Dendritic Spine Pathology in Schizophrenia

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Abstract

Schizophrenia is a neurodevelopmental disorder whose clinical features include impairments in perception, cognition and motivation. These impairments reflect alterations in neuronal circuitry within and across multiple brain regions that are due, at least in part, to deficits in dendritic spines, the site of most excitatory synaptic connections. Dendritic spine alterations have been identified in multiple brain regions in schizophrenia, but are best characterized in layer 3 of the neocortex, where pyramidal cell spine density is lower. These spine deficits appear to arise during development, and thus are likely the result of disturbances in the molecular mechanisms that underlie spine formation, pruning, and/or maintenance. Each of these mechanisms may provide insight into novel therapeutic targets for preventing or repairing the alterations in neural circuitry that mediate the debilitating symptoms of schizophrenia.

Schizophrenia is a devastating and complex psychiatric disorder characterized by impairments in multiple domains, including perception, affect and cognition. This range of clinical features suggests that the pathophysiology of schizophrenia reflects altered connectivity within and between multiple brain regions. Many of these connections involve dendritic spines, small protrusions from dendritic shafts that are the synaptic targets of axon terminals. Dendritic spine number undergoes substantial changes during development, and abnormalities in these processes likely contribute to the pathology of a number of brain disorders, including schizophrenia. In this review, we consider 1) findings of dendritic spine abnormalities in schizophrenia, 2) evidence that these abnormalities reflect the disease process, 3) possible anatomical and molecular mechanisms underlying spine abnormalities in schizophrenia, 4) the potential role of altered developmental trajectories in these abnormalities, and 5) the implication of these findings for understanding the disease process of schizophrenia and for the development of novel therapeutic interventions.

Schizophrenia

Clinical Features

Schizophrenia affects approximately 0.5–1.0% of the world's population, and the care and treatment of schizophrenia is associated with large economic, societal and family burdens (Wu et al., 2005; Awad and Voruganti, 2008). The clinical signs and symptoms of schizophrenia can be divided into three categories: positive, negative, and cognitive. Positive symptoms include hallucinations, delusions, and thought disorder. Negative

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symptoms include altered emotional expression (e.g., flat affect), inability to derive pleasure from activities that were previously enjoyable (i.e., anhedonia), poverty of speech (i.e., alogia), and inability to initiate and persist in goal-directed activities (i.e., avolition) (American Psychiatric Association, 1994). Cognitive symptoms include deficits in multiple domains such as executive functioning, attention, and working memory (Elvevag and Goldberg, 2000; Piskulic et al., 2007). The positive and negative diagnostic features generally appear in late adolescence or early adulthood (Lewis and Lieberman, 2000), while cognitive impairments are usually present years before the clinical diagnosis is made (Lesh et al., 2011).

The staple treatment for schizophrenia is antipsychotic drugs (APDs). Although these medications can suppress the positive symptoms experienced by patients (Kane, 1996; Lieberman and Stroup, 2011), they have little to no effect on negative and cognitive symptoms (Keefe et al., 2007; Harvey, 2007). Importantly, cognitive impairments are the best predictor of factors underlying recovery such as employment, social integration, and relapse (Green, 2006). Thus, while the discovery of antipsychotic drugs has improved the outcome and quality of life of many individuals diagnosed with schizophrenia, the limited efficacy of these drugs clearly indicates the need to identify new biological targets and therapeutics for schizophrenia patients (Insel and Scolnick, 2006).

Risk Factors

Schizophrenia is more commonly diagnosed in males (male:female ratio 1.4:1) (Aleman et al., 2003; McGrath et al., 2004); and males have more severe symptoms, including an earlier age of onset, poorer response to treatment, and worse outcomes (Grossman et al., 2008). People born in urban environments have twice the risk for developing schizophrenia as those born in rural environments (Marcelis et al., 1998; Mortensen et al., 1999; Pedersen and Mortensen, 2001), and some studies suggest an increased risk for those living in cities irrespective of their birthplace (McGrath et al., 2004; Saha et al., 2005). Migrant populations, especially those belonging to an ethnic minority in their new location, are at a significantly increased risk for schizophrenia (Fearon et al., 2006; Morgan et al., 2010). Finally, epidemiological data suggest a significantly increased risk for developing schizophrenia later in life in individuals who chronically use marijuana during early adolescence (Casadio et al., 2011).

Genetic factors also clearly contribute to the etiology of the illness as the relative risk of schizophrenia is 6 – 17 times greater among first degree relatives, and 40 – 50 times greater in the monozygotic twin of an affected individual than in the general population (Gottesman, 1991; Cardno et al., 1999). Both common allelic variants of small effect and rare copy number variants (i.e., large deletions or duplications of DNA) of apparently large effect have been associated with the illness, but identification of specific genetic causes remains an ongoing challenge (Kim et al., 2011).

Finally, schizophrenia has a clear developmental component; many symptoms appear or worsen during adolescence (Lewis and Lieberman, 2000), a time of great transition and refinements in brain structure and function (Casey et al., 2010; Chu-Shore et al., 2011). A proposed integrated conceptualization of schizophrenia as a disorder of neurodevelopment includes the interaction of genetic predisposition and environmental exposures, which lead to cascading effects of altered neurodevelopment, resulting in the behavioral syndrome (Lewis and Levitt, 2002).

Pathology

Structural imaging studies have shown smaller whole brain volumes in the prodromal stage, at the first episode of psychosis, and in chronically ill patients (Lawrie and Abukmeil, 1998; Steen et al., 2006; Levitt et al., 2010). For example, a recent eight year longitudinal magnetic resonance imaging (MRI) study demonstrated that people at high genetic risk for schizophrenia have greater reductions over time in whole brain, prefrontal cortex (PFC), and temporal lobe volumes than those with no genetic risk. Moreover, those who eventually converted to schizophrenia showed an even greater reduction in PFC volume (McIntosh et al., 2011). Smaller hippocampal volumes have also been identified at these early stages of the illness (Harrison, 2004; Tamminga et al., 2010), in agreement with the temporal lobe findings. Decreased volume in schizophrenia appears to be especially pronounced in cortical areas; in contrast, results from structural imaging studies of the basal ganglia (Bogerts et al., 1985; Brandt and Bonelli, 2008; Horga et al., 2011) and cerebellum (Supprian et al., 2000; Andersen and Pakkenberg, 2003; Kakeda and Korogi, 2010) have been mixed.

Reductions in grey matter may underlie the smaller cortical and hippocampal volumes in schizophrenia (Glahn et al., 2008). Although not conclusive, smaller grey matter volumes are frequently reported in individuals at high genetic risk (Cannon et al., 2002; Hulshoff Pol et al., 2004; Borgwardt et al., 2010; Mechelli et al., 2011), and in both first-episode and chronically ill subjects with schizophrenia relative to healthy comparison subjects (Honea et al., 2005; Takahashi et al., 2009; Levitt et al., 2010). Some longitudinal MRI studies have found that high risk subjects who convert to psychosis have larger deficits in grey matter volume than those who do not (Pantelis et al., 2003; Fornito et al., 2008; Sun et al., 2009); however, a recent large, multicenter study found that grey matter reductions in converters and non-converters were virtually indistinguishable (Mechelli et al., 2011). Finally, many studies indicate that deficits in grey matter may be progressive through the initial phases of the disease (Kasai et al., 2003b; Takahashi et al., 2009; Yoshida et al., 2009; Olabi et al., 2011).

Neuronal somal size is correlated with dendritic tree (Hayes and Lewis, 1996; Jacobs et al., 1997) and axonal arbor (Lund et al., 1975; Gilbert and Kelly, 1975) complexity, whose components (dendritic shafts, dendritic spines, axons, and axon terminals) contribute to the cortical neuropil. Studies using postmortem human tissue suggest that smaller pyramidal cell bodies and decreased neuropil, rather than neuron loss, may be the primary contributor to smaller cortical grey matter volumes in the dorsolateral prefrontal cortex (DLPFC) and auditory cortices in schizophrenia. On average, pyramidal cell somal volume is ~10% smaller in layer 3 of the DLPFC (Rajkowska et al., 1998; Glantz and Lewis, 2000; Pierri et al., 2001), and primary and association auditory cortices (Sweet et al., 2003; Sweet et al., 2004); and neuronal packing density is increased each of those regions in schizophrenia in some studies (Selemon et al., 1995; Selemon et al., 1998; Selemon et al., 2003; Dorph-Petersen et al., 2009). Together, these data suggest that schizophrenia is associated with diminished cortical neuropil (Selemon and Goldman-Rakic, 1999; Dorph-Petersen et al., 2009), and as summarized below, studies from multiple cortical areas indicate that lower dendritic spine density contributes to the reduced cortical neuropil in schizophrenia.

Spines are morphologically and biochemically discrete compartments that protrude from the dendritic shafts of cortical and hippocampal pyramidal cells, cortical spiny stellate cells, cerebellar Purkinje cells, and medium spiny neurons of the striatum (Gray, 1959; Harris and Kater, 1994). The vast majority (80 – 95%) of excitatory synapses in the central nervous system are formed onto dendritic spines (DeFelipe and Farinas, 1992; Wilson, 2007); and, as such, spines perform a significant role in regulating neuronal excitability. Each spine typically receives one glutamatergic synapse; thus spine density reflects the amount of excitatory drive a neuron receives (Yuste, 2011), though spines may also be innervated by

other neurotransmitter and neuropeptide systems (Goldman-Rakic et al., 1989; Kung et al., 1998) (Figure 1). In experimental models, spine deficits are associated with impairments in working memory, attention, sensory-motor processing, and sociability (Liston et al., 2006; Cahill et al., 2009; Hains et al., 2009; Brennaman et al., 2011); such findings suggest that deficits in dendritic spines may contribute to the clinical features of schizophrenia. Indeed, the diverse symptomatology of schizophrenia suggests that a common alteration is present across many different brain regions and leads to impaired connectivity within and between regions; thus, alterations in dendritic spines could play a key role as a neural substrate for schizophrenia.

Spine Alterations in Schizophrenia

Neocortex

Direct quantification of neocortical dendritic spines in schizophrenia subjects has been performed in four studies using either Golgi impregnation of pyramidal cells or immunohistochemical labeling of spine markers (Table 1). All findings converge on the conclusions that spine density is lower in multiple neocortical areas in schizophrenia, and that these alterations might be most robust for pyramidal neurons located in layer 3, a major site for cortico-cortico and thalamo-cortical integration (Jones, 1984; Kritzer and Goldman-Rakic, 1995; Melchitzky et al., 1999). For example, layer 3 pyramidal cells receive both feed-forward and intrinsic excitatory cortical inputs, as well as excitatory inputs from the thalamus. Thus, lower spine density in layer 3 pyramidal cells may reflect, or contribute to, alterations in multiple types of excitatory connections in the cortex. The first Golgi study quantified spine density in pyramidal cells whose somata were located in layer 3 in various prefrontal and temporal cortical areas. In these multiple areas, spine density was significantly ~ 60% lower in the schizophrenia subjects (Garey et al., 1998).

Subsequent work quantified spine density in triad cohorts of schizophrenia, healthy comparison, and psychiatric comparison subjects. Relative to both comparison subject groups, spine density in the subjects with schizophrenia was ~20% lower on the basilar dendrites of pyramidal neurons located in layer deep 3, but did not differ for pyramidal neurons in superficial layer 3, layer 5 or layer 6 of area 46, or in layer 3 of primary visual cortical area 17 (Glantz and Lewis, 2000; Kolluri et al., 2005) (Figure 2). Interestingly, within layer deep 3 of area 46, the total dendritic length (TDL) was also significantly lower in schizophrenia subjects, and analysis of spine density controlling for TDL increased the significance of the between group difference. Importantly, spine density in subjects in the psychiatric comparison group who had been treated with APD did not differ from healthy comparison subjects, suggesting that decreased DLPFC spine density in schizophrenia is not a consequence of APD treatment.

Finally, one study examined spine density in primary and association auditory cortices areas 41 and 42 by quantifying spinophilin-immunoreactive (SP-IR) puncta in matched pairs of schizophrenia and healthy comparison subjects (Sweet et al., 2009). The density of layer deep 3 SP-IR puncta was significantly 27% lower in area 41 and 22% lower in area 42 of schizophrenia subjects. Using the presence or absence of immunoreactivity to identify whether a neuronal structure is present or absent has some methodological limitations. For example, the spine may still be present, but no longer contains SP-immunoreactivity at detectable levels, resulting in an erroneous interpretation of decreased spine density. However, studies of cortical SP mRNA and protein expression have found either increased or unchanged levels in schizophrenia (Weickert et al., 2004; Baracskay et al., 2006), supporting the interpretation that lower SP-IR puncta density is reflective of decreased spine density, and not undetectable levels of SP-immunoreactivity per spine.

Non-cortical areas

Spine pathology has also been reported in the striatum and hippocampus of schizophrenia subjects (Table 1). In the striatum, spines on GABAergic medium spiny neurons (MSN) have been examined by electron microscopy in schizophrenia in several studies from the Roberts' group. Overall, the studies indicate that axospinous synapse density may be increased in the dorsal striatum (Table 1). For example, a 3D reconstruction analysis of over 4,000 and 2,000 synapses in schizophrenia and healthy comparison subjects, respectively, found significantly higher densities of all types of synapses, including asymmetric axospinous, in the caudate of schizophrenia subjects. These findings were present in subjects receiving either typical or atypical APD, and they were especially pronounced in the two subjects off APD at the time of death, suggesting that medication effects were not driving the increase in synaptic density (Roberts et al., 2005b). To further examine which afferent sources may be contributing to increased axospinous synapse density, two subsequent studies quantified synaptic density in the patch and matrix compartments of the striatum (Roberts et al., 2005a; Roberts et al., 2008). A significant increase in total synaptic density in the putamen patch of subjects with schizophrenia was observed, and this difference was driven by a selective increase in the density of asymmetric axospinous synapses. Importantly, subjects on typical APD had normal levels of putamen patch axospinous synaptic density, those on atypical APDs had higher densities, and the two subjects not on APDs at the time of death had the highest density. Together, these results suggest that increased axospinous synaptic density in the putamen patch compartment may not be a consequence of APD treatment. Because patch compartments receive cortico-limbic inputs (Bolam et al., 2000), these findings may reflect increased glutamatergic inputs from corticolimbic regions onto MSNs in the putamen patch compartment in schizophrenia. Interestingly, putamen patch MSNs project to the substantia nigra pars compacta, where they inhibit dopaminergic neurons. Thus, enhanced excitation of inhibitory MSN may be a compensatory response to quell overactive nigral dopaminergic neurons in schizophrenia. However, whether increased axospinous synapse density, and presumably increased excitatory drive, reflects a cause of the illness, compensation to some other upstream pathology, or a consequence of treatment remains to be determined.

In the hippocampal formation, the major glutamatergic pathways consist of projections from the entorhinal cortex to the dentate gyrus via the perforant pathway, dentate gyrus to CA3 via the mossy fiber projections, CA3 to CA1 via the Schaffer collateral, and CA1 to the subiculum. Dendritic spine density in these pathways has only been reported in one study of schizophrenia. Apical spine density was significantly ~70% lower in schizophrenia subjects and significantly ~50% lower in mood disorder subjects relative to the healthy comparison group (Rosoklija et al., 2000). Importantly, because subjects in the mood disorder group, all of whom had all been treated with APD, also had significantly lower subicular spine density, an effect of APD treatment on spine density cannot be ruled out. Moreover, in contrast to many other postmortem studies of schizophrenia, all of the schizophrenia and mood disorder subjects were institutionalized in state hospitals for lengthy periods, and lack of environmental enrichment can decrease hippocampal spine density (Moser et al., 1994; Leuner and Gould, 2010).

Two studies using EM techniques have examined mossy fiber terminations (MFT) onto CA3 pyramidal cell spines in schizophrenia subjects. In the first study, subject groups did not differ in the volume fraction of spines, total number of invaginated spines, nor the number of spines receiving a synapse per MFT (Kolomeets et al., 2005). In a subsequent study, those authors found a significant 25% reduction in the mean number of synaptic contacts per MFT, though analysis was not restricted to axospinous synapses (Kolomeets et al., 2007). Whether these results differ from the previous study due to the inclusion of axodendritic synapses and/or the different characteristics of the subject cohorts is unclear. Thus, while

imaging studies of the hippocampus have convincing data regarding smaller volume and altered activity during some memory tasks (Steen et al., 2006; Tamminga et al., 2010), studies on morphological changes of dendritic spines are mixed and preliminary.

Methodological & Medication Considerations

In interpreting the results of the studies that used Golgi impregnation methods to quantify spine density or dendritic length, it is important to keep in mind several potential limitations of this technique. First, only a small proportion of neurons are labeled using Golgi staining, and the number labeled can vary considerably across samples (Pasternak and Woolsey, 1975). However, the process by which cells are labeled is stochastic, and as such, labeled neurons are likely representative of the population. Second, because the reaction product of Golgi impregnation is opaque, labeled spines could be obscured behind dendritic shafts and not counted. Thus, differences in dendrite diameter between diagnostic groups could contribute to the findings (Horner and Arbuthnott, 1991), and this issue should be considered when interpreting Golgi studies which do not report dendritic diameter [(Garey et al., 1998; Rosoklija et al., 2000; Kolluri et al., 2005)]. However, Glantz and Lewis (2000) reported no difference in mean dendrite diameter across schizophrenia and comparison subjects, suggesting that lower spine density in schizophrenia is not a consequence of hidden spines. Finally, although Golgi-labeled neurons that are fully impregnated can be identified following postmortem intervals (PMI) of up to 24 hours, longer PMIs can contribute to incomplete Golgi impregnation; indeed, even at 12 hour PMIs, spine density appears to be reduced, with superficial cortical layers reported to be preferentially affected (Williams et al., 1978; Buell, 1982). The longer PMIs in the schizophrenia relative to comparison subjects in the Garey et al (1998) and Rosoklija (2000) studies may have contributed to the larger between subject group differences in spine density identified in these two studies relative to those found in the shorter PMI study of Glantz and Lewis (2000).

Golgi studies of cortical spine density all demonstrate decreased number of spines per μm of dendrite in schizophrenia subjects relative to healthy comparison subjects, and this density measure is likely reflective of a decrease in the total number of spines. Total spine number can be altered by changes in the number of spines per dendritic length, and/or decreased dendritic length. By measuring the number of spines/μm, these studies confirm that spine deficits are not only due to shorter dendrites in schizophrenia. However, the decrease in schizophrenia may be reflective of both of these processes, given other reports of decreased dendritic complexity in the subiculum (Rosoklija et al., 2000) and PFC (Kalus et al., 2000; Broadbelt et al., 2002). Indeed, lower TDL was identified in the DLPFC (Glantz and Lewis, 2000) of schizophrenia subjects along with decreased spine density. Sweet et al (2009) found lower spine density in schizophrenia auditory cortex using the number of SP-IR puncta/μm^3 of tissue. Given that structural imaging studies consistently report smaller gray matter volumes in schizophrenia, these density measures may actually underestimate the reduction in cortical dendritic spine number in schizophrenia.

Dendritic spines are dynamic structures, whose morphology and density can change in response to many factors, including circulating hormone levels, changes in environmental enrichment, drug use, learning, and synaptic activity (Yuste and Bonhoeffer, 2001; Fiala et al., 2002), and thus the potential impact of such factors on the findings of decreased spine density in schizophrenia must be kept in mind. Two studies which found lower spine density in schizophrenia statistically examined the effects of comorbid substance abuse diagnosis and duration of illness, and found no effect of these factors on spine density (Glantz and Lewis, 2000; Sweet et al., 2009). In addition, psychiatric comparison subjects, which may have similar hospitalization experiences as schizophrenia subjects, did not have altered cortical spine density (Glantz and Lewis, 2000; Kolluri et al., 2005). Moreover,

experimental data demonstrate that the vast majority of spines in mouse cortex persist for over 13 months (Grutzendler et al., 2002), that persistent spines are more prevalent in adult animals (Holtmaat et al., 2005), and that dendritic spine density is relatively stable in adult monkey and human DLPFC (Anderson et al., 1995; Petanjek et al., 2011).

The possible effect of APD on spine measures is of potential concern in all the postmortem studies described above. In addition to statistically accounting for APD usage, animal studies have provided information about the effects of chronic APD treatment on spine measures. In rats chronically treated with haloperidol for six months, mean striatal spine density was decreased (Roberts et al., 1995; Kelley et al., 1997), whereas many of the striatal postmortem findings suggest increased striatal spine density in schizophrenia. Sweet et al (2009) included a control experiment comparing SP-IR puncta density across two groups of sex-, age- and weight-matched monkeys: one group was chronically administered haloperidol for 9 – 12 months at doses that produced serum levels comparable to those associated with therapeutic efficacy in humans, and the other group received vehicle. Quantification of SP-IR puncta density revealed no difference between the two groups. Finally, rats treated with clinically-relevant doses of haloperidol or olanzapine showed no changes in PFC pyramidal cell spine density (Wang and Deutch, 2008), and rats chronically treated with haloperidol for one year also did not show a change in cortical spine density (Vincent et al., 1991). Thus, while not conclusive, the available data suggest that the striatal and cortical spine findings are likely not an artifact of APD treatment.

Potential mechanisms underlying spine deficits in schizophrenia

Markers of molecular mechanisms important for dendritic spine formation and maintenance are altered in schizophrenia. Stabilization of the actin cytoskeleton is essential for spine shape and density (Calabrese et al., 2006; Tada and Sheng, 2006; Bourne and Harris, 2008), and transcript and protein levels of molecules important for spine cytoskeletal stabilization are altered in multiple cortical areas in schizophrenia. Rho GTPases, small proteins that bind to GDP and GTP, are important for intracellular signaling and actin remodeling (Negishi and Katoh, 2005; Calabrese et al., 2006). Activity of the Rho GTPases Cdc42 (cell division cycle 42) and Rac1 (Ras-related C3 botulinum toxin substrate 1) increases spine formation in culture and *in vivo* (Nakayama et al., 2000; Irie and Yamaguchi, 2002; Scott et al., 2003; Kreis et al., 2007; Cerri et al., 2011; Bongmba et al., 2011). In schizophrenia, Cdc42 mRNA levels are lower, and the decrease is strongly correlated with DLPFC layer 3 spine deficits (Hill et al., 2006). Cdc42 has numerous effector proteins, and mRNA for Cdc42 effector protein 3 (Cdc42EP3), which is preferentially expressed in layer 3 of human DLPFC (Arion et al., 2007), is upregulated in schizophrenia (Ide and Lewis, 2010). Interestingly, current evidence suggests that activation of Cdc42 by glutamate stimulation inhibits Cdc42EP3 activity which in turn dissociates the complex of septin filaments in spine necks, enabling the movement from the parent dendrite of molecules (e.g., cytoskeletal proteins, second messengers, etc) required for synaptic potentiation (Ide and Lewis, 2010). The combination of lower levels of CDC42 and higher levels of Cdc42EP3 might lead to a reduced capacity for glutamatergic stimuli to open the septin filament barrier in the spine neck, impairing synaptic plasticity and contributing to spine loss (Figure 3).

Promotion of RhoGTPase interaction with effector proteins is mediated via guanine exchange factors (GEFs), including Kalirin, a Rac1 GEF that is concentrated in spine heads (Penzes et al., 2001) and regulates cortical spine density (Cahill et al., 2009). In schizophrenia, Kalirin mRNA expression (using a probe that identifies Kalirin-5 and Kalirin-7) is lower in DLPFC layer 3, and this decrease is correlated with DLPFC layer 3 spine deficits in the same subjects (Hill et al., 2006). Interestingly, a recent study demonstrated no change in the protein levels of Kalirin-5, -7, and -12 and a significant 11%

increase in Kalirin-9 expression in total auditory cortex grey matter (Deo et al., 2011b). Kalirin-9 overexpression in mature cultured cortical neurons decreases dendritic length, without changing spine number (Deo et al., 2011a). Importantly, the *KALRN* locus has been associated with risk for schizophrenia (Ikeda et al., 2011); missense mutations in *KALRN* are reported in individuals with schizophrenia (Kushima et al., 2010); and the *KALRN* protein product interacts with those of other putative schizophrenia risk genes (e.g., *DISC1, NRG, ERBB4*) in regulating dendritic morphology and spine plasticity (Hayashi-Takagi et al., 2010; Cahill et al., 2012). While additional studies examining Kalirin mRNA and protein expression in a laminar-specific manner in DLPFC and auditory cortex are needed, these results suggest that alterations in Kalirin promotion of Rho GTPase activity, and subsequent spine formation and stabilization (Cahill et al., 2009; Xie et al., 2010), may contribute to the neocortical spine deficits in schizophrenia subjects.

Decreased presynaptic activity and/or fewer afferent inputs is another potential factor that could contribute to decreased cortical spine density in schizophrenia (Fiala et al., 2002). In mature neural systems, pharmacological blockade of AMPA receptors or surgical deafferentation of glutamatergic inputs results in decreased spine density (Hamori, 1973; Matthews et al., 1976; Cheng et al., 1997; McKinney et al., 1999; Smart and Halpain, 2000; Jacobs et al., 2003; Sa et al., 2010), and two recent studies showed that a constitutive reduction in NMDA receptor activity results in decreased spine density and cortical volume in PFC and sensory cortex (DeVito et al., 2011; Balu et al., 2011). Though the results of studies examining presynaptic transcript and protein levels in total cortical grey matter have been mixed (Bauer et al., 2008; Corradini et al., 2009; Fung et al., 2011), results from microscopy studies quantifying presynaptic protein levels suggest that cortical axon terminal density is likely to be decreased in schizophrenia. For example, synaptophysin immunoreactivity is decreased in all cortical layers of the DLPFC (Glantz and Lewis, 1997), and the density of synaptophysin-IR puncta is also decreased in auditory cortex (Sweet et al., 2007). Importantly, DLPFC spines receive glutamatergic inputs from local and long-range pyramidal cell projections, as well as projections from the mediodorsal (MD) nucleus of the thalamus (Melchitzky et al., 1999; Melchitzky et al., 2001; Negyessy and Goldman-Rakic, 2005). Determining whether spines postsynaptic to a specific afferent source are affected in schizophrenia will help to illuminate potential mechanisms for spine deficits in schizophrenia. Initial evidence suggested that the DLPFC received fewer inputs from the MD thalamus (Pakkenberg, 1990; Young et al., 2000; Popken et al., 2000; Byne et al., 2002), and since these axons preferentially innervate DLPFC deep layers 3 and 4, fewer inputs from the MD thalamus might explain the tendency for the deficit in spine density to be most marked on the basilar dendrites of deep layer 3 pyramidal cells. However, subsequent studies using unbiased stereological methods and larger samples of subjects failed to find evidence of fewer neurons in the MD thalamus in schizophrenia (Cullen et al., 2003; Dorph-Petersen et al., 2004; Young et al., 2004; Kreczmanski et al., 2007). Furthermore, thalamocortical inputs represent a small proportion of all glutamatergic synapses in the cortex (Ahmed et al., 1994; Peters, 2002), so even a complete loss of thalamic inputs would likely not result in the observed decrease in spine density. Thus, decreased density of spines is more likely to reflect a deficit in cortico-cortico projections.

DLPFC spines also receive inputs from dopaminergic axons projecting from the ventral tegmental area (VTA) (Goldman-Rakic et al., 1989). VTA lesions in adult rats result in decreased PFC pyramidal cell basilar spine density, with no change in motor cortex spine density, and this decrease may be mediated by both D_1 and D_2 dopamine receptors (Wang et al., 2009a). Interestingly, prefrontal dopaminergic signaling is also important for WM ability (Goldman-Rakic et al., 2000), and is thought to play a role in cognitive dysfunction in schizophrenia (Goldman-Rakic, 1994). For example, DLPFC dopamine D1-family receptors are more abundant in schizophrenia subjects (Abi-Dargham et al., 2002; Abi-Dargham et al.,

2011), and this increase is thought to reflect a compensatory upregulation due to decreased DLPFC dopaminergic innervation. However, a postmortem examination of dopaminergic inputs to the DLPFC only found a deficit in layer 6, where spine density is reportedly unchanged (Akil et al., 1999). Further examination of dopaminergic afferents to the DLPFC in human postmortem tissue will be important to determine whether diminished dopamine signaling could contribute to altered spine density in schizophrenia.

Another potential mechanism underlying decreased spine density and presynaptic inputs in schizophrenia is impaired mitochondrial functioning or trafficking within neurons. Because the brain relies fully upon glycolysis and mitochondrial respiration for adenosine triphosphate generation, deficits in mitochondrial function would be expected to strongly affect neuronal systems. Indeed, maintenance of dendritic and axonal arborization requires targeted, sufficient energy production from mitochondria (Mattson et al., 2008; Cheng et al., 2010). For example, impairing mitochondrial transport to dendrites by inhibiting mitochondrial fission decreases neuronal spine density (Li et al., 2004; Ishihara et al., 2009; Wang et al., 2009b), as does altering the mitochondrial membrane potential and cytochrome c release (Tsai et al., 2009). Multiple sources of information point to mitochondrial dysfunction in schizophrenia (Clay et al., 2011), including altered lactate levels in cerebrospinal fluid (Regenold et al., 2009), genetic linkage studies (Washizuka et al., 2006), altered levels of transcripts and proteins crucial to mitochondrial functioning (Martins-de-Souza et al., 2011; Gigante et al., 2011; Rosenfeld et al., 2011; Regenold et al., 2012), and altered brain metabolics (Khaitovich et al., 2008; Shao et al., 2008). However, mitochondria dysfunction has also been implicated in other psychiatric illnesses, such as bipolar disorder (Clay et al., 2011), which have not as yet been shown to have lower spine density.

Other molecular mechanisms that could contribute to decreased spine density in schizophrenia are being investigated (Lin and Koleske, 2010; Penzes et al., 2011; Bennett, 2011). For example, a candidate susceptibility gene for schizophrenia, disrupted in schizophrenia 1 (DISC1) (Chubb et al., 2008), is involved with mitochondrial trafficking (Atkin et al., 2011), and regulates spine formation via Kalirin-7 and Rac1 (Hayashi-Takagi et al., 2010). Neuregulin-1 and ErbB4 are also candidate susceptibility genes for schizophrenia (Walsh et al., 2008; Mei and Xiong, 2008), and their activity is associated with changes in spine density (Penzes et al., 2011). Finally, astroglia can enhance spinogenesis, and deficits in markers of glial functioning are identified in schizophrenia (Allen and Barres, 2005; Bernstein et al., 2009). Thus, multiple molecular or anatomical mechanisms, many of which interact with each other, may contribute to decreased cortical spine density in schizophrenia. Understanding which of these mechanisms are most relevant for schizophrenia may be informed by knowledge of when during development the spine deficits in individuals with schizophrenia arise.

Developmental trajectory of cortical spine density

The density of cortical dendritic spines goes through a protracted developmental trajectory defined by excessive production early in life, followed by pruning and elimination, and finally stabilization (Huttenlocher, 1979; Bourgeois et al., 1994; Huttenlocher and Dabholkar, 1997; Zhang and Benson, 2000). For example, pyramidal cell spine density in human DLPFC increases rapidly after birth and peaks in childhood, at which point spine density begins to decline until stabilizing in the third decade of life (Petanjek et al., 2011). Spine morphology also changes across development, transitioning from filopodia-shaped thin spines early in development to larger spines with a defined head and neck (commonly referred to as mushroom spines) (Garcia-Lopez et al., 2010), one hallmark of a stable axospinous synapse. Cortical axospinous synapses which survive pruning are generally less dynamic than those present earlier in development, becoming relatively stable in both shape

and density (Lin and Koleske, 2010). Thus, spine density and morphology reflect neuronal development, as well as plasticity and connectivity within a given region.

The developmental time point at which spine density deficits arise in schizophrenia is unclear. Experimental evidence suggests that adult spine density can be affected by manipulations that begin *in utero* (Mukai et al., 2008; DeVito et al., 2011), childhood or adolescence (Silva-Gomez et al., 2003; Rubino et al., 2009), and even adulthood (Wang and Deutch, 2008; Liston and Gan, 2011). However, the developmental trajectory of schizophrenia symptoms suggests that spine deficits may arise from impaired spinogenesis during early childhood and/or enhanced pruning during adolescence. For example, deficits in general knowledge, language skills, and verbal and visual reasoning are already emerging by age seven in individuals who later develop schizophrenia (Reichenberg et al., 2010). Furthermore, these individuals subsequently manifest deficits in processing speed and working memory by early adolescence. This longitudinal study indicates that cortical dysfunction is already present early in childhood in individuals who will later receive a schizophrenia diagnosis, perhaps reflecting abnormal spinogenesis, and that dysfunction of the affected cortical circuits might be exacerbated during adolescence when spines are pruned.

Further insight could come from longitudinal MRI studies of grey matter volume in individuals at genetic risk for schizophrenia, as cortical grey matter volume and spine density follow similar developmental trajectories (Bennett, 2011). MRI studies of 22q11 deletion syndrome (22q11 DS), a strong risk factor for developing schizophrenia (Drew et al., 2011), have been performed in children. While adults with 22q11 DS show smaller frontal lobe volumes (Tan et al., 2009), results from children have been mixed, showing increases or no difference (Eliez et al., 2000; Kates et al., 2001; Simon et al., 2005; Baker et al., 2011; Kates et al., 2011). Thus, studies from this patient population suggest spinogenesis may be unaffected in schizophrenia, though 22q11 DS-associated schizophrenia may not be generalizable to all forms of the illness. However, a recent MRI study found no difference in grey matter volume between infants of mothers with schizophrenia and those born to healthy comparison mothers (Gilmore et al., 2010). Thus, the available structural data suggests that spinogenesis may not be grossly impaired in individuals at high risk for developing schizophrenia. However, because the majority of these high risk individuals will not eventually develop schizophrenia, additional longitudinal structural MRI studies comparing converters and non-converters will help to clarify whether spinogenesis is impaired in schizophrenia.

Because cortical dendritic spine density decreases substantially throughout adolescence, enhanced spine pruning may contribute to decreased cortical spine density in schizophrenia. Feinberg first proposed abnormal synaptic pruning as a potential cause for schizophrenia (Feinberg, 1982), and seven years later Hoffman and Dobscha posited that over-pruning of PFC spines leads to schizophrenia (Hoffman and Dobscha, 1989). Excessive spine pruning is now considered a potential factor underlying reduced cortical grey matter volume in schizophrenia. This hypothesis is supported by 1) MRI studies showing that high-risk subjects who convert to schizophrenia may have greater reductions in grey matter volumes of the PFC and other cortical regions than non-converters (Pantelis et al., 2003; Borgwardt et al., 2007; Sun et al., 2009; McIntosh et al., 2011; Mechelli et al., 2011), and that grey matter loss may be progressive through the initial phases of the illness (Kasai et al., 2003b; Salisbury et al., 2007; Takahashi et al., 2009; Yoshida et al., 2009); 2) magnetic resonance spectroscopy studies suggesting an increased breakdown of plasma membrane phospholipids in the early stages of the illness (Keshavan et al., 2004); and 3) the observation that the emergence of schizophrenia symptoms generally occur during the period of spine pruning.

Over-elimination of cortical spines in schizophrenia may be due to pathologically enhanced pruning mechanisms, or an over-abundance of immature axospinous synapses that are normally pruned. The molecular mechanisms underlying pruning are not fully understood, though synaptic activity plays an important role (Trachtenberg et al., 2002; Lin and Koleske, 2010), and as such, many of the molecules and processes implicated in pruning are also implicated in spinogenesis and spine maintenance (Segal, 2005). Thus, alterations in one process are likely to affect the others, and decreased spine density in schizophrenia may represent a global problem in the formation, maturation, and maintenance of axospinous synapses, rather than a specific impairment in the generation, elimination or stabilization of spines.

Future Directions

The findings summarized above indicate that schizophrenia is associated with lower spine density that is best documented in the cerebral cortex, that this deficit may be most marked in layer 3, that a number of potential molecular mechanisms underlying this deficit exist, and that this deficit may reflect disturbances in the normal developmental trajectory of cortical spine number. Understanding the role of lower cortical spine density in the disease process of schizophrenia, and its treatment, requires answers to a number of important questions about 1) the circuits mediated by the affected spines, 2) the developmental timing of the deficit in the affected spines, and 3) the functional role of the affected spines.

The existing findings support the idea that dendritic spine density deficits in schizophrenia are layer specific, raising the possibility that certain cortical afferent circuits are affected. Layer 3 pyramidal cells receive afferents from four major sources: 1) local axon collaterals from neighboring pyramidal cells, 2) long-distance axon collaterals that travel through the grey matter from pyramidal cells in the same cortical region, 3) association and colossal projections from pyramidal neurons in other cortical regions, and 4) projections from the thalamus. Given that layer 3 pyramidal neurons are smaller in both the DLPFC and other regions that project to the DLPFC (Rajkowska et al., 1998; Glantz and Lewis, 2000; Pierri et al., 2001; Sweet et al., 2003; Sweet et al., 2004), any or all of the three cortical sources of inputs to layer 3 pyramidal cells could be affected. As discussed above, the number of neurons from the mediodorsal thalamus does not appear to be altered in schizophrenia, although fewer neurons have been reported in the pulvinar nucleus which also projects to the DLPFC (Dorph-Petersen and Lewis, 2011).

The distribution of spine deficits across the dendritic tree of the affected neurons could provide insight into both the affected afferents and whether the spine deficits are cell autonomous or independent of cell type. For example, lower spine density in all portions of the dendritic tree of a given class of cortical pyramidal neuron would suggest that the spine deficit is cell autonomous (Fig 4B), and thus possibly due to a cell type-specific, intrinsic deficit in the molecular machinery required for spine production/maintenance. A cell autonomous spine deficit restricted to deep layer 3 pyramidal cells would be predicted to result in the loss of targets for certain types of afferents, and thus would have the following downstream consequences for the affected pyramidal cells: fewer inputs from feed-forward cortical projections, fewer inputs from the intrinsic axon collaterals of layer 3 pyramidal cells, and fewer inputs from thalamic projections. In contrast, the connections furnished by these sources onto the dendritic spines of unaffected pyramidal cells, such as those with cell bodies are located in layers 5 and 6, would not be reduced (Fig 4B). Alternatively, a cell type-independent spine deficit in deep layer 3 would be associated with a different pattern of altered connectivity (Fig 4C). For example, an upstream deficit in feed-forward cortical projections would lead to a loss of spines on *all* dendrites in layers deep 3 and 4, but no change in the number of inputs from the intrinsic axon collaterals of layer 3 pyramidal cells

or from thalamocortical projections (Fig 4C). Importantly, these two models provide testable hypotheses as to the upstream cause of spine deficits in schizophrenia.

Knowing when during the course of the illness cortical spine deficits arise in schizophrenia may have substantial implications for therapeutic interventions designed to restore or maintain normal spine density and plasticity. For example, if spine deficits arise in adolescence during the prodromal phase of the illness, when spine pruning predominates, then interventions that forestall or blunt this decline may be effective in delaying or preventing the cognitive symptoms of the illness. On the other hand, if spine deficits arise during birth or early childhood, when spinogenesis predominates, then early identification of individuals at high genetic risk and regular assessments of proxy markers of dendritic spine density (e.g., cortical grey matter thickness) becomes critical. A high genetic risk person with decreased cortical grey matter in early childhood may be a prime candidate for an intervention that bolsters spinogenesis. For example, the adrenergic 2 agonist guanfacine increases spine density in cultured cortical neurons (Hu et al., 2008; Ren et al., 2011), and local infusion of guanacine into the DLPFC of awake, behaving monkeys restores delay period pyramidal cell firing in aged monkeys (Wang et al., 2011). In addition, systemic administration of guanfacine improves working memory performance in young and aged monkeys (Arnsten et al., 1988; Rama et al., 1996; Franowicz and Arnsten, 1998; O'Neill et al., 2000). However, a double-bind, placebo-controlled clinical trial in chronically-ill schizophrenia subjects found no effect of adjunctive guanfacine treatment on performance in multiple cognitive domains (Friedman et al., 2001). Although discouraging, the results of this negative trial may highlight the importance of timing in the delivery of therapeutic interventions for schizophrenia, as early interventions to enhance spine number and function may be much more likely to be successful than when the deficit in circuitry function has been present for years.

Because spines have distinct morphologies that reflect different types of synaptic plasticity (Kasai et al., 2010), a preferential loss of one morphological class in schizophrenia would indicate which type of synaptic plasticity is altered. For example, small, thin spines have been described as "learning" spines (Kasai et al., 2003a), as they are transient and critical for rapid plasticity (Arnsten et al., 2010a). In contrast, large, mushroom spines are have been described as "memory" spines (Kasai et al., 2003a), as they are stable and engage in long-term synaptic plasticity (Bourne and Harris, 2007). Recently, thin spines have been proposed to be critical for "dynamic network connectivity," an ongoing, rapid process by which PFC connections are strengthened or eliminated, providing the mental flexibility characteristic of the PFC (Arnsten et al., 2010b). Indeed, PFC thin spine density is positively correlated with working memory ability in monkeys (Dumitriu et al., 2010). These findings suggest the testable hypothesis that the impairments in working memory function that are common in schizophrenia reflect a preferential deficit in thin spines in the PFC.

If a lower density of thin spines in the PFC contributes to impaired cognitive ability 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 the DLPFC of both younger and aged ovariectomized monkeys (Tang et al., 2004; Hao et al., 2006; Hao et al., 2007). Importantly, aged ovariectomized monkeys who received estrogen treatment did not display the normal age-related decline in DLPFC-dependent cognition (Rapp et al., 2003). Indeed, the findings that age of onset of diagnosis of schizophrenia is later in women (Riecher-Rossler and Kulkarni, 2011), and that women have a second period of increased rate of diagnosis after age 40 (Riecher-Rossler et al., 1997), have lead to the suggestion that estrogen has a protective effect in this illness. Interestingly, clinical trials of estrogen receptor modulators in postmenopausal women have shown improvements in schizophrenia symptoms (Kulkarni et al., 2010; Usall et al., 2011). Thus, these findings are

consistent with the hypothesis that schizophrenia is associated with a deficit in thin spines and suggest that cyclical estrogen treatment might be a viable therapeutic intervention for the prevention of thin spine loss, and cognitive impairments, in schizophrenia.

Finally, identification of effective therapeutics also depends upon determining whether decreased dendritic spine density is a cause or consequence of the disease process of schizophrenia. Because spine density is not associated with the duration of psychotic illness, use of APDs, or presence of a psychiatric illness, spine deficits are not likely to be simply a consequence of the disease. On the other hand, excessive pruning of spines during late childhood/ adolescence could account for both the greater than normal decline in cortical grey matter during this time (Rapoport et al., 1999; Sporn et al., 2003) and the observation that cognitive impairments progress during this timeframe in individuals later diagnosed with schizophrenia (Reichenberg et al., 2010; Seidman et al., 2010). Moreover, spine deficits and associated reductions in network activity could drive the multiple changes identified in DLPFC GABA neurons in schizophrenia subjects (Lewis et al., 2012) that are thought to underlie the impaired cortical network oscillations and cognitive performance of the illness (Cho et al., 2006; Uhlhaas et al., 2008). Thus, while not conclusive, the existing evidence supports the idea that dendritic spine deficits are likely to represent the neural substrate for cognitive impairments in schizophrenia, and not to be a secondary consequence of the illness.

In summary, we have reviewed the evidence indicating that dendritic spine alterations are present in multiple brain regions in subjects with schizophrenia, but are best characterized in layer 3 of the neocortex, where pyramidal cell spine density is lower. These spine deficits appear to arise during development and thus are likely the result of disturbances in the molecular mechanisms that underlie spine formation, pruning, and/or maintenance. The conduct of definitive experiments that can reveal exactly where, how and when cortical spine deficits arise, and which schizophrenia symptoms can be attributed to these deficits, will provide a major step forward in the identification of novel therapeutic strategies for the prevention and treatment of schizophrenia.

Highlights

1. Impaired perception, cognition and motivation are clinical features of schizophrenia

2. These symptoms reflect neural circuitry abnormalities, including spine deficits

3. Spine density is best characterized and lower in layer 3 of the neocortex

4. Altered spinogenesis or pruning during development likely underlies spine deficits

5. These processes represent possible novel therapeutic targets for schizophrenia

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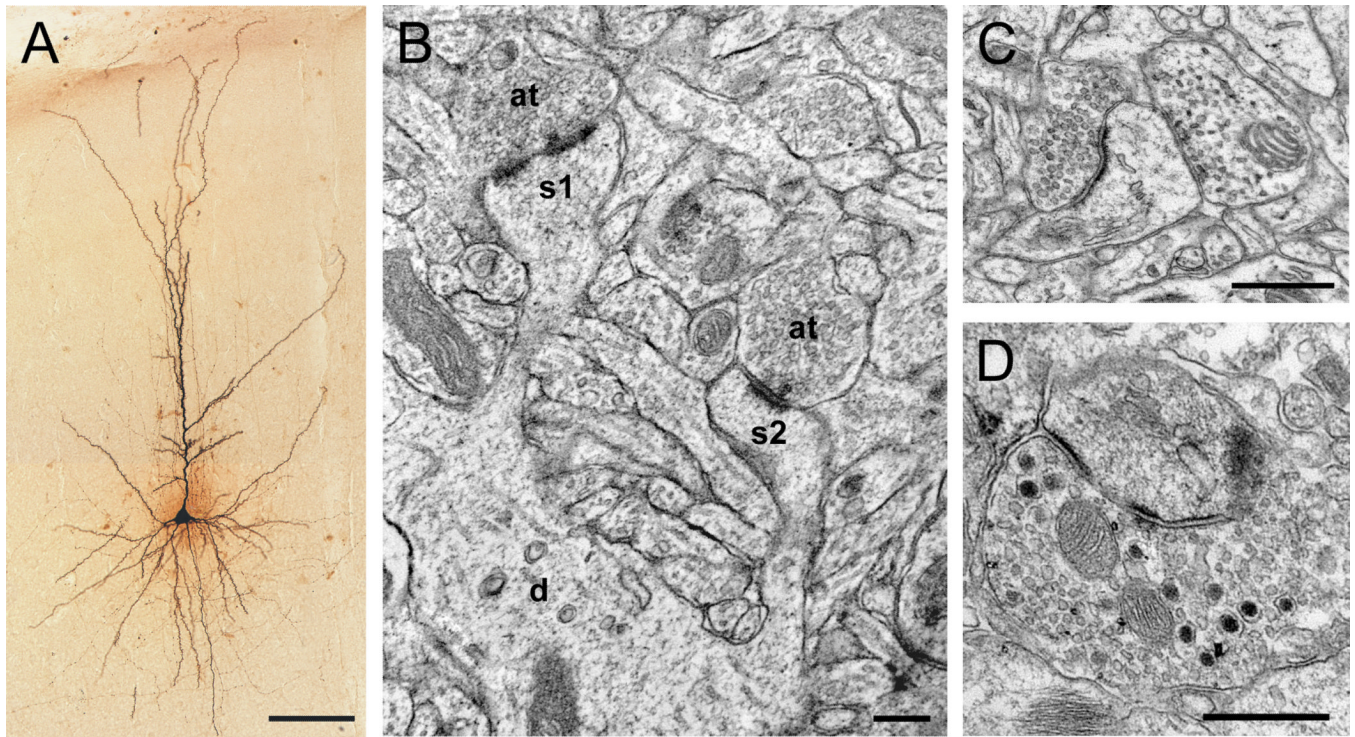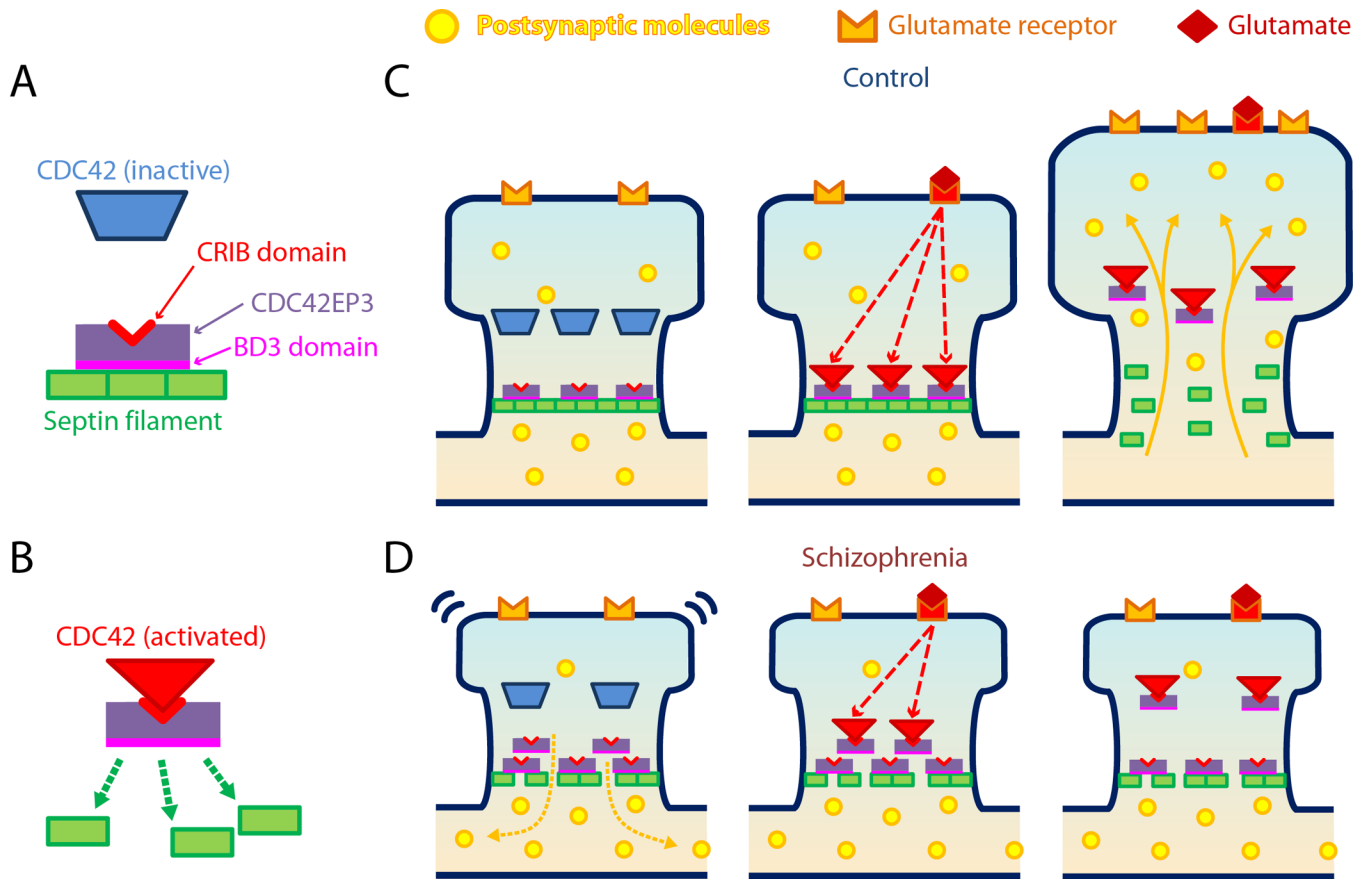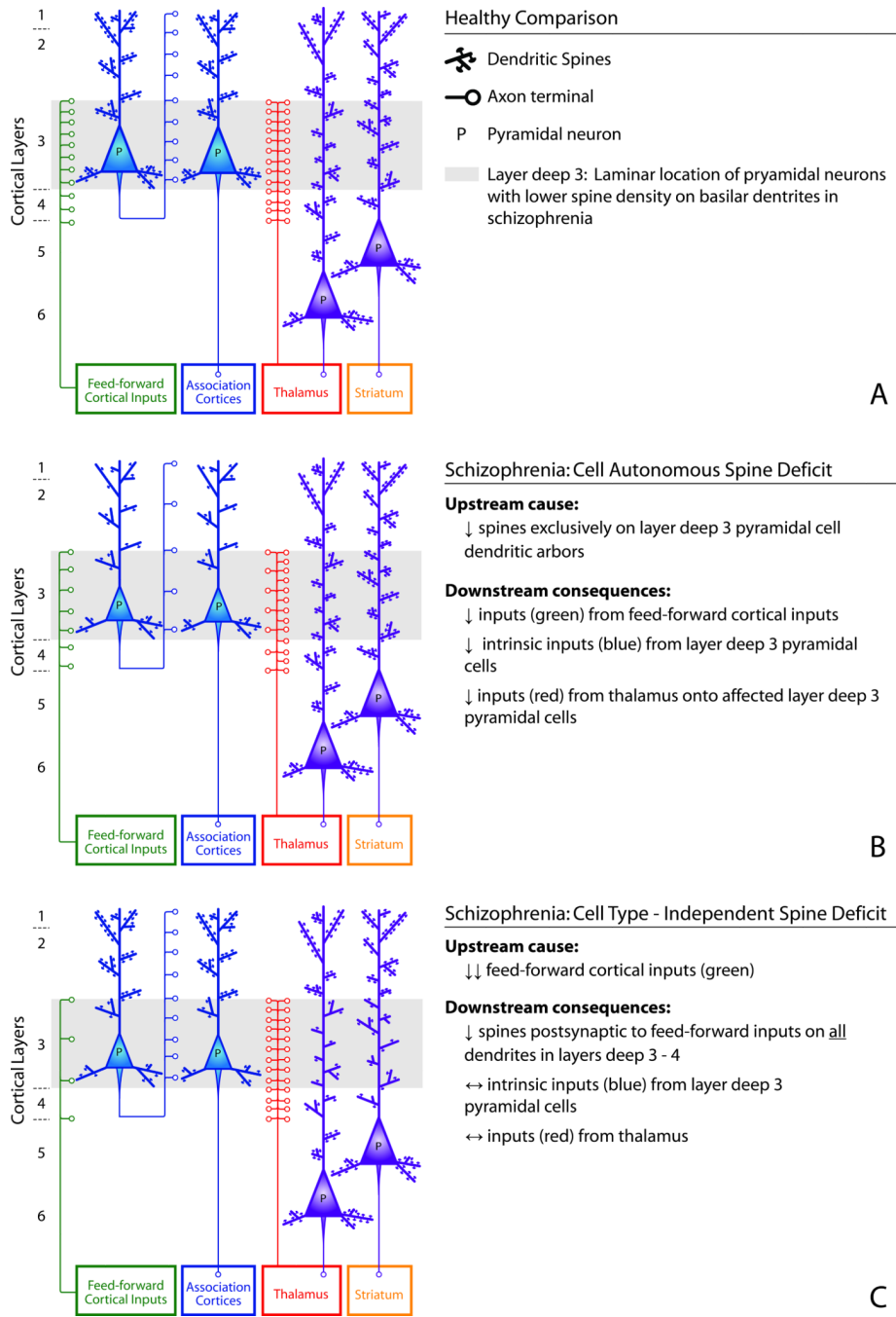
Figure 1.
Micrographs of pyramidal cell dendritic spines in the primate prefrontal cortex. A) Light micrograph of a biocytin-filled pyramidal cell showing the cell body, and basilar and apical dendritic shafts. B) Electron micrograph showing two spines (s1, s2) protruding from a dendritic shaft (d). Spine s1 is receiving a perforated asymmetric (presumably glutamatergic) synapse. C) Dendritic spine receiving an asymmetric (presumably glutamatergic) synapse and a symmetric (inhibitory or catecholaminergic) synapse. Note the difference in the appearance of the synaptic vesicles in each presynaptic axon terminal. D) Axon terminal containing small, round vesicles characteristic of glutamate, and large, dense-core vesicles characteristic of neuropeptides, forming an asymmetric synapse onto a spine. Scale bar is 100 μm in A, 200 nm in B, and 500 nm in C–D.
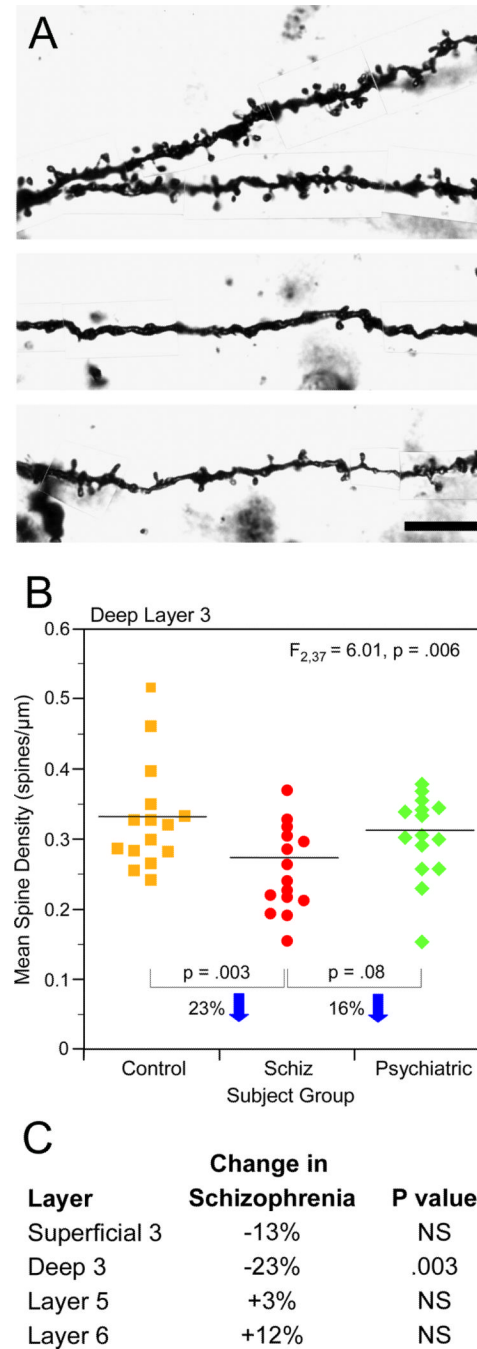
Figure 2.
Decreased layer 3 spine density in the dorsolateral prefrontal cortex (DLPFC) of schizophrenia subjects. A) Golgi-impregnated basilar dendrites and spines from a healthy comparison subject (top) and two schizophrenia subjects (bottom). Spine density is qualitatively decreased in the schizophrenia subjects relative to the healthy comparison subject. B) Scatter plot demonstrating lower layer deep 3 spine density in schizophrenia subjects relative to healthy comparison and psychiatrically ill subjects. C) Within the same subjects, lower DLPFC spine density is specific to layer deep 3. Scale bar is 10 µm in A. Adapted from Lewis and Gonzalez-Burgos (2008).

Figure 3.
Schematic diagram of Cdc42-Cdc42EP3-septin interactions and their proposed roles in spine dysfunction in schizophrenia. A) Cdc42EP3 binds to septins via a BD3 domain, inducing the assembly of septin filaments. Inactive Cdc42 cannot bind to Cdc42EP3. B) Once activated, Cdc42 can bind to and inhibit Cdc42EP3 via its CRIB domain, disrupting septin filament formation. C) In the normal state, Cdc42EP3 consolidates septin filaments in the spine neck, effectively forming a barrier for molecular diffusion with the parent dendrite (left). Transient activation of Cdc42 by glutamate stimulation inhibits the Cdc42EP3-mediated assembly of the septin filament barrier (middle), enabling molecular diffusion with the parent dendrite (right). C) In schizophrenia, decreased expression of septin 7 mRNA contributes to impaired septin filament formation at the spine neck, limiting the retention of postsynaptic molecules that are critical for spine structure and function in the spine head (left). Furthermore, lower levels of Cdc42 and increased levels of Cdc42EP3 lead to a reduced capacity for glutamatergic signaling to open the septin barrier (middle), limiting synaptic plasticity and possibly contributing to spine loss (right). Cell division cycle 42 (Cdc42), Cdc42 effector protein 3(Cdc42EP3). Adapted from Ide and Lewis 2010.

Figure 4.
Two alternative models of potential cause and consequences of layer deep 3 spine deficits in schizophrenia.

Table 1

Summary of reported dendritic spine alterations in schizophrenia

Anatomical Regions	Schizophrenia/Healthy Comparison Subjects	Methods	Measures	Reported Significant Differences in Schizophrenia	Reference
Frontal Cortex	13/11	Golgi	Spine density	66% Decrease, Layer 3	Garey et al 1998
Temporal cortex	13/11	Golgi	Spine density	59% Decrease, Layer 3	Garey et al 1998
BA46	15/15	Golgi	Spine density	23% Decrease, Layer deep 3	Glantz and Lewis 2000
BA46	15/15	Golgi	Spine density	No difference, Layers 5–6	Kolluri et al 2005
BA17	15/15	Golgi	Spine density	No difference, Layer 3	Glantz and Lewis 2000
BA41	15/15	IHC	Spinophilin-IR puncta density	27% Decrease, Layer deep 3	Sweet et al 2009
BA42	15/15	IHC	Spinophilin-IR puncta density	22% Decrease, Layer deep 3	Sweet et al 2009
Striatum	6/6	EM	Spine cross-sectional area	30% Decrease	Roberts et al 1996
Caudate	17/10	EM	Axospinous synapse density	26% Increase	Roberts et al 2005b
Putamen	17/10	EM	Axospinous synapse density	No difference	Roberts et al 2005b
Caudate Patch & Matrix	14/8	EM	Axospinous synapse density	No difference	Roberts et al 2005a
Putamen Matrix	14/8	EM	Axospinous synapse density	No difference	Roberts et al 2005a
Putamen Patch	14/8	EM	Axospinous synapse density	44% Increase	Roberts et al 2005a
Caudate Patch & Matrix	16/10	EM	Axospinous synapse density	No difference	Roberts et al 2008
Putamen Matrix	16/10	EM	Axospinous synapse density	No difference	Roberts et al 2008
Putamen Patch	16/10	EM	Axospinous synapse density	44% Increase	Roberts et al 2008
Subiculum	13/8	Golgi	Spine density	35% Decrease, Apical dendrites	Rosoklija et al 2000
CA3	9/10	EM	Mossy fiber axospinous synapse density	No difference	Kolomeets et al 2005