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Synapse-specific contributions in the cortical pathology of schizophrenia

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Abstract

Schizophrenia (SZ) is often described as a disease of neuronal connectivity. Cognitive processes such as working memory, which are particularly dependent on the proper functioning of complex cortical circuitry, are disturbed in the disease. Reciprocal connections between pyramidal neurons and interneurons, as well as dopaminergic innervations, form the basis for higher cognition in the cortex. Nonetheless, only a few review articles are available which address how each synapse operates, and is possibly disturbed in SZ, at least in part by mechanisms involving genetic susceptibility factors for SZ. In this review, we provide an overview of cortical glutamatergic, GABAergic, and dopaminergic circuitry, review SZ-associated deficits at each of these synapses, and discuss how genetic factors for SZ may contribute to SZ-related phenotypes deficits in a synapse-specific manner. Pinpointing the spatially and temporally distinct sites of action of putative SZ susceptibility factors may help us better understand the pathological mechanisms of SZ, especially those associated with synaptic functioning and neuronal connectivity.

Keywords

schizophrenia; synapse; connectivity; genetic factors; DISC1; dysbindin; neuregulin-1

1. Introduction

Disturbances in neuronal connectivity are frequently thought to be a key pathology associated with schizophrenia (SZ) (Hayashi-Takagi and Sawa, 2010). At the neuroanatomical level, SZ patients exhibit reductions in frontal gray matter volume, mainly shown by magnetic resonance imaging (MRI), and in structural integrity of cortico-cortical white matter tracts, shown by diffusion tensor imaging (DTI) (Glahn et al., 2008; Honea et al., 2005; Mathalon et al., 2001; Phillips et al., 2011). At the clinico-physiological level, deficits in cortical synchrony (particularly in gamma-band oscillations, which are brought about by functional connectivity of excitatory and inhibitory neurons) have been found in the prefrontal cortex of SZ patients (Farzan et al., 2010; Lee et al., 2003). At the cellular level, a number of postmortem studies in SZ brains point to cytoarchitectural and protein expression deficits which could contribute to altered excitatory-inhibitory balance in the

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disease. For example, reduced density of dendritic spines, which are excitatory synaptic structures on pyramidal neurons, has been reported in SZ patients (Garey, 2010; Glantz and Lewis, 2000; Kolluri et al., 2005). Reduced mRNA expression of glutamic acid decarboxylase (GAD67), a synthetic enzyme for the inhibitory neurotransmitter GABA, is consistently observed in SZ patient brains (Akbarian et al., 1995; Knable et al., 2002). In addition, studies of gene expression by microarray analysis show reduced expression of synapse-regulating proteins in SZ patient tissue (Horvath et al., 2011).

A combination of genetic susceptibility factors and environmental insults is likely to underlie the disruptions in connectivity associated with SZ pathology (Jaaro-Peled et al., 2009). For the past decade, many studies have identified candidate genetic susceptibility factors for SZ, including disrupted in schizophrenia 1 (*DISC1*) (Brandon and Sawa, 2011), Neuregulin-1 (*NRG1*) (Mei and Xiong, 2008; Rico and Marin, 2011), dysbindin (Mullin et al., 2011), zinc finger protein (*ZNF*)804a (Williams et al., 2011), and the voltage-dependent calcium channel alpha 1C subunit (*CACNA1C*) (Hamshere et al., 2012; Ripke et al., 2011). Polymorphisms in the genes of *NRG1*, *ErbB4*, and *dysbindin* have associated with altered structural connectivity in the cortex (Konrad et al., 2009; Nickl-Jockschat et al., 2012; Winterer et al., 2008). A recent study also found that a common missense variant of the *DISC1* gene is associated with impaired network connectivity in the brain, measured by diffusion MRI (Li et al., 2012b). We have to acknowledge that the individual contribution of each factor, by itself, to the disease is still debated. Nonetheless, many investigators believe that these factors can serve as useful “probes”, and that understanding their functioning may provide insight into disease-associated molecular pathways and disease mechanisms.

Our current understanding of SZ-associated pathophysiology has largely been shaped by studies of individual neurotransmitter systems. Early pharmacological observations of the psychotomimetic effects of glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) and ketamine, and the antipsychotic effects of dopamine D2 receptor antagonists, such as chlorpromazine and haloperidol, originally led to the oversimplified conceptual models of NMDA hypofunction and dopamine hyperfunction for SZ, respectively. However, a wealth of subsequent evidence has indicated that the pathophysiology of the disease is not so straightforward (Abi-Dargham, 2004; Kantrowitz and Javitt, 2010). It has been found that administration of antagonists to excitatory NMDA receptors primarily leads to suppression of interneuronal activity, leading to disinhibition and increased activity of cortical pyramidal neurons, at least in the rat prefrontal cortex (Homayoun and Moghaddam, 2007). Since NMDA receptors mediate excitatory neurotransmission by glutamate, it is surprising that blocking these receptors increases firing of pyramidal neurons, the predominant cell type in the cortex, rather than decreasing it. Positron emission tomography (PET) studies on dopamine have suggested that reduced cortical and increased subcortical (e.g., striatal) dopaminergic signaling may be characteristics of SZ patients (Abi-Dargham, 2004; Davidson and Heinrichs, 2003). This is also an unexpected result: if reduced cortical dopamine signaling is a key pathophysiology of SZ, it is not obvious how further suppressing dopamine signaling using a D2 receptor antagonist could be useful in SZ treatment. These results highlighted the complex nature of SZ pathophysiology, and were the first indications that a brain region, cell type-, and ultimately synapse-specific approach may be necessary to understand how deficits in signaling and connectivity bring about the disease state.

Individual neurons form different types of synapses which differ greatly in their contributions to brain functioning, depending on the cells, neurotransmitters, and receptors involved pre- and post-synaptically. Here, we will overview the characteristics that distinguish individual synapses from each other in the cerebral cortex, and how each type of synapse may uniquely contribute to SZ. We pay particular attention to reciprocal pyramidal

neuron-interneuron connections and input from dopaminergic neurons in the cortex (Fig. 1). This brain region is the focus of this article, because many of the higher cognitive functions impaired in SZ, such as working memory, are controlled by the cortex (Arnsten, 2011; Fleming et al., 1997; Gold et al., 1997; Goldman-Rakic, 1995). To address the mechanisms by which such cell type- and synapse-specific connectivity deficits contribute to disease susceptibility and pathophysiology, we propose the utility of studying candidate genetic susceptibility factors for SZ. By using these molecular “probes,” we can combine frontline mouse genetic engineering technology, viral vectors, *in utero* electroporation, and other *in vivo* techniques in order to target specific cells and neurocircuits. Evidence from mouse models may not be directly relevant to human brain functioning, but a large degree of similarity in brain structure and gene expression patterns between the human and mouse brain has been demonstrated (Zeng et al., 2012).

2. Different types of synapses

Several functionally distinct synapses exist between different types of cells in the cerebral cortex (Fig. 1). Based on the synapses depicted in Fig. 1, pathological observations from SZ patients are organized in a synapse-specific manner (Table 1). Here, we will discuss each synapse type in more detail, including synapse-specific deficits observed in SZ, in conjunction with possible roles of SZ genetic susceptibility factors in these deficits.

2.1. Glutamatergic synapses on pyramidal neurons

Pyramidal neurons are the most abundant cell type in the cortex, and form extensive networks of excitatory glutamatergic synapses. The main function of these cells is integration of information, specifically the timing and strength of excitation of other connected neurons in the network, in order to coordinate higher brain functioning (Spruston, 2008). Pyramidal neurons receive excitatory inputs from other pyramidal neurons via synapses on their apical and basal dendrites. These synapses are located at dendritic spines, which are highly plastic, cytoskeletally maintained structures at which postsynaptic proteins localize (Fig. 2A). Neurotransmitter binding at these synapses modifies depolarization of the neuron, which in turn determines output of the pyramidal neuron, that is, the action potentials fired along a single axon. This axon is often densely branched, to enable each pyramidal neuron to influence many other synapses, on other pyramidal neurons as well as interneurons, simultaneously.

Individual glutamatergic synapses on pyramidal neurons differ from each other in several aspects. These include the “sources” of presynaptic inputs, the “distance” of a synapse from the soma along the dendrite, and the “morphology” of the spine. First, the “sources” of presynaptic input include pyramidal neurons in a different cortical layer or hemisphere, or a different brain region, such as the thalamus, amygdala, or hippocampus. Projections from the cortex and hippocampus innervate pyramidal neurons in layers I–VI of the cortex; thalamocortical afferents target mainly pyramidal neurons in layers III and IV; and amygdalocortical afferents target pyramidal neurons in layers II–VI (Bacon et al., 1996; De Gois et al., 2005; Jay and Witter, 1991; Spruston, 2008). Second, the “distance” of a synapse from the soma along the dendrite affects its ability to control axonal output. The voltage change induced by neurotransmitter binding and depolarization at a synapse becomes weaker while traveling along the length of the dendrite to the cell body and axon hillock, where firing of an action potential may occur if a physiologically defined “threshold” potential is reached. Therefore, if a synapse is located proximally to the cell body, such a synapse may be expected to have a greater influence on firing of the neuron (Katz et al., 2009). Pyramidal neurons can be subdivided into apical and basal dendrites (Spruston, 2008). Experiments done in rat cortical slices show that even within the basal dendritic arbor, nonuniform integration of input (i.e. linear vs. non-linear integration) occurs between

synapses located on different dendrites or those at different locations on the same dendrite (Branco and Hausser, 2011; Polsky et al., 2004). Thus, the dendritic location of a synapse affects its influence on firing of the pyramidal neuron. Third, the strength of a synapse is determined by the size and shape of the dendritic spine, a cytoskeletally maintained synaptic structure. Spine enlargement precedes incorporation of neurotransmitter receptors to the spine surface and synaptic strengthening, or long term potentiation (LTP), in rat slice cultures (Kopec et al., 2006). Individual spines, even on the same mature dendrite, differ in size and composition in an activity-dependent manner (Matsuzaki et al., 2004; Sorra and Harris, 2000). This diversity in composition includes the subunit composition of AMPA and NMDA receptors (O'Rourke et al., 2012).

Postmortem studies in the brains from SZ patients have shown reductions in the volume of the neuropil (the intercellular space thought to contain dendritic spines), soma size, and dendritic arborization of layer V pyramidal neurons compared to normal controls (Black et al., 2004; Selemon and Goldman-Rakic, 1999). Other studies have reported reduced dendritic spine density in layer III neurons in SZ patients (Garey, 2010; Glantz and Lewis, 2000; Kolluri et al., 2005). The laminar specificity of some of these deficits may provide mechanistic clues to SZ pathology: for example, reduced thalamic input to layer III may underlie impairment in sensorimotor gating, which is frequently observed in SZ patients (Braff et al., 1992). At a molecular level, reduced expression of receptor molecules at glutamatergic synapses, including NMDA-type glutamate receptor subunits GluN1, GluN2A, and GluN2C, as well as impaired processing and trafficking of subunit GluN2B, have been reported in the prefrontal cortex of SZ patients (Beneyto and Meador-Woodruff, 2008; Kristiansen et al., 2010a; Kristiansen et al., 2010b). Furthermore, reduced expression of α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA)-type glutamate receptor subunits, particularly GluR1, has been reported in postmortem studies of SZ cortices (Eastwood et al., 1995; Mirnics et al., 2000; Sokolov, 1998). However, it remains elusive at which specific synapses these expression levels are changed; the expression change of these molecules may affect glutamatergic synapses on pyramidal neurons (discussed here) as well as those on interneurons (which will be discussed in the next subsection).

Genetic susceptibility factors involved in SZ participate in glutamatergic synapses on pyramidal neurons. The localization of DISC1 in the spines of some, but not all synapses in the cortex has been demonstrated by studies of immunoelectron microscopy in human and primate brains (Kirkpatrick et al., 2006; Paspalas et al., 2012). DISC1 binds to postsynaptic density protein PSD-95 and Kalirin-7, a guanine nucleotide exchange factor (GEF) for the small GTPase protein Rac1. This binding is released by NMDA receptor activation, resulting in free access of Kalirin-7 to Rac1, the resultant activation of Rac1, and spine enlargement. This demonstrates a cell-autonomous role for DISC1 in regulating activity-dependent structural plasticity of the spine. Long-term disturbance of DISC1 leads to constitutive overactivation of Rac1, which eventually results in the spine shrinkage (Hayashi-Takagi et al., 2010). A significant reduction in size of pyramidal neurons in DISC1 mutant mice has been reported (Lee et al., 2011). These results from mouse models suggest that loss of function of DISC1 can produce SZ-like phenotypes in pyramidal neuron morphology. DISC1 binding to Traf2 and Nck-interacting kinase (TNK), postsynaptically at glutamatergic synapses on neurons, plays an important role in stabilizing protein expression and regulating the composition of the postsynaptic density; this mechanism may occur at glutamatergic synapses on interneurons as well as pyramidal neurons (Wang et al., 2010). Loss of function of another SZ risk factor, dysbindin, which is expressed both pre- and postsynaptically at excitatory synapses on pyramidal neurons, leads to a decrease in GluN1 mRNA expression and reduction in NMDA-evoked currents in pyramidal neurons in the prefrontal cortex, as measured by RT-PCR and electrophysiology in brain slices from *dysbindin* mutant mice (Karlsborg et al., 2011; Mullin et al., 2011). Dysbindin protein levels

are reduced in the prefrontal cortex of SZ patients (Tang et al., 2009). A dysbindin-mediated mechanism may therefore contribute to excitatory dysfunction in the disease via impaired cortical GluN1 expression and NMDA receptor functioning. In pyramidal neurons, the intracellular domain of cleaved type III NRG1 regulates dendritic growth and branching and possibly affects their ability to form synaptic connections with other neurons, including other pyramidal neurons (Chen et al., 2010). Formation of these circuits is critical to proper functioning of the cortex.

2.2. Glutamatergic synapses on interneurons

Pyramidal neurons also form excitatory glutamatergic synapses on interneurons. Excitation at these synapses stimulates release of the inhibitory neurotransmitter GABA, resulting in feedback or feedforward inhibition of pyramidal neurons, depending on the source of excitation (i.e., the pyramidal neuron targeted by the interneuron, or a third pyramidal neuron, respectively). Due to the absence of dendritic spines on interneurons, glutamatergic synapses on these cells form along the dendritic shaft (Fig. 2B). The postsynaptic mechanisms by which these synapses mature are similar to those seen in pyramidal neurons, including clustering of postsynaptic density protein (PSD)-95 and AMPA receptor subunits (El-Husseini et al., 2000).

Systemic pharmacological blockade of NMDA receptors using the antagonist MK-801 in adult rats results in reduced parvalbumin (PV) immunoreactivity in the hippocampus (Keilhoff et al., 2004). Acute MK-801 treatment in adult rats causes reduced PV expression in the prefrontal, orbitofrontal, and entorhinal cortices (Romon et al., 2011). These results can be interpreted as a sign of dysfunction in PV-interneurons elicited by blocking the activity of NMDA receptors on the cells. To extend these observations, investigators have shown that MK-801 treatment induces a reduction in the activity of fast-spiking interneurons, such as PV-interneurons, and a subsequent increase in the firing rate of pyramidal neurons, in the cortex of the awake rats (Homayoun and Moghaddam, 2007). Furthermore, chronic systemic injection of an antagonist to the NMDA receptor GluN2A subunit (NVP-AAM077) impairs expression of PV and maturation of fast-spiking interneurons in the mouse cortex (Zhang and Sun, 2011). Studies of genetic manipulation in mice also verify that loss of excitatory input from NMDA receptors leads to interneuron deficits: mice with PV-positive interneuron-specific knockout of the NMDA receptor GluN1 subunit showed reduced expression of PV and GAD67, along with a loss of synchronous firing of cortical pyramidal neurons, a downstream result of these interneuron deficits (Belforte et al., 2010; Carlen et al., 2011). These pharmacological and genetic models also show behavioral changes relevant to SZ at the preclinical level (Belforte et al., 2010; Stefani and Moghaddam, 2005). Based on these results, NMDA receptors at glutamatergic synapses on interneurons are currently postulated as one of the most important molecular mediators of the pathophysiology of SZ (Lewis et al., 2012; Rotaru et al., 2012).

Glutamatergic synapses on interneurons represent another site at which synapse-specific contributions of SZ susceptibility genes may take place. ErbB4 is almost selectively expressed in interneurons, including 80% of PV-positive interneurons (Fazzari et al., 2010; Vullhorst et al., 2009). The formation of excitatory synapses onto cortical PV-positive interneurons is impaired in mice with genetically encoded interneuron-specific knockout of ErbB4 (Fazzari et al., 2010). In addition, excitatory transmission at these synapses is enhanced by NRG1-ErbB4 signaling: treatment with NRG1 in rat primary cultures increases the number and size of excitatory synapses on interneurons via ErbB4, and enhanced interneuronal miniature excitatory postsynaptic current (mEPSC) frequency and amplitude (Abe et al., 2011; Ting et al., 2011). Also at these synapses in neuron culture, binding of the extracellular domain of ErbB4, expressed by interneurons, to presynaptic NRG1 in pyramidal neurons, increased the size of the presynaptic terminal and led to enhancement of

interneuron activation (Krivosheya et al., 2008). The above observations illustrate several mechanisms by which NRG1/ErbB4 signaling may consistently facilitate excitatory transmission to interneurons. Interestingly, data from postmortem SZ patient brains shows that NRG1 and ErbB4 mRNA and protein expression are increased (Hahn et al., 2006; Law et al., 2007; Law et al., 2006; Silberberg et al., 2006). Treatment of postmortem SZ brains with NRG1 leads to greater ErbB4 activation compared with normal control brains (Hahn et al., 2006). If these data from biospecimens from SZ patients are correct, the expected pathophysiology is the opposite of what drug-induced models for SZ have suggested (i.e. interneuronal hyperactivation vs. hypoactivation). This discrepancy is an important question to be addressed in SZ research. As a first step, some groups have recently generated mice with transgenic overexpression of NRG1, which demonstrate SZ-like behavioral phenotypes, however the mechanism by which elevated NRG1 brings about these phenotypes remains to be determined (Deakin et al., 2009; Deakin et al., 2012; Kato et al., 2010). Finally, disruption of dysbindin has also been shown to decrease excitability of fast-spiking interneurons in the prefrontal cortex and, in turn, impair gamma-band oscillations (Carlson et al., 2011).

2.3. GABAergic synapses on pyramidal neurons

Excitatory output of pyramidal neurons is intensively regulated by input from inhibitory interneurons in the cortex via inhibitory synapses. These synapses all inhibit pyramidal neuron firing using the neurotransmitter GABA, however their features differ significantly based on the characteristics of the presynaptic interneurons and the subcellular locations of these synapses on the pyramidal neurons. There are several subtypes of interneurons, distinguished by morphology and marker expression. Two types of PV-positive fast-spiking interneurons, basket cells and chandelier cells, build inhibitory synapses onto pyramidal neurons (DeFelipe, 1999; Freund, 2003). Basket cells innervate the soma and proximal dendrites of pyramidal neurons, which are particularly important for integration of excitatory inputs and are major sites of synaptic plasticity; and chandelier cells form synapses targeting the axon initial segment of the pyramidal neurons to directly affect pyramidal cell outputs (Benes and Berretta, 2001; Lewis et al., 2005). Cholecystokinin (CCK)-positive basket cells also exist, however these are mainly non-fast-spiking cells which are unlikely to mediate gamma-band pyramidal neuron synchrony (Freund, 2003). In addition to these perisomatic inputs, non-fast-spiking interneurons (a subtype of interneurons which also includes somatostatin- and calbindin-positive cells) innervate distal dendrites, and play an important role in modulating integration of excitatory input in the dendrite (Kawaguchi and Kubota, 1998). In addition to GABAergic synapses on pyramidal neurons, some interneurons, including calretinin-positive cells, also target other interneurons; such interneuron-interneuron connections can disinhibit pyramidal neurons to provide further temporal control of pyramidal neuron activity (Conde et al., 1994). Rather than using specialized structures like dendritic spines, inhibitory synapses are formed by interneurons directly onto the pyramidal neuron cell body or the shaft of pyramidal dendrites (Fig. 2C).

Impairment of GABAergic inhibition onto pyramidal neurons in the pathophysiology of SZ has been suggested by several lines of evidence. GABAergic neurotransmission in SZ appears to be disrupted at the presynaptic, synaptic, and postsynaptic compartments. As described earlier, the presynaptic mechanism includes a decrease in the expression of interneuron markers, such as GAD67 and PV, which has been reproducibly reported in SZ (Akbarian et al., 1995; Fung et al., 2008; Gabriel et al., 1996; Hashimoto et al., 2008; Hashimoto et al., 2003; Knable et al., 2002). At the synaptic level, a reduction in the number of GABA transporter GAT1-positive inhibitory synapses, formed by chandelier cells on the axon initial segment (AIS) of cortical pyramidal neurons, has been observed in the brains of

SZ patients (Woo et al., 1998). Increased GABA(A) receptor $\alpha 2$ subunit expression has been observed in the pyramidal neuron AIS in SZ patients, likely as a compensatory response to reduced presynaptic GABA release from chandelier cells (Volk et al., 2002). Some, but not all, reports suggest a reduction of GABA in the cortex of SZ patients by magnetic resonance spectroscopy (MRS) (Asada et al., 1997; Yoon et al., 2010). At the postsynapse, SZ patients show a reduction in expression of the GABA(A) receptor $\alpha 1$ subunit, which is expressed in pyramidal neurons postsynaptic to PV-interneurons (Glausier and Lewis, 2011; Klausberger et al., 2002). In addition, reduced GABA(A) receptor $\alpha 5$ and $\beta 2$ subunit mRNA expression has been reported in the dorsolateral prefrontal cortex (PFC) in SZ, though these studies might not precisely address the cell-type specificity (Beneyto et al., 2011; Duncan et al., 2010). Treatment with a GABA(A) receptor $\alpha 2$ and $\alpha 3$ subunit agonist was observed to lead to improved gamma-band power in SZ patients, implying that activation of these subunits may be impaired in SZ (Lewis et al., 2008). Altogether, the above findings indicate that there is impairment in the ability of interneurons, particularly fast-spiking interneurons, to effectively inhibit pyramidal neurons in SZ.

Only a few studies have addressed how SZ susceptibility genetic factors may be involved at inhibitory synapses on pyramidal neurons. Elevated interneuronal activation is expected to produce increased activity-induced GABA release. In human studies, an SZ risk polymorphism for ErbB4 predicted ErbB4 mRNA expression *in vivo* as well as cortical GABA levels measured by MRS, suggesting a link between the two (Marenco et al., 2011). Consistent with this idea, NRG1 signaling, mediated by ErbB4 in fast-spiking interneurons, was found to promote activity-dependent GABA release in mice (Wen et al., 2010). In preclinical studies, NRG1-ErbB4 signaling has been shown to enhance inhibition of pyramidal neurons, as an outcome of increased interneuronal activation. As described above, PV-interneuron-specific knockout of ErbB4 resulted in reduced frequency and amplitude of mEPSCs in mature fast-spiking interneurons (Fazzari et al., 2010). Consequently, the same mice showed the reduced miniature inhibitory postsynaptic current (mIPSC) frequency and increased firing rate in pyramidal neurons (Fazzari et al., 2010; Wen et al., 2010).

Several studies, while not directly addressing synaptic mechanisms, have suggested that modulation of SZ susceptibility factors leads to interneuron deficits which may eventually cause synaptic dysfunction. For example, expression of a dominant-negative form of DISC1, in either a pyramidal neuron-specific or endogenous manner, leads to reduction of PV-positive interneurons in the prefrontal cortex (Hikida et al., 2007; Shen et al., 2008). DISC1 knockdown can impair migration of interneurons to the cortex (Steinecke et al., 2012). NRG1-ErbB4 signaling regulates tangential migration of interneurons to the cortex as well as activity-dependent dendritic outgrowth (Anton et al., 2004; Cahill et al., 2012; Li et al., 2012a). Proper placement and maturation of interneurons in the developing cortex is critical to the formation of functional cortical inhibitory circuitry. These neurodevelopmental deficits, particularly in migration, may therefore have important consequences on connectivity at later stages.

2.4 Dopaminergic synapses on pyramidal neurons and interneurons

Dopaminergic neurons provide extrinsic input to the cortex from a mesocortical pathway originating in the ventral tegmental area (VTA). Mesocortical dopaminergic neurons project to pyramidal neurons and interneurons of the cortex, where their activity modulates circuit excitation (Fig. 1) (Floresco and Tse, 2007). This regulation plays a critical role in cognitive functioning, including working memory, in which dopamine release modulates activation of pyramidal neurons directly and indirectly via interneurons (Goldman-Rakic et al., 2000).

The dopamine D1 receptor (D1R) is expressed at excitatory postsynapses and at axon terminals of both pyramidal neurons and interneurons (Bergson et al., 1995; Paspalas and

Goldman-Rakic, 2005). Signaling by D1Rs can enhance firing of pyramidal neurons and interneurons (by modulating excitability), as well as reduce their excitatory or inhibitory output (by modulating neurotransmitter release), depending on the synaptic site at which they are activated, i.e. glutamatergic postsynapses or axon terminals respectively. At dendritic spines of pyramidal neurons in the cortex, activity of postsynaptic D1Rs enhances NMDA receptor surface expression and downstream signaling, as well as excitability of the pyramidal neuron, in dissociated neurons and slice cultures from rats (Lei et al., 2009; Tseng and O'Donnell, 2004). In contrast, at axon terminals of these pyramidal neurons, hyperactivation of presynaptic D1Rs attenuates glutamate release in the monkey cortex (Gao et al., 2001). D1R signaling can therefore enhance excitation of pyramidal neurons, and also reduce their excitatory output. Meanwhile, at glutamatergic synapses on fast-spiking interneurons, postsynaptic D1R activation enhances excitability of interneurons *in vivo* (Gao and Goldman-Rakic, 2003; Seamans et al., 2001). However, at axon terminals of fast-spiking interneurons, presynaptic D1R activation depresses inhibition of postsynaptic pyramidal neurons (Gao et al., 2003). This bidirectional modulation of circuit activity suggests that tightly regulated D1R-mediated signaling can act to maintain a balance of excitation and inhibition in the cortex.

The dopamine D2 receptor (D2R) is expressed presynaptically at inhibitory axon terminals and postsynaptically at excitatory and inhibitory synapses, as well as presynaptically at dopaminergic axon terminals, where D2R activation plays a role in regulating dopamine release (Fitzgerald et al., 2012; Negyessy and Goldman-Rakic, 2005; Plantje et al., 1987). These receptors also contribute to maintaining cortical excitatory-inhibitory balance. D2R signaling can decrease pyramidal neuron excitation (by reducing pyramidal neuronal excitability and increasing interneuronal excitability) or increase pyramidal neuron excitation. At glutamatergic synapses on cortical pyramidal neurons, the D2R agonist quinpirole activates postsynaptic D2Rs and inhibits AMPA receptor-mediated pyramidal neuron excitability, in rat brain slices (Tseng and O'Donnell, 2004). At glutamatergic synapses on interneurons, quinpirole treatment enhances interneuronal excitation, which increases activity-induced GABA release, and as above, reduces excitation of pyramidal neurons (Tseng and O'Donnell, 2004). In contrast, at inhibitory synapses on pyramidal neurons, activation (using quinpirole) of postsynaptic D2Rs expressed by pyramidal neurons increases their excitation, by causing a reduction in GABA(A) receptor mediated mIPSC amplitude, in rat PFC slices (Seamans et al., 2001). Also at these synapses, treatment with multiple D2R agonists increases excitation of postsynaptic pyramidal neurons, by activating presynaptic D2Rs expressed by interneurons and reducing GABA release by axon terminals (Retaux et al., 1991; Seamans et al., 2001). These apparently contradictory data can be reconciled by taking into account the overall developmental trajectory of dopamine signaling in the PFC. The D2R effects that enhance interneuron activation are acquired during adolescence (Tseng et al., 2007), while the D2R effects that suppress inhibition of pyramidal neurons are present in the juvenile PFC (Seamans et al., 2001; Seamans and Yang, 2004; Tseng and O'Donnell, 2004).

The dopamine D4 receptor (D4R), a member of the D2-like family of dopamine receptors, is expressed by both pyramidal neurons and interneurons in the cortex (Mrzljak et al., 1996; Rivera et al., 2008). Several *in vitro* studies using the selective D4R agonist PD168077 indicate that D4R signaling can enhance pyramidal neuron excitation and reduce inhibition of cortical pyramidal neurons by interneurons. At glutamatergic synapses on pyramidal neurons, activation of postsynaptic D4Rs enhances pyramidal neuron excitation, by promoting phosphorylation of the AMPA receptor GluR1 subunit by the pyramidal neuron-specific kinase α CaMKII, in rat dissociated PFC cultures (Gu et al., 2006). At glutamatergic synapses on interneurons, activation of postsynaptic D4Rs reduces excitation of interneurons, by modulating AMPA receptor trafficking, in rat PFC slices (Yuen and Yan,

2009). Finally, at inhibitory synapses on pyramidal neurons, stimulation of postsynaptic D4Rs reduces inhibitory currents in pyramidal neurons, by reducing surface expression of GABA(A) receptor $\beta 2/3$ subunits in an actin-dependent manner, in rat dissociated PFC cultures (Graziane et al., 2009).

Dopamine-mediated transmission is critical for prefrontal cortex functioning, which is impaired in SZ (Goldman-Rakic et al., 2000). Dopaminergic innervation, particularly to layer VI of the cortex, has been found to be reduced in postmortem SZ brains (Akil et al., 1999). These observations suggest that a hypodopaminergic state, at least in the cortex, is associated with SZ. PET neuroimaging for D1R and D2R has been used to address this question. Disruption of D1R expression and binding in the cortex of SZ patients has been reported, but is still under debate, with several groups addressing the nature and mechanism of SZ-related D1R dysfunction (Abi-Dargham et al., 2002; Abi-Dargham and Moore, 2003; Cropley et al., 2006; Okubo et al., 1997). More than one study has reported reductions in D2R density and binding in different regions of the cortex (Buchsbaum et al., 2006; Kegeles et al., 2010; Suhara et al., 2002; Tuppurainen et al., 2003). Several pharmacological studies in monkeys have examined the role of cortical dopamine signaling in cognitive processes, including those known to be disturbed in SZ, such as working memory. Cortical infusion of a general dopamine antagonist or selective D1R antagonist impairs working memory, whereas a D1R agonist improved working memory performance (Arnsten et al., 1994; Sawaguchi and Goldman-Rakic, 1991). However, treatment with dopamine D1R or D4R antagonists also prevented stress-induced impairment of working memory performance in monkeys, suggesting that hyperdopaminergia (in this case, caused by environmental stress) is also detrimental to cognitive functioning (Arnsten and Goldman-Rakic, 1998; Arnsten et al., 2000). These observations have led to the theory that dopamine signaling must be present in an optimal range (at the center of an “inverted u-shaped” curve) for cortical functioning to proceed normally (Arnsten, 1997; Seamans and Yang, 2004). The developmental time point can also influence the dopaminergic contribution to mental illness: as described above, the net effect on interneuron activation by dopamine is moderate in the juvenile PFC, with D1R and D2R exerting opposing effects. In mental disorders that emerge during adolescence, such as SZ, genetic factors which may have altered dopaminergic circuitry earlier in development may give rise to behavioral phenotypes, downstream of such disturbed circuits, when peri-adolescent maturation occurs (O'Donnell, 2011). For example, D2R activation suppresses interneuronal activation in the juvenile PFC, but enhances this activation and subsequent inhibition of pyramidal neurons following adolescence (Tseng et al., 2007; Tseng and O'Donnell, 2004), and certain SZ susceptibility factors that alter D2R signaling may have a role in such developmental trajectory.

Genetic susceptibility factors for SZ may affect neurotransmission via dopaminergic synapses, in ways that are relevant to SZ pathophysiology. Knockdown of DISC1 in pyramidal neurons during neurodevelopment results in impaired maturation of mesocortical dopaminergic projections and decreased levels of dopamine in the cortex in adulthood, which may be consistent with the observation from autopsied brains of SZ patients (Akil et al., 1999; Niwa et al., 2010). NRG1-ErbB4 signaling stimulates growth and survival of midbrain dopaminergic neurons *in vitro* and *in vivo*, a neurodevelopmental effect which might indirectly link to the disturbance of dopaminergic neurons in the adult cortex (Carlsson et al., 2011; Zhang et al., 2004). Treatment of neonatal mice with NRG1 also results in a hyperdopaminergic state in the cortex which persists until adulthood, though the implications of this observation in SZ pathology are not clear (Kato et al., 2011). As described earlier, expression of dysbindin is reduced in the PFC of SZ patients (Tang et al., 2009). A *dysbindin* mutant mouse model, which expresses negligible levels of dysbindin, exhibits decreased dopamine levels and impaired dopamine release in the cortex, as measured by Western blotting and *in vivo* microdialysis (Murotani et al., 2007; Nagai et al.,

2010). Loss of expression of dysbindin alters intracellular trafficking of D2R and leads to increased neuronal cell-surface expression of the receptor in cultures and mice (Iizuka et al., 2007; Ji et al., 2009). Furthermore, a greater increase in interneuronal firing, and subsequent decrease in pyramidal neuron firing, is observed in this condition compared with normal controls, in response to the D2R agonist quinpirole (Ji et al., 2009; Papaleo et al., 2012).

3. Discussion

The above discussions demonstrate that it is critical to be conscious of the specific type of synapse being studied when drawing conclusions about the pathophysiology of SZ. This may also be true for other mental disorders, such as autism and bipolar disorder, which share some genetic risk factors with SZ. Glutamatergic synapses on pyramidal neurons and interneurons, GABAergic synapses on pyramidal neurons, and dopaminergic synapses on pyramidal neurons and interneurons each play distinct roles in neuronal connectivity in the cortex, which may individually mediate cognitive deficits and other symptoms of SZ. In the mature brain, genetic susceptibility factors for SZ are likely to participate in synapse-specific mechanisms. We took DISC1, NRG1/ErbB4, and dysbindin as examples of useful probes to study SZ-associated synaptic mechanisms, and showed how they have distinct roles in each synapse in the present article. Though not discussed here, it is important to keep in mind that other types of synapses, in particular those releasing the neurotransmitters serotonin and acetylcholine, also modulate these circuits and likely contain their own unique genetic mechanisms contributing to SZ symptoms.

Treating each synapse as a distinct, individual contributor to SZ pathology may help pinpoint the site of action of various molecular factors within the framework of synaptic connectivity. Cell type-specific genetic modulation is a useful tool for selectively targeting different types of synapses. Several experimental approaches exist to achieve this goal: *in utero* electroporation into the ventricular zone affects pyramidal neurons, while electroporation into the medial ganglionic eminence can be used to target interneurons which will migrate into the cortex (Kubo et al., 2010; Yozu et al., 2005). The availability of a variety of mice expressing Cre recombinase under the control of cell type-specific promoters has made it possible to alter gene expression in specific cells during neurodevelopment as well as in adulthood (Murray et al., 2011). Certain viral vectors containing cell-type specific promoters are also available (Fazzari et al., 2010; Peel et al., 1997). Understanding the mechanisms by which SZ genes act in distinct cells to bring about the disease state may help in the development of novel therapeutic strategies targeting individual synapses, rather than the entire brain.

Synaptic deficits occur not only due to the disturbances of functioning of mature circuits, but also by problems in the developmental trajectory of the neurons which comprise those circuits. In several instances described above, SZ genetic susceptibility factors not only directly affect functional signaling involving synaptic transmission but also have roles in neurodevelopmental trajectory, which can in turn affect circuit formation and connectivity in the adult brain. Thus, SZ genetic factors can serve as a particularly useful tool to address SZ-associated synaptic pathology, including the influences of developmental trajectory. In order to determine the distinct contributions of SZ genetic factors to the pathology during development and in adulthood, the ability to temporally restrict gene modulation is necessary. Several experimental techniques exist to pre- and postnatally control timing of gene modulation *in vivo* (Kamiya, 2009; Pletnikov, 2009; Sawa, 2009; Seshadri and Hayashi-Takagi, 2009).

One more important point to be noted is that key SZ susceptibility factors have large networks of binding partners, and it is important to consider the context-dependence of

individual molecular interactions. For example, DISC1 interacts with several proteins whose expressions are spatially and temporally segregated (Camargo et al., 2007), many of which could represent distinct mechanisms mediating its contribution to SZ pathology. Convergence of multiple genetic risk factors seems increasingly likely to be an explanation for the complex genetic nature of SZ, and efforts to explore cross-talk among such factors have been made, at least at the cellular level (Jaaro-Peled et al., 2009; Mead et al., 2010; Ottis et al., 2011; Seshadri et al., 2010). Any attempt to understand how these convergent pathways influence circuit formation *in vivo*, and its impairment in SZ-related pathology, should address the cell type- and synapse-specificity of their effects.

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Fig. 1.

Schematic representation of synaptic connections made by a cortical layer II/III pyramidal neuron (blue). These cells receive excitatory glutamatergic input from other pyramidal neurons, as well as inhibitory GABAergic input from fast-spiking (FS) and non-fast-spiking (NFS) interneurons (orange). Dopaminergic afferents (pink) innervate both pyramidal neurons and interneurons. Layer II/III pyramidal neurons form excitatory projections to other areas of the brain, including layer V of the cortex, the basolateral amygdala (BLA), lateral hypothalamus (LH), and ventral striatum (VS). Synapses of particular interest are circled in green; they are: 1) glutamatergic synapse on pyramidal neuron; 2) glutamatergic synapse on interneuron; 3) GABAergic synapse on pyramidal neuron; 4) dopaminergic synapse on pyramidal neuron; and 5) dopaminergic synapse on interneuron. Other abbreviations: PFC, prefrontal cortex; AIS, axon initial segment; VTA, ventral tegmental area; TH, thalamus.

Fig. 2. Schematic representations of three major types of synapses, depicting pre- and postsynaptic terminals, major neurotransmitter receptors and other synaptic proteins. A) Diagram of glutamatergic synapse on pyramidal neuron, including dopaminergic innervation; B) Diagram of glutamatergic synapse on interneuron; C) Diagram of GABAergic synapse on pyramidal neuron, including dopaminergic innervation.

Overview of evidence for altered gene expression in SZ. Available evidence from expression studies for various SZ-associated molecules is organized based on which neurotransmitter system and which synapses (numbered based on labeling in Fig. 1) are most affected by altered expression.

Table 1

Neurotransmitter system	Molecule/Pathological characteristic	Context	Expression studies	Direction of change	Synapses affected
Glutamatergic	NMDA receptor activation	Postmortem	(Hahn et al., 2006)	Decreased	1,2
	GluN1	Postmortem	(Sokolov, 1998)	Decreased	1,2
	mGluR1	Postmortem	(Gupta et al., 2005)	Increased	1,2
	mGluR5	Postmortem	(Crook et al., 2002)	Increased	1,2
	mGluR2/3	Postmortem	(Gupta et al., 2005)	Increased	1,2
	Dendritic spine density	Postmortem	(Garey, 2010; Glantz and Lewis, 2000; Kolluri et al., 2005)	Decreased	1
	Soma size	Postmortem	(Selemon and Goldman-Rakic, 1999)	Decreased	1,2
	Dendritic arborization	Postmortem	(Black et al., 2004)	Decreased	1,2
GABAergic	GAD67	Postmortem	(Hashimoto et al., 2003; Knable et al., 2002)	Decreased	3
	GAT1	Postmortem	(Volk et al., 2001; Woo et al., 1998)	Decreased	3
	GABA(A) receptor	Postmortem	(Hashimoto et al., 2008)	Decreased	3
	PV	Postmortem	(Hashimoto et al., 2003)	Decreased	3
Dopaminergic	COMT	Postmortem	(Ye et al., 2012)	Decreased	4,5
	DARPP-32	Postmortem	(Albert et al., 2002)	Decreased	4,5
	D2R	PET	(Wong et al., 1986)	Increased	4,5
	D4R	PET, Postmortem	(Lahti et al., 1998; Murray et al., 1995; Seeman et al., 1993)	Increased	4,5
	DAT positive axon terminals	Postmortem	(Akil et al., 1999)	Decreased	4,5