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GABAergic interneuron origin of schizophrenia pathophysiology

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Abstract

Hypofunction of N-methyl-D-aspartic acid-type glutamate receptors (NMDAR) induced by the systemic administration of NMDAR antagonists is well known to cause schizophrenia-like symptoms in otherwise healthy subjects. However, the brain areas or cell types responsible for the emergence of these symptoms following NMDAR hypofunction remain largely unknown. One possibility, the so-called "GABAergic origin hypothesis," is that NMDAR hypofunction at GABAergic interneurons, in particular, is sufficient for schizophrenia-like effects. In one attempt to address this issue, transgenic mice were generated in which NMDARs were selectively deleted from cortical and hippocampal GABAergic interneurons, a majority of which were parvalbumin (PV)-positive. This manipulation triggered a constellation of phenotypes—from molecular and physiological to behavioral—resembling characteristics of human schizophrenia. Based on these results, and in conjunction with previous literature, we argue that during development, NMDAR hypofunction at cortical, PV-positive, fast-spiking interneurons produces schizophrenia-like effects. This review summarizes the data demonstrating that in schizophrenia, GABAergic (particularly PV-positive) interneurons are disrupted. PV-positive interneurons, many of which display a fast-spiking firing pattern, are critical not only for tight temporal control of cortical inhibition but also for the generation of synchronous membrane-potential gamma-band oscillations. We therefore suggest that in schizophrenia the specific ability of fast-spiking interneurons to control and synchronize disparate cortical circuits is disrupted and that this disruption may underlie many of the schizophrenia symptoms. We further argue that the high vulnerability of corticolimbic fast-spiking interneurons to genetic predispositions and to early environmental insults—including excitotoxicity and oxidative stress—might help to explain their significant contribution to the development of schizophrenia.

Keywords

schizophrenia; fast-spiking interneuron; NMDA receptor hypofunction; parvalbumin; oxidative stress; transgenic mice

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1. Introduction

Cortical and hippocampal neural circuits comprise both excitatory neurons (the vast majority of which are pyramidal neurons) and several classes of GABAergic inhibitory interneurons (Kawaguchi and Kubota 1997, reviewed in Petilla Interneuron Nomenclature Group 2008). These GABAergic interneurons are often subdivided into distinct subtypes based on morphology (e.g., basket cells, chandelier cells), electrophysiology (e.g., fast-spiking, low-threshold spiking), synaptic connectivity (e.g., soma, distal dendrites), and gene expression (e.g., parvalbumin, somatostatin) (reviewed in Markram et al. 2004). Of these, the parvalbumin (PV)-containing interneurons, which innervate hundreds of pyramidal neurons mainly at the soma and proximal dendrites, control these neurons' output and synchrony (Williams et al. 1992, Cobb et al. 1995, Miles et al. 1996). Activation of PV-containing fast-spiking interneurons is known to be critical for the generation of the gamma-frequency oscillations (Cardin et al. 2009, Sohal et al. 2009) that may organize functional neural ensembles (reviewed in Bartos et al. 2007 & Mann and Paulsen 2007). On the other hand, somatostatin (SST)-expressing Martinotti cells are low-threshold spiking (LTS) interneurons that project extensively to distal dendrites' pyramidal cells and control dendritic excitability (de Lima and Morrison 1989; Kawaguchi and Kubota 1996), and calretinin-containing double-bouquet cells symmetrically synapse predominantly on the dendritic shafts of other GABA neurons and may act to disinhibit pyramidal neurons (Meskenaite 1997, Gonchar and Burkhalter 1999). GABAergic interneuron subtypes appear to support cortical circuit functions—including proper synaptic inhibition at somata and dendrites (reviewed in Huang 2009), network oscillations (reviewed in Bartos et al. 2007), and the balancing of excitation and inhibition (Shu et al. 2003).

In addition to their role in maintaining normal cortical function, GABAergic neurons play a fundamental role in the proper maturation of neural circuitry during postnatal development. Cortical GABAergic circuits are highly immature at birth and GABAergic inhibition develops in a protracted postnatal period (Micheva and Beaulieu 1996, Reynolds and Beasley 2001, Chattopadhyaya et al. 2004). Proper GABAergic inhibition during cortical maturation is essential for the refinement of cortical circuitry. For instance, during this protracted period of postnatal development, it is crucial to regulate the timing of external stimuli to develop ocular-dominance plasticity in the visual cortex (reviewed in Hensch 2005). In weeks 1-4, rodents' basket-cell axon arbors in the dentate gyrus of the hippocampus undergo marked maturation, which contributes to the enhanced coherence of gamma oscillation during this period (Doischer et al. 2008). This enhanced coherence may also be supported by the maturation of fast-spiking basket neurons' intrinsic excitability during this same period, characterized by a decrease in membrane resistance, a hyperpolarization of the resting-membrane potential, and an increase in the membrane-potential oscillation frequency towards the gamma range (Goldberg et al. 2010). In the primate prefrontal cortex, maturation of GABAergic innervation patterns often extends well into the post-adolescent period (Cruz et al. 2009, Hashimoto et al. 2009). It is therefore plausible that impaired maturation of GABAergic neurons could lead to neuropsychiatric disorders including schizophrenia.

We aim here to provide a general framework to explain PV-containing interneurons' involvement in the etiology of schizophrenia. Building upon past literature, we hope to confirm the link between NMDA hypofunction and interneuron theories of schizophrenia and to explain how dysfunctions in cortical-PV interneurons' ability to synchronize disparate neural networks can behaviorally manifest as schizophrenia symptoms. We will also highlight how these neurons are especially susceptible to early environmental insults known to contribute significantly to schizophrenia pathophysiology. Finally, it is important to note that while PV-positive interneurons are prevalent throughout the brain (including in the

thalamic reticular nuclei, also implicated in schizophrenia [Zhang et al. 2010]), this review is mainly focused on the function and effects of corticolimbic interneurons.

2. Dysfunction of cortical interneurons in schizophrenia

Converging experimental and clinical evidence suggests that dysfunction of proper GABAergic inhibition and the consequent imbalance between excitation and inhibition in the cerebral cortex underlies at least part of the pathophysiological process of several neuropsychiatric disorders (reviewed in Levitt et al. 2004), including epilepsy (reviewed in Cossart et al. 2005 & Maglóczky and Freund 2005), schizophrenia (reviewed in Benes and Berretta 2001 & Guidotti et al. 2005 & Lewis et al. 2005), mood disorders (reviewed in Brambilla et al. 2003 & Sanacora and Saricicek 2007), and autism spectrum disorders (reviewed in Rubenstein and Merzenich 2003 & Belmonte et al 2004). But while misspecification or dysfunction of specific subtypes of interneurons may account for a portion of the etiology of such disorders, the attribution of specific diseases to the abnormal function of cortical GABAergic neurons is far from established. Morphologically and neurochemically heterogeneous interneurons comprise a relatively small fraction of the total cells in the cortex and hippocampus. In seeking to shed light on which particular minor disturbances, in which interneuron subtypes, located in which brain areas, and occurring at which developmental time points contribute most to the selective malfunction that eventually triggers the pathophysiology of schizophrenia, we have chosen to focus on evidence for the dysregulation of cortical GABAergic neurons.

Schizophrenia is a complex psychiatric disorder with a strong genetic component that affects roughly ~1% of the world population (Sullivan et al. 2003). To date, the diagnosis of schizophrenia relies solely on the presentation of an array of clinical symptoms, which encompasses positive attributes (delusions, hallucinations, thought disorder), negative attributes (anhedonia, blunted affect, social withdrawal), and cognitive deficits (in attention, executive function, and working memory). While schizophrenia has been shown to have a prominent genetic component, no single gene has been found to exert a strong effect. It rather appears that the disorder emerges through the interaction of genetic, developmental, and environmental factors. Genetic mutations, epigenetic changes, and other cellular deficits have all been shown to disturb given brain circuits and—singly or together—may result in similar clinical manifestations.

In the realm of neurotransmitters alone, the evidence points to abnormalities in glutamate, GABA, dopamine, and acetylcholine pathways. The theory that dysfunction of GABAergic transmission is related to the symptoms of schizophrenia arose from early findings that in schizophrenia patients, both the concentration of cortical GABA (Perry et al. 1979) and the activity of the rate-limiting synthetic enzyme glutamic-acid-decarboxylase (GAD) (Bird 1985) are reduced. These observations were confirmed and extended in subsequent studies showing alteration in several presynaptic and postsynaptic components of the GABAergic systems. In particular, a number of studies consistently found reduced GAD67 levels in the postmortem brain tissue of patients with schizophrenia (reviewed in Akbarian and Huang 2006 & Gonzalez-Burgos et al. 2010).

GABAergic neurons express two homologous forms of GAD, with protein sizes of 67 and 65 kDa, each encoded by a different gene—Gad1 (for GAD67) and Gad2 (for GAD65). It is estimated that in the mouse brain, GAD67 accounts for up to 80–90% of overall GABA levels (Asada et al. 1997, Condie et al. 1997). Genetic studies show that a single-nucleotide-polymorphism (SNP) in the 5′ untranslated region of Gad1 is associated with decreased expression of Gad1 mRNA in the prefrontal cortex (PFC) of the schizophrenic brain (Straub et al. 2007). Reductions of several other interneuron proteins—including PV, SST, Reelin,

and GABA transporter-I—are also reported in schizophrenic brains (Guidotti et al. 2000, reviewed in Lewis and Gonzalez-Burgos 2006).

Importantly, these GABAergic deficits do not affect all interneuron subtypes equally (Benes et al. 1991). Reduced expression of GAD67-mRNA in the dorsolateral PFC is perhaps the most widely and consistently replicated pathological disturbance in schizophrenia (reviewed in Akbarian and Huang 2006, Gonzalez-Burgos et al. 2010). A microarray study using postmortem dorsolateral PFC tissues of subjects with schizophrenia detected significant expression deficits of GABA-neuron-related-mRNAs, including mRNAs of the neuropeptides somatostatin, neuropeptide Y, and cholecystokinin (Hashimoto et al. 2008). This finding suggests that in schizophrenia, a variety of interneuron cell-types is affected. The question remains: Why does a deficit in cortical PV interneurons appear to be critical for schizophrenia pathophysiology?

3. Fast-spiking PV-interneurons are critical for generating synchronous gamma oscillations

Accumulating evidence implicates disturbances in gamma-frequency neuronal synchrony as a major physiological feature of schizophrenia (reviewed in Uhlhaas and Singer 2010). Importantly, inhibition from PV-containing basket cells projecting to the perisomatic regions of excitatory neurons is essential for the synchronization of neural activity (Bartos et al. 2007, Mann and Paulsen 2007). The exact mechanisms for gamma-frequency oscillations involving PV neurons, however, are still unclear. Two theories have been proposed as to the principal mechanisms underlying gamma oscillations: (1) feedback loops from principal neurons onto PV neurons, and (2) oscillations in mutual PV neuronal networks via chemical or electrical transmission. Because gamma power is diminished when excitatory drive onto PV neurons is selectively reduced, the former circuitry model appears to be the more dominant (Fuchs et al. 2007)—although not when synaptic inhibition in PV neurons is ablated (Wulff et al. 2009).

Regardless of the exact generation mechanisms, PV-positive basket cell involvement appears to be critical for the generation of synchronous gamma oscillations. Their unique, fast-spiking, action-potential phenotype is precisely phase-locked to gamma oscillation (Jonas et al. 2004), and regardless of the stimulation frequency, their sub-threshold membrane-potential oscillations showed resonance at the gamma frequency (Pike et al. 2000). Recent optogenetic studies of virally engineered PV neurons, moreover, have shown that light-driven activation of fast-spiking interneurons selectively amplifies gamma oscillations (Cardin et al. 2009, Sohal et al. 2009).

Several inherent properties of fast-spiking basket cells contribute to the synchronous oscillation of postsynaptic membrane potentials (Goldberg et al. 2010). (1) They depolarize and repolarize rapidly and accurately, which allows them to fire at high frequency (Hu et al. 2010). (2) They release GABA efficiently, fast, and with precision (Bucurenciu et al. 2008). (3) They can depolarize membranes through the gap junctions among PV neurons, thereby amplifying the magnitude of the gamma oscillation within the PV-interneuronal network (Hormuzdi et al. 2001). Taken together, these properties synergistically narrow the time window for temporal summation of the membrane potentials in postsynaptic principal neurons, which appears to contribute to the generation of high frequency, synchronous, membrane-potential oscillations (Bartos et al. 2007). Fast-spiking (mostly PV-positive) interneurons therefore seem to play a central role in generating synchronous gamma oscillations.

Cortical PV-positive interneurons, which often display fast-spiking patterns (but see Blatow et al. 2003), are classified into at least two distinct morphological subtypes: cortical *basket cells*, which innervate perisomatic areas of principal neurons and other PV-positive basket cells, and *axo-axonic cells* (or chandelier neurons), a minor population of cortical cells that project onto the axon-initial segment (AIS) of pyramidal cells. In schizophrenia, both types of PV interneurons appear to be impaired, with dysfunctions that include reduced expression of PV, Gad1, and the GABA transporter (GAT)-1 mRNAs (Lewis and Gonzalez-Burgos 2008) and a decrease in the number of GAT-1 immuno-reactive cartridges in axo-axonic cell terminals, suggesting decreased GABA-release by axo-axonic cells (Woo et al. 1998). Because PV-containing basket cells project to the perisomatic area (controlling the output and synchrony of pyramidal neurons, as mentioned above), deficits in basket cells should lead to impaired cortical inhibition and the disruption of synchronized firing.

Indeed, reduction in cortical inhibitory tone (Daskalakis et al. 2007) and impaired synchronized activity (Kwon et al. 1999, Spencer et al. 2004) has been reported in the brains of schizophrenia patients. Furthermore, converging evidence suggests that, measured by EEG, the synchronized oscillatory activity, in particular in the gamma range is abnormal in schizophrenia patients (Ferrarelli et al. 2008). Recently, the activity of PV-positive interneurons was shown to be causally related to the generation of gamma oscillations in mice in vivo (Cardin et al. 2009, Sohal et al. 2009). Although clearly important, the transmission mode and function of axo-axonic cells remains to be clarified. Whereas the axo-axonic cells in the hippocampus hyperpolarize the pyramidal neurons (Glickfeld et al. 2009), for instance, recent reports suggest that in the rodent cortex, axo-axonic cells depolarize the AIS (Szabadics et al. 2006, Khirug et al. 2008, Woodruff et al. 2009) in contrast to cortical basket cells, which clearly contribute to GABAergic inhibition (or shunting) and to the generation of synchronous oscillatory activity.

While PV-containing interneurons are fundamental for generating normal synchronous activity and appear to be impaired in schizophrenia, it remains to be seen whether or not impairments in interneuron networks are a primary cause of schizophrenia or a secondary effect arising from alterations in other neurotransmitter systems.

4. Cortical interneurons and the ‘NMDAR hypofunction theory’ of schizophrenia

In schizophrenia research, the hypothesis that NMDAR hypofunction is the chief mechanism behind the disease's pathophysiology has gained considerable support. The discovery that the psychotomimetic drug phencyclidine (PCP) acts as a non-competitive antagonist of NMDA-receptors (Lodge and Anis 1982) helped establish the glutamatergic hypothesis of schizophrenia (see reviews by Javitt 1987, Deutsch et al. 1989, Olney and Farber 1995, Coyle 1996, Tamminga 1998). At low doses in normal volunteers, other non-competitive NMDAR antagonists (such as ketamine and MK-801) were also found to induce a range of schizophrenia symptoms, both positive and negative, including the disease's characteristic cognitive deficits (Krystal et al. 1994, Lahti et al. 1995b). In stabilized schizophrenia patients, moreover, NMDAR antagonists have been shown to reinstate pre-existing symptoms (Lahti et al. 1995b).

Genetic studies provide further evidence of NMDAR hypofunction's association with schizophrenia. For instance, an NR1 hypomorph mouse, in which expression of the NR1 (Grin1) subunit protein of NMDARs is reduced to 5-10%, displays deficits in social interaction and impairment in prepulse inhibition (PPI) of the acoustic startle reflex (Mohn et al. 1999, Duncan et al. 2004). The results obtained after the global genetic manipulations support the notion of a NMDAR malfunction involved in the pathophysiology of

schizophrenia. Since the global manipulation of NMDAR subunits often disturbs primary sensory or motor functions, however, it cannot be used to elucidate the mechanisms underlying abnormal behaviors (Belforte and Nakazawa 2011). Fundamental questions regarding NMDAR's role in the pathophysiology of schizophrenia that cannot be addressed using conventional global manipulations include: In which brain areas would an NDMAR deficit lead to behavioral symptoms? Do all cell types contribute equally to the development of the disorder? Are developmental changes involved?

The possibility that cortical GABAergic interneurons are a prime target for NMDAR hypofunction (Olney and Farber 1995) is supported by three different lines of evidence. First, acute systemic administration of NMDAR antagonists results in hyperactivity of cortical pyramidal neurons (Suzuki et al. 2002, Jackson et al. 2004) and spillover of cortical glutamate (Moghaddam et al. 1997, Lorrain et al. 2003). These paradoxical cellular changes concur with brain imaging data showing net cortical excitation after NMDAR-antagonist treatment in human subjects (Lahti et al. 1995a, Breier et al. 1997, Vollenweider et al. 1997) and in rodent brains (Duncan et al. 1998, Miyamoto et al. 2000, Väisänen et al. 2004). Second, whereas the results in the cortex have been inconsistent (Li et al. 2002, Hull et al. 2009), hippocampal GABAergic interneurons are disproportionally more sensitive to NMDAR antagonists than pyramidal neurons (Ling and Benardo 1995, Grunze et al. 1996). Thus, excitation induced by NMDAR antagonists may be due to a preferential reduction in the firing of fast-spiking interneurons, resulting in the disinhibition of excitatory neurons (Homayoun and Moghaddam 2007). Third, repeated administration of NMDAR antagonists decreases the expression of GAD67 and PV in cortical GABAergic neurons (Cochran et al. 2003, Keilhoff et al. 2004, Rujescu et al. 2006, Behrens et al. 2007, Morrow et al. 2007), linking NMDAR hypofunction to dysfunction of GABAergic neurons.

5. Postnatal NMDAR ablation in corticolimbic interneurons confers schizophrenia-like phenotypes

To test the theory that corticolimbic NMDAR hypofunction in GABAergic interneurons produces elements of schizophrenia pathophysiology, Belforte et al. (2010) created a conditional knockout mouse strain in which the NR1 subunit was selectively ablated in approximately half of cortical and hippocampal GABAergic neurons, a majority of which contain PV. Using the newly generated Cre line, Ppp1r2 (Protein phosphatase 1, regulatory subunit 2)-Cre, the NR1 subunit was successfully ablated in 40-50% of cortical and hippocampal interneurons, predominantly PV-positive ones, in early postnatal development. This result was confirmed by double *in situ* hybridization histochemistry and patch-clamp recordings of NMDA-mediated currents. Consistent with the theory of interneuron-based NMDAR hypofunction (Olney and Farber 1995), distinct schizophrenia-like symptoms emerged in mutants after adolescence (Table). Symptoms included novelty-induced hyper-locomotion (possibly reflecting psychomotor agitation), a reduced preference for sweet solution (suggestive of anhedonia), deficits in nesting and mating (suggestive of social withdrawal), and deficits in spatial working and short-term social memory (cognitive impairments). Taken together, these deficits are reminiscent of the positive, negative, and cognitive symptoms of human schizophrenia. Mutants also showed impaired sensorimotor gating, as assessed by the PPI of the startle reflex. In addition, as in the stress-precipitation of psychotic states in schizophrenia, social isolation stress exacerbated mutants' deficits in social nest-building, anxiety-like behaviors, and anhedonia-like behaviors. Furthermore, the phenotypes of disrupted nest-building and mating and the anhedonic and anxiety-like behaviors were most prominent after 12 weeks of age, suggesting the existence of a latent period before their emergence. The fact that deficits in mutants' spatial working memory and PPI were ameliorated by the antipsychotic risperidone, moreover, confers some degree of predictive validity to the model. Also consistent with schizophrenia post-mortem brain

pathology, the mutant mice exhibited reduced GAD67 and PV levels in the NR1-deleted cortical GABAergic neurons.

By contrast, post-adolescent deletion of NR1 subunit in the same interneuron population did not result in schizophrenia-like abnormalities, demonstrating NMDARs' fundamental role during the early postnatal stages with regard to the development of schizophrenia-like phenotypes in later adulthood (Belforte et al., 2010). Recently, PV neuron-specific NR1 deletion mutant mice were shown to be impaired in spatial working memory as well as in atropine-resistant theta oscillations (Korotkova et al. 2010). In this mutant line, however, the NR1-deletion appeared after the third postnatal week and these mice did not show abnormal social behavior. This result appears once again (albeit speculatively) to confirm the critical postnatal period in which NR1 deletion can result in the development of schizophrenia-like phenotypes.

In summary, the postnatal NR1 mutant model created by Belforte et al. (2010) not only reproduces positive, negative, and cognitive aspects of schizophrenia but also mirrors three additional characteristics of human schizophrenia: stress-dependent precipitation of symptoms, a latency period before the development of symptoms, and a critical period for disease acquisition. It also exhibits non-behavioral features (such as decreases in GAD67 and PV) compatible with schizophrenia, increasing the face validity of the model. It is striking that Ppp1r2-Cre/NR1 KO mutants with selective genetic NMDAR deletion from cortical and hippocampal interneurons developed a constellation of phenotypes—molecular, physiological, and behavioral—resembling many of the characteristics of human schizophrenia (Figure 1). These results suggest that in schizophrenia, NMDAR hypofunction in the cortical GABAergic interneurons is one of the major “shared” pathophysiological pathways originating from malnutrition, infection, obstetric complications during development, and a variety of other possible etiological factors.

6. Is a corticolimbic interneuron origin probable given that schizophrenia is in part a genetic disease?

As suggested by the above animal model, an obvious question is whether the pathological changes seen in human schizophrenia originate primarily from cortical GABAergic interneurons. Given that schizophrenia is in part a genetic disease, it is unlikely that genetic predispositions of schizophrenia are manifested solely in corticolimbic GABAergic neurons. Indeed, reduced spine density and dendritic morphology of cortical glutamatergic excitatory neurons is one of the most consistent findings of schizophrenia postmortem brain tissue pathology (Garey et al. 1998, Glantz and Lewis 2000, Kalus et al. 2000). This does not however rule out the possibility that schizophrenia originates in GABAergic neurons. Many genetic predispositions and environmental insults can induce an early pathology and impair normal development over time, which may then be manifested behaviorally at a much later date. Cortical GABAergic neurons (especially PV neurons), which have a protracted development period, seem to be especially vulnerable to this type of developmental disruption.

Because disruption in cortical (including PV-containing) interneurons is associated with many different mental illnesses—including major depressive and bipolar disorders (Benes and Berretta 2001, Torrey et al. 2005) and autism spectrum disorders (Selby et al. 2007, Gibson et al. 2008, Gogolia et al. 2009), this feature alone is insufficient to explain specificity to schizophrenia. We suggest that in schizophrenia, the ability of fast-spiking (mostly PV-containing) interneurons to control and synchronize the disparate neural circuits that support higher order cognition (including working memory) is uniquely disrupted. We

further suggest that this specific type of disruption is triggered by NMDAR hypofunction in fast-spiking neurons.

7. Corticolimbic PV neuronal dysfunction manifests as diverse symptoms of schizophrenia

While schizophrenia is characterized by episodic positive symptoms and persistent and progressive negative symptoms, it is the cognitive symptoms which are the disease's core feature. Indeed, almost all (>98%) patients assessed to have deficits in verbal memory, working memory, processing speed, attention, reasoning, and problem-solving are impaired overall (Keefe et al. 2005). For this reason, substantial research has focused on the mechanisms of working memory, typically defined as the ability to hold the information needed to do complex cognitive tasks (such as reasoning, comprehension, and learning) actively in the mind.

Seeking the mechanisms underlying impaired working memory and recognizing that normal function depends on the correlated activity of principal cortical neurons, schizophrenia researchers have largely focused on the abnormal synchronized oscillatory activity of cortical neurons in the dorsolateral PFC (reviewed in Salinas and Sejnowski 2001) and concomitant local-field potential (LFP) synchronization, particularly in the gamma-frequency range (reviewed in Fries 2009). Since the ability of PV-containing fast-spiking interneurons to drive synchronous oscillatory activity at gamma frequency is being acknowledged as a cellular basis for cognitive and executive brain function, it is clear that dysfunction in PV interneurons could induce cognitive symptoms. Less clear is whether the special properties of fast-spiking interneurons are also associated with other schizophrenia symptoms, especially the positive ones.

The emergence of psychosis, a characteristic of the positive symptoms, is known to be linked to hyper-dopaminergic neurotransmission in the ventral striatum (Laruelle et al. 1996, Breier et al. 1997). In experiments with rats, excess dopamine in the striatum (including nucleus accumbens) is induced mainly by causing aberrant activity in either the medial PFC or ventral subiculum. Local infusion of the NMDAR antagonist CPP into the rat medial PFC, for instance, increases the release of dopamine in the nucleus accumbens and also increases motor activity (Del Arco et al. 2008), which appears to be mediated by cortical disinhibition (Del Arco et al. 2010). On the other hand, ventral subicular stimulation increases the activity of ventral tegmental area (VTA) dopamine neurons and the release of dopamine in the accumbens (Lodge and Grace 2007), which appears to be mediated by dysregulation of PV-containing neurons (Lodge and Grace 2010).

The mechanisms underlying aberrant activity in the PFC or subiculum that lead to excess dopamine in the accumbens are highly debatable. One prominent possibility is that a deficit in intrinsic GABAergic signaling elicits the aberrant activity while somehow decreasing cortical or hippocampal output tone. This in turn would disinhibit VTA dopaminergic neuronal activity and increase dopamine release in the accumbens. The prediction of augmented dopaminergic tone following reduction in cortical output is based on Carr and Sesack's neurotracing study. This study demonstrated that the PFC axon terminals synapse selectively on the mesocortical dopaminergic neurons and on the mesoaccumbens GABAergic interneurons. This could result in feed forward inhibition of mesoaccumbens dopaminergic neurons within the VTA (Carr and Sesack 2000). It would follow then that reductions in PFC output could disinhibit the VTA and increase accumbens dopamine. It is also plausible that the dopaminergic tone increase is mediated by an impaired feed-forward inhibition via nucleus accumbens.

How, then, could dysregulation of PV-containing fast-spiking neurons decrease cortical or hippocampal output, while apparently disinhibiting aberrant activity? It is possible that this functional reduction in cortical output could be due to the desynchronized activity of principal neurons attributed to GABAergic dysfunction (Belforte et al. 2010). This cortical desychronization could disinhibit mesoaccumbens activity (Figure 2). We recently tested this hypothesis by administering the psychostimulant methamphetamine to Ppp1r2-Cre/NR1 mutant mice and found them exceptionally susceptible to methamphetamine-induced hyperlocomotion (unpublished). This finding suggests that cortical GABAergic dysfunction alone is sufficient to cause a functional reduction in cortical output, thereby inducing a subcortical hyper-dopaminergic state. Note that impaired axo-axonic cells, which can excite principal neurons directly, might also contribute to the reduction in cortical output. In any case, since these putative mechanisms for cortical—subcortical dysregulation in schizophrenia, future studies are clearly warranted.

8. The vulnerability of cortical interneurons in schizophrenia pathophysiology

Is there any evidence that cortical PV-interneurons are especially vulnerable to an initial or earlier pathology? Supporting literature is sparse, in part because it is difficult to obtain schizophrenia postmortem brain tissue during the premorbid stage. In addition, the limits of current brain imaging technology make it difficult to pinpoint metabolic or molecular changes with single-cell resolution. Circumstantial evidence, however, appears to support the contention.

The vulnerability of cortical interneurons in schizophrenia is suggested by patients' reduced cortical inhibition (Daskalakis et al. 2002, Eichhammer et al. 2004, Wobrock et al. 2008). Clinically, cortical inhibition is assessed by paired-pulse transcranial magnetic stimulation (TMS). TMS involves stimulating with a lower-intensity pulse a few milliseconds before a higher-intensity pulse, thereby inhibiting the size of the evoked potential in the motor cortex produced by the higher-intensity pulse. Importantly, this short-interval cortical inhibition is a function of GABAergic inhibition, because $GABA_A$ agonists enhance cortical inhibition (reviewed in Ziemann 2004). As measured by TMS, therefore, the origin of reduced cortical inhibition in schizophrenia is likely to be an impaired function of GABAergic interneurons. Recently, similar evidence has also been obtained by functional MRI.

Recent fMRI imaging studies of baseline functional connectivity during periods of “rest” have found activation and increased functional connectivity in the “default mode network” (DMN), which includes the ventromedial prefrontal cortex and regions of the parietal and cingulate cortex (Raichle et al. 2001). Conversely, during tasks that require goal-directed behavior (such as working memory tasks), there is a suppression of DMN activity. In healthy subjects, the degree to which DMN activity is inhibited is correlated with performance (Kelly et al. 2008). Interestingly, schizophrenia patients, as well as their first-degree relatives, show a lack of the normal suppression and hyperconnectivity of DMN activity during working memory tasks (Whitfield-Gabrieli et al. 2009), again suggesting a genetic predisposition for impaired cortical inhibition in schizophrenia.

Other evidence that schizophrenia pathophysiology might originate in the interneurons comes from accumulated data suggesting that NMDAR hypofunction occurs more robustly in interneurons than in pyramidal neurons. This is particularly significant in light of the theory that schizophrenia symptoms reflect NMDAR hypofuction. In one elegant study, systemic *in vivo* injection of MK-801 preparations demonstrated that in awake rats, prefrontal cortex interneurons and pyramidal neurons showed opposite responses (Homayoun and Moghaddam 2007). A one-shot administration of MK-801 initially

decreased the firing rates of putative fast-spiking interneurons. Then, with a significant delay of minutes, it increased the firing of the majority (over 80%) of surrounding pyramidal neurons. These results suggest that systemic NMDAR blockade causes overall cortical excitation by disinhibiting pyramidal neurons.

While the precise mechanisms for this differential sensitivity are still unknown, several potential explanations have been proposed (Greene 2001, Homayoun and Moghaddam 2007). Of particular relevance here is the difference between interneurons and pyramidal cells in the composition of their NMDAR subunits. At a physiological concentration of Mg^{2+}_{o}, memantine (non-competitive NMDAR antagonist) and ketamine have been reported to block NR1/2C and NR1/2D preferentially (Kotermanski and Johnson 2009). Importantly, in cortical and hippocampal non-pyramidal neurons, NR1/2C (Monyer et al. 1994, Xi et al. 2009) and NR1/2D (Monyer et al. 1994) are known to be major subunits of NMDARs. Non-competitive NMDAR antagonists may therefore manifest stronger potency to “interneuron-type” NMDARs, which could account for cortical disinhibition by NMDAR antagonists.

From the physiological standpoint, moreover, NMDARs in cortical interneurons appear to participate in their basal synaptic transmission (Jones and Bühl 1993, Goldberg et al. 2003). It is therefore plausible that NMDAR hypofunction in interneurons may result in decreased action-potential firing, reducing recurrent IPSP and causing disinhibition (Greene 2001). On the other hand, in the prefrontal cortex, NMDARs' pyramidal neurons appear to be required for the generation of sustained bursting (Shi and Zhang 2003, Gao and Goldman-Rakic 2006, Polsky et al. 2009). Although NMDAR antagonists suppress pyramidal neuron's burst firing (Shi and Zhang 2003, Polsky et al. 2009), they appear to have a minimal effect on the generation of simple spikes.

Despite these findings, however, it remains unclear which cortical interneuron cell-types are most sensitive to NMDAR antagonists and therefore produce cortical disinhibition, especially during adulthood. As animals mature, the majority of cortical PV neurons lose their synaptic NMDAR component (Wang and Gao 2009 2010, Rotaru et al. 2011). Even before adolescence, fast-spiking neurons sometimes produce NMDAR-independent disynaptic IPSPs (Hull et al. 2009, Pouille et al. 2009). Another factor is that, since a single interneuron projects to hundreds of pyramidal neurons (Cobb et al. 1995), NMDAR hypofunction of a single interneuron could disinhibit the firing of a large number of cortical pyramidal neurons and thereby exceed the impact of an NMDAR blockade of individual pyramidal neurons (Homayoun and Moghaddam 2007).

9. Cortical disinhibition preferentially affects cortical PV-positive interneurons

There is converging evidence that the GABAergic deficits discovered in schizophrenia postmortem brains did not affect all classes of cortical interneurons equally (Benes et al. 1991, reviewed in Lewis and Gonzalez-Burgos 2008). These differences suggest the existence of cell-type specific mechanisms for interneuron vulnerability. Notably, in individuals with schizophrenia the immunoreactivity (IR) of Ca^{2+}-binding protein calretinin (an interneuron cell-type marker that covers approximately 50% of cortical GABAergic interneurons) is unaffected. Conversely, postmortem studies of schizophrenic brains consistently find deficits of cortical PV-positive interneurons.

In animal pharmacological models of schizophrenia, the acute systemic administration of NMDAR antagonists (including PCP, ketamine, and MK-801) is known to produce deficits specific to different interneuron cell-types. Postnatal PCP administration in rats selectively reduces PV-positivity in the cortex, whereas no densitometric changes in calretinin- or

calbindin-positive interneurons have been observed in any brain areas (Wang et al. 2008). This heightened sensitivity of PV-containing neurons to NMDAR antagonists compared to the non-PV interneurons has been consistently reported across animals and the timing and dose of administration (Bubeníková-Valesová et al. 2008) and in cell cultures of interneurons (Kinney et al. 2006).

At higher doses of NMDAR antagonists, pyramidal neurons as well as interneurons display a significant vulnerability to the excitotoxic action of NMDAR antagonists (Ikonomidou et al. 1999). In fact, early postnatal administration of MK-801 (1 mg/kg) causes apoptotic cell death in ~50% of PV-positive interneurons and also in ~42% of pyramidal neurons (Coleman et al. 2009). By contrast at lower doses, NMDAR antagonists that elicit cortical disinhibition may elicit glutamate-mediated toxicity in PV neurons that is reversible. Ischemia-induced glutamate toxicity, for instance, has been reported to impair primarily the excitability and GABAergic transmission of interneurons but not pyramidal neurons (Wang 2003).

In another pharmacological animal model of schizophrenia—the methylazoxymethanol acetate (MAM) G17 model—the mitotoxin MAM is injected into pregnant rats on gestational day 17 disrupt development of the ventral hippocampus. This model also shows a loss of PV-containing interneurons, leading to diminished oscillatory activity (Lodge et al. 2009).

Why are cortical PV-positive neurons so vulnerable to cortical disinhibition and to excitotoxicity? One major factor could be oxidative stress. Due to their high frequency firing property, PV-positive fast-spiking neurons function at a high metabolic cost and with concomitant reduced efficiency (Gulyás et al. 2006, Carter and Bean 2009). Compared to other cell-types, therefore, mitochondria in the fast-spiking neurons produce much more abundant reactive oxygen species (ROS) and ATP. Under normal conditions, actual ROS produced in PV neurons appears to be limited by the neurons' potent anti-oxidation mechanism. PV neurons, for instance, highly express PGC-1α (peroxisome proliferator-activated receptor γ coactivator-1α, [Lucas et al. 2010]), which is a master regulator of mitochondria energy metabolism and anti-oxidation (Lin et al. 2005). PGC-1α in concert with other proteins is known to increase the expression of ROS-detoxifying enzymes (St-Pierre et al. 2006). When this anti-oxidation system fails to function, dysfunction is caused in fast-spiking neurons. Indeed, upon transient deficit in anti-oxidant glutathione with dopamine-induced oxidative stress condition in early postnatal development, specific reduction of PV-IR, but not calbindin-IR nor calretinin-IR, was evident in rat anterior cingulated cortex (Cabungcal et al. 2006).

Interestingly, oxidative stress or impaired redox regulation has been suggested as a pathophysiological (Mahadik and Mukherjee 1996,, Prabakaran et al. 2004) or even an etiological factor in schizophrenia (reviewed in Do et al. 2009). Oxidative stress is also implicated in a pharmacological model of the NMDAR-hypofunction theory for schizophrenia. Repetitive ketamine exposure has been shown to activate the superoxide-producing enzyme NADPH oxidase (Nox2), leading to a robust decrease in the expression of GAD67 and PV— but not of other interneuron calcium-binding proteins (Behrens et al. 2007). This increase in Nox2, and subsequent decrease in GAD67, ultimately leads to decreased inhibitory activity in the prefrontal cortex (Zhang et al. 2008).

Other mechanisms in and attributes of PV neurons could synergistically contribute to the susceptibility of PV-positive fast-spiking neurons against excitotoxicity. For instance, abundant expression of Ca^{2+}-permeable AMPA receptors in PV neurons may be responsible for their selective susceptibility to excitotoxicity (McBain and Dingledine 1993, Koh et al.

1995, Moga et al. 2002, Goldberg et al. 2003, Wang and Gao 2010). Activation of Ca^{2+}-permeable AMPA receptors by disinhibited glutamatergic afferents may elicit excess amount of Ca^{2+} influx, thereby leading to the exacerbation of hypofunction of PV neurons and cortical disinhibition. In schizophrenia pathophysiology, however, the involvement of Ca^{2+}-permeable AMPA receptors following cortical disinhibition has yet to be determined. The unique micro-circuitry of PV neurons may also make them more vulnerable. In the hippocampus, for instance, PV neurons receive more glutamatergic input than other interneuron cell types (Gulyás et al. 1999). In the rat cortex, moreover, the number of perisomatic excitatory inputs to PV neurons is also exceptionally higher than to any other cell types (Y. Kubota, personal communication), putting PV neurons at potentially greater risk from excitotoxic insults.

10. The role of NMDAR hypofunction in PV neuron dysfunctions

The three main hypotheses of schizophrenia etiology – the dopamine hypothesis (Klawans et al. 1972, Snyder 1972, Meltzer and Stahl 1976, Davis et al. 1991), the NMDAR hypofunction (Javitt 1987, Deutsch et al. 1989, Coyle 1996, Tamminga 1998) hypothesis and the GABAergic origin hypothesis (Benes and Berretta 2001, Guidotti et al. 2005, Lewis et al. 2005) – have traditionally been viewed as separate and rarely merged into a single theory. One notable exception is the proposal by Olney and Farber's (1995) persuasive hypothesis that NMDAR hypofunction at cortical interneurons synapses could account for cortical excitotoxicity following systemic NMDAR antagonist treatment. The present review extends this argument by demonstrating how selective dysfunction of corticolimbic PV-positive interneurons could account for the varied pathophysiological alterations characteristic of schizophrenia— including impaired synchronized gamma oscillations. We further suggest that the increases in subcortical dopamine (the basis for the dopamine hypothesis of schizophrenia) could arise as a function of cortical GABAergic dysfunction. In particular, we argue that specific deficits in cortical synchronization following impaired development of cortical PV-containing fast-spiking interneuron networks could manifest behaviorally as the symptoms of schizophrenia. Evidence of minimal synaptic expression of NMDARs in matured PV neurons (Wang and Gao 2009 2010, Rotaru et al. 2011), as well as almost no schizophrenia-like findings in mice following post-adolescent NMDAR deletion (Belforte et al, 2010), are also consistent with the neurodevelopmental theory of schizophrenia (Weinberger 1987).

Based on the evidence presented in this review, the authors suggest two major directions for future research. In order to explain the mechanisms underlying impaired synchronized activity and gamma oscillations, researchers need to delineate the cellular and molecular consequences of NMDAR hypofunction in fast-spiking neurons. It is equally necessary to uncover the cellular and molecular pathways responsible for reduced NMDAR function in those fast-spiking interneurons where there is currently little human evidence of genetic mutations or epigenetic alterations to explain NMDAR hypofunction (Nestler and Hyman 2010). It is hoped that new insights into the pathogenesis of schizophrenia as a function of dysfunction in the fast-spiking cortical GABAergic interneurons will one day lead to a unified understanding of the disease and to the development of novel treatment—targeted to specific cellular pathways—for this devastating psychiatric disease.

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Abbreviations

AIS	axon-initial segment
DMN	default mode network
GAD	glutamic acid decarboxylase
IR	immunoreactivity
NMDAR	NMDA receptor
PCP	phencyclidine
PFC	prefrontal cortex
PPI	prepulse inhibition
PV	parvalbumin
ROS	reactive oxygen species
SST	somatostatin
TMS	transcranial magnetic stimulation
VTA	ventral tegmental area

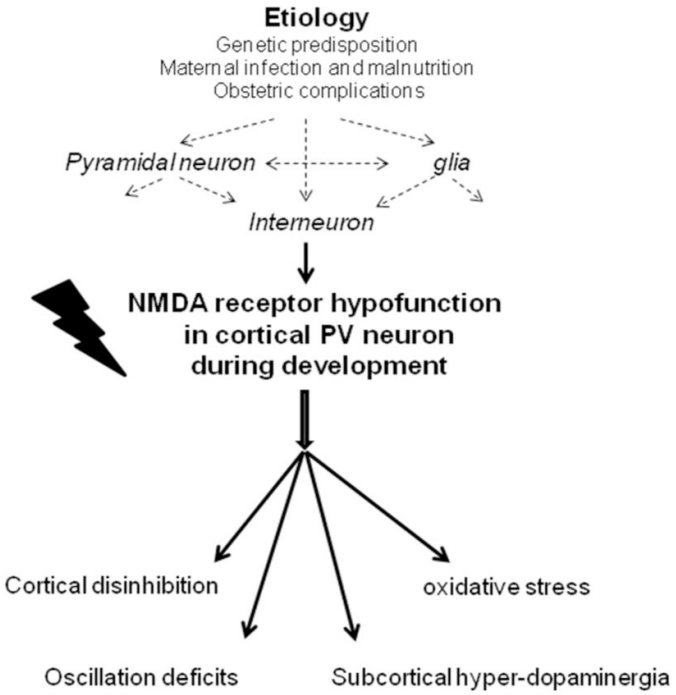

Figure 1. The GABAergic neuronal dysfunction hypothesis of schizophrenia pathophysiology

According to this hypothesis, precipitating factors may include any combination of genetic disposition, maternal infection or malnutrition, and obstetric complications. When these insults lead to NMDAR hypofunction of cortical interneurons, especially parvalbumin (PV)-containing fast-spiking neurons, during development, pathophysiological phenotypes (cortical disinhibition, impaired oscillatory activity, dopaminergic dysregulation, and oxidative stress) may arise, precipitating the emergence of major schizophrenia-like symptoms after adolescence.

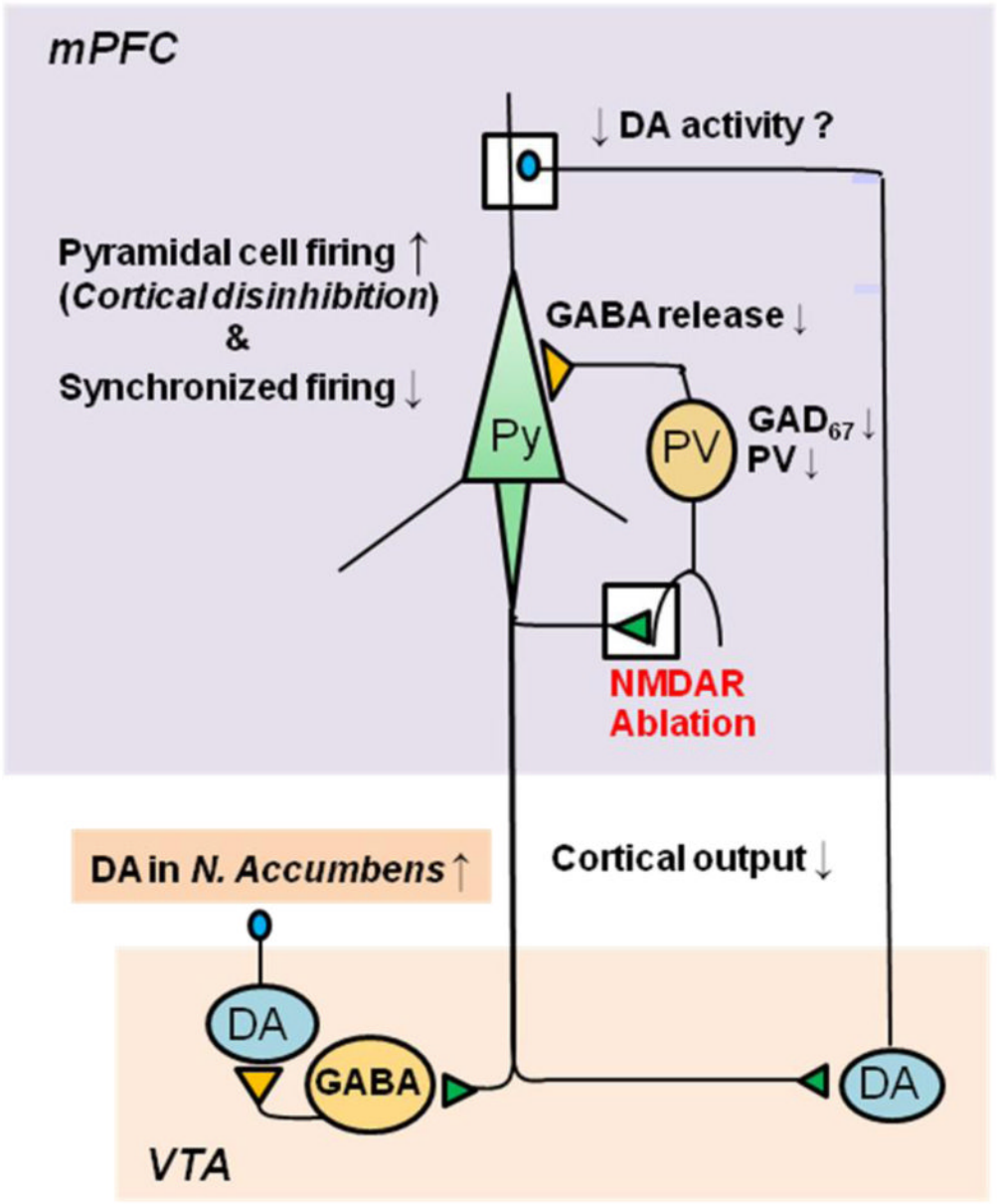

Figure 2. Mechanism by which NMDAR deletion in cortical parvalbumin (PV) neurons could alter cortical activity, leading to the emergence of subcortical dopamine hyperactivity in mice

NMDAR deletion in cortical PV neurons down-regulates their GABA synthesis and release, which not only results in cortical disinhibition but also impairs the synchronized activity of principal neurons. This may reduce the cortical output to VTA and thereby increases dopamine activity in the nucleus accumbens.

DA = dopamine, mPFC = medial prefrontal cortex, VTA = ventral tegmental area. Diagram is modified from Lewis and Gonzalez-Burgos 2006.

Table 1
Schizophrenia-related behaviors of *Ppp1r2*-Cre/NR1 KO mouse mutants

Behavioral phenotype observed	Onset of symptom	Effect of social isolation
Novelty-induced hyperlocomotion	N/D	
Nest building impairment	After 12 week old	Exacerbated
Mating deficit	After 12 week old	
Impaired saccharine preference test	N/D	Exacerbated
Deficit in spontaneous Y maze alternation	N/D	
Deficit in social short-term memory	N/D	
Deficit in prepulse inhibition (PPI)	N/D	No effect
Anxiety-like behaviors	After adolescence	Exacerbated

N/D: Not determined.