood, Light, Swerdlow, Radant, & Braff, 2012; Sun et al., 2010) and observations that decreasing NMDAR levels in mice through genetic manipulations leads to schizophrenia-associated symptoms (hyperlocomotor activity, impaired learning, reduced social interactions, and altered neuronal oscillations) (Halene et al., 2009; Mohn et al., 1999).

Precisely how NMDAR blockade induces schizophrenia symptoms is unclear, but many studies support the proposal that blockade of NMDARs in GABAergic interneurons containing parvalbumin (PV) is responsible for the psychotomimetic actions of NMDAR antagonists (Guillermo Gonzalez-Burgos & David A Lewis, 2008; Joshua T Kantrowitz & Daniel C Javitt, 2010; John E Lisman et al., 2008). Because PV-interneurons provide negative feedback to pyramidal neurons, inhibition of NMDAR in PV cells causes an excitation of pyramidal neurons by disinhibition and thus alters the excitatory/inhibitory balance in cortical circuits (Homayoun & Moghaddam, 2007; Q. Li, Clark, Lewis, & Wilson, 2002; Nakazawa et al., 2012). PV cell activity also contributes to gamma frequency band neuronal network oscillations that are important for cortical processing, working memory, and perceptual integration (Korotkova et al., 2010; Sohal, Zhang, Yizhar, & Deisseroth, 2009; Yizhar et al., 2011). Thus, acute administration of ketamine or

phencyclidine (PCP) enhances excitatory activity in corticolimbic structures and increases basal levels of gamma oscillations (Homayoun & Moghaddam, 2007; Hunt & Kasicki, 2013; Bernat Kocsis, 2012; Nakazawa et al., 2012). Accordingly, selective reduction of the common GluN1 NMDAR subunit in PV cells, increases basal gamma oscillations, decreases NMDAR antagonist-induced gamma oscillations, and promotes schizophrenia-associated behavioral symptoms (Belforte et al., 2010; Billingslea et al., 2014; Carlen et al., 2012; Korotkova et al., 2010). Some of these effects could also be mediated by PV-containing interneurons in the thalamic reticular nucleus (Frassoni et al., 1991; Llinas, Urbano, Leznik, Ramirez, & van Marle, 2005). In schizophrenia, NMDAR-hypofunction may thus disturb excitatory/ inhibitory balance, thereby altering neuronal oscillations and disrupting cognitive function (Joshua T Kantrowitz & Daniel C Javitt, 2010; John E Lisman et al., 2008; Uhlhaas & Singer, 2013).

The roles played by NMDARs with different subunit combinations in cortical processing and schizophrenia-related symptoms are unknown. Such information is necessary for resolving individual pathophysiologic components of schizophrenia and for defining appropriate therapeutics. NMDARs are tetrameric complexes composed of two GluN1 subunits and two subunits from among the GluN2A-D and GluN3A-B subunits (Ikeda et al., 1992; Ishii et al., 1993; Mishina et al., 1993; Monyer et al., 1994; Traynelis et al., 2010). Pharmacologic studies in vivo have indicated a predominant role for GluN2A subunits in NMDAR antagonist-induced neuronal oscillations (B. Kocsis, 2012). However, in vitro experiments suggest a greater role for GluN2B subunits (McNally et al., 2011), and the roles of GluN2C and GluN2D subunits are unclear. Our group and others recently demonstrated that GluN2D NMDA receptors are mainly expressed in PV positive interneurons in various brain regions which suggests a critical role of GluN2D NMDA receptors in generating and modulating gamma oscillations, thus a critical role on schizophrenia pathology. We hypothesized that GluN2D-containing NMDARs may contribute to ketamine-induced schizophrenia symptoms because GluN2D NMDAR subunits are localized in PV-containing

GABAergic interneurons in cortex, reticular nucleus of thalamus, and hippocampus (Alsaad et al., 2018; Monyer et al., 1994; Standaert et al., 1996; von Engelhardt et al., 2015; Yamasaki et al., 2014) and because ketamine has a higher affinity for GluN2D-containing NMDARs than for NMDARs containing the more widely expressed GluN2A and GluN2B subunits (Kotermanski & Johnson, 2009). GluN2D involvement in schizophrenia could potentially also be mediated by altering neuronal-oligodendrocyte signaling (Fields, 2008; Micu et al., 2016). Thus, in the present study, we sought to determine whether ketamine-induced gamma oscillations are reduced in GluN2D-KO mice. Meanwhile, since the PPI response was not altered in GluN2D-KO mouse (Sapkota et al., 2016), we also sought to determine if MMN response is influenced by GluN2D-containing NMDARs.

3.3 Materials and Methods

3.3.1 Animals

GluN2D-KO mice (Ikeda et al., 1995) that had been backcrossed onto a C57BL/6 background to 99.9% homogeneity (Hizue, Pang, & Yokoyama, 2005) were used for these studies. The background strain was confirmed to be congenic with C57BL/6 (Charles River Laboratories genetic testing service; Willington, MA). Mouse genotype was confirmed by polymerase chain reaction followed by sequencing of the reaction product and by Western blot analysis. Male C57BL/6 WT and GluN2D-KO mice 10 to 12 weeks of age were used for studies; 10- to 15-week-old male mice were used for ECoG studies. Mice were handled in accordance with University of Nebraska Medical Center's Institutional Animal Care and Use Committee (IACUC) guidelines. In accordance with these guidelines, efforts were made to minimize animal suffering and the number of animals used.

3.3.2 Surgery

All procedures were approved by the IACUC in compliance with National Institutes of Health guidelines. 12-16 weeks old WT and GluN2D-KO mice were surgically implanted with tripolar electrodes (MS333/2; Plastics One, Roanoke, VA) under xylazine/ketamine/acepromazine anesthesia as required by IACUC regulations. Two holes were made in the skull 3mm posterior to bregma at 1mm and 2.5mm lateral. Two electrodes were placed in the medial hole onto the dura surface near the retrosplenial cortex, and the third electrode was placed in the lateral hole for ground. The electrodes were secured to the skull as described elsewhere (Jeffrey et al., 2013). After 7 days of recovery, electroencephalographic (ECoG) recordings were made with a DP-311 differential amplifier (Warner Instruments, Hamden, CT) with high-pass/low-pass filters set at 0.1 and 300 Hz and digitized/recorded (Digidata 1400, pClamp 10; Molecular Devices, Sunnyvale, CA).

3.3.3 Drugs

We used the general NMDAR antagonists: ketamine (30mg/kg, Par Pharmaceutical, Spring Valley, New York or Hospira, Inc., Lake Forrest, IL), MK-801 (0.2mg/kg, kindly provided by Merck & Co.), memantine (20mg/kg), and PCP (3mg/kg, Sigma-Aldrich, St. Louis, MO). All drugs were dissolved in the saline. The dosage of each drug was determined by prior experiments and literature value (M. J. Hunt et al., 2006). These concertation gave similar signal response in WT animals.

3.3.4 ECoG Recordings

At least one-week after electrode implant surgery, animals in their home cage were placed inside a surrounding Faraday cage. The electrode assembly was then connected to the commutator by a cable and the animals were allowed to acclimate for 10 minutes. After 30 minutes of baseline recordings, the animals were injected i.p. with NMDA antagonists or saline and recorded for the period between 5 and 90 minutes after the injection.

3.3.5 Oddball response recordings design

Mice were tested for one half-hour session each day, for three days. The awake mouse recovered after 7 days from the surgery was placed in the experimental chamber for 15 min before each session to acclimatize. Each session consisted of an ascending and a descending oddball sequence separated by a 3 min break. The order of the two sequences alternated for each mouse across test sessions. Two sequences were presented in the experiment. These were oddball sequences where the roles of the deviant and standard were reversed (flip-flop condition) resulting in either an ascending deviant sequence (low frequency standard and high frequency deviant) or a descending deviant sequence (high frequency standard and low frequency deviant). In the ascending and descending oddball sequences, 87.5% of the tones were standards and 12.5% deviants. For all sequences, tones had a 10 ms rise and fall time and a stimulus onset asynchrony

(SOA) of 500 ms. Two tones of 100 ms duration were used: a low frequency tone of 9000 Hz and a high frequency tone of 13000 Hz, Each of the sequences consisted of 1800 tones and ran for 20 minutes.

3.3.6 Data Analysis

A power spectrum analysis was performed with Clampfit (Molecular Devices) using a Hamming window with 50% overlap. Spectrogram analysis was performed by Neuroexplorer software. Data are expressed as mean of individual experiments along with the standard error of the mean. Statistical comparisons were made using one- or two-way ANOVA and multiple t-test. Graphpad Prism was used for statistical analysis and graphing the data.

3.4 Results

ECoG recording of awake WT and GluN2D-KO mice displayed mostly typical ECoG traces before and after ketamine administration (Figure 3.1). The GluN2D-KO mice displayed a more obvious slow oscillation (~ 4 Hz). Average baseline absolute power of the WT and GluN2D-KO mice are displayed in (Figure 3.2) and values normalized by WT values are shown in (Figure 3.3). Relative to WT mice, GluN2D-KO mice had reduced power in the 5 – 30 Hz range (which may account for the distinct appearance of slow oscillations) and higher basal power above 50 Hz (Figure 3.3).

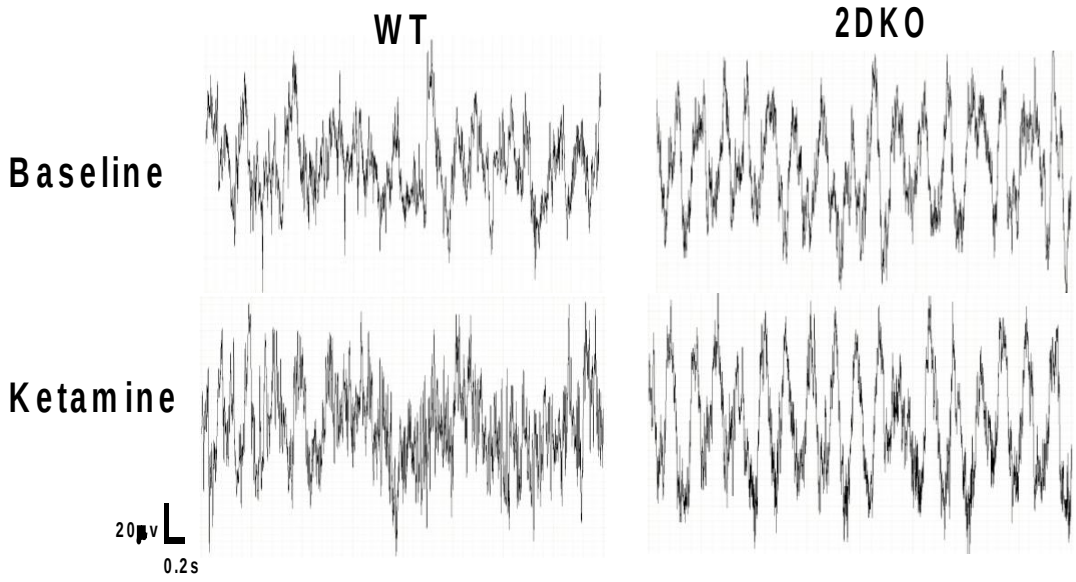


Figure 3. 1 Example traces of ECoG recordings of wildtype and GluN2D-KO mice before (baseline) and after ketamine administration.

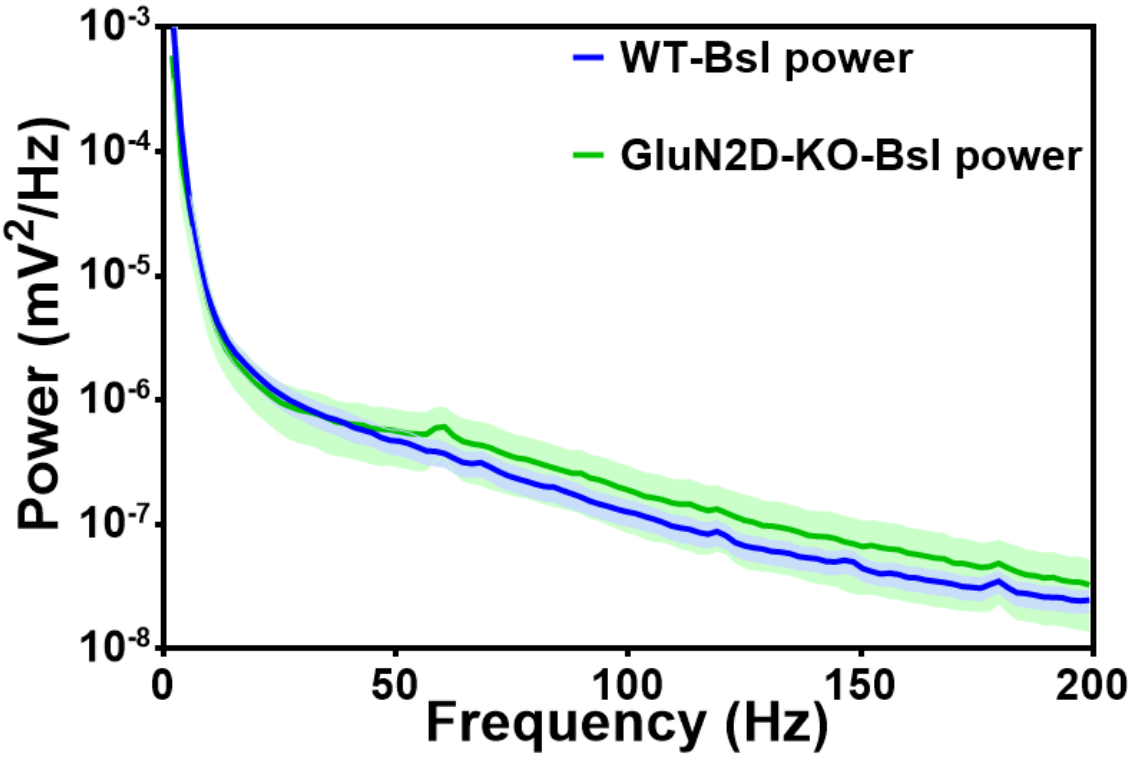


Figure 3. 2 Baseline power spectrum of WT, GluN2D-KO animals.

GluN2D-KO mice (n=8) display higher spontaneous oscillatory power than wildtype mice (n=22), especially in high-gamma frequency range (60-140 Hz). SEMs are shown by light shading.

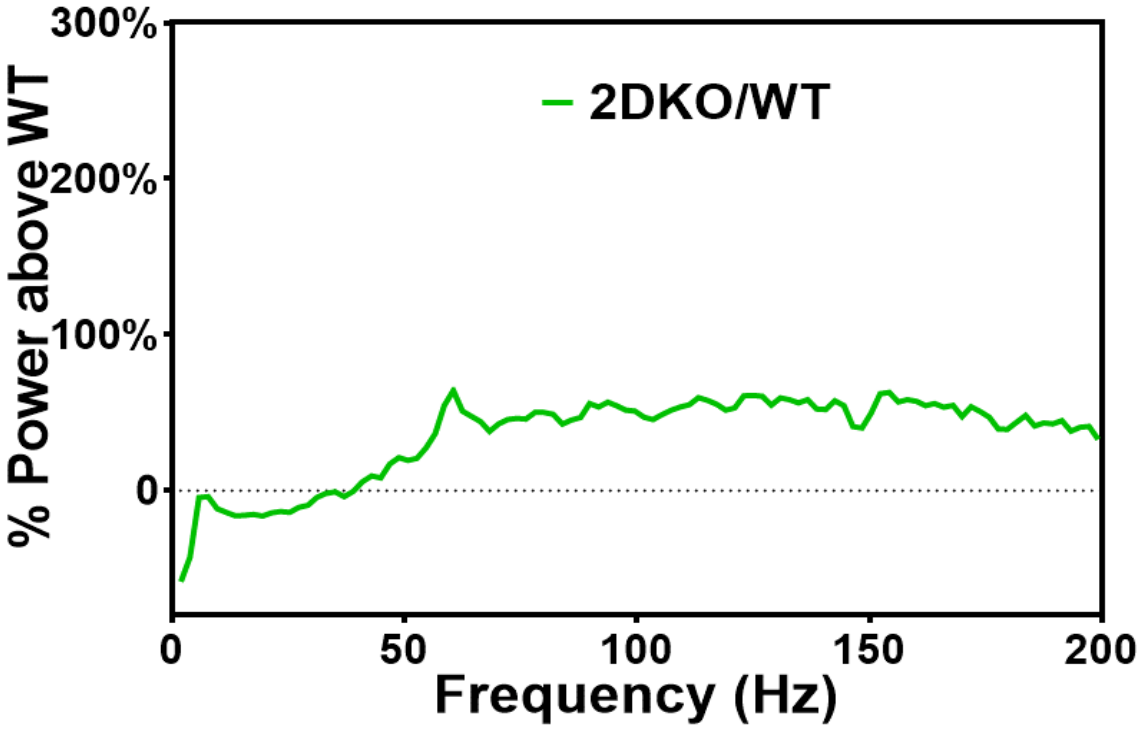


Figure 3. 3 % Power of oscillations in GluN2D-KO normalized by WT mice values.

GluN2D-KO mice display reduced oscillatory power from 5-30 Hz range, whereas display higher oscillatory power than WT mice above 50 Hz.

Ketamine administration is followed by increased cortical neuronal oscillations in rodents, as we (Sapkota et al., 2016) and others (for review see Hunt et al.) have reported. The ketamine response in WT and GluN2D KO mice is rapid (~1-2 minutes) and decays with a half-life of 15-20 minutes, consistent with the known half-life for ketamine in mice (Sato et al 2004) (Figure 3.4). This suggests that these actions are mediated by ketamine and not an active metabolite of ketamine. The ketamine-induced increase in oscillatory power seen in WT mice was significantly reduced in the high gamma frequencies in GluN2D-KO mice (Figure 3.5).

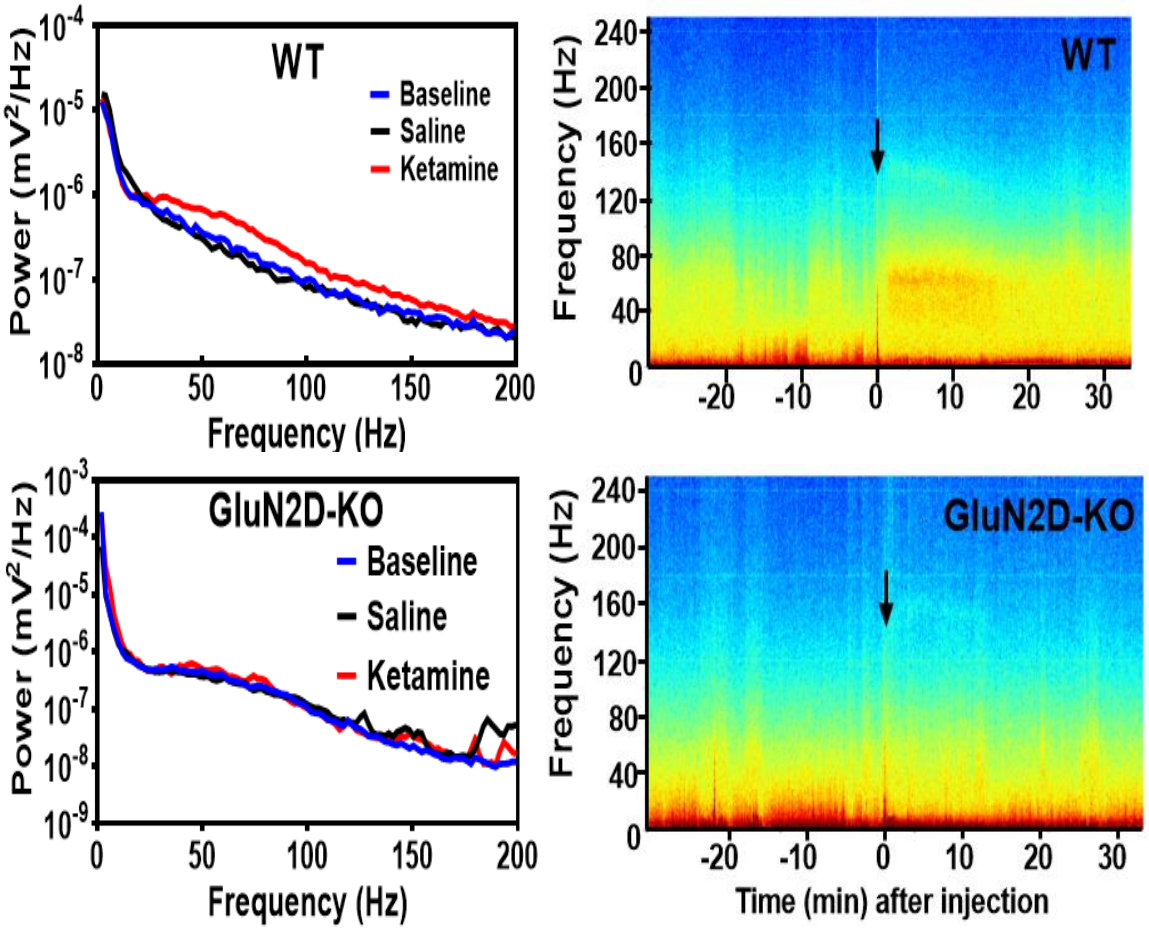


Figure 3. 4 Ketamine-induced gamma oscillations increase is abolished in GluN2D-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2D-KO mice before and after ketamine administration. Ketamine was injected at time = 0 (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

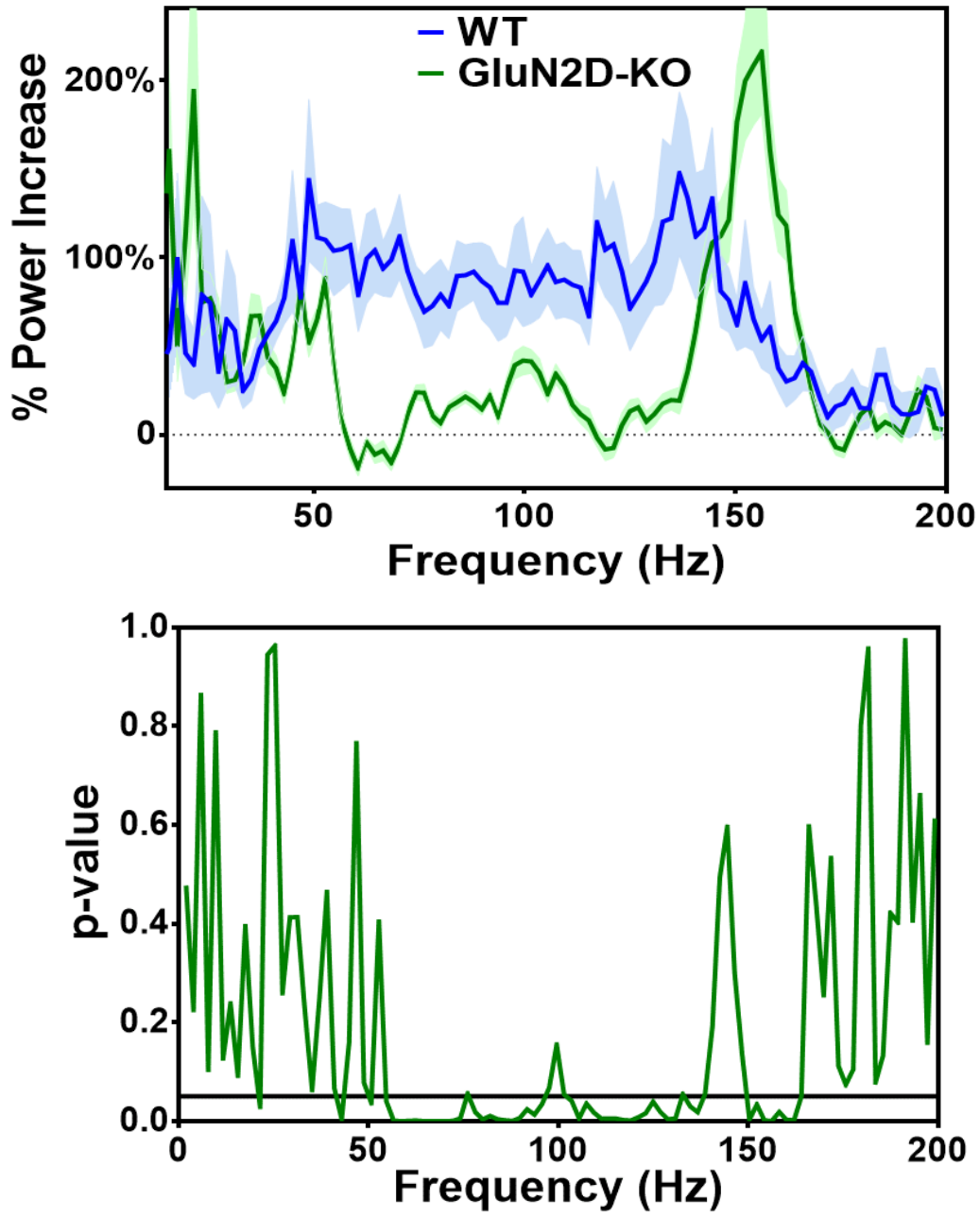


Figure 3. 5 The average % oscillatory power increase of WT and GluN2D-KO mice after ketamine administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. Ketamine induced an increase of ~100% between 50 to 145 Hz in the WT (blue line, n = 10) while ketamine only produced ~20% increase in GluN2D-KO (green line, n = 9) mice in the same frequency band. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

We next compared the ability of the potent NMDAR blocker MK-801 to induce oscillations in WT and GluN2D-KO mice. MK-801-induced augmentation of oscillations is greatly diminished in GluN2D-KO mice compared to WT (Figure 3.6). In a manner generally similar to ketamine, MK-801-induced oscillations were weaker in GluN2D-KO mice than WT mice with $p < 0.05$ (Figure 3.7) at most frequencies between 75 and 120 Hz and variably promoted high frequency oscillations (~155 Hz) in GluN2D-KO mice (Figure 3.6 and Figure 3.7).

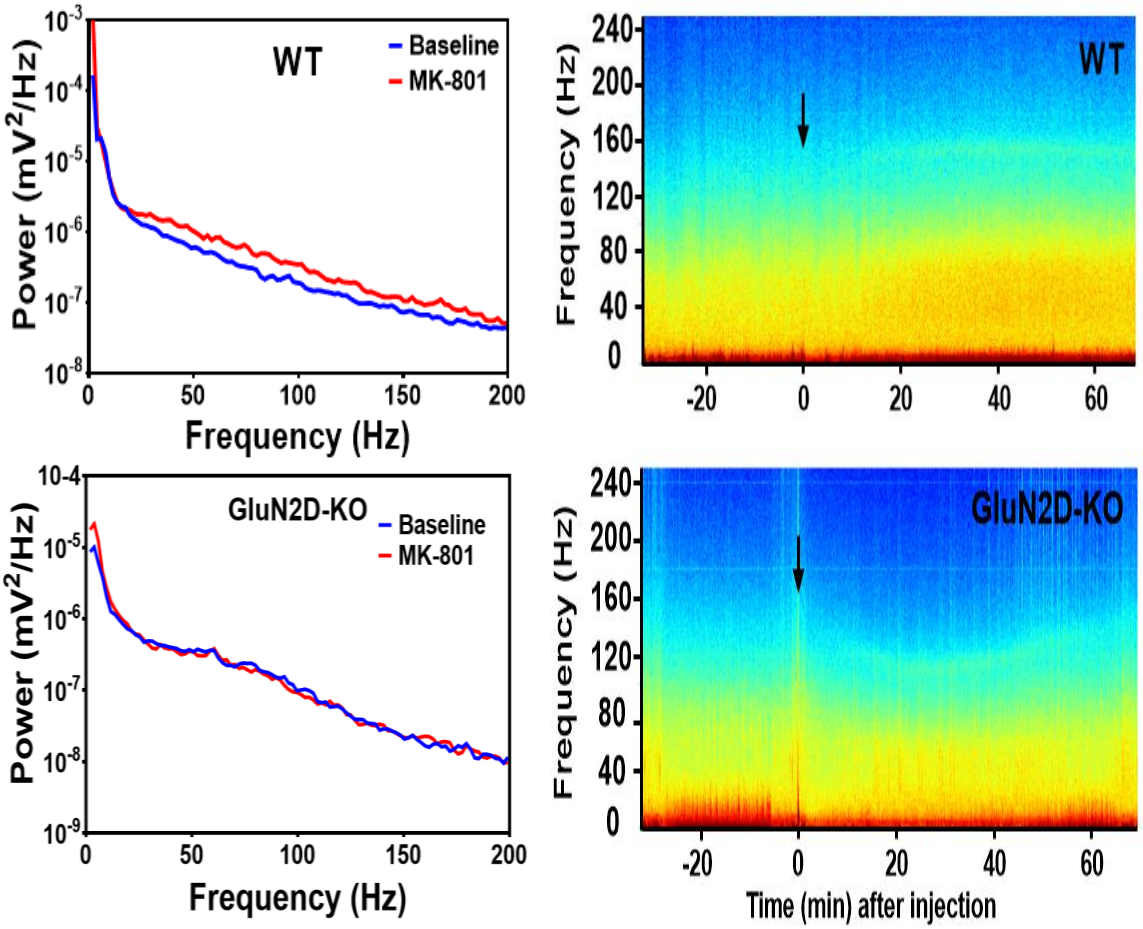


Figure 3. 6 MK-801-induced gamma oscillations increase is abolished in GluN2D-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2D-KO mice before and after MK-801 administration. MK-801 was injected at time = 0 (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

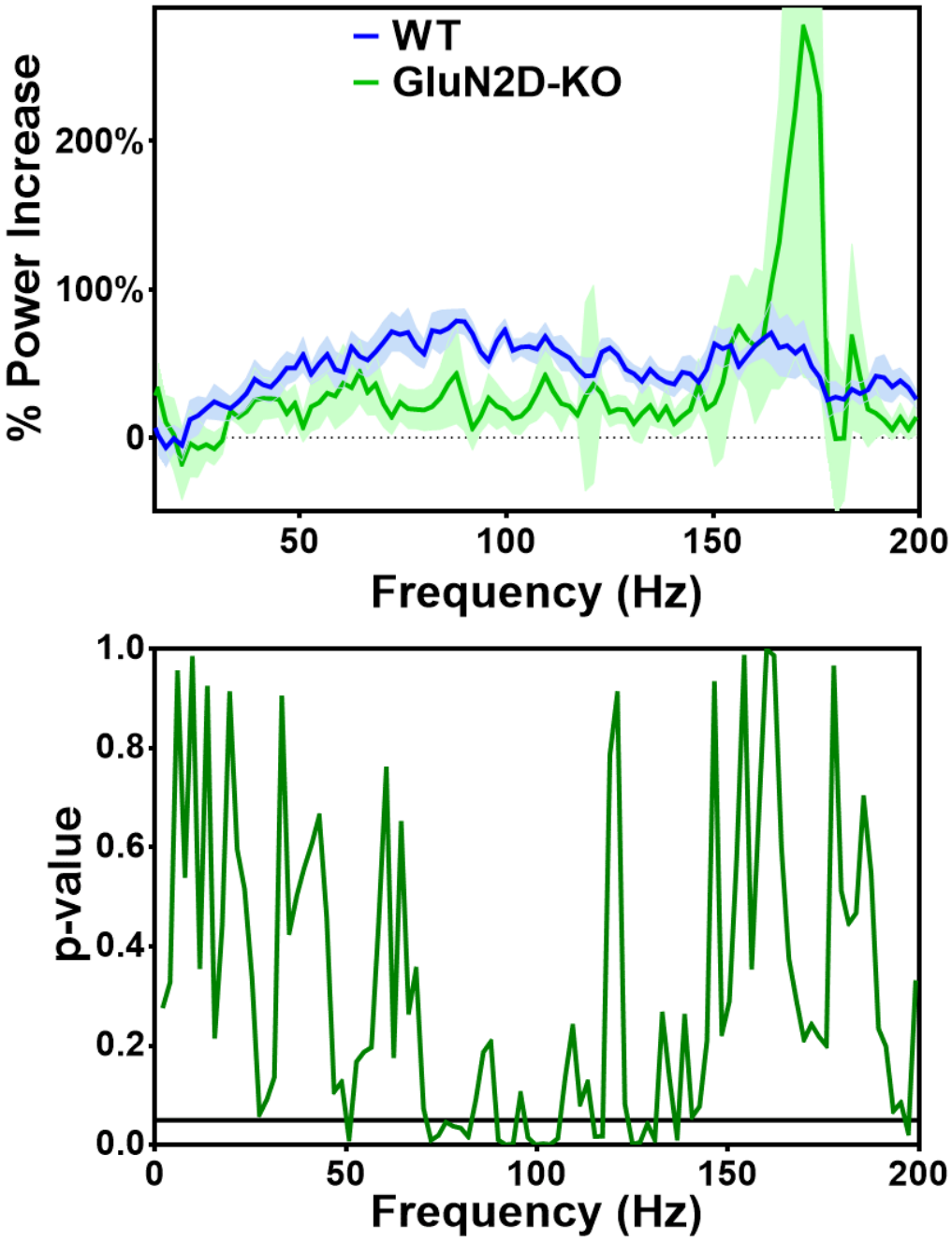


Figure 3. 7 The average % oscillatory power increase of WT and GluN2D-KO mice after MK-801 administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. MK-801 induced an increase of ~80% between 50 to 145 Hz in the WT (blue line, n = 12) while MK-801 only produced ~20% increase in GluN2D-KO (green line, n = 7) mice in the same frequency band. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

PCP-induced oscillations were also largely diminished in GluN2D-KO mice compared to WT mice (Figure 3.8). PCP-induced oscillations appeared mostly eliminated in GluN2D-KO mice (Figure 3.9) with $p < 0.05$ for frequencies 50 – 70 Hz (Figure 3.9).

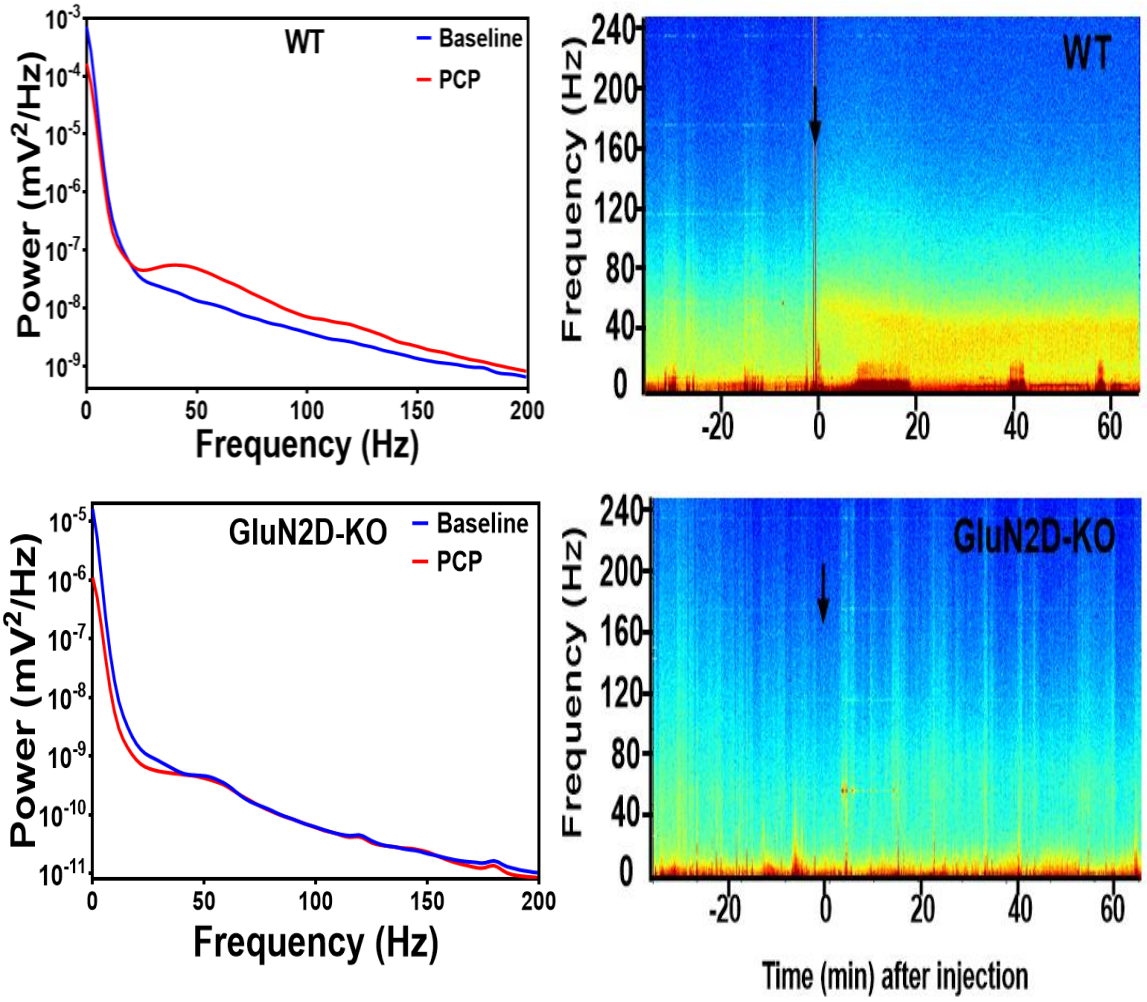


Figure 3. 8 PCP-induced gamma oscillations increase is abolished in GluN2C-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT and GluN2D-KO mice before and after PCP administration. PCP was injected at time = 0 (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

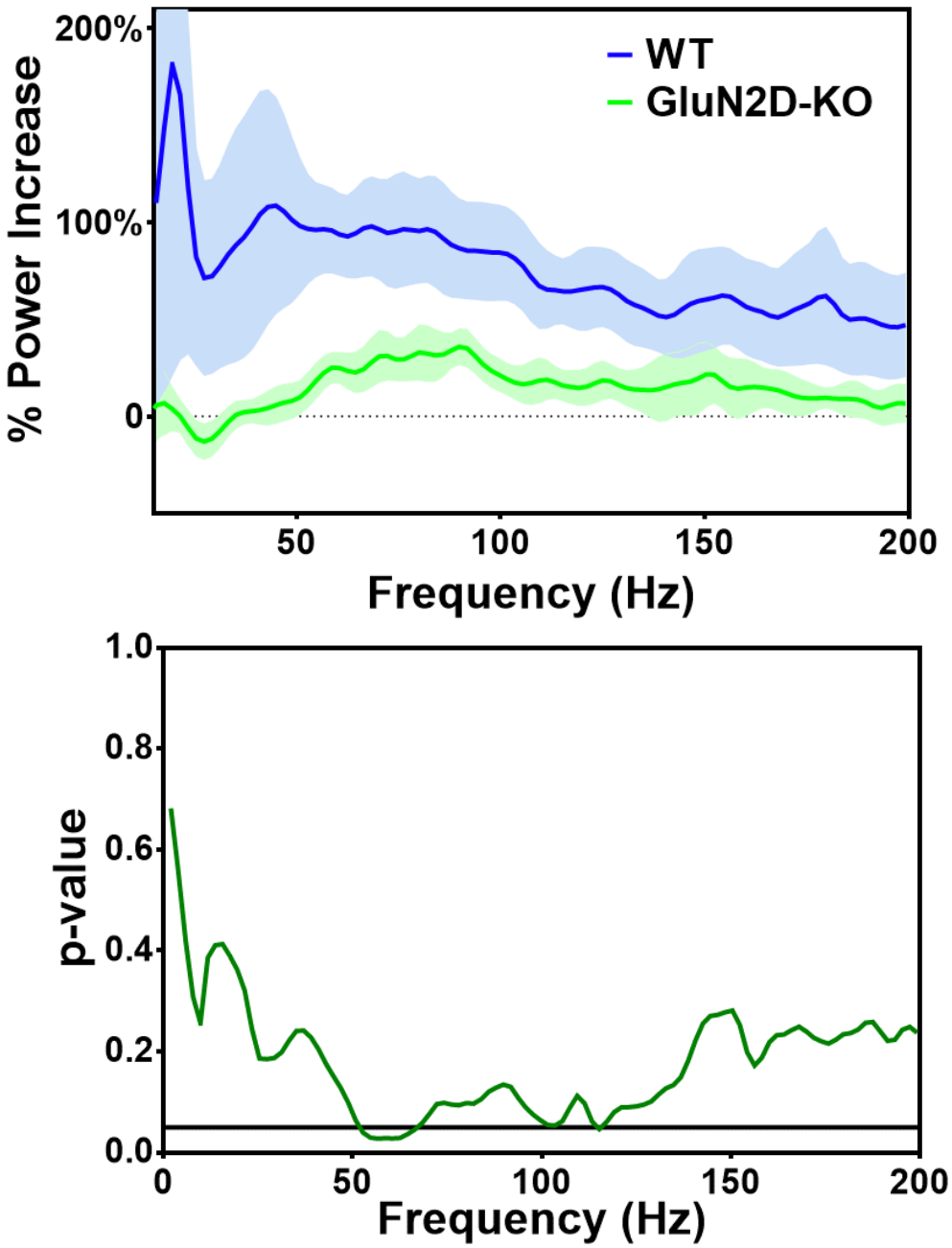


Figure 3. 9 The average % oscillatory power increase of WT and GluN2D-KO mice after PCP administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. PCP induced an increase of ~100% over a broad range of frequency in the WT (blue line, n = 5) while PCP only produced ~30% increase in GluN2D-KO (green line, n = 4) mice in the same frequency band. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

Memantine augmented neuronal oscillations to a similar extent as do other general NMDAR antagonists, an approximately 100% increase especially over the gamma frequency band (Figure 3.10 and Figure 3.11). The majority of this increase was eliminated in GluN2D-KO mice with the average GluN2D-KO response less than the WT response for all frequencies between 30 and 200 Hz (Figure 3.11). P-values were < 0.05 for all frequencies between 45 and 94 Hz (Figure 3.11). High frequency oscillations (~140 – 160 Hz) were variably present after ketamine and MK-801 administration, but not observed after PCP or memantine.

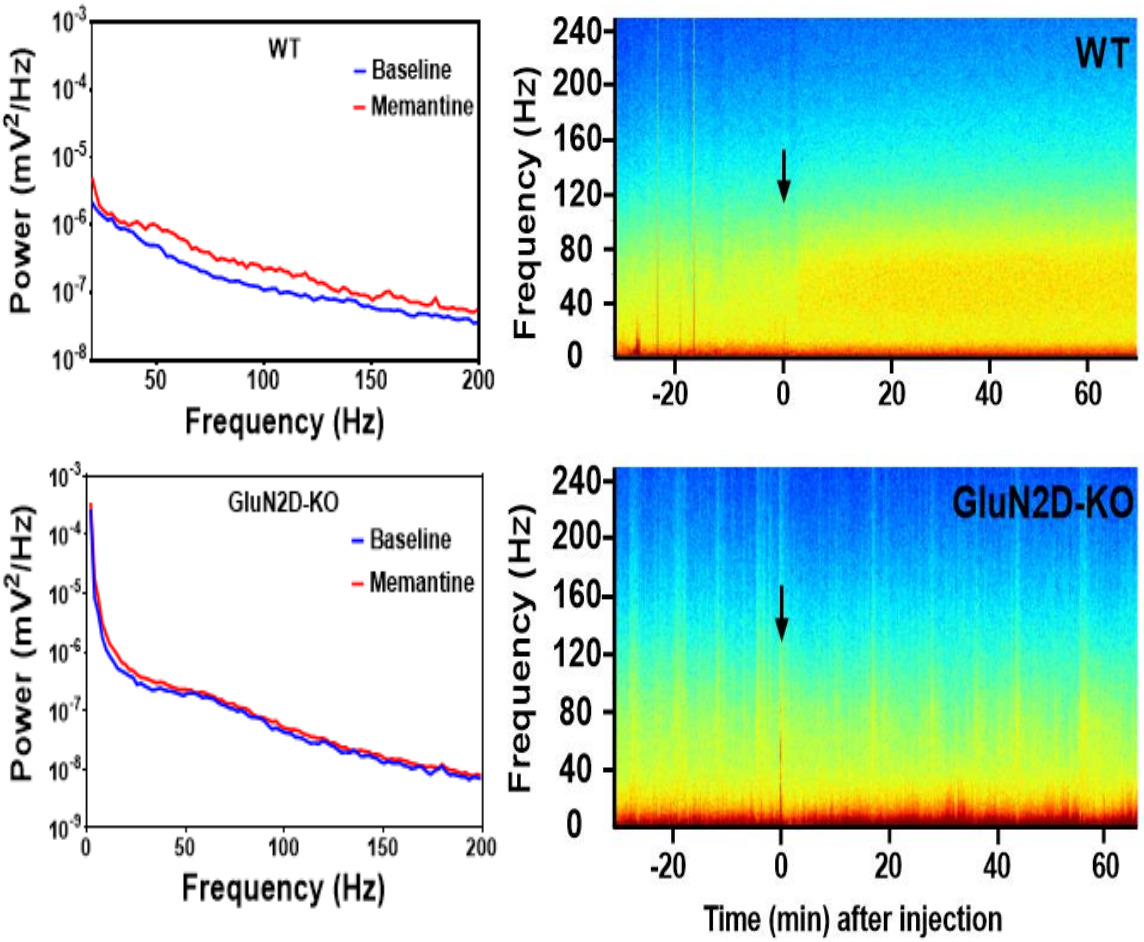


Figure 3. 10 Memantine-induced gamma oscillations increase is augmented in GluN2D-KO mice.

Representative power spectrum (left) and time-frequency spectrogram (right) of WT, GluN2D-KO mice. Memantine was injected at time = 0 (arrow). The color of the spectrogram (from blue to red) represent the power (low to high) of the oscillations.

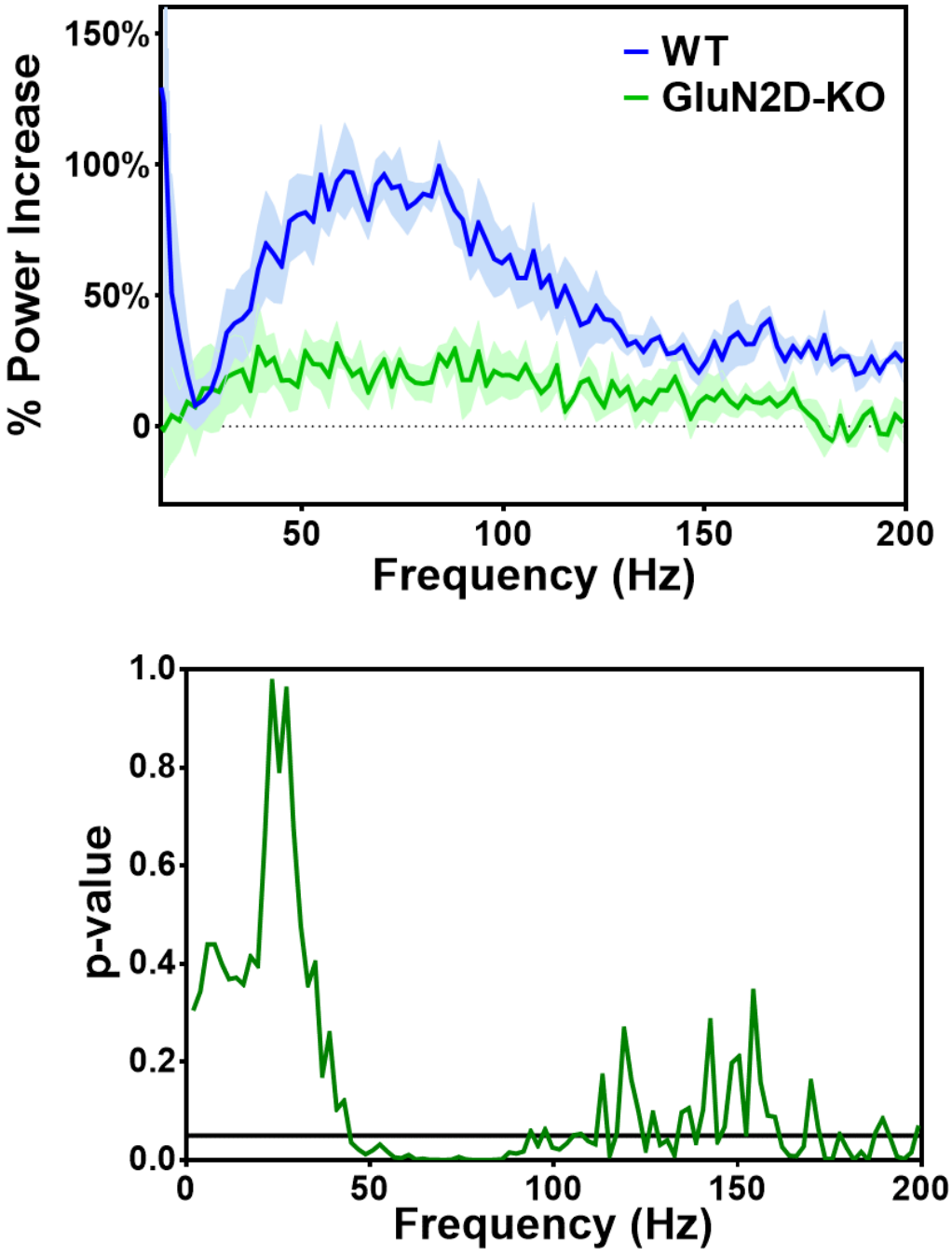


Figure 3. 11 The average % oscillatory power increase of WT and GluN2D-KO mice after memantine administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. Memantine induced an increase of ~100% between 50 to 100 Hz in the WT (blue line, n = 5) while memantine only produced ~15% increase in GluN2D-KO (green line, n = 4) mice in the same frequency band. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

The oddball response in GluN2D-KO mouse is intact. The GluN2D-KO mouse display classic oddball response (Figure 3.12) which the deviant tone induced a larger peak response, and the latency of each peak is: P1 ~ 19 ms, N1 ~ 31 ms.

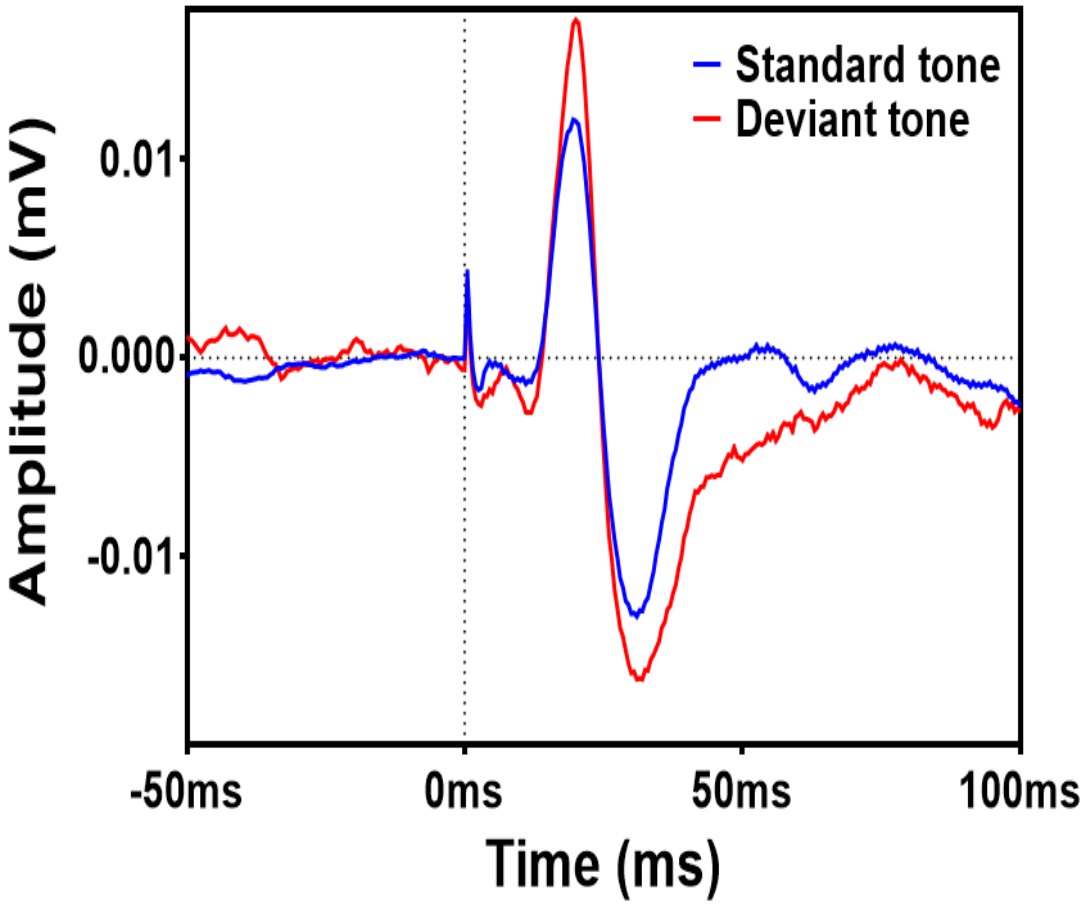


Figure 3. 12 GluN2D-KO Oddball auditory-evoked response.

In an ECoG recording from above the GluN2D-KO mouse cortex, the classic auditory evoked response is enhanced when an oddball tone is presented. The average of the 13K Hz responses is shown for when the tone is presented as a standard (8:1) or a deviant (1:8). The latency of the N1 peak left-shifted compared to WT mouse. The P1 wave is at ~19 ms, N1 ~31 ms. As found for WT mice, the deviant tone generated a larger amplitude response.

3.5 Discussion

Our finding that GluN2D deletion reduces NMDAR antagonist-induced gamma oscillations suggests that GluN2D-containing NMDARs have an important role in modulating neuronal network oscillations. This has significant implications for schizophrenia. Neuronal oscillations in the gamma frequency band are thought to be integral to cognition and perception, and their impairment has been proposed to underlie the symptoms of schizophrenia (Gonzalez-Burgos, Hashimoto, & Lewis, 2010; G. Gonzalez-Burgos & D. A. Lewis, 2008; Uhlhaas & Singer, 2013). Because NMDARs in PV positive cells are important for the modulation of gamma oscillations (Carlen et al., 2012; Uhlhaas & Singer, 2013), these results are also consistent with a key role of GluN2D subunits in cortical PV cell function. In addition, GluN2D subunits in the thalamus are likely to contribute to ketamine-induced dysrhythmias. Nucleus reuniens participates in circuits involved in schizophrenia-related symptoms (prefrontal cortex, hippocampus, and ventral tegmentum) (Duan et al., 2015; Griffin, 2015; Ito, Zhang, Witter, Moser, & Moser, 2015; Lisman, Pi, Zhang, & Otmakhova, 2010) and is enriched in GluN2D subunits (Buller et al., 1994; M. Watanabe et al., 1993a). Additionally, inhibition of NMDAR in the reticular nucleus, which contains GluN2D and GluN2C subunits (M. Watanabe et al., 1993a; Yamasaki et al., 2014), generates telencephalic delta oscillations and potentially schizophrenia-related symptoms (Y. Zhang et al., 2009). Thus, GluN2D subunit-containing NMDARs may have an essential role in the pathophysiologic expression of NMDAR hypofunction that underlies schizophrenia's cognitive symptoms. This suggestion is consistent with studies associating genetic variants of GluN2D subunits with schizophrenia risk (Makino, Shibata, Ninomiya, Tashiro, & Fukumaki, 2005) and with reduced GluN2D expression in schizophrenia (Sodhi, Simmons, McCullumsmith, Haroutunian, & Meador-Woodruff, 2011) and in an animal model of schizophrenia(Bullock, Bolognani, Botta, Valenzuela, & Perrone-Bizzozero, 2009) .

Ketamine also produced an increase in oscillations at frequencies corresponding to high-frequency oscillations (HFO), as previously reported elsewhere (Hunt & Kasicki, 2013). In GluN2D-KO mice, the ketamine-induced peak appeared at a higher frequency (~155 Hz) than in WT mice (~135 Hz). Interestingly, other groups have reported a similar finding in the methylazoxymethanol acetate neurodevelopmental model of schizophrenia. In both the nucleus accumbens (Goda et al., 2015) and motor cortex (Phillips et al., 2012), ketamine elicited HFO with a higher peak frequency in the methylazoxymethanol-treated animals. The significance of this shift in peak frequency is unclear, but it may be noteworthy that the atypical antipsychotics (Olszewski, Piasecka, Goda, Kasicki, & Hunt, 2013) and glycine (Hunt et al., 2015) were found to reduce the peak frequency of NMDAR antagonist-induced HFOs. Thus HFOs peak frequency may be a biomarker suitable for monitoring antipsychotic drug activity.

From our previous experiment, the PPI was not changed in GluN2D-KO mouse. It is not a surprise that the MMN response was also not affected by GluN2D. However, proper controls should be taken into consideration in obtaining the MMN response. In our experiments, we use one control (flip-flop design) to exclude to effect of the frequency of the tones itself. We will use a multi-standards control to distinguish between true deviance detection and adaptation in future studies. Current GluN2D-KO data show a trend of unchanged oddball response, more experiments will be needed to quantify the changes of the peak amplitude and the shifts of the latency to make a solid conclusion.

The ability of GluN2D-deletion to nearly eliminate NMDAR antagonist-induced high gamma oscillations may be due to the loss of GluN2D subunits which are normally expressed in GABAergic interneurons containing parvalbumin (PV) (Alsaad et al., 2018; Perszyk et al., 2016; Standaert et al., 1999; von Engelhardt et al., 2015; Y. Watanabe et al., 2015) PV cells participate in generating gamma oscillations (Buzsáki & Wang, 2012; Cardin et al., 2009) and the blockade (Hunt and Kasicki 2013) or the genetic deletion of NMDARs in these cells (Carlen et al., 2012;

Korotkova et al., 2010) augments gamma oscillations. These findings are consistent with the observation that NMDAR channel blockers preferentially block interneurons (Homayoun & Moghaddam, 2007; Q. Li et al., 2002) thus causing disinhibition of downstream excitatory neurons. This greater sensitivity of PV interneurons to NMDAR antagonists may be due to the greater sensitivity of GluN2D-containing NMDARs to channel blockers such as ketamine and memantine (J. W. Johnson & Kotermanski, 2006).

Thus, GluN2D-containing NMDARs could be a promising therapeutic target for treating schizophrenia. The negative allosteric modulators that act selectively on GluN2D-containing NMDARs have the potential to become a new-generation anti-schizophrenia drug.

Chapter 4

The role of CDKL5 (cyclin-dependent kinase-like 5) in modulating the neuronal oscillations

4.1 Abstract

CDKL5 (cyclin-dependent kinase-like 5) is a protein with homology to the serine-threonine kinases whose function is not-fully characterized. CDKL5 is expressed in the cortex, hippocampus, and striatum, localized to synaptosomes and nuclei. Mutations in the CDKL5 gene, encoding CDKL5, have been identified in CDKL5 disorder which is a devastating neurodevelopmental disorder associated with early-onset epileptic encephalopathy, severe intellectual disability, autism, and related phenotypes. Since many of the symptoms of CDKL5 disorder are similar to schizophrenia and autism, we hypothesized that there may be NMDA receptor hypofunction in inhibitory interneurons. Consequently, we hypothesized that mice with CDKL5 loss-of-function may serve as a model for this disorder and that measured oscillations might serve as a biomarker for the disorder. If so, then there may be a change in the basal oscillatory power, a reduced impact of NMDAR antagonists on oscillatory power, and hopefully an improvement in the behavior in the presence of NMDAR potentiators. In this project, we have tested the first two hypotheses. Using mice in which CDKL5 has been knockout conditionally, we measured the basal and drug-induced neuronal oscillations from CDKL5-KO mice and wildtype mice; our data have shown that CDKL5-KO mice display reduced basal oscillations in frequency <45 Hz and augmented basal oscillations in frequency range > 45 Hz. Moreover, our data also show that both ketamine and pentylenetetrazol (PTZ) induce oscillations with reduced power in CDKL5-KO mice compared to WT mice. Taken together, these data support the idea that CDKL5 deficient mouse a reduced NMDAR function in inhibitory interneurons which may be responsible for some of the symptoms.

4.2 Introduction

CDKL5 disorder is a devastating neurodevelopmental disorder associated with early-onset epileptic encephalopathy (Bodian, Schreiber, Vilboux, Khromykh, & Hauser, 2018; C. Kilstrup-Nielsen et al., 2012), severe intellectual disability, autism, and related phenotypes (Posar, Faggioli, & Visconti, 2015). CDKL5 is a protein with homology to the serine-threonine kinases. Structurally, the protein has a kinase domain and putative nuclear localization and nuclear export signals. The functional roles of CDKL5 are not fully characterized, but it has been shown to play critical roles in regulating postsynaptic localization of NMDA receptors (K. Okuda et al., 2017), surface expression of AMPA receptors (Tramarin et al., 2018), neuronal polarization (Nawaz et al., 2016), synaptic connectivity in the cortex (Pizzo et al., 2016), dendritic spine stability (Della Sala et al., 2016), and dendritic architecture (Fuchs et al., 2014). Loss of CDKL5 in mouse models leads to phenotypes associated with CDKL5 disorder, including autistic phenotypes (I. T. Wang et al., 2012), memory impairment (Tang et al., 2017), increased seizure susceptibility (K. Okuda et al., 2017), and sleep apnea (Lo Martire et al., 2017). Thus, CDKL5 is a critical regulator of neural circuit function, and disruption of these functional roles in CDKL5 disorder likely contributes to neural circuit deficits and behavioral outcomes associated with the disorder. Schroeder and colleagues (Schroeder et al., 2018) demonstrated that loss of CDKL5 has distinct effects on mTOR signaling and synaptic compositions on excitatory neurons and inhibitory neurons.

Neuronal oscillations are modulated by a group of inhibitory neurons that synchronize excitatory neuronal assemblies at the same time, and they are related to many higher brain functions, such as cognition and perception. Thus, CDKL5 disorder phenotypes might caused by its regulation of NMDARs function in both the excitatory neurons and inhibitory neurons. A reliable indicator of NMDARs function *in vivo* is the neuronal oscillations. Since CDKL5-KO upregulates the GluN2B subunits of NMDAR in excitatory neurons, it is plausible that CDKL5 knockout mouse

model will display elevated basal neuronal oscillations thus contributes to the neurological phenotypes. Additionally, CDKL5 loss-of-function is related to increased seizures, thus by giving a sub-convulsive dose of PTZ to CDKL5-KO, we would expect an increase in seizure susceptibility and maybe an enhanced augmentation of neuronal oscillations. PTZ, as a GABA receptor antagonist, blocking GABA receptors will disinhibit the excitatory neurons and thus make the E/I balance shift to more excitatory direction, as such this may increase the neuronal oscillations.

Our data have shown that CDKL5-KO mice display reduced basal oscillations in frequency <45 Hz and augmented basal oscillations in frequency range > 45 Hz. Moreover, our data also show that both ketamine and pentylenetetrazol (PTZ) induce oscillations with reduced power in CDKL5-KO mice compared to WT mice. Our basal oscillatory power data from CDKL5-KO and WT mice suggest that loss of CDKL5 function reflect a hypofunction state of NMDARs in inhibitory interneurons. From our previous studies, the oscillatory power increase caused by NMDAR antagonism may depends on the extent of total NMDARs function that had been inhibited. Taken together, our data indicate that CDKL5 disorder associated neurological phenotypes may caused by its role in regulating the neuronal oscillations and NMDARs function.

4.3 Methods and materials

4.3.1 CDKL5-KO mouse line generation

The CDKL5-KO mouse line was generated in the Dr. Arikkath laboratory as previously described (Schroeder et al., 2018). In the mouse CDKL5 gene, the fourth exon was targeted for creating a conditional knockout allele. The targeting construct was commercially synthesized that contained a left and right homology arms along with the upstream LoxP site in intron 3. Upon Cre-mediated deletion of the exon 4, the transcript will undergo nonsense-mediated decay due to frameshift in the protein coding sequence of the downstream exons. A genotyping PCR assay was developed for detecting the conditional knockout allele. The floxed mice were bred to Cre mice to generate neuronspecific conditional knockout allele for CDKL5.

4.3.2 Animals

All animal experiments were approved by Institutional Animal Care and Use Committee of the University of Nebraska Medical Center. Mice were housed with 12/12-h dark/light cycle with free access to food and water. The heterozygous CDKL5fl females were mated with homozygous CaMKIIα-Cre (the Jackson Laboratory, Stock No. 005359) or Gad2-IRES-Cre (the Jackson Laboratory, Stock No. 019022) male. Three offspring from homozygous CDKL5fl female and heterozygous Gad2-IRES-Cre male were also included and no significant difference were observed. Only male mice were included in this study.

4.3.3 Surgery

All procedures were approved by the University of Nebraska Medical Center's Institutional Animal Care and Use Committee (IACUC) in compliance with the National Institutes of Health guidelines. 12-16 weeks old WT, CDKL5-KO mice were surgically implanted with tripolar electrodes (MS333/2; Plastics One, Roanoke, VA) under xylazine/ketamine/ acepromazine anesthesia as required by IACUC regulations. Two holes were made in the skull 3mm posterior to

bregma at 1mm and 2.5mm lateral. Two electrodes were placed in the medial hole onto the dura surface near the retrosplenial cortex, and the third electrode was placed in the lateral hole for ground. The electrodes were secured to the skull as described elsewhere (Jeffrey et al., 2013). After 7 days of recovery, electroencephalographic (ECoG) recordings were made with a DP-311 differential amplifier (Warner Instruments, Hamden, CT) with high-pass/low-pass filters set at 0.1 and 300 Hz and digitized/recorded (Digidata 1400, pClamp 10; Molecular Devices, Sunnyvale, CA).

4.3.4 Drugs

We used the general NMDAR antagonist: ketamine (30mg/kg, Par Pharmaceutical, Spring Valley, New York or Hospira, Inc., Lake Forrest, IL), and the GABAergic antagonist: Pentylenetetrazol (PTZ) (15mg/kg, from our cooperator, Dr. Olga Taraschenko). All drugs are dissolved in the saline. The dosage of each drug was determined by prior experiments and literature values(Mark Jeremy Hunt, Beryl Raynaud, & Rene Garcia, 2006).

4.3.5 ECoG Recordings

At least one-week after electrode implant surgery, animals in their home cage were placed inside a surrounding Faraday cage, the electrode assembly was connected to a commutator by a cable and the animals were allowed to acclimate for 10 minutes. After 30 minutes of baseline recordings, the animals were injected i.p. with ketamine or PTZ and recorded for 60-90 minutes after the injection. Some recordings were pause during drug administration and then resumed within 2 minutes using the same recording conditions.

4.3.6 Data Analysis

A power spectrum analysis was performed with Clampfit (Molecular Devices) using a Hamming window with 50% overlap. Spectrogram analysis was performed by Neuroexplorer software. Data are expressed as mean of individual experiments along with the standard error of the mean. Statistical comparisons were made using one- or two-way ANOVA and multi-

comparison t-tests if the standard deviations varied with frequency. Graphpad Prism was used for statistical analysis and graphing the data.

4.4 Results

Relative to WT mice, CDKL5-KO mice, displayed higher average basal oscillatory power at frequencies above 45 Hz. In contrast, CDKL5-KO mice had reduced power in the 5 – 45 Hz range (Figure 4.1).

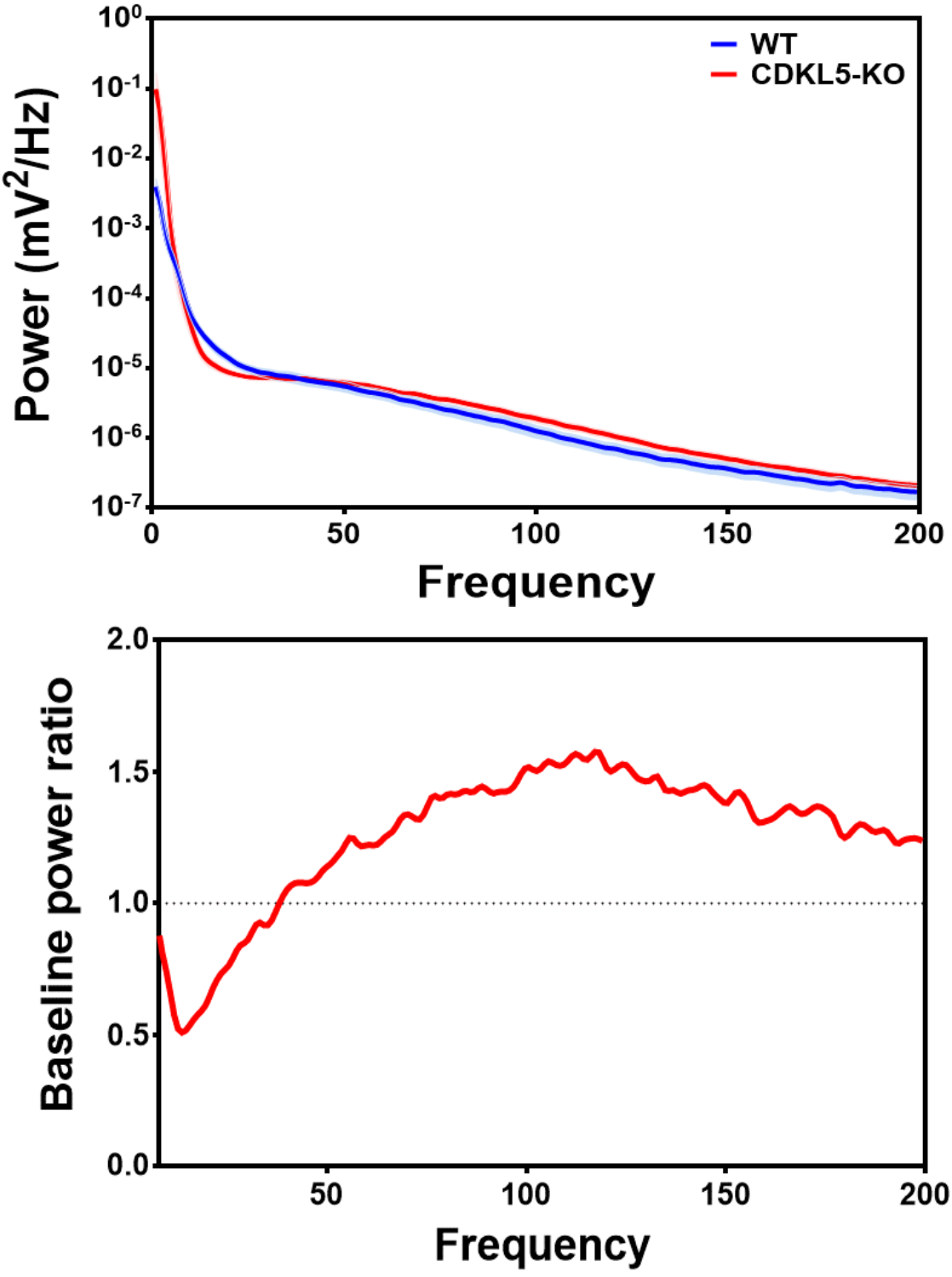


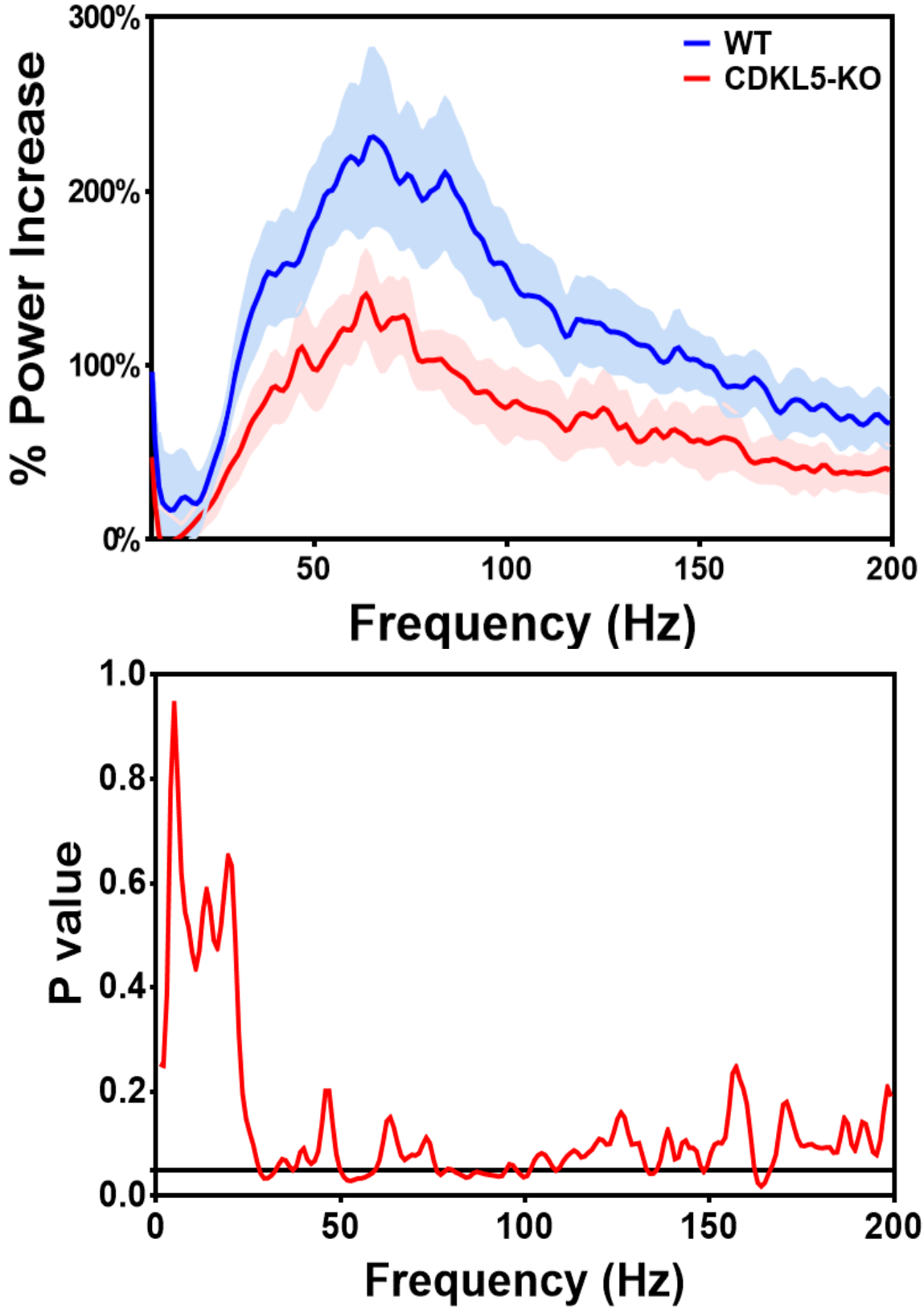
Figure 4. 1 Baseline oscillations are elevated in CDKL5-KO mice.

Upper panel: ECoG analysis of baseline power spectrum of WT and CDKL5-KO animals before drug administration. SEMs are shown by light shading. Bottom panel: % Power of oscillations in CDKL5-KO mice compared to WT mice.

The ketamine-induced increase in oscillatory power was greater in WT mice than in CDKL5-KO mice at all frequencies between 5 and 200 Hz (Figure 4.2). The differences between WT and CDKL5-KO mice were most prominent between 50 to 60 Hz and between 80 to 100 Hz; all frequencies in this range showed p values < 0.05 by both multiple t-test and two-way ANOVA.

Figure 4. 2 Ketamine induced power increase on gamma oscillations in CDKL5-KO and WT mice.

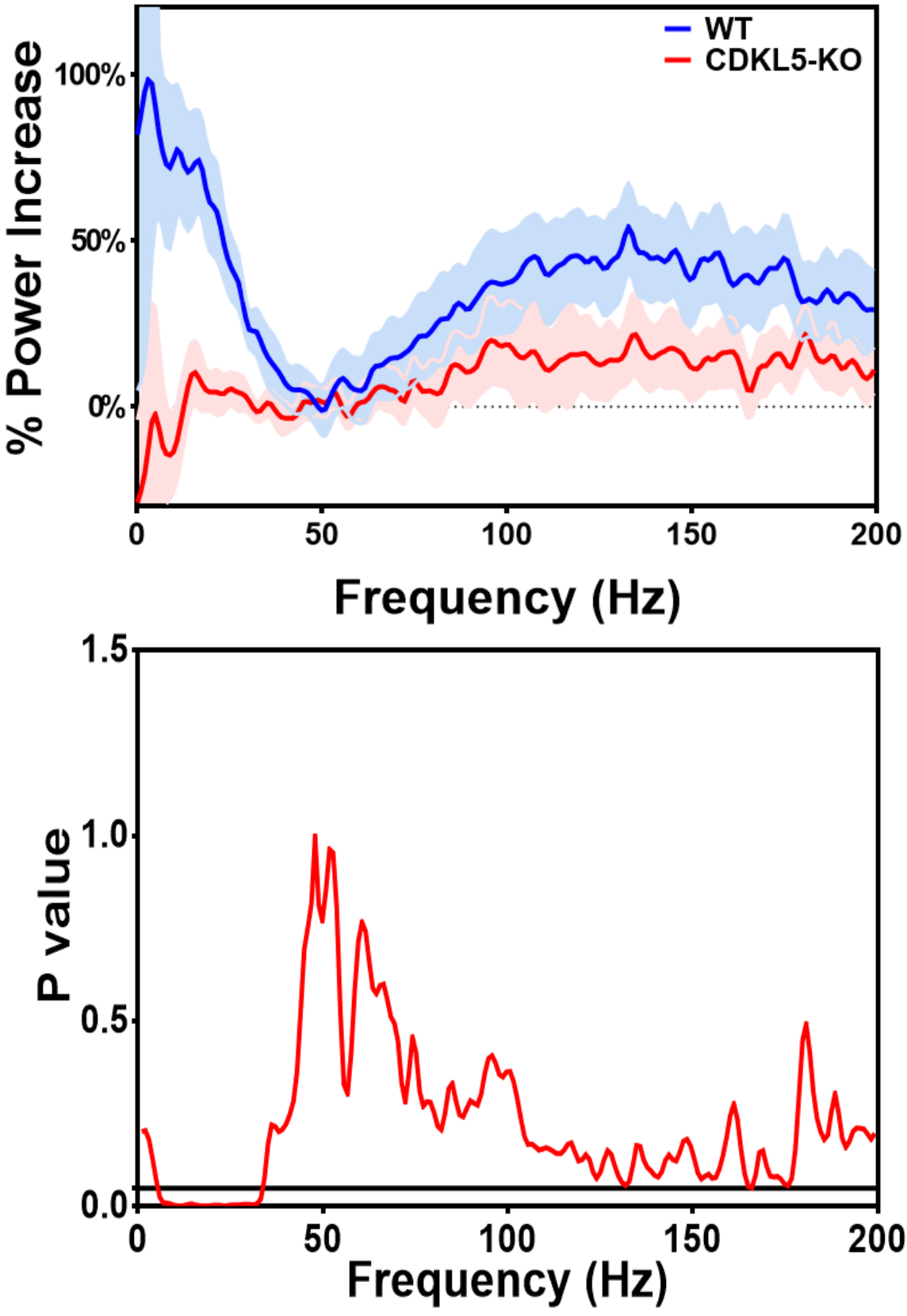
Upper panel: the average % increase in oscillatory power is shown for different frequencies in response to ketamine injection for WT (blue line, n = 10) and CDKL5-KO (red line, n = 9). SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.


300%
200%
100%
0%
% Power Increase
WT
CDKL5-KO
50
100
150
200
Frequency (Hz)
1.0
0.8
0.6
0.4
0.2
0.0
P value
0
50
100
150
200
Frequency (Hz)

The PTZ-induced increase in oscillatory power was greater in WT mice than in CDKL5-KO mice at all frequencies between 5 and 200 Hz (Figure 4.3). The differences between WT and CDKL5-KO mice were most prominent between 5 and 35 Hz; all frequencies in this range showed p values < 0.05 by both multiple t-test and two-way ANOVA.

Figure 4. 3 PTZ-induced power increase on gamma oscillations in CDKL5-KO and WT mice.

Upper panel: the average % increase in oscillatory power is shown for different frequencies in response to PTZ injection for WT (blue line, n = 10) and CDKL5-KO (red line, n = 9). SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.


WT
CDKL5-KO
% Power Increase
100%
50%
0%
0
50
100
150
200
Frequency (Hz)
P value
1.5
1.0
0.5
0.0
0
50
100
150
200
Frequency (Hz)

4.5 Discussion

NMDAR hypofunction in inhibitory interneurons may contribute to the mechanism by which CDKL5 loss-of-function leads to behavioral impairments. A reliable electrophysiological indicator of NMDARs function *in vivo* is the change of oscillatory power resulting from NMDAR antagonists. From our previous experiments, we propose that the enhancement of oscillatory power is directly related to NMDAR hypofunction caused by deletion/blockade to NMDARs by genetic modification or pharmacological antagonism. CDKL5-KO is known to cause an upregulation in GluN2B-containing NMDAR in excitatory neurons. However, our studies are consistent with a hypofunction of NMDAR in inhibitory interneurons. These two actions are not mutually exclusive and, both would contribute to increasing the E/I balance and favor seizure generation. The upregulation of GluN2B subunits in excitatory neurons may contributes to the enhanced basal power of CDKL5-KO mice compared to WT mice. Having a higher basal oscillatory power, it is not surprising that the NMDAR antagonists-induced neuronal oscillations increase in CDKL5-KO mice is not as strong as in WT mice. This could be due to other factors and that the reduced impact of NMDAR antagonism could be due to a ceiling effect where the higher basal levels limit how much oscillations can be further augmented. However, as shown in chapter 2, in the GluN2C-KO, the NMDAR antagonist induced more neuronal oscillations increase than WT, even though GluN2C-KO also displayed higher basal neuronal oscillations. Thus, the brain is capable of stronger oscillations even with elevated basal oscillations.

Many neurological deficits such as schizophrenia, autism are also associated with impaired long-range synchrony. CDKL5 disorder displays various phenotypes, including seizures, autism. To test our hypothesis, one future direction is to measure the long-range synchrony when the CDKL5-KO mouse is performing cognitive task (e.g. food forging). Additionally, the possibility that the CDKL5-KO mouse has NMDA hypofunction is consistent with the behavioral symptoms of these mice.

Finally, if our hypothesis is correct, NMDAR potentiators of GluN2D-containing NMDARs should restore the abnormal neuronal oscillations and improve the behavioral deficits in CDKL5-KO mouse. CDKL5-KO mouse could possibly be used to test NMDA receptor modulators using neuronal oscillations and behavioral studies.

Chapter 5

Subunit-selective drug-induced neuronal oscillations in GluN2C and GluN2D knockout mice

5.1 Abstract

The aim of this chapter is to confirm the findings from chapter 2 & 3. By using GluN2C-KO, GluN2D-KO mouse, and NMDAR subunits selective antagonists, we are able to confirm the opposing roles of GluN2C- and GluN2D- containing NMDARs in modulating neuronal oscillations. Specifically, we used NVP-AAM077 (GluN2A-subunit preferring antagonist), Ro25-6981 (GluN2B-selective antagonist), UBP791 (GluN2C and GluN2D selective antagonist), and SDZ-220,581 (a general antagonist with higher potency at GluN2A>2B>2C>2D) to determine the effect of these drugs on neuronal oscillations in GluN2C- and GluN2D-KO mice. We found that both NVP-AAM077 and Ro25-6981 induced power increase in WT mice and that the increased oscillations were not altered in GluN2C- and GluN2D-KO mice. In contrast, the increase in oscillations induced by UBP791 in WT mice was eliminated in GluN2D-KO mice and augmented in the GluN2C-KO. Lastly, SDZ-220,581 induced an obvious oscillatory power increase in the high-gamma range in GluN2C-KO mouse whereas did not induce an ambient change in GluN2D-KO and WT mouse. Taken together, these results suggest that inhibition of GluN2A- or GluN2B-containing NMDARs can enhance gamma oscillations independently of GluN2C/D-containing receptors whereas altered oscillatory power due to NMDAR channel blockers (e.g., PCP, ketamine) and GluN2C/D-selective competitive antagonists are dependent upon GluN2C/D-containing receptors.

5.2 Methods and materials

5.2.1 Drug preparation

We used the subunit-selective NMDAR antagonists: NVP-AAM077 (20mg/kg), Ro25-6981 (30mg/kg, Tocris), SDZ220,581 (3mg/kg), and UBP791 (30mg/kg). All drugs were dissolved in the saline. The dosage of each drug was determined by prior experiments and literature (Bernat Kocsis, 2012; N. Lozovaya et al., 2014; Phillips et al., 2012).

5.2.2 ECoG recordings

See details in chapter 2, 3, and 4

5.2.3 Surgery

See details in chapter 2, 3, and 4

5.2.4 Date analysis

See details in chapter 2, 3 and 4

5.3 Results

We compared the ability of the GluN2A-selective antagonist NVP-AAM077 to induce oscillations in WT, GluN2C-KO, and GluN2D-KO mice. NVP-AAM077 induced ~50% oscillatory power increase in the three mouse lines from 30 Hz to 60 Hz (Fig 5.1). Statistical analysis indicates that there is no significant difference between WT and KOs among all frequency range.

The GluN2B-selective antagonist Ro25-6981 displayed similar effects as NVP-AAM077, Ro25-6981 induced ~50% oscillatory power increase in the three mouse lines from 60 Hz to 120 Hz, except it did not induce as much of an increase in oscillatory power at frequencies above ~120 Hz in GluN2D-KO mice (Fig 5.2).

We next compared the ability of the GluN2C and GluN2D-preferring competitive antagonist UBP791 to induce oscillations in WT, GluN2C-KO, and GluN2D-KO mice. UBP791 induced ~80% power increase in GluN2C-KO mouse, while it only induced ~50% power increase in WT mouse, and it minor alter the oscillatory power in GluN2D-KO mouse (Fig 5.3).

Lastly, SDZ-220,581 induced a maximal 300% oscillatory power increase in the high-gamma range in GluN2C-KO mouse whereas did not induce an ambient change in GluN2D-KO and WT mouse (Fig 5.4).

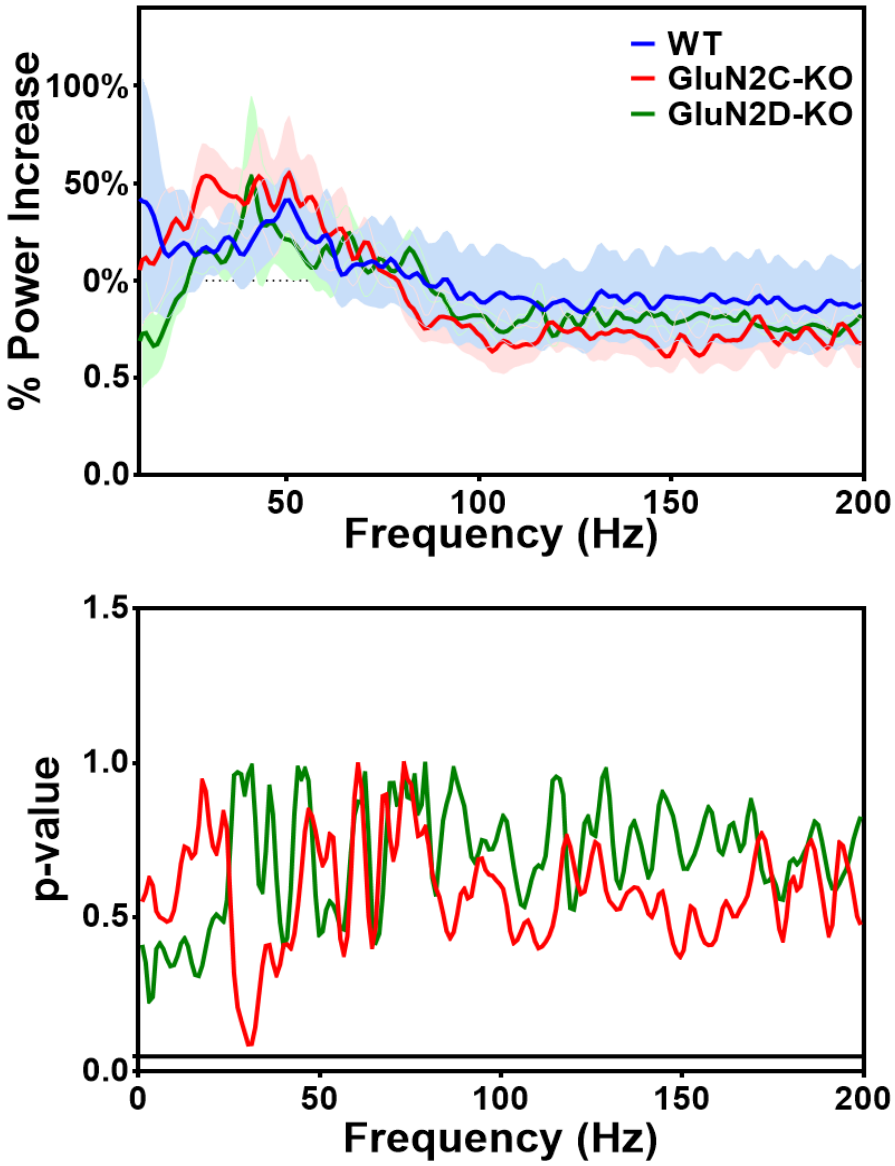


Figure 5. 1 The average % oscillatory power increase of WT, GluN2C-KO mice and GluN2D-KO mice after NVP-AAM077 administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. NVP-AAM077 induced an increase of ~40% between 30 to 60 Hz in the WT (blue line, n = 6), NVP-AAM077 induced an increase of ~50% between 30 to 60 Hz in GluN2C-KO (red line, n = 4) while NVP-AAM077 produced ~30% increase in GluN2D-KO (green line, n = 4) mice between 30-60 Hz. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

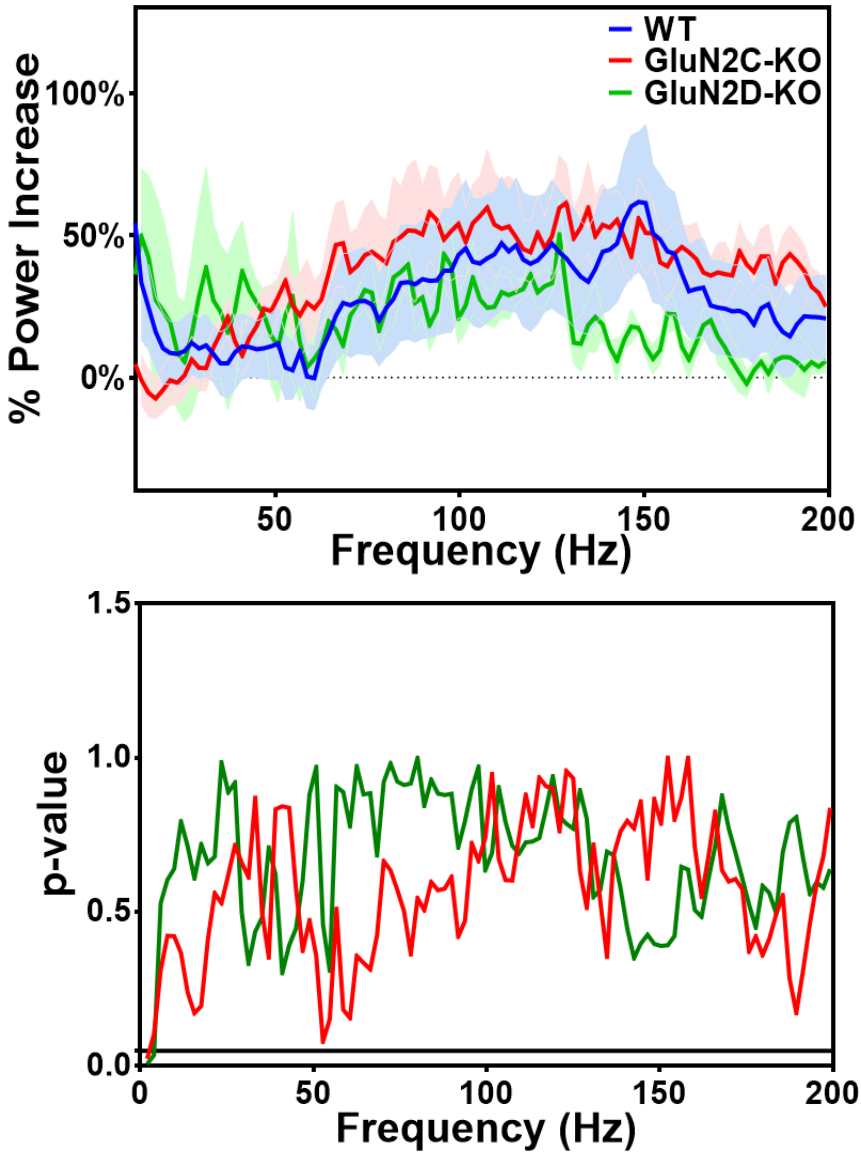


Figure 5. 2 The average % oscillatory power increase of WT, GluN2C-KO mice and GluN2D-KO mice after Ro25-6981 administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. Ro25-6981 induced an increase of ~40% between 60 to 150 Hz in the WT (blue line, n = 12), drug induced an increase of ~50% between 60 to 150 Hz in GluN2C-KO (red line, n = 7) while Ro25-6981 produced ~30% increase in GluN2D-KO (green line, n = 3) mice between 60-130 Hz. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

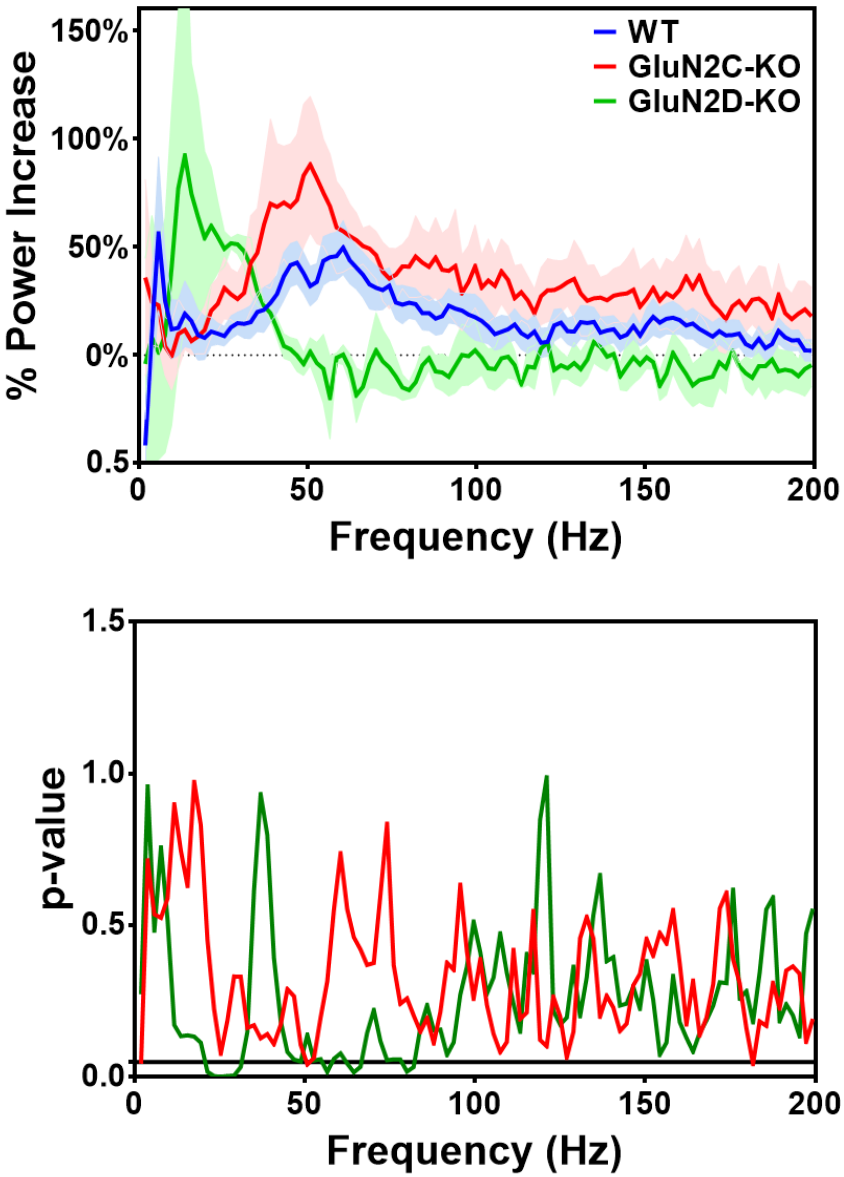


Figure 5. 3 The average % oscillatory power increase of WT, GluN2C-KO mice and GluN2D-KO mice after UBP791 administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. UBP791 induced an increase of ~80% between 40 to 60 Hz in the WT (blue line, n = 12), UBP791 induced an increase of ~50% between 40 to 60 Hz in GluN2C-KO (red line, n = 6) while UBP791 produced ~0% increase in GluN2D-KO (green line, n = 3) mice between 40-60 Hz. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

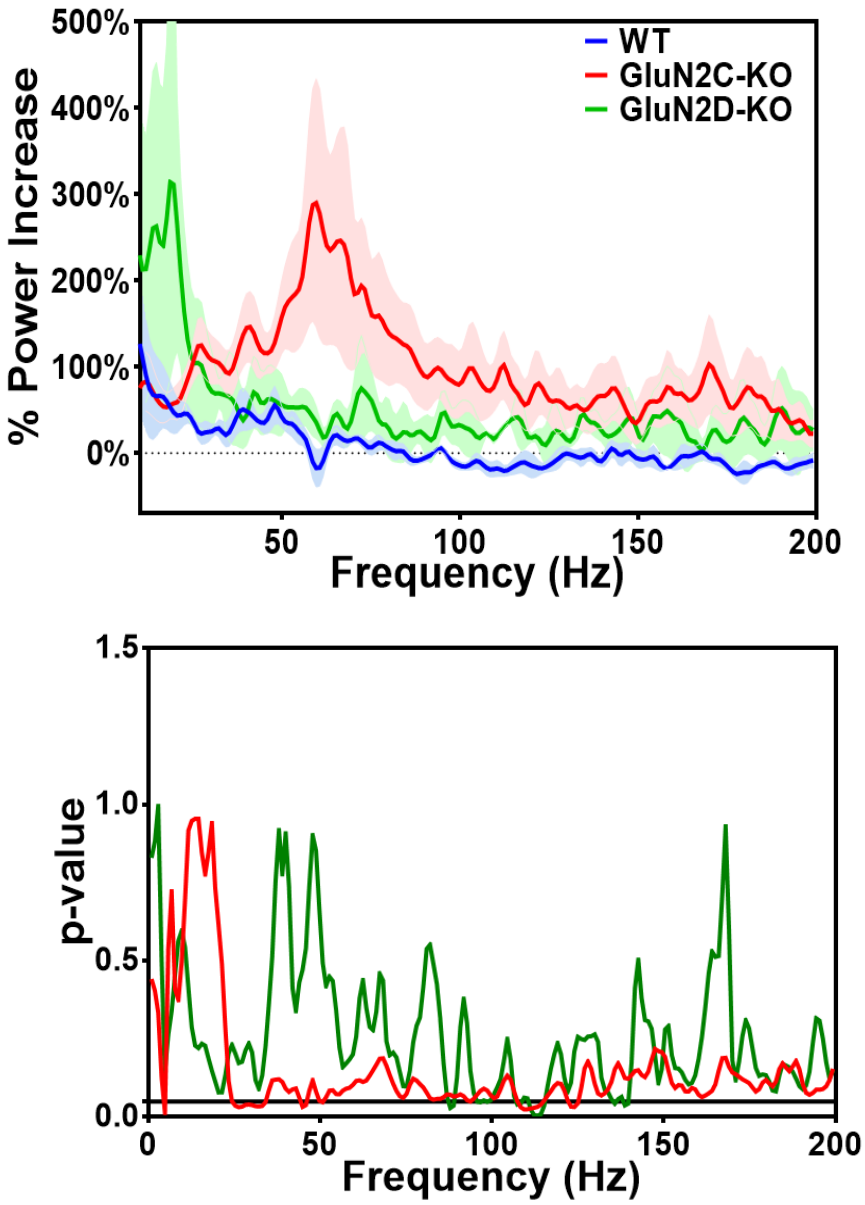


Figure 5. 4 The average % oscillatory power increase of WT, GluN2C-KO mice and GluN2D-KO mice after SDZ administration.

Upper panel: the average increase in drug-induced oscillatory power relative to the proceeding baseline condition as a function of frequency. SDZ induced an increase of ~0% between 40 to 60 Hz in the WT (blue line, n = 4), SDZ induced an increase of ~200% between 40 to 60 Hz in GluN2C-KO (red line, n = 5) while SDZ produced ~0% increase in GluN2D-KO (green line, n = 2) mice between 40-60 Hz. The dotted line represents 0% increase, no drug-induced change in power. SEMs are shown by light shading. Bottom panel: the statistical significance of the difference between WT and KO animals in oscillatory power at different frequencies is shown by a graph of the p values, the dotted line represents p = 0.05.

5.4 Discussion

The present studies are consistent with the results found in Chapters 2 and 3. Only the GluN2C/D-selective antagonist UBP791 enhanced neuronal oscillations that were augmented / reduced in the GluN2C-KO and GluN2D-KO, respectively. The work is also consistent with prior studies looking at the ability of NMDAR subtype-selective antagonists to elicit oscillations. In other work, NVP-AAM077 and Ro25-6981 were able to elicit oscillations (Bernat Kocsis, 2012). This study, however, reported that GluN2C/D antagonist does not enhance oscillations since the compound phenanthrene piperadine 2,3-dicarboxylic acid (PPDA), a GluN2C/D "preferring" antagonist did not augment oscillations. This is the only one study that investigates the effect of subunit-selective NMDAR antagonists in modulating neuronal oscillations. Although PPDA has a slightly higher affinity for GluN2C- and GluN2D-containing receptors, given the higher affinity of L-glutamate for GluN2C/D-containing receptors, this competitive antagonist has very similar IC50s for all four GluN2 subunits. Thus, the inability of PPDA to induce neuronal oscillations may be due to the inability of PPDA to cross the blood-brain barrier. This is consistent with the doses needed to get the structurally-related compound UBP141 into the brain (N. Lozovaya et al., 2014). From chapter 2, 3 and 5, we are able to show that both GluN2C and GluN2D subunits play critical roles in modulating neuronal oscillations. NVP-AAM077 and Ro25-6981-induced oscillations increase are not altered in the GluN2C- and GluN2D-KO mice, which suggest that GluN2A- and Glu2B-containing NMDARs can contribute to oscillations but these oscillations may be independent of those caused by NMDAR channel blockers (e.g. PCP). In contrast, UBP791 which blocks GluN2C and GluN2D-containing NMDARs, increase oscillations in WT and this effect is eliminated in the GluN2D-KO and augmented in the GluN2C-KO. Thus, these results are consistent with GluN2D blockade causing increase in neuronal oscillations and GluN2C blockade causing a decrease in neuronal oscillations. Interestingly, SDZ-220,581 failed to augment oscillations in WT mice, but did enhance oscillations in the GluN2C-KO. This agent is also a competitive antagonist,

its ability to block GluN2C in astrocytes may be relatively enhanced since glutamate concentrations near GluN2C-containing receptors is likely to be much lower than at GluN2A/B containing receptors in the synapse. SDZ also has its lowest affinity at GluN2D-containing receptors, and these receptors are in excitatory synapses on inhibitory interneurons which have relatively high glutamate concentrations. So one would expect that SDZ-220,581 would not be able to induce oscillations by blocking GluN2D-containing receptors. The difference between NVP-AAM077 and SDZ-220,581 in the ability to augment oscillations in WT mice may be due to relative doses; higher concentrations of SDZ-220,581 may show oscillations. Perhaps the most important observation for this chapter is that the psychotomimetic, general NMDAR channel blockers such as PCP and ketamine have their actions eliminated in the GluN2D-KO while blockade of GluN2A/B-containing receptors is not affected by eliminating GluN2D. Taken together, this suggests that the psychosis-producing effects of PCP may be due to blockade of GluN2D while these results do not provide a prediction for the impact of blocking GluN2A/B-containing receptors.

Chapter 6
Discussion and conclusions

The coordination of neuronal activity into neuronal oscillations is thought to be necessary for cognition, perception and memory formation (P. J. Uhlhaas et al., 2008; Uhlhaas & Singer, 2012). The molecular mechanisms that underlie their apparent disruption in neuropsychiatric disorders such as schizophrenia, autism spectrum disorders and intellectual disability may be the dysfunction of NMDARs. The numerically minor GluN2C- and GluN2D- containing NMDAR subtypes are ideally situated for modulating oscillations for therapeutic benefit while minimally impacting the major populations of NMDARs that are involved in a variety of other processes such as synaptic plasticity and whose overactivation is detrimental.

NNMARs have a central role in the major hypotheses regarding neuropsychiatric disorders. They significantly contribute to different neuronal oscillatory generators, they greatly affect the E/I balance (both long-lasting changes after developmental NMDAR activity and acutely in the adult) and they are central to the NMDAR hypofunction hypothesis of SCZ and ASD (J. T. Kantrowitz & D. C. Javitt, 2010; J. E. Lisman et al., 2008). The role played by NMDAR subtypes in each of these diseases is still unknown. NMDARs are a subfamily of neurotransmitter receptors for the primary excitatory neurotransmitter, L-glutamate. They are tetrameric complexes composed of two GluN1 subunits and two subunits from among four GluN2A-2D (which bind glutamate) and two GluN3A-3B subunits which form $Ca^{2+}/Na^{+}/K^{+}$-permeable ion channel gated by L-glutamate and glycine (or D-serine) (Dingledine, Borges, Bowie, & Traynelis, 1999; Traynelis et al., 2010). While NMDARs are most well known for their roles in synaptic plasticity, learning, and initiating cell death in pathological states, NMDAR activity markedly affects working memory, perception, and cognition quite possibly through modulating neuronal oscillations. Thus, it is not surprising that NMDAR antagonists and GluN1 depletion, mimic the symptoms of SCZ and ASD and that many psychiatric disease-related genes affect NMDAR function either directly or indirectly (D. T. Balu & J. T. Coyle, 2011; Sun et al., 2010).

GABAergic interneurons are essential in producing neuronal oscillations (Bartos et al., 2002; Bartos, Vida, & Jonas, 2007; T. Kim et al., 2015; Sohal et al., 2009). Each interneuron innervates a large population of local excitatory neurons and provides a strong simultaneous inhibition of that population when excited in a feedback loop from excitatory neurons. Optogenetic studies have confirmed these conclusions (T. Kim et al., 2015; Sohal et al., 2009). Even PV downregulation by itself leads to increased basal gamma oscillatory power and asynchrony (Vreugdenhil, Jefferys, Celio, & Schwaller, 2003) and mimics the core symptoms of ASD (Wohr et al., 2015). PV expression and E/I balance are also altered in MeCP2 (-/y) mice (Calfa, Li, Rutherford, & Pozzo-Miller, 2015; Tomassy, Morello, Calcagno, & Giustetto, 2014), Down's syndrome (K. Kobayashi et al., 1990), Angelman's syndrome (Saunders et al., 2013). Confirming a central role for NMDARs in PV cell function, many studies have examined the effects of deleting the obligatory GluN1 subunit from PV cells and overall, they find altered neuronal function and behaviors consistent with these diseases (Belforte et al., 2010; Carlen et al., 2012; Korotkova et al., 2010; Saunders et al., 2013). Discrepancies between studies may involve the developmental timing of the deletion and behavioral study methodology (Bygrave et al., 2016). However, which types of NMDAR are in PV cells and what are their functions is unknown.

Many studies have characterized the effects of NMDA antagonists on the power of neuronal oscillations; generally, antagonists increase the power of oscillations in most frequency bands (for a review see (Hunt & Kasicki, 2013)). The most common hypothesis used to explain the effects of antagonists on gamma oscillations follows from the observation that commonly used NMDAR antagonists (PCP, ketamine, MK-801) preferentially inhibit NMDARs on cortical PV cells (Homayoun & Moghaddam, 2007; Q. Li et al., 2002; Nakazawa et al., 2012). This action reduces GABAergic inhibitory activity and thus disinhibits downstream excitatory pyramidal cells leading to an augmentation of basal gamma oscillations and impaired synchrony (Hunt & Kasicki, 2013). This is consistent with the well-documented NMDAR antagonist-induced increase in

activity in corticolimbic structures as reflected by 2-deoxyglucose uptake (G. E. Duncan, Miyamoto, Leipzig, & Lieberman, 1999; M. A. Duncan & Spiller, 2002). Thus, it is significant that in the GluN2D knockout mouse, we find that NMDAR antagonist-augmented high gamma oscillations are nearly eliminated and that there is a complete loss of ketamine-induced glucose uptake. These results clearly suggest that GluN2D subunits contribute largely to NMDAR antagonist-induced oscillations and to brain activation. This finding is consistent with recent neuroanatomical studies which show that GluN2D subunits, although rare in the telencephalon, are localized in PV cells in the cerebral cortex and hippocampus (Alsaad et al., 2018; Standaert et al., 1996; Swanger et al., 2018; von Engelhardt et al., 2015; Yamasaki et al., 2014). We have also shown that GluN2C and GluN2D do not co-localize in cortex or hippocampus and that GluN2D co-localize with neuronal markers in the telencephalon whereas GluN2C does not (Alsaad et al., 2018).

One recent discovery has demonstrated that glutamate release from astrocytes is essential for maintaining low-gamma oscillations (H. S. Lee et al., 2014). Our group found that GluN2C-containing NMDARs are mainly found in astrocytes in the cortex (Alsaad et al., 2018), so it is reasonable to propose that astrocytic GluN2C-containing NMDARs activated by the spillover of glutamate from synaptic cleft, can cause intracellular Ca^{2+} influx, which then causes astrocytes to release glutamate as a gliotransmitter to modulate the circuitry excitability and gamma oscillations.

NMDARs also regulate delta oscillations and high frequency oscillations (HFOs). GluN2C-containing NMDARs in the thalamic reticular nucleus have been proposed to control of delta oscillations directed to the hippocampus (Y. Zhang, Buonanno, et al., 2012; Y. Zhang et al., 2009; Y. Zhang, Yoshida, et al., 2012). NMDAR antagonists can also alter the interactions between high gamma band and low gamma band oscillations in hippocampus and entorhinal cortex (Middleton et al., 2008). Additionally, NMDAR antagonists generate HFOs (80-200 Hz) in the nucleus accumbens that can be recorded from cortex and hippocampus (Hunt et al., 2011). Interestingly, we find that in the GluN2D-KO mouse, ketamine-induced HFOs are enhanced and

have a peak shift in HFO frequency (from ~145 to ~155 Hz), which is consistent with the results seen in a MAM SCZ disease model (Phillips et al., 2012).

Receptors containing GluN2C and GluN2D subunits have several distinct mechanistic properties that make them ideal to be a tonic modulator of oscillations. They have higher affinity for L-glutamate than the major NMDAR populations (GluN2A and GluN2B); they are much less sensitive to Mg^{2+}, therefore can be activated without concurrent depolarization; they also do not desensitize and therefore can retain their activity under tonic or fast-spiking activity. These mechanisms explain how neurons in the thalamic reticular nucleus containing GluN2C are hyperpolarized by NMDAR antagonists. This shift in the membrane potential can then deinactivate T-type Ca^{2+} channels resulting in the delta oscillations (Y. Zhang, Buonanno, et al., 2012; Y. Zhang et al., 2009; Y. Zhang, Yoshida, et al., 2012). Compared to GluN2C, GluN2D-containing receptors have two additional key distinctions, their deactivation time is > 10X longer and they are expressed in PV cells (Alsaad et al., 2018; Standaert et al., 1996; Swanger et al., 2018). Taken together, we propose the hypothesis that GluN2D-containing NMDARs generate tonic modulation of the PV cell membrane potential due to ambient extracellular glutamate reflecting averaged excitatory activity and this determines PV cell excitability and modulates oscillations. This feature may account for GluN2D's disproportionate contribution to gamma oscillations and brain activation (Sapkota et al., 2016) despite the presence of other NMDAR subunits in these cells. Thus, this is similar to that proposed for GluN2C modulation of thalamic delta generation (Y. Zhang et al., 2009), but different because of the differing resulting output (high gamma oscillations).

It is virtually certain that there are multiple subtypes of NMDAR in PV cells given the strong in situ hybridization, RNA sequencing and pharmacology evidence that GluN2A, GluN2B, and GluN2D are present. Thus, there could be six different NMDAR subtypes 2A, 2B, 2D, 2A/2B, 2A/2D, and 2B/2D receptors present. Arguably, the only one of these that has been tested is GluN1/GluN2B heterodimeric receptors by the use of 2B-NAM (Bernat Kocsis, 2012). Only one study has evaluated if either GluN2C or GluN2D are involved in NMDAR antagonist-induced

oscillations. Since the GluN2C/2D "selective" antagonist PPDA did not cause oscillations, they concluded that neither GluN2C or GluN2D is involved (Bernat Kocsis, 2012). However, even though it was the first competitive antagonist to have higher affinity (Ki) for GluN2C/2D than GluN2A/2B, this compound has very similar IC_{50}s for GluN2A-2D after adjusting for glutamate affinities (Feng et al., 2004). As such, PPDA can be useful, but it is not a "selective" agent. Thus, the absence of a CNS effect they observed after i.p. injection indicates a lack of brain penetration for PPDA at this concentration and does not necessarily suggest the exclusion of GluN2C and GluN2D-containing NMDARs in modulating the neuronal oscillations.

Schizophrenia and NMDAR hypofunction are associated with a reduction in mismatch negativity (MMN). In MMN, a component of the auditory-evoked response is larger for an unexpected tone than an expected, repeated tone (Featherstone, Melnychenko, & Siegel, 2018; P. T. Michie, Malmierca, Harms, & Todd, 2016; J. Todd, Harms, Schall, & Michie, 2013). As this is reliably reduced in SCZ patients, and even in asymptomatic siblings of SCZ, it is thought to be a highly sensitive measure and is also seen with even partial NMDAR knockdown (R. E. Featherstone et al., 2015). NMDAR antagonists likewise cause an impairment in MMN (Ehrlichman, Maxwell, Majumdar, & Siegel, 2008; D. C. Javitt, M. Steinschneider, C. E. Schroeder, & J. C. Arezzo, 1996), but little is known about the role of different NMDAR subtypes. General NMDAR antagonists can cause an enhancement in an early MMN component (P13) while higher doses can cause an inhibition of a later component of MMN (N55) (L. Harms et al., 2018). Thus NMDAR contribution to MMN modulation is complex and may involve multiple NMDAR subtypes. This conclusion is consistent with studies using ketamine and CP-101,606, a GluN2B-selective NAM. Ketamine reduced MMN by increasing the standard evoked response while CP-101,606 reduced the deviant response (D. V. Sivarao et al., 2014). While GluN2B-NAMs inhibit MMN, they do not readily augment gamma oscillations (Keavy et al., 2016; Bernat Kocsis, 2012). Conversely to GluN2B's actions, we have observed an intact oddball response in the GluN2D-KO mouse while GluN2D deletion greatly reduces NMDAR antagonist-induce gamma oscillations.

MMN may be similar to prepulse inhibition (PPI) which we and others have found to be unaltered in the GluN2D-KO mouse (Sapkota et al., 2016; Takeuchi et al., 2001). Our results shown that GluN2D-KO mice display a normal MMN, while GluN2C-KO mice's MMN response is reduced and display abnormal peak distribution at the same time.

In the GluN2C-KO, memantine only augmented the oscillatory power in the high-gamma range, whereas ketamine, PCP, and MK-801 all increase oscillatory power in either the low-gamma range (ketamine and PCP) or both in the high and low-gamma range (MK-801). This is potentially significant because memantine does not cause psychosis as do ketamine, MK-801, and PCP. Thus, the effect of memantine on neuronal oscillatory generators may be distinct from the effect of the psychotomimetic NMDAR antagonists. Understanding this mechanism may allow the design of drugs that are better tolerated in the clinic.

All in all, the above work has demonstrated that both GluN2C and GluN2D-containing NMDARs play critical roles in generating and modulating the neuronal oscillations, particularly, GluN2C-containing NMDARs is associated with low-gamma oscillations and GluN2D-containing NMDARs is associated with high-gamma oscillations and HFOs. Given the expression pattern of GluN2C and GluN2D subtypes and relevant evidence regarding the role of astrocytes and PV cells in neuronal oscillations, we propose that GluN2C- and GluN2D-containing NMDAR subtypes have distinct, critical roles in modulating neuronal oscillations due to their distinctive physiological and anatomical properties (Figure 6.1). Compared to GluN2A/B-containing NMDARs, GluN2C- and GluN2D-containing NMDARs have higher affinity for L-glutamate, show less voltage-dependency due to reduced Mg^{2+} sensitivity, and they do not desensitize (Glasgow et al., 2015; Johannes J Krupp et al., 1998; Traynelis et al., 2010; Wyllie et al., 2013). Thus these receptors are well suited for being activated by low concentrations of extracellular glutamate and they can retain their activity under tonic or fast-spiking activity. With GluN2C in astrocytes, and GluN2D in PV-positive GABAergic interneurons, these receptors can provide excitatory feedback, or inhibitory feedback, respectively, to the local ensemble of excitatory neurons in response to excitatory drive thus

modulating the neuronal oscillations (Figure 6.1). These subtypes represent numerically minor NMDAR subtypes in the forebrain. Thus, their potential ability to differentially modulate neuronal oscillations, while minimally impacting the major populations of NMDARs that are involved in a variety of other processes, suggests that these receptors could be useful targets for therapeutic applications.

From chapter 4, CDKL-KO mice displayed elevated basal oscillatory power compared to WT mice. Besides, both NMDAR non-selective channel blocker ketamine and the GABA receptor antagonist PTZ did not induce as much oscillatory power increase in CDKL5-KO mice as in WT mice. CDKL5-KO is known to cause an upregulation in GluN2B-containing NMDAR in excitatory neurons which may contribute to the elevated basal neuronal oscillations. This effect would also increase excitatory activity and increase the E/I balance. Ketamine and PTZ induce a greater oscillatory power increase in WT mice than CDKL5-KO mice which is consistent with a hypofunction of NMDAR in inhibitory interneurons. With NMDAR hypofunction in GABAergic cells there would be less of an effect of inhibiting NMDARs and there would be less GABA output, so PTZ would have less of an effect by blocking GABA receptors. With NMDAR hypofunction and decreased inhibitory output, there would be increased excitatory activity of excitatory neurons, thus increasing the E/I balance. Added to this effect may be the reported upregulation of GluN2B-containing receptors in excitatory cells, again leading to increased excitatory activity and thus a lowering of seizure threshold as seen in this disorder.

Overall, these studies suggest that neuronal oscillations can serve as an *in vivo* readout for testing subtype-selective NMDAR modulators. Additionally, as the power and synchrony of oscillations also reflect dysfunction in neuropsychiatric animal models, ECoG analysis in CDKL5-KO mouse model might be useful for testing the effectiveness of NMDAR drugs for restoring normal function along with behavioral studies.

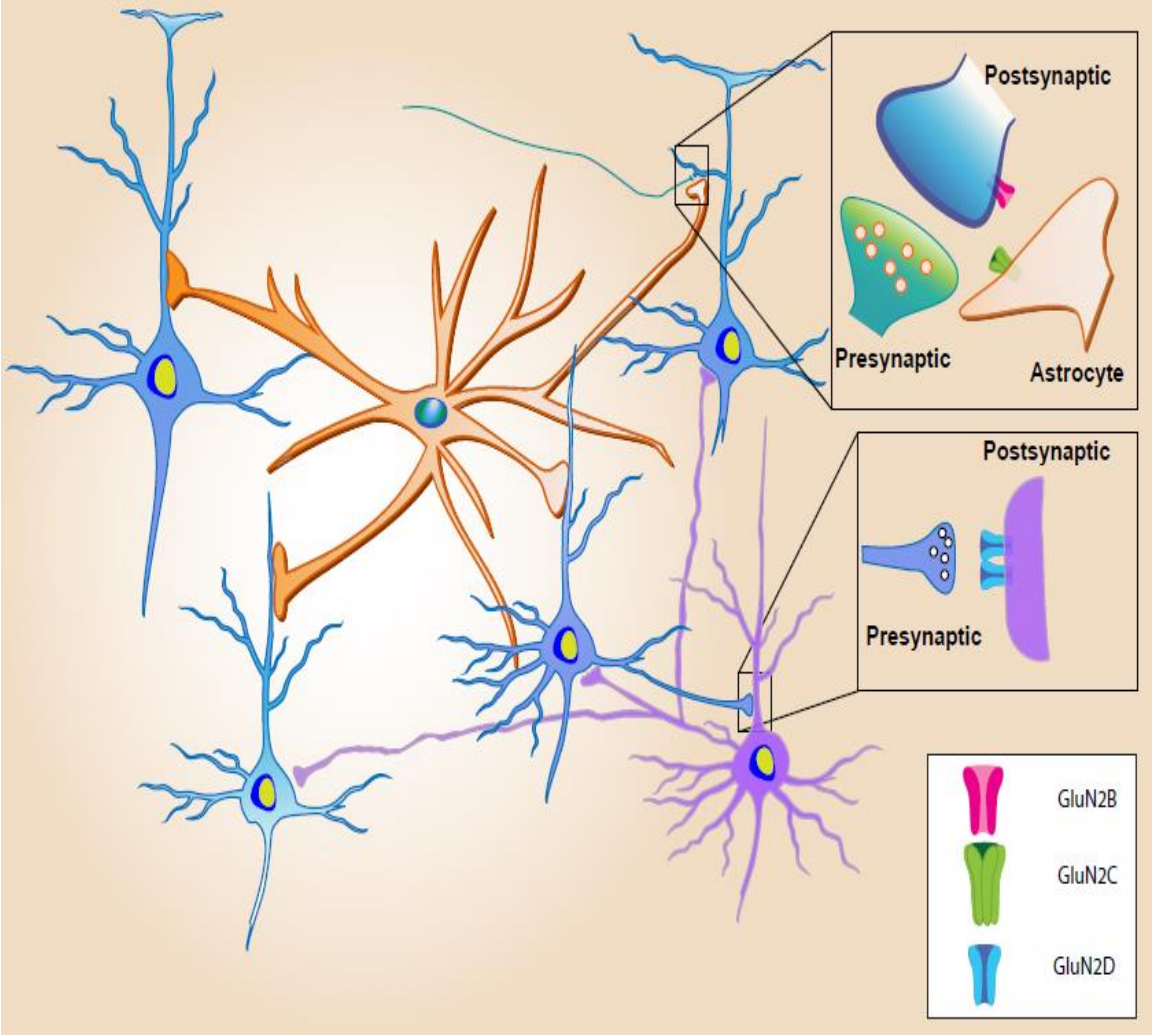


Figure 6. 1 Hypothesis for the opposing roles of GluN2C-and GluN2D-containing NMDARs in modulating neuronal oscillations.

(Upper insert) Astrocytic GluN2C-containing NMDARs: With sufficient synaptic activation, glutamate spillover activates GluN2C-containing NMDARs on astrocytes, leading to increased cytoplasmic calcium levels. In response to elevated intracellullar calcium from intracellular stores, and possibly from GluN2C currents, astrocytes release glutamate (and other gliotransmitters) which acts on extrasynaptic GluN2B-containing NMDARs on the postsynaptic structure, and potentially additional neurons, to modulate excitability and synchronize the activity of a group of neurons thus causing oscillatory power enhancement. (Lower insert) GluN2D-containing NMDARs in PV inhibitory interneurons: Glutamate released from presynaptic nerve of excitatory neurons activates GluN2D-containing NMDARs on the postsynaptic dendrite of inhibitory interneurons. With sufficient synaptic activation, inhibitory interneurons release GABA back onto excitatory neurons. This negative feedback mechanism can thus synchronize the firing of an assembly of excitatory neurons and by decreasing their membrane potential, decrease the magnitude of the population spike and oscillatory power for that group of neurons.

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