Published in final edited form as:

Eur J Neurosci. 2012 June ; 35(12): 1871–1878. doi:10.1111/j.1460-9568.2012.08156.x.

Cortical circuit dysfunction and cognitive deficits in schizophrenia: Implications for preemptive interventions

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Abstract

Schizophrenia is a devastating disorder that is common, usually chronic, frequently associated with substantial co-morbidity for addictive and medical disorders, and, as a consequence, very costly in both personal and economic terms. At present, no proven means for preventing or modifying the course of the illness exist. This review discusses evidence supporting the ideas 1) that impairments in certain cognitive processes are the core feature of schizophrenia, 2) that these cognitive impairments reflect abnormalities in specific cortical circuits, and 3) that these circuitry abnormalities arise during childhood-adolescence. The implications of these findings for the development and implementation of safe, preemptive, disease-modifying interventions in individuals at high risk for a clinical diagnosis of schizophrenia are considered.

Keywords

Gamma oscillations; humans; parvalbumin neurons; prefrontal cortex; pyramidal neurons; working memory

Introduction

The identification of individuals at high risk for a major psychiatric illness, and the development of novel interventions that can change the course of the illness before its debilitating signs and symptoms emerge, represent critical current challenges in public health. This article considers these challenges for schizophrenia, a leading cause of years of life lost to disability and premature mortality in developed countries (Lopez et al., 2006). Schizophrenia is now considered to be a neurodevelopmental disorder in which psychosis actually represents a late, and potentially preventable, outcome of the illness (Insel, 2010); that is, the appearance of the diagnostic clinical features of schizophrenia (psychosis) represents not the onset of the illness, but the downstream product of years of pathogenic processes at work. From this perspective, the development of effective preemptive treatments for schizophrenia (i.e., interventions that modify disease pathogenesis in order to prevent or delay the appearance of psychosis) requires knowledge of 1) the abnormalities in brain circuitry that underlie the core functional disturbances of the illness, 2) when during the course of development these abnormalities in brain circuitry arise, and 3) a means to detect these abnormalities in brain circuitry when their functional impact is still subclinical.

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Disclosures

The author currently receives investigator-initiated research support from Bristol-Myers Squibb, Curridium Ltd and Pfizer and in 2009-2011 served as a consultant in the areas of target identification and validation and new compound development to BioLine RX, Bristol-Myers Squibb, Merck and SK Life Science.

This review summarizes some of the evidence supporting the ideas that 1) impairments in certain cognitive processes are the core feature of schizophrenia, 2) these cognitive impairments reflect abnormalities in specific cortical circuits, and 3) these circuitry abnormalities arise during childhood-adolescence. The implications of these findings for the development and implementation of safe, preemptive, disease-modifying interventions in individuals at high risk for a clinical diagnosis of schizophrenia are considered.

Clinical features of schizophrenia

Schizophrenia, which affects 0.5–1% of the world's population, is associated with marked impairments in social and occupational functioning that emerge from the convergence of disturbances in perception, attention, volition, inferential thinking, fluency and production of language, and the recognition and expression of emotion (Lewis & Sweet, 2009). Many individuals with schizophrenia also experience severe depression (Buckley et al., 2009), excessively use nicotine, alcohol and cannabis (Dixon, 1999), and carry increased risk for both cardiovascular disease (Osborn et al., 2007) and diabetes (Chien et al., 2009). Approximately 5% of people with schizophrenia die by suicide (Palmer et al., 2005). As a result of these factors, the average life expectancy of individuals diagnosed with schizophrenia is reduced by approximately 25 years (Saha et al., 2007).

The clinical features of schizophrenia cluster in three categories (Lewis & Sweet, 2009). Positive or psychotic symptoms include delusions (false beliefs firmly held in the face of contradictory evidence), hallucinations (most commonly experienced as hearing voices distinct from one's own thoughts), thought disorder (e.g., loose associations), and abnormal psychomotor activity (e.g., grossly disorganized behavior, posturing or catatonia). Negative symptoms include social withdrawal, impairments in initiative and motivation, a reduced capacity to recognize and express emotional states, and poverty in the amount or content of speech. Cognitive symptoms include disturbances in selective attention, working memory, executive control, episodic memory, language comprehension and social-emotional processing.

Of the cognitive impairments in schizophrenia, substantial research has focused on working memory, typically defined as the ability, in the absence of sensory cues, to transiently maintain and manipulate a limited amount of information in order to guide thought or behavior (Barch & Smith, 2008). Performance on working memory tasks depends, at least in part, upon the neural circuitry of the dorsolateral prefrontal cortex (DLPFC) (Miller & Cohen, 2001), and in schizophrenia, the DLPFC exhibits altered activation during working memory tasks (Van Snellenberg et al., 2006; Deserno et al., 2012). These impairments in working memory function and DLPFC activation are present in both medicated and unmedicated subjects, in both early and chronic phases of the illness, and in a manner that cannot be attributed to nonspecific factors such as lack of effort or interest (Barch & Smith, 2008).

Cognitive deficits as the core feature of schizophrenia

The marked disruptions in managing interpersonal relationships and in navigating the challenges of life in society that accompany the typical emergence of psychosis during late adolescence or early adulthood usually lead to the first clinical encounter and subsequent diagnosis of schizophrenia. However, impairments in working memory and other types of cognitive processes may be present for years prior to the diagnosis of the illness (Lesh et al., 2011). Indeed, cognitive impairments have been found throughout the life span of affected individuals, including during childhood and adolescence as well as at the initial onset of psychosis (Davidson et al., 1999; Cosway et al., 2000). In addition, in individuals diagnosed with schizophrenia, cognitive deficits occur with high frequency, are relatively stable over

time, and are independent of psychotic symptoms (Keefe & Fenton, 2007). Although, on average, individuals score 1.5–2 standard deviations below normative means on tests of cognition (Keefe & Fenton, 2007), some individuals diagnosed with schizophrenia (e.g., those with prominent paranoid features) may have relatively preserved cognitive function. Perhaps most importantly, the degree of cognitive impairments, and not the severity of psychosis, is the best predictor of long-term functional outcome for affected individuals (Green, 1996). The unaffected relatives of individuals with schizophrenia also exhibit similar, although milder, cognitive deficits (Egan et al., 2001), suggesting that cognitive abnormalities reflect the genetic risk for the illness. The combination of these findings has led to the view that cognitive deficits are the core abnormalities of the illness that set the stage for the later emergence of psychosis.

The evidence that cognitive impairments are present, and in at least some individuals are progressive, before the onset of psychosis suggests that they may reflect an early and ongoing pathogenic process. For example, as early as the 4th grade of school, individuals who would later be diagnosed with schizophrenia scored, on average, more poorly than their peers on standardized tests of scholastic performance, and in many domains their performance relative to peers worsened through the school years (Keefe & Fenton, 2007). Similarly, mean childhood IQ scores were lower in individuals who grew up to meet diagnostic criteria for schizophrenia relative to comparison groups composed of either those who were later diagnosed with major depression or those who did not develop a psychiatric illness (Reichenberg et al., 2010). In particular, relative to both of these comparison groups, individuals later diagnosed with schizophrenia failed to show the normal degree of improvement in working memory between ages 7 and 13 years (Reichenberg et al., 2010).

The findings that working memory impairments are a core feature of schizophrenia, that they appear to be present and progressive during childhood-adolescence, and that they are associated with abnormalities in activation of the DLPFC, raise two critical questions: 1) What abnormalities in DLPFC circuitry are present in individuals diagnosed with schizophrenia? 2) Which of these abnormalities are likely to reflect alterations in the normal developmental trajectories of DLPFC circuitry? These questions are addressed in the following two sections.

Alterations in DLPFC circuitry in schizophrenia

Individuals diagnosed with schizophrenia have smaller whole brain volumes in the prodromal stage, at the first episode of psychosis, and during the chronic phase of the illness (Lawrie & Abukmeil, 1998; Steen et al., 2006; Levitt et al., 2010). In addition, young individuals who, by virtue of having an affected first degree relative carry an elevated genetic risk for schizophrenia, have greater reductions over time in the volumes of the prefrontal and temporal lobes, and in some but not all studies, the decline in prefrontal volume was most marked in those eventually diagnosed with schizophrenia (Pantelis et al., 2003; Borgwardt et al., 2007; Sun et al., 2009; McIntosh et al., 2011; Mechelli et al., 2011). Consistent with these findings, individuals with childhood onset schizophrenia show an increased rate of the decline in prefrontal gray matter that normally occurs during adolescence (Giedd & Rapoport, 2010).

Smaller prefrontal gray matter volumes in individuals diagnosed with schizophrenia appear to be due to less cortical neuropil (i.e., small dendritic shafts, dendritic spines, axons, and axon terminals) (Selemon & Goldman-Rakic, 1999), and not to fewer cortical neurons (Akbarian et al., 1995; Thune et al., 2001). The reduced neuropil in the DLPFC appears to reflect fewer axon terminals, as suggested by findings in postmortem studies of schizophrenia of lower levels of proteins present in axon terminals (Glantz & Lewis, 1997),

and of fewer dendritic spines (Garey et al., 1998; Glantz & Lewis, 2000). These alterations appear to be particularly pronounced in layer 3. For example, in the DLPFC of subjects with schizophrenia, basilar dendritic spine density was significantly lower on deep layer 3 pyramidal cells relative to both normal and psychiatrically-ill comparison subjects, but spine density was only modestly lower on superficial layer 3 pyramidal neurons and unchanged on pyramidal neurons in layers 5 and 6 (Glantz & Lewis, 2000; Kolluri et al., 2005). Consistent with these findings, the mean somal volume of layer 3 pyramidal neurons was smaller in subjects with schizophrenia in the DLPFC and in other cortical regions (Arnold et al., 1995; Rajkowska et al., 1998; Pierri et al., 2001; Sweet et al., 2003), whereas the volume of layer 5 pyramidal neurons was unchanged (Sweet et al., 2004). Importantly, none of these findings appeared to be attributable to medication use or length of illness (Lewis & Gonzalez-Burgos, 2008).

In addition to these alterations in excitatory pyramidal neurons, multiple studies have reported alterations in markers of inhibitory GABA neurotransmission. For example, lower levels of the mRNA for the 67 kDa isoform of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67) have been consistently found in the DLPFC of subjects with schizophrenia (Gonzalez-Burgos et al., 2010). This deficit in GAD67 mRNA appears to be particularly pronounced in the subset of DLPFC GABA neurons that express the calcium-binding protein parvalbumin (PV), as about 50% of PV neurons lacked detectable levels of GAD67 mRNA in individuals with schizophrenia (Hashimoto et al., 2003). Importantly, the number of PV neurons in the DLPFC appears to be unchanged (Lewis et al., 2005), although the expression of PV mRNA per neuron is decreased (Hashimoto et al., 2003). The latter finding, in addition to methodological confounds, appears to explain the reports in some studies of a lower density of cortical PV-immunoreactive neurons in schizophrenia (Stan & Lewis, 2012).

PV neurons can be subdivided into two major classes based on the principal target of their axon terminals. The axon terminals from the basket cell class of PV neurons target the cell body and proximal dendrites of pyramidal neurons. Both pre- and post-synaptic alterations in PV basket cell-pyramidal cell connectivity in the DLPFC, especially in layer 3, appear to be present in schizophrenia. First, the density of PV-labeled axon terminals, presumably from basket neurons, is reduced in DLPFC layer 3 in schizophrenia (Lewis et al., 2012). Second, the level of GAD67 protein is markedly lower in these terminals (Curley et al., 2011), suggesting that basket cells represent the population of PV neurons with undetectable levels of GAD67 mRNA (Hashimoto et al., 2003). Third, mRNA expression of the GABA_A receptor $\alpha 1$ subunit, which is postsynaptic to PV basket cell inputs, is preferentially lower in layer 3 in schizophrenia (Beneyto et al., 2011), and this deficit is selective for pyramidal neurons and is not present in GABA neurons (Glausier & Lewis, 2011).

The other major class of PV neurons, chandelier cells, gives rise to axon terminals that form distinctive vertical arrays, termed cartridges, which exclusively target the axon initial segments (AIS) of pyramidal neurons. In the DLPFC of subjects with schizophrenia, the density of cartridges immunoreactive for the GABA membrane transporter (GAT1) is lower than comparison subjects (Woo et al., 1998), whereas the density of pyramidal cell AIS immunoreactive for the GABA_A receptor $\alpha 2$ subunit, the dominant GABA_A receptor α subunit present in pyramidal cell AIS in layer 3, is markedly increased (Volk et al., 2002). In addition, the density of AIS immunoreactive for ankyrin-G, a protein that plays a key role in the structure and plasticity of the AIS, is also lower in the DLPFC in schizophrenia (Cruz et al., 2009). Importantly, both the chandelier and PV basket cell alterations appear to be specific to the disease process of schizophrenia since they are not observed in individuals with other psychiatric disorders or in monkeys exposed chronically to antipsychotic medications (Lewis et al., 2012).

Each of the alterations in markers of PV basket and chandelier neuron connectivity is most pronounced in layer 3, the same laminar location where the morphological abnormalities in pyramidal cells are most striking. Interestingly, studies in nonhuman primates have shown that neural activity in the DLPFC is particularly pronounced in layer 3 during working memory tasks, and that the pattern of neural connections in this layer is well-suited to support the sustained firing of DLPFC neurons observed during the delay period of working memory tasks (Goldman-Rakic, 1995). Thus, the alterations in pyramidal neuron-PV neuron connectivity are likely to contribute to the working memory impairments in schizophrenia.

Consistent with this interpretation, the working memory impairments in schizophrenia are associated with lower power of frontal lobe gamma oscillations (Cho et al., 2006; Minzenberg et al., 2010), which in at least other association regions of the primate neocortex, are most prominent in layer 3 (Buffalo et al., 2011). Furthermore, both computational models (Gonzalez-Burgos & Lewis, 2008) and experimental data in rodents (Cardin et al., 2009; Sohal et al., 2009) indicate that pyramidal neuron-PV neuron connectivity is essential for the generation of gamma oscillations, supporting the interpretation that alterations in this local circuitry contribute to the neural substrate for working memory impairments in the illness. However, these findings leave open the question of whether the alterations in pyramidal neurons or PV neurons are the proximal cause of the disturbance in neural network activity. Recent data in humans, reviewed in detail elsewhere (Lewis et al., 2012), converge on the hypothesis that an intrinsic deficit in pyramidal neuron dendritic spines, the associated loss of excitatory synapses, and the resulting reduction in cortical network activity leads to a homeostatic reduction in inhibition from PV basket neurons in order to restore excitatory-inhibitory balance. While a direct examination of this hypothesis in individuals with schizophrenia faces the usual constraints associated with experimental studies in humans, studies in model animal systems can be used to provide proof-of-concept tests of the cause and effect relationships between observations made in postmortem human studies. For example, genetic manipulations in mice that selectively reduce dendritic spines in pyramidal neurons would be predicted to recapitulate the pattern of other circuitry alterations seen in schizophrenia, whereas the selective reduction of GAD67 expression in PV basket would not.

Developmental trajectories of the components of DLPFC circuitry altered in schizophrenia

Given that both working memory performance and associated patterns of DLPFC activity continue to mature through late adolescence (Luna et al., 2010), and that working memory impairments are detectable in individuals with schizophrenia years before the onset of psychosis (Reichenberg et al., 2010), how might the schizophrenia-associated alterations in DLPFC circuitry arise during postnatal development? Although opportunities to directly study circuitry development at the cellular level in humans are quite limited, macaque monkeys provide an excellent model system. Similar to humans, monkeys progressively improve in working memory ability from early childhood through late adolescence (Goldman-Rakic, 1987), and this improvement is associated with an increased engagement of DLPFC circuitry in task performance (Alexander & Goldman, 1978; Alexander, 1982).

This maturational increase in working memory dependence on DLPFC circuitry is associated with substantial developmental refinements in layer 3 pyramidal neurons and PV neurons, the same cell types that are altered in schizophrenia. For example, in monkey DLPFC, the density of basilar dendritic spines on layer 3 pyramidal increases substantially during late gestation and the postnatal period, reaches a plateau that is maintained until late childhood, and then declines during adolescence until stable adult levels are achieved (Anderson et al., 1995). Similarly, pyramidal cell spine density in human DLPFC increases

rapidly after birth, peaks in childhood, and then declines across adolescence until stabilizing in the third decade of life (Petanjek et al., 2011). Consistent with the fact that dendritic spines are the main site of excitatory synaptic input onto pyramidal cells, the number of layer 3 excitatory synapses changes in a similar age-related fashion in both monkey and human DLPFC (Bourgeois et al., 1994; Huttenlocher & Dabholkar, 1997).

Electrophysiological studies suggest that this adolescence-related remodeling of excitatory connectivity in layer 3 of primate DLPFC primarily involves the elimination of mature synapses, and that some factor, such as the neuronal source of input or the postsynaptic target, somehow tags mature synapses for pruning (Gonzalez-Burgos et al., 2008).

The axon terminals of both PV basket and chandelier neurons in monkey DLPFC layer 3 also undergo substantial refinements during postnatal development. For example, the density of PV-immunoreactive axon terminals, putatively from basket neurons, progressively increases childhood through adolescence (Erickson & Lewis, 2002). The density of chandelier neuron axon cartridges immunoreactive for either PV or GAT1 increases from birth to reach a peak during childhood and then declines markedly during adolescence to stable adult levels, whereas the density of pyramidal cell AIS immunoreactive for the GABA_A receptor $\alpha 2$ subunit is very high in the postnatal period, and then steadily declines through adolescence (Cruz et al., 2003). Whether these findings reflect developmental shifts in the number of basket and chandelier cell inputs to pyramidal cells or in the amount of pre- and post-synaptic proteins at these inputs remains unclear.

The protracted postnatal refinements in the connectivity of pyramidal and PV neurons in layer 3 of primate DLPFC suggest that there may be multiple sensitive periods during which adverse environmental events or exposures could alter these developmental trajectories (Hoftman & Lewis, 2011). Indeed, a range of environmental exposures occurring at different stages of development (e.g., *in utero* infections, obstetrical complications, minority group position and urban residence during childhood, and frequent cannabis use during early adolescence (Lewis & Levitt, 2002; van Os et al., 2010)) have all been associated with an increased risk for the later appearance of schizophrenia.

Identification of individuals at risk for schizophrenia

The findings summarized above suggest that core cognitive impairments in schizophrenia are present, and in some individuals are progressive, before the onset of psychosis and that these impairments might reflect, at least in part, disturbances in the developmental trajectories of components of DLPFC circuitry. However, the implementation of any type of preemptive, disease-modifying intervention based on these findings requires the ability to identify children and adolescents who are at high risk for a clinical diagnosis of schizophrenia.

Genetic risk factors

The risk of schizophrenia is directly proportional to the percentage of genes shared with an affected person (Gottesman, 1991). For example, the relative risk of schizophrenia is ~10 times greater among first degree relatives, and ~45 times greater in the monozygotic twin of an affected individual than in the general population (Gottesman, 1991; Cardno et al., 1999). Consistent with these findings, the risk of schizophrenia in adopted individuals is associated with the presence of the illness in the biological but not in the adoptive parents (Gottesman, 1991). However, the inheritance of schizophrenia is clearly complex and does not conform to a typical mode of inheritance such as autosomal dominant, sex-linked or mitochondrial (Sullivan, 2008). Both common allelic variants of small effect and a number of rare copy number variants (e.g., large deletions or duplications of DNA), both inherited and de novo, of apparently large effect have been associated with the illness (Kim et al., 2011). Increased

rates of de novo copy number variants might help explain the persistence of schizophrenia despite reduced fertility and reproduction (Haukka et al., 2003). However, at present, neither family history nor genetic markers have sufficient positive predictive power for the reliable identification of individuals with a high likelihood of manifesting the diagnostic features of schizophrenia.

Environmental risk factors

A number of adverse events occurring at different stages of development have been associated with an increased risk of schizophrenia later in life (Lewis & Levitt, 2002). These putative risk factors include severe physical or emotional maternal stress during the first trimester of pregnancy (Susser et al., 1996; Khashan et al., 2008), maternal influenza during the second trimester of pregnancy (Mednick et al., 1989), labor and delivery complications (Geddes & Lawrie, 1995), high population density at the place of birth and rearing (Pedersen & Mortensen, 2001), frequent cannabis use during adolescence (Moore et al., 2007), and immigration, especially of individuals belonging to a racial or ethnic minority in their new residence (Morgan et al., 2010). However, some of these factors require additional replication to be established as risk factors and none of them has sufficient specificity and sensitivity to identify at-risk individuals with high probability (Cannon et al., 2002; van Os et al., 2010).

Biomarkers of risk for psychosis

Given the limited positive predictive value of both genetic and environmental risk factors for the later diagnosis of schizophrenia, recent studies have focused on other methods for detecting individuals at high risk for conversion to psychosis. For example, in treatment-seeking individuals with prodromal symptoms of schizophrenia, about one-third will convert to psychosis over the next several years. However, about two-thirds of treatment-seeking individuals who have 2 or more of certain characteristics (e.g., genetic risk with recent deterioration in function, high levels of unusual thought content or paranoia, social impairment, or history of substance use) will convert (Cannon et al., 2008). Other lines of evidence suggest that deviations from normal developmental trajectories in task-related patterns of brain activation (Gee et al., 2012) or the presence of neurophysiological alterations known to be associated with schizophrenia (Ziermans et al., 2012; Shaikh et al., 2012) predict conversion. These studies represent important examples of the progress being made in identifying at-risk individuals, and in predicting conversion to clinical schizophrenia, but further studies are needed before pre-emptive interventions can be reliably applied, especially if those interventions carry potential for adverse medical effects or stigma.

The future of preemptive interventions for schizophrenia

The successful use of preemptive interventions for schizophrenia requires not only the ability to identify at-risk individuals, but also knowledge of when and how to intervene. Consider, for example, the potential contribution of a deficient number of dendritic spines on DLPFC layer 3 pyramidal neurons to the deficits in working memory that are present before the onset of psychosis. If these spine deficits reflect a failure in the normal exuberant spine proliferation during the third trimester of gestation or early childhood, then preemptive interventions might need to be delivered quite early in life and targeted to molecular pathways that regulate spine formation. Alternatively, if spine deficits reflect excessive spine pruning during late childhood-adolescence (Feinberg, 1982; Hoffman & Dobscha, 1989), then preemptive interventions could be delivered later and directed at molecular pathways that regulate spine maintenance. The idea that a deficit in the excitatory connectivity of DLPFC layer 3 pyramidal neurons, which is critical for normal working

memory function (Goldman-Rakic, 1995), arises during late childhood-adolescence is consistent with evidence that individuals who are later diagnosed with schizophrenia have normal working memory function at age 7, but then fail to show the typical age-related improvement in working memory performance (Reichenberg et al., 2010). In addition, teenagers at high risk for schizophrenia, especially those who later became psychotic, had poorer performance on neurocognitive measures than comparison subjects, although this dysfunction was milder than in individuals in their first psychotic episode (Seidman et al., 2010). Finally, many studies indicate that high-risk subjects who convert to schizophrenia have greater reductions in PFC grey matter volume during adolescence than do non-converters (Pantelis et al., 2003; Borgwardt et al., 2007; Sun et al., 2009; McIntosh et al., 2011; Mechelli et al., 2011), an expected finding if spines are being excessively pruned. Furthermore, the expression of gene products that have been implicated in spine maintenance are altered in schizophrenia, providing both a potential molecular basis for excessive spine pruning and novel drug targets (Hill et al., 2006; Ide & Lewis, 2010).

The design of preemptive interventions directed against spine deficits might also be informed by knowledge of the types of spines that are affected. Spines have distinct morphologies that reflect different types of synaptic plasticity; small, thin (“learning”) spines are considered to be transient and critical for rapid plasticity, whereas large, mushroom-shaped (“memory”) spines are thought to be stable and essential for long-term plasticity (Kasai et al., 2003). Thin spines have been proposed to be key elements in “dynamic network connectivity,” an ongoing and rapid strengthening or elimination of excitatory connections in the DLPFC that provides the mental flexibility characteristic of working memory (Arnsten et al., 2010). Consistent with this hypothesis, thin spine density in monkey DLPFC is positively correlated with working memory ability (Dumitriu et al., 2010). If a lower density of thin spines in the DLPFC contributes to impaired working memory in individuals with schizophrenia, then it may be possible to reverse this deficit through pharmacological means. For example, estrogen treatment increases thin spine density in monkey DLPFC (Tang et al., 2004; Hao et al., 2007), and estrogen receptor modulators have been reported to improve symptoms in postmenopausal women with schizophrenia (Kulkarni et al., 2010; Usall et al., 2011).

The decrease in presynaptic GAD67 (Curley et al., 2011) and postsynaptic GABA_A α 1 subunit-containing receptors (Glausier & Lewis, 2011) at PV basket neuron inputs to layer 3 pyramidal neurons in schizophrenia suggest that PV basket cell inhibition is lower in schizophrenia. Such a reduction in inhibition has been hypothesized to represent a compensatory response to an upstream deficit in layer 3 pyramidal cell excitation (due to their dendritic spine deficit) that would help re-balance DLPFC excitation and inhibition (Lewis et al., 2012). The presynaptic down-regulation of GAT1 (Woo et al., 1998) and the postsynaptic up-regulation of GABA_A α 2 subunit-containing receptors (Volk et al., 2002) at PV chandelier cell-pyramidal cell inputs are also thought to be compensatory to the spine deficit, since in “quiet” circuits GABA inputs from chandelier cells can be excitatory (Woodruff et al., 2011). Consistent with this hypothesis, in proof-of-concept studies a novel compound that enhances GABA neurotransmission at GABA_A receptors containing α 2 subunits was associated with improved working memory performance in subjects with schizophrenia (Lewis et al., 2008) and in an animal model of the cognitive deficits of schizophrenia (Castner et al., 2010), although a larger clinical trial in chronically-ill subjects with schizophrenia did not show evidence of benefit (Buchanan et al., 2011). The possibility that this or a related therapeutic strategy would be of benefit at an early stage of the illness, especially prior to the onset of psychosis, remains to be determined (Lewis, 2011).

The alterations in cortical circuits that underlie the cognitive abnormalities in schizophrenia might also be targeted through behavioral interventions. For example, recent studies using

different behavioral approaches have reported functional improvements in individuals with schizophrenia. Subjects with chronic schizophrenia who participated in 80 hours of computerized training of cognitive processes, compared to those engaged in a computer games control condition, exhibited improvement in reality monitoring and improved social functioning 6 months later (Subramaniam et al., 2012). Relative to patients with chronic schizophrenia who received standard treatment alone, those who also received up to 18 months of cognitive therapy focused on correcting dysfunctional beliefs and adapted for neurocognitive impairments exhibited improvements in global functioning and reductions in both avolition and positive symptoms (Grant et al., 2012). A two year trial of cognitive enhancement therapy, which combines computer-assisted neurocognitive training and group-based social cognition exercises, was associated with both improvement in social cognition and greater preservation of gray matter volume in patients with schizophrenia treated within the first 5 years of onset of psychosis (Eack et al., 2010). The effectiveness of these interventions might actually be greater if used in individuals at risk, but before the onset of psychosis, since the intervention would be delivered at a stage of life when the targeted neural circuits normally have greater plasticity, and before the function of these circuits has borne the brunt of illness chronicity. In addition, relative to pharmacological approaches, behavioral interventions offer potential advantages in terms of a lower risk of adverse side effects and less stigma.

The use of behavioral interventions might be particularly powerful in improving cognition when used in combination with pharmacological approaches designed to enhance the function of pyramidal neuron-PV neuron connectivity. Such pharmacological interventions might be synapse-specific and chronic (e.g., increasing the slow depolarization of pyramidal neurons via inputs from PV chandelier cells with a positive allosteric modulator of $\alpha 2$ subunit-containing GABA_A receptors (Lewis et al., 2012)) in order to improve the functional capacity of the neural circuitry engaged by the cognitive training. Alternatively, a drug that broadly enhances synaptic plasticity might be administered only at the time of cognitive training in order strengthen connections in those specific circuits that are activated by the training regimen.

Finally, it is also important to recognize that although the positive predictive power of identified risk factors for schizophrenia is low at the level of the individual, they may still inform public health initiatives that could be preemptive. For example, cannabis use has before the age of 16 has been reported to increase the risk for, and lower the age of onset of, schizophrenia in a dose-dependent manner (Moore et al., 2007). In fact, epidemiological findings estimate that 8–14% of cases of schizophrenia can be attributed to cannabis use (Moore et al., 2007). Thus, public health measures designed to reduce or delay the use of cannabis during the early teen years could have a substantial impact on the appearance of the psychosis of schizophrenia. Unfortunately, use of cannabis among US teenagers has increased in recent years in association with a decline in its perceived risk in this age group (Johnston et al., 2012).

In summary, advancements in our understanding 1) that impairments in certain cognitive processes as the core feature of schizophrenia, 2) of the neural circuitry basis for these impairments, and 3) of the developmental nature of these circuitry abnormalities offer promise for the future development and implementation of safe, preemptive, disease-modifying interventions in individuals at high risk for schizophrenia.

Acknowledgments

Cited work conducted by the author was supported by NIH grants MH051234, MH43784, and MH084053.

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