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The impact of NMDA Receptor hypofunction on GABAergic interneurons in the pathophysiology of schizophrenia

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Abstract

While the dopamine hypothesis has dominated schizophrenia research for several decades, more recent studies have highlighted the role of fast synaptic transmitters and their receptors in schizophrenia etiology. Here we review evidence that schizophrenia is associated with a reduction in N-methyl-D-aspartate receptor (NMDAR) function. By highlighting post mortem, neuroimaging and electrophysiological studies, we provide evidence for preferential disruption of GABAergic circuits in the context of NMDAR hypo-activity states. The functional relationship between NMDARs and GABAergic neurons is realized at the molecular, cellular, microcircuit and systems levels. A synthesis of findings across these levels explains how NMDA-mediated inhibitory dysfunction may lead to aberrant interactions among brain regions, accounting for key clinical features of schizophrenia. This synthesis of schizophrenia unifies observations from diverse fields and may help chart pathways for developing novel diagnostics and therapeutics.

Keywords

NMDA receptor; GABA; inhibitory interneuron; schizophrenia

Introduction

Findings from clinical and postmortem investigation into the pathophysiology of schizophrenia coupled with advances in molecular and systems neuroscience increasingly point to a complex neurodevelopmental etiology. For example, it is now estimated that 6,000 to 12,000 single nucleotide polymorphisms (SNPs) may contribute to risk for

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Contributors

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Conflict of Interest

All authors declare that they have no conflicts of interest.

schizophrenia (Andreassen et al., 2014; Ripke et al., 2013). Among the many molecules, pathways and circuits that have been implicated, postmortem evidence for abnormalities of GABAergic inhibitory interneurons has been among the most compelling and consistent, whereas behavioral models based on disruption of glutamate signaling via NMDAR antagonists have dominated recent efforts at drug discovery. Because NMDARs are critical for the development and function of GABAergic interneurons (De Marco Garcia et al., 2011) and NMDARs localized on interneurons may also play an important role in the behavioral effects of NMDA antagonists, the interaction between NMDARs and GABAergic interneurons has received considerable attention. Recent advances in our understanding of intracellular pathways linking NMDAR activation with use-dependent gene expression and neuroplasticity of interneurons (Moreau and Kullmann, 2013), as well as studies linking NMDARs on interneurons to functional connectivity (Spellman and Gordon, 2014) promise to provide new insights regarding cognitive functions that are compromised in schizophrenia.

Early models of schizophrenia posited a hyperdopaminergic state, based on the finding that affinity of D2 receptor antagonists correlates with their clinical potency (Creese et al., 1976; Snyder, 1981). Excessive activity at D2 receptors was demonstrated by the dysregulation of amphetamine-induced striatal dopamine release (Cohen and Servan-Schreiber, 1992; Howes et al., 2012; Meltzer and Stahl, 1976; Weinberger et al., 1986). The dopamine model subsequently was extended to include a reciprocal hypoactivation of D1 receptors in prefrontal cortex (PFC) (Davis et al., 1991). Abnormal dopamine release remains highly relevant to deficits in reward response, novelty detection, attention and neuroplasticity in schizophrenia (Goto et al., 2010; Lisman et al., 2011). However, abnormal dopamine signaling may be a consequence of other primary modulatory abnormalities, including NMDAR dysregulation (Kegeles et al., 2000). Among relevant receptor systems, NMDARs have drawn attention in large part due to historical observations that the NMDAR antagonist phencyclidine (PCP) produces a syndrome resembling schizophrenia in healthy individuals (Luby et al., 1959). More than 20 years ago, investigators proposed models linking NMDAR hypofunction to schizophrenia (Carlsson and Carlsson, 1990; Deutsch et al., 1989; Javitt and Zukin, 1991; Olney and Farber, 1995). The model proposed by Carlsson (Carlsson and Carlsson, 1990) emphasized interactions between glutamate and dopamine signaling in the processing and transmission of sensory information. Experiments by Olney and Farber (Olney and Farber, 1995) demonstrated corticolimbic neurodegenerative changes following exposure to NMDAR antagonists and focused attention on midline structures, including anterior cingulate and thalamus, while providing evidence for a developmental vulnerability consistent with the neurodevelopmental pattern of onset of schizophrenia. Of note is the discovery by Benes and colleagues of a reduced density of small interneurons in cingulate cortex (Benes et al., 1991), followed by their finding of a 73% reduction in GABAergic neurons expressing the NR2A subunit of the NMDAR in cingulate cortex, identified by co-localization of glutamic acid decarboxylase 67 (GAD67) and NR2A mRNA (Woo et al., 2004). These studies of brain samples from affected individuals provided critical evidence linking NMDARs and GABAergic interneurons to schizophrenia.

Here, we will discuss the contribution of NMDAR dysfunction to schizophrenia etiology. NMDARs are glutamatergic receptors with unique gating and kinetic properties that expand

the ability of neurons to encode and transmit information as well as modify their connectivity. At the cellular and microcircuit levels, NMDAR activation can support the generation of local rhythmic activity. While their expression on cortical pyramidal neurons is necessary for the generation of slow oscillations (<1 Hz) (Fellin et al., 2009), NMDAR function in interneurons supports the generation of gamma oscillations (30-100 Hz), dynamics important for local synchrony of cortical microcircuits (Buzsáki and Wang, 2012; Korotkova et al., 2010; Moore et al., 2010). At the level of large scale network organization, NMDAR blockade is known to produce a functional dysconnectivity syndrome, observed in neuroimaging studies. This effect may be exerted through disruption of cortico-cortical and cortico-hippocampal interactions, some of which depend on thalamic mechanisms (Blot et al., 2013; Saalman, 2014; Woodward et al., 2012). Indeed, there is growing consensus that NMDARs contribute to brain development and function at multiple levels of organization: molecular, cellular, circuit, and systems, and that understanding their role in GABAergic neuronal physiology may be particularly relevant to the clinical attributes of schizophrenia. Addressing their involvement at all these levels of organization may help chart a path towards development of diagnostics and therapeutics for this important brain disorder.

The unique molecular properties of NMDARs make their dysfunction particularly relevant for the pathophysiology of schizophrenia

To put NMDARs into context, excitatory synaptic transmission is mediated by multiple ionotropic glutamate receptors, including NMDA, AMPA, and kainate receptors. Several characteristics make NMDARs unique (see Figure 1). In contrast to AMPARs, which mediate current flow across the membrane in response to glutamate, NMDARs act as coincidence detectors of pre- and post-synaptic activity due to a voltage dependent Mg^{2+} blockade, allowing ion flux only at depolarized membrane potentials (Collingridge et al., 1988). In addition, NMDARs require the presence of a co-agonist along with glutamate. At the glycine binding site, D-serine potentiates NMDAR function (Halassa et al., 2007; Mothet et al., 2000; Wolosker et al., 1999) whereas kynurenic acid, a metabolite of tryptophan, acts as an antagonist at the glycine binding site (Schwarcz et al., 2012). Both D-serine and kynurenic acid are released from astrocytes and dysregulation of their synthesis and release has been implicated in schizophrenia (Panatier et al., 2006; Potter et al., 2010). The functional properties are rooted in molecular structure. NMDARs are tetrameric complexes assembled from obligatory NR1 subunits which contain the glycine binding site and variable NR2 subunits which contain the glutamate binding site. The various NR2 subunits confer distinct functional properties (Dingledine et al., 1999). NR2A subunits, which are present mainly at synaptic sites, are associated with neuroprotection and synaptic potentiation (Hardingham et al., 2002). In contrast, NR2B subunits are mainly extrasynaptic (Rumbaugh and Vicini, 1999), and their activation promotes cell death (Hardingham et al., 2002) and synaptic depression (Liu et al., 2013). The synaptic NR2A/ NR2B ratio is known to increase in excitatory cortical neurons throughout development (Flint et al., 1997; Stocca and Vicini, 1998), which is important for novel forms of synaptic plasticity involved in transferring new information into long term memories (Cui et al., 2013). NR2C and NR2D subunits are both expressed in forebrain interneurons and likely distributed at both synaptic and extrasynaptic sites (Monyer et al., 1994; Standaert et al., 1996; Wenzel et al., 1996; Xi

et al., 2009). NR2C/ NR2D-containing NMDARs exhibit a particularly high affinity for ketamine, which may be mechanistically related to ketamine-induced psychosis (Greene, 2001; Homayoun and Moghaddam, 2007; Kotermanski and Johnson, 2009; Lisman et al., 2008). NR3A and NR3B subunits are much less studied and their functional role remains to be clarified (Piña-Crespo et al., 2010).

Once activated by glutamate, NMDARs generate long excitatory postsynaptic currents (EPSCs), with a time constant approximately an order of magnitude greater than those generated by AMPARs ($\tau_{\text{NMDA}} \sim 6\text{--}350\text{ms}$ $\tau_{\text{AMPA}} \sim 0.34\text{--}1\text{ms}$) (Bellingham et al., 1998; Götz et al., 1997; Faber and Korn, 1980; Perouansky and Yaari, 1993). These long EPSCs are specifically important for the generation of spike bursts in the hippocampus and ventral tegmental area (Grienberger et al., 2014; Tong et al., 1996). NMDAR channels are permeable to Ca^{2+} , a highly important second messenger. Ca^{2+} flux through NMDAR-gated channels is critical for refinement of synaptic connections (Bourne and Nicoll, 1993; Constantine-Paton et al., 1990) and for the induction of synaptic long term potentiation (LTP) and long term depression (LTD), cellular correlates of memory (Bliss and Collingridge, 1993; Collingridge et al., 2010). By coupling to Ca^{2+} -calmodulin (CaM) dependent kinases (CaMKs), NMDAR regulation of Ca^{2+} influx can modulate gene expression necessary for the maintenance of synaptic structure (Bradley et al., 2006; Hardingham et al., 2001). Numerous signaling proteins working downstream of NMDARs have been implicated in schizophrenia, including nitric oxide synthase (Reif et al., 2006), calcineurin (Gerber et al., 2003; Liu et al., 2007; Miyakawa et al., 2003) and βCaMKII (Novak et al., 2000). Altered NMDAR function in different brain regions could lead to different symptomatology; for example, disruption of NMDAR signaling specifically in the PFC (Goto et al., 2010) and the hippocampus (Wiescholleck and Manahan-Vaughan, 2013) may lead respectively to altered cognition and psychosis.

NMDAR antagonists as a model for schizophrenia

Examples of NMDAR antagonists include APV, CPP and CPPene (competitive) and PCP and MK-801 (use-dependent uncompetitive), ketamine (non-competitive), and kynurenic acid, (antagonist at the glycine binding site). Ketamine and PCP have been shown to produce a schizophrenia-like behavioral phenotype in healthy individuals (Javitt and Zukin, 1991; Krystal et al., 1994). In addition, ketamine provokes a transient recurrence of behavioral symptoms in schizophrenia patients stabilized on D2 antagonist antipsychotics (Lahti et al., 1995). Unlike dopamine agonists, which selectively produce psychotic symptoms, subanesthetic doses of ketamine produce the full syndrome, characterized by withdrawal, blunted affect, psychomotor retardation, delusions, and cognitive impairment (Krystal et al., 1994). NMDAR antagonists bind to other neurotransmitter/ neuromodulator receptors, with variable affinity. Ketamine and phencyclidine both have high affinity for D(2) and 5-HT(2) receptors (Kapur and Seeman, 2002), and ketamine binds to allosteric sites on the nicotinic cholinergic receptor complex, which complicates interpretation of studies employing these agents as behavioral models for schizophrenia. Moreover, the agents differ in their affinity for the NMDAR and hence are not interchangeable. While caution must be used when interpreting results from experiments using NMDAR

antagonists, these studies can provide valuable insight about the role of NMDARs in producing behavioral phenotypes that approximate schizophrenia.

NMDAR antagonists may produce behavioral effects via several mechanisms, including disinhibition of glutamate and dopamine release and disruption of plasticity and functional connectivity. In humans, ketamine's psychotomimetic effects are blocked by agents that reduce glutamate release (Anand et al., 2000; Krystal et al., 2005) but not by D2 antagonists (Krystal et al., 1999). Imaging studies have demonstrated that ketamine administration leads to an increase in cortical glutamate concentrations (Stone et al., 2012), cortical perfusion (Holcomb et al., 2001) and glucose metabolism (Vollenweider et al., 1997) and a decrease in PFC GABA concentrations (Scheidegger et al., 2013). Ketamine also increased global measures of functional connectivity in correlation with positive and negative symptoms (Driesen et al., 2013), consistent with resting-state hyperconnectivity in schizophrenia (Chai et al., 2011; Guller et al., 2012; Woodward et al., 2011, 2012). In mice, the use-dependent NMDA channel blocker, MK801, enhanced excitability of prefrontal cortex (Moghaddam et al., 1997), first appearing as reduced activity of GABAergic interneurons, followed by increased activity of pyramidal neurons and disruptions in patterns of spontaneous bursts and loss of variability in spike trains (Homayoun et al., 2005; Homayoun and Moghaddam, 2007). NMDA antagonists preferentially impact inhibitory interneurons, in part because of they exhibit higher baseline activity compared to pyramidal neurons. The contribution of NMDAR channel currents may be accentuated in inhibitory neurons because their average membrane potential is more depolarized and thus more favorable to removal of pore block by Mg^{2+} (Lewis and Moghaddam, 2006).

NMDARs regulate inhibitory interneurons, whose deficiency is implicated in schizophrenia

NMDARs are critical to both the development and adult function of GABAergic interneurons. In cultured cortical neurons, NMDAR antagonism with ketamine reduces expression of GAD67, a GABA synthesizing enzyme that defines a major population of inhibitory interneurons (Kinney et al., 2006). This same manipulation in PFC slices reduces inhibitory synaptic transmission (Zhang et al., 2008). NMDARs also regulate expression of parvalbumin (PV) (Kinney et al., 2006), a Ca^{2+} binding protein that defines a subpopulation of interneurons and modulates its firing properties (shown in thalamic reticular nucleus [TRN]; Albéri et al., 2013) and plasticity (shown in cerebellum; Caillard et al., 2000). The causal link between PV and GAD67 levels and behavior is reinforced by bidirectional manipulation of PV and GAD67 protein levels in the hippocampus of the awake mouse; learning is improved by pharmacogenetic enhancement of PV expression, and diminished by its pharmacogenetic reduction (Donato et al., 2013). Genetic ablation of NMDARs reduces GAD67 and PV in the intact mouse cortex and hippocampus, a deficit that is associated with schizophrenia-like behaviors such as novelty-induced hyperlocomotion and impaired prepulse inhibition (Belforte et al., 2010). These studies show that NMDAR signaling is required for GABAergic cell development and behavior, suggesting that NMDAR hypofunction contributes to abnormalities in GABAergic markers seen in schizophrenia.

Molecular evidence for both NMDAR and GABAergic dysfunction is consistently found in post-mortem schizophrenia studies. Decreased levels of GAD67 mRNA and protein are highly reproducible postmortem findings (Akbarian et al., 1995; Bird et al., 1978; Knable et al., 2002; Lewis et al., 2005; Volk et al., 2000). NMDAR expression levels are globally reduced, with selective decreases in NR1 and NR2C subunits in PFC (Beneyto and Meador-Woodruff, 2008; Weickert et al., 2013) and thalamus (Meador-Woodruff et al., 2003). Post-mortem studies have shown that NMDAR dysfunction may specifically affect GABAergic neurons. A reduction in the density of NR2A expressing GAD67+ neurons in the anterior cingulate cortex (Woo et al., 2004) suggests that NMDAR hypofunction may contribute to reduced GABAergic markers, through excitation-transcription coupling (Lewis et al., 2005). Layers of the medial cingulate cortex that show no change in NR2A do not show a reduction in GAD67+ neurons (Woo et al., 2004). These results, in combination with the efficacy of an NR2A specific antagonist to reduce GAD67 and PV levels in cultured cortical neurons (Kinney et al., 2006), supports the contention that NR2A-dependent glutamatergic input onto GABAergic interneurons contributes to reduced levels of GAD67 and PV expression characteristic of schizophrenia. In agreement, levels of NR2A (Bitanirwe et al., 2009), GAD67 and PV (Beasley et al., 2002; Hashimoto et al., 2003; Woo et al., 1997) are decreased in basket and chandelier cells, two major PV-expressing cortical interneuron types. Selective reduction in excitability of PV+ interneurons may also be related to other ion channel deficits, such as the α subunit of Kv9.3 potassium channels in PFC (Georgiev et al., 2014). In addition to changes in excitability, dysfunction of PV+ neurons in schizophrenia may be caused by increased oxidative stress secondary to reduced perineuronal nets (seen in amygdala and entorhinal cortex; Cabungcal et al., 2013; Pantazopoulos et al., 2010). Consistent with this model, Behrens and colleagues (Behrens and Sejnowski, 2009) demonstrated that ketamine may produce a reduction in PV expression indirectly, via an inflammatory increase in oxidative stress. In addition to compelling evidence for aberrant PV+ interneuron function in schizophrenia, changes in molecular markers have been observed in other inhibitory interneuron subtypes, including somatostatin (Beneyto et al., 2012; Hashimoto et al., 2008a; 2008b; Morris et al., 2008) and VIP (Levinson et al., 2011; Moreno-De-Luca et al., 2010; Mulle et al., 2010; Vacic et al., 2011). It seems reasonable to think that abnormalities in GABAergic interneurons beyond the specific PV+ subtype may also contribute to deficits associated with schizophrenia.

The role of NMDARs in gene expression and neuroplasticity

Activity dependent gene expression is a mechanism that allows cells to couple their electric activity to long term changes in their functional properties. This process of excitation-transcription (E-T) coupling is essential for developmental plasticity and is thought to be the underlying mechanism for how sensory enrichment can rescue abnormalities stemming from early deprivation (Maurer et al., 1999; Nelson et al., 2007). Experience-induced neuronal activity modulates circuit development by controlling specific cellular characteristics, including neuronal excitability and survival (Zhang et al., 2002), growth of dendritic and axonal arbors (Chattopadhyaya et al., 2004; Chen et al., 2011), and development of synapses (Bloodgood et al., 2013; Spiegel et al., 2014). Importantly, different pathways exhibit distinct kinetics, and can thereby couple neurotrophins, neurotransmitters, and

neuromodulators to a multitude of neuronal responses at multiple timescales (Cohen and Greenberg, 2008; West et al., 2002; Wu et al., 2001). For example, the CaMK pathway couples local Ca^{2+} flux through Ca_v1 (L-type) channels to the formation of a Ca^{2+} /CaM complex that translocates to the nucleus to activate the transcription factor CREB (Bito et al., 1996; Deisseroth et al., 1998; Ma et al., 2014; Wheeler et al., 2008; 2012). The Ras-mitogen associated protein kinase (MAPK/ERK) pathway, activated by Ca^{2+} flux through voltage gated Ca^{2+} channels and NMDARs, or by growth factors such as BDNF, also results in the phosphorylation of CREB (Impey et al., 1998; Sheng et al., 1991). The coupling of NMDAR signaling to gene expression is known to involve such biochemical pathways, which may explain how NMDARs influence interneuron development and function. Activation of the MAPK/ERK pathway is critical for expression of PV and GAD65/67 in slice cultures from mouse visual cortex (Patz et al., 2003; 2004). BDNF, acting through this pathway (Gottschalk et al., 1999), is important for the maturation of physiological properties of PV+ cells (Itami et al., 2007) and for development of inhibitory cortical networks (Hong et al., 2008). NMDAR signaling activates this pathway in a manner that is modulated by interactions with scaffold proteins. In inhibitory interneurons, it is specifically modulated by ErbB4 and its receptor Neuregulin 1 (Nrg1) (Hahn et al., 2006; Vullhorst et al., 2009). The relevance of these molecules to pathophysiology is highlighted by genetic and post-mortem studies connecting Nrg-ErbB4 signaling to schizophrenia (Agim et al., 2013; Hahn et al., 2006; Stefansson et al., 2002; Yang et al., 2003). In fact, many proteins involved in these pathways, including the Ca_v1 channel, calcineurin, $\text{CaMKII}\beta$ and $\text{CaMKII}\gamma$, and BDNF and its receptor TrkB have all been linked to schizophrenia and related neuropsychiatric disorders such as autism (Gerber et al., 2003; Glausier and Lewis, 2011; Hamshere et al., 2012; Lewis et al., 2011, 2012; Voineagu et al., 2011). Understanding the mechanism by which interneurons use Ca^{2+} influx through NMDARs to regulate gene expression will help clarify the molecular link between NMDAR and GABAergic function in schizophrenia.

The role of NMDARs on interneurons: disinhibition and reduced gamma oscillations

Electrophysiological findings provide additional support for a link between NMDA and GABA in schizophrenia, as reduced NMDAR-dependent inhibitory drive results in the increased excitability that characterizes schizophrenia (Wobrock et al., 2007). In the cortical slice preparation, exposure to MK-801 reduces inhibitory post-synaptic currents (IPSCs) on pyramidal neurons (Li et al., 2002). In animal models, the administration of ketamine enhances excitability of PFC (Moghaddam, et al., 1997). This is surprising, as one would expect a blocker of excitatory transmission to reduce excitability. It has been proposed that NMDAR antagonists preferentially impact inhibitory interneurons, partially because of their higher baseline activity compared to pyramidal neurons, which lessens Mg^{2+} dependent block of their NMDARs (Homayoun and Moghaddam, 2007). Consequently, MK-801 decreases activity of GABAergic interneurons and thereby increases pyramidal neuron excitability in prefrontal regions, which may contribute to the disinhibition associated with psychosis (Homayoun and Moghaddam, 2007; Jackson et al., 2004).

One consequence of reduced inhibitory drive in schizophrenia is the disruption of gamma oscillations, 30-100 Hz activity that is important for spike timing synchrony in local cortical microcircuits (Bartos et al., 2007; Cardin et al., 2009; Klausberger and Somogyi, 2008; Lodge et al., 2009; Sohal et al., 2009). PV+ cortical interneurons are particularly important for their role in the generation of these oscillations. Optogenetic stimulation of these cells is sufficient to generate gamma oscillations, while their inhibition attenuates gamma (Sohal et al., 2009). Importantly, pharmacologic blockade or genetic ablation of NMDARs on PV+ cells results in disruption of the gamma rhythm, a physiological phenotype found in schizophrenia patients, and one that correlates with schizophrenia-like symptoms in animals (Carlén et al., 2012; Gonzalez-Burgos et al., 2010; Kocsis, 2012; Korotkova et al., 2010; Lisman et al., 2008). This phenotype is only seen following postnatal and not post-adolescent NMDAR ablation, suggesting that NMDAR activity on PV+ interneurons during development may be important for the maturation of physiological function necessary to support gamma oscillations (Belforte et al., 2010).

Disrupted functional connectivity in schizophrenia may be downstream of NMDA and GABA hypofunction

Functional neuroimaging studies using magnetic resonance spectroscopy (MRS) have linked GABA and NMDARs to the abnormal functional connectivity seen in schizophrenia. The observation of resting-state hyperconnectivity in schizophrenia (Chai et al., 2011; Guller et al., 2012; Woodward et al., 2011, 2012) may explain task-related dysconnectivity in these conditions; diminished recruitment of certain circuits in behavior may be related to their difficulty in disengaging from hyper-connected resting-state networks. In schizophrenia patients, GABA concentration is reduced in visual cortex, an attribute that correlates with aberrant visual sensory processing (Yoon et al., 2010). Levels of GABA are inversely correlated with resting-state functional connectivity in the motor cortex (Stagg et al., 2014), supporting the relationship between inhibition and inter-regional interactions. As ketamine is known to alter cognition in a manner mimicking many of the symptoms of schizophrenia, its effect on brain activity has been assayed in several MRS studies. Ketamine administration in healthy subjects both induces resting-state hyperconnectivity (Driesen et al., 2013) and reduces prefrontal GABA concentration (Scheidegger et al., 2013), completing the loop between NMDA, GABA, and schizophrenia symptomatology.

On a global level, it is therefore interesting to speculate that the behavioral phenotypes seen in schizophrenia can be explained by deficits in functional connectivity among large scale networks, a phenomenon which depends on GABAergic inhibition in the motor cortex (Stagg et al., 2014) and NMDAR activity in the PFC and striatum (Dandash et al., 2014; Driesen et al., 2013). Functional connectivity is critical for the emergence of the default mode network (DMN, also referred to as the task-negative network), a collection of correlated cortical regions including the medial PFC, which is active when the brain is at wakeful rest and is associated with stimulus-independent thought and internally guided cognition (Raichle et al. 2001). DMN is known to be hyperactive in schizophrenia patients, a measure that is correlated with both positive and negative symptoms (Whitfield-Gabrieli et al., 2009). When the brain shifts its information processing mode to externally-guided

cognition, DMN is suppressed, and instead the dorsal attentional network (DAN, also referred to as task-positive network, which includes dorsolateral PFC (dlPFC) is activated (Fox et al., 2006). DMN and DAN are mutually anticorrelated networks, whose respective engagement may reflect the dominant mode of information processing in the brain. Similar to DMN, DAN is also disrupted in schizophrenia at rest, evident by its aberrant interactions with executive cortical regions (Woodward et al., 2011). During working memory tasks, appropriate DAN activation and DMN suppression is impaired in schizophrenia (Garrity et al., 2007; Pomarol-Clotet et al., 2008; Woodward et al., 2011), a phenomenon that is mimicked by ketamine administration to healthy subjects (Anticevic et al., 2012). These findings are highly significant, as they suggest a mechanism by which hypo-NMDA states translate to clinical phenomenology. In addition, augmenting inhibition with a GABA agonist in humans (Fingelkurts et al., 2004) or optogenetics in mice (Hamilton et al., 2013) results in increased functional connectivity in the cortex. By impairing large scale cortical networks involved in telling apart internal vs. external stimuli, such states may help explain hallucinations in schizophrenia where it is often difficult to distinguish internal from external events.

As large scale cortical network interactions are detected through blood-oxygen-level dependent (BOLD) neuroimaging, an indirect measure of neural activity, the underlying circuit mechanisms are unclear. In recent years, much attention has been focused on the role of the thalamus in coordinating multiple cortical regions through rhythmic interactions. For example, during top-down visual attention in primates, the pulvinar (higher order thalamic nucleus) coordinates visual cortical areas through alpha-band synchrony, a physiological measure that correlates with successful performance (Saalmann et al., 2012). The thalamus is especially relevant to this model because of the importance of thalamic inhibition for regulating rhythmic interactions. Specifically, thalamic inhibition is mediated by the TRN, a thin shell of GABAergic neurons that surrounds thalamic relay nuclei. While the role of TRN in attentional processing is established (Cohen and Servan-Schreiber, 1992; Halassa et al., 2014; McAlonan et al., 2006, 2008), it is unclear whether it regulates thalamic-mediated cortico-cortical interactions as a mechanism of attentional regulation. Despite this lack of knowledge, it is worth considering that TRN dysfunction, evident as a reduction in spindles (Halassa et al., 2011), may contribute to disrupted thalamic coordination of functional cortical connectivity. Indeed disrupted sleep spindles in schizophrenia have been used to link schizophrenia to the TRN (Ferrarelli et al., 2007, 2010).

TRN neurons are notable for high expression of NR2C containing NMDARs, which significantly contribute to their overall excitability. A hypo-NMDA functional state, characteristic of schizophrenia, would lead to reduced TRN excitability. Because these neurons exhibit unique biophysical properties, including T-type Ca^{2+} channel expression, hyperpolarization may result in their de-inactivation and engagement in low-frequency rhythms in the delta range (1-4 Hz) via rhythmic bursting (Zhang et al., 2012). In schizophrenia patients, increased delta oscillations (normally seen in sleep) are observed in the awake PFC (Clementz et al., 1994). This electrophysiological abnormality is similarly observed upon APV administration, which also produces rhythmic bursting in the TRN (Zhang et al., 2009). Elevated waking delta would diminish PFC recruitment during waking behavior and may partly explain cognitive deficits in schizophrenia.

Targeting NMDARs and interneurons as a potential therapeutic strategy

While current pharmacologic management of schizophrenia is dependent on D2 blockers, the evolving understanding of NMDAR and GABA interactions in schizophrenia holds promise for future therapeutics. As subunit-specific positive and negative allosteric modulators become available, this approach will increasingly be guided by selective targeting of subpopulations of NMDARs in an approach consistent with their neurodevelopmental expression. Several drugs acting at the glycine binding site of NMDARs have been tested with mixed results over the past 20 years (Tuominen et al., 2005). Increasing glycine via dietary supplementation (Costa et al., 1990; Heresco-Levy et al., 1999; Javitt et al., 1994; Rosse et al., 1989) or by inhibiting glycine reuptake with the competitive inhibitors sarcosine (Tsai et al., 2004) or bitopertin (Umbricht et al., 2014) has been shown to ameliorate negative symptoms of schizophrenia, although results have been inconsistent (Buchanan et al., 2007; Goff, 2014). Other trials have supported the efficacy of high dose D-serine (Heresco-Levy et al., 2005; Kantrowitz et al., 2010; Tsai et al., 1998) and low dose D-cycloserine (Goff et al., 1999b) but again, negative results have also been reported (Buchanan et al., 2007; Goff et al., 2005; Weiser et al., 2012). The difficulty in replicating early positive findings may reflect the larger problem of heterogeneity in schizophrenia and the unreliability of clinical trials in this population. In addition, clozapine and possibly other second generation antipsychotics may enhance glutamatergic transmission, thereby complicating pharmacologic add-on strategies (Fumagalli et al., 2008; Goff et al., 1999a; 2002; Wittmann et al., 2005). Repeated dosing with glycine site agonists may produce tachyphylaxis via endocytosis of NMDARs (Nong et al., 2003; Parnas et al., 2005) which has led to intermittent dosing strategies (Goff et al., 2008; Cain et al., 2014). Intracellular pathways downstream of NMDARs may also present targets for pharmacologic intervention, as exemplified by nitric oxide augmentation by nitroprusside infusion (Hallak et al., 2013). Of note, clozapine reverses the loss of PV in interneurons produced by repeated administration of NMDAR antagonists in adult mice (Cochran et al., 2003) and differs from other antipsychotics in showing efficacy for the glycine site of the NMDAR (Schwielers et al., 2008). Another promising new pharmacologic approach targets the Kv3.1 channel which is primarily localized on PV+ interneurons (Yanagi et al., 2014). It remains to be established whether newer strategies, such as interneuron precursor transplants (Gilani et al., 2014) and transcranial electrical stimulation (Filmer et al., 2014) will prove effective in correcting interneuron functional deficits. Given the many genetic links between schizophrenia and NMDAR pathways, a personalized medicine approach may produce larger and more consistent therapeutic benefits which could fundamentally advance our understanding of the illness and expand our available therapeutic options.

Conclusion

The past two decades have produced a wealth of evidence for dysfunction of both GABAergic interneurons and NMDARs in schizophrenia (Figure 2). While deficits were first seen in postmortem studies, recent experiments using electrophysiology, neuroimaging, and animal models have provided mechanistic links between these two abnormalities. Recent studies have shown that NMDAR activity is critical for proper development and adult function of GABAergic interneurons, and that both micro and macroscopic functional

brain organization is dependent on proper inhibition. The relationship between NMDAR and GABAR, clearly seen on different scales of analysis, can provide insight into how they are normally required for cognition and how their dysfunction contributes to schizophrenia phenomenology. Specifically, we hypothesize that NMDAR hypofunction on GABAergic interneurons may result in underdeveloped GABAergic circuitry and reduced inhibition, and thus support many symptoms of schizophrenia. This overview unifies findings from multiple fields and thus provides a schizophrenia framework that can help launch novel therapeutic directions.

Abbreviations

BOLD	blood-oxygen-level dependent
CaM	calmodulin
CaMK	Ca ²⁺ /CaM dependent protein kinase
DMN	default mode network
DAN	dorsal attentional network
EPSC	excitatory postsynaptic current
GAD67	glutamic acid decarboxylase 67
IPSC	inhibitory postsynaptic current
LTP	long term potentiation
LTD	long term depression
MRS	magnetic resonance spectroscopy
PV	parvalbumin
PFC	prefrontal cortex
TRN	thalamic reticular nucleus

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Figure 1.

Schematic description of functional properties of the NMDA receptor. Features that distinguish NMDA receptors from other glutamate receptors, unique properties of subunits, and relevance to schizophrenia are presented.

Figure 2.

Evidence that hypo-NMDA states and GABA dysfunction contribute to the schizophrenia phenotype at multiple levels. Findings from schizophrenia patients are juxtaposed with studies in humans or rodents where NMDAR antagonism (green) or reduced GABA (red) is associated with the same finding. Orange lettering represents studies where NMDAR hypofunction on GABAergic interneurons mimics a schizophrenia state. Delta oscillations are 1-4 Hz and gamma oscillations are 30-100 Hz.