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# Synaptic changes in the brain of subjects with schizophrenia

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## Abstract

Clinical, epidemiological, neuroimaging and postmortem data all suggest schizophrenia is a neurodevelopmental disorder, and that synaptic disturbances might play a critical role in developing the disease. In 1982 Feinberg proposed that the schizophrenia might arise as a result of abnormal synaptic pruning. His hypothesis has survived 40 years of accumulated data, and we review the critical findings related to synaptic dysfunction of schizophrenia. While it is clear that synaptic disturbances are integral and important for understanding the pathophysiology of schizophrenia, it has also become obvious that synaptic disturbances cannot be studied and understood as an independent disease hallmark, but only as a part of a complex network of homeostatic events. Development, glial-neural interaction, changes in energy homeostasis, diverse genetic predisposition, neuroimmune processes and environmental influences all can tip the delicate homeostatic balance of the synaptic morphology and connectivity in a uniquely individual fashion, thus contributing to the emergence of the various symptoms of this devastating disorder. Finally, we argue that based on a predominant change in gene expression pattern we can broadly sub-stratify schizophrenia into “synaptic” “oligodendroglial”, “metabolic” and “inflammatory” subclasses.

### Keywords

schizophrenia; synapse; pruning; postmortem; gene expression

Schizophrenia is a devastating mental disorder with a complex etiology that arises as an interaction between genetic and environmental factors (Carpenter and Buchanan, 1994; Lewis and Levitt, 2002; Marenco and Weinberger, 2000). Clinical, epidemiological, neuroimaging and postmortem data all suggest schizophrenia is a neurodevelopmental disorder, and that normal brain development and function is impaired long before the onset of the first full-blown clinical symptoms.



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Research Highlights

>Synaptic disturbances are integral and important part of schizophrenia pathophysiology. >Synaptic disturbances cannot be studied and understood as an independent disease. >We propose a molecular sub-stratification of schizophrenia into “synaptic” “oligodendroglial”, “metabolic” and “inflammatory” subclasses.

In 1979 Huttenlocher quantified the density of synaptic profiles in layer III of the frontal gyrus in 21 brains ranging from newborn to 90 years in age (Huttenlocher, 1979), and came to conclusion that the synaptic density in the neonatal brain was already comparable to those seen in adulthood. Furthermore, he reported that in infanthood there was a sharp increase in the number of synapses to about 150% of that seen in adulthood, followed by a progressive decline in synaptic density between the ages of 2-16. Based on findings of progressive postnatal "synaptic pruning" and the clinical presentation of the disease, in 1982 Feinberg (Feinberg, 1982; Keshavan et al., 1994) formulated a radically new theory on the cause of schizophrenia, proposing that that the disease presentation might arise from abnormal synaptic pruning in the affected individuals. While Feinberg hypothesized that altered cortical pruning is critical for developing the disease, he was uncommitted about the precise mechanism by which the pathophysiology might occur, stating that "... as a result of some abnormality in this process, too many, too few, or the wrong synapses are eliminated. Regrettably, we have no basis to choose among these abnormalities". The initial Feinberg hypothesis was further expanded by Hoffman and Dobscha (Hoffman and Dobscha, 1989), who proposed that hyperpruning of collateral axons in the prefrontal cortex (PFC) leads to the clinical manifestation of schizophrenia, and by Jernigan and colleagues (Jernigan et al., 1991), who proposed that defective pruning of certain brain structures underlies schizophrenia. Almost 30 years later, these initial hypotheses are still very intriguing and are supported by multiple lines of indirect evidence.

## Pruning in the central nervous system

After the initial Huttenlocher reports (Huttenlocher, 1979; Huttenlocher et al., 1982; Huttenlocher and de Courten, 1987), synaptic pruning in the CNS attracted a considerable research interest. It has been established that synaptic pruning is 1) present in virtually all brain regions, including the prefrontal, visual, motor and associative cortices, hippocampus and cerebellum (Bourgeois and Rakic, 1993; Eckenhoff and Rakic, 1991; Innocenti, 1995; Rakic et al., 1994; Takacs and Hamori, 1994); 2) proceeds coarsely from caudal to frontal regions (Rakic et al., 1994), 3) is present in more than one mammalian species (human, monkey, cat, rat) (Bourgeois and Rakic, 1993; Eckenhoff and Rakic, 1991; Innocenti, 1995; Rakic et al., 1994; Takacs and Hamori, 1994), although with a different time-course, and 4) represents an experience-dependent process (Roe et al., 1990; Stryker and Harris, 1986). Importantly, these changes could not be explained by enlargement of brain volume over development (Rakic et al., 1994).

### Structural brain changes in schizophrenia

Defining neuropathology of schizophrenia has been challenging, with findings that often did not reproduce across various cohorts. However, most of the studies to date suggest that the disease is characterized by: 1) a mild enlargement of ventricles, 2) decreased cortical thickness; 3) altered neuronal density and decreased neuron size in limbic, temporal, and frontal regions; 4) abnormal dendritic spine densities in the cortex; 5) altered cortical cytoarchitecture, perhaps related to abnormal neuronal migration, differentiation, and/or cell pruning; and 6) molecular changes that encompass altered expression of genes related to synaptic function, energy metabolism, immune system activation, and oligodendrocyte transcripts (reviewed by (Harrison, 1999; Harrison and Weinberger, 2005; Hof and Schmitz, 2009; Iritani, 2007; Mirnics et al., 2006)). However, it is important to point out that most of the postmortem studies to date did not uncover progressive neurodegenerative disease lesions or ongoing astrocytosis that would indicate post-maturational neural injury (Arnold and Trojanowski, 1996). At least theoretically, all these changes can be directly related to altered synaptic pruning in schizophrenia, arising from a complex interplay of genetic predisposition and adverse environmental influences (Horvath and Mirnics, 2009).

In 1976, Johnstone and colleagues, using computerized tomography (CT) noted a significant ventricular enlargement in a group of chronic schizophrenics (Johnstone et al., 1976). These data were later replicated in both the lateral and 3rd ventricles by multiple groups of investigators with a prevalence rates ranging from 18-40% (Maser and Keith, 1983; Okasha and Madkour, 1982; Weinberger et al., 1979). Furthermore, based on a comprehensive meta-analysis study of 39 datasets Van Horn and McManus concluded that "that there is a difference in ventricle:brain ratio between schizophrenics and controls which would seem to be an indisputable characteristic of schizophrenia" (Van Horn and McManus, 1992). However, the findings also suggested that the changes were too small to be of practical significance for establishing a patient diagnosis. Follow-up studies also suggested that ventricular enlargement might be correlated with disease symptoms, where patients with ventricular enlargement showed predominantly negative symptoms and impaired functioning, while patients without ventricular enlargement tended to have a preponderance of positive symptoms and a normal sensorium (Andreasen et al., 1982). Furthermore, ventricular enlargement is present in unmedicated, first-break patients, suggesting that the findings are not a result of disease progression or medication effects (Niemann et al., 2000; Vita et al., 2006). The ventricular enlargement is accompanied by an overall loss of brain tissue averaging ~3% (Lawrie and Abukmeil, 1998), albeit the degree of ventricular enlargement and the decrease in the brain volume do not appear to be correlated. Magnetic resonance imaging (MRI) studies suggest that the temporal lobes and medial temporal structures are the most affected (Nelson et al., 1998), and that gray matter reduction is more prominent than the decrease in white matter volume. Furthermore, more recent data suggest that genetic vulnerability factors and disease-associated gene alleles (e.g. RGS4 and NRG1) contribute to structural alterations in the brain of patients with schizophrenia (Mata et al., 2009; Prasad et al., 2009). All these structural changes can arise as a result of various factors and cellular deficits, however, in the absence of marked neuronal loss in schizophrenia, the findings are consistent with the idea that reduction in dendrites and synapses might be an important contributor to the cortical volume reduction (McGlashan and Hoffman, 2000).

## Synapse-related neuroanatomical and molecular changes

To date, multiple studies have examined cellular and synaptic morphology in postmortem tissue of subjects with schizophrenia. Golgi-impregnation studies revealed a region- and disease-specific decrease in dendritic spine density in dorsolateral prefrontal cortex layer 3 pyramidal cells in subjects with schizophrenia (Glantz and Lewis, 2000). Importantly, these synapse-related changes do not appear to be a result of chronic antipsychotic medication: 1) monkeys receiving chronic antipsychotic medication do not show reduced expression of synaptic markers, 2) schizophrenic subjects not receiving antipsychotic medications at the time of death show synaptic alterations, and 3) antipsychotic medication treated subjects with diagnoses other than schizophrenia show no apparent synapse-related pathology. Furthermore, ultrastructural studies suggest that striatal spines in schizophrenics are reduced in size by ~30% when compared to the control population, raising the possibility that this change might be directly related to aberrant synaptic conductance and/or efficacy in the subcortical gray matter (Roberts et al., 1996). Kung and colleagues (Kung et al., 1998) also pointed out that the density and/or proportion of symmetric synaptic profiles was primarily affected in the caudate nucleus (and not the putamen) arguing for an imbalance in inhibitory synaptic transmission between these two structures. In addition, the density of perforated synaptic profiles, cortical afferents thought to be involved in synaptic turnover and cognition, was lower in the striatum of the schizophrenic subjects compared to the control groups. Finally, the same study found that density of axodendritic synaptic profiles, particularly of the asymmetric type, was decreased in the caudate, but not the putamen.

While Golgi-studies and cellular density measurements suggest that the reduced synaptic marker expressions are a result of structural deficits related to the neuropil, these studies cannot exclude the possibility that many of the observed deficits are of functional nature. The anatomical substrate might be preserved (e.g. presynaptic terminal), and the studies reporting deficient presynaptic mRNA/protein levels (revealed by bulk tissue assessment methods or immunohistochemistry) often cannot distinguish between the "reduced expression in a synaptic terminal" and "reduced number of synaptic terminals" scenarios. Regardless, it is obvious that both mechanisms (reduced number of synapses or synapses expressing sub-threshold levels of presynaptic genes) are likely to have a significant impact on brain function. While the causality of the schizophrenia-related presynaptic deficits is somewhat open to interpretation, the research data suggest that multiple key transcripts and proteins of the presynaptic secretory machinery are reduced in schizophrenia. For example, quantitative western blot analysis of human postmortem hippocampus from the brains of schizophrenics and age-matched controls revealed reduced levels of synapsin I in the diseased subjects (Browning et al., 1993). Similarly, synaptophysin immunostaining revealed a reduction in protein levels in prefrontal, but not visual cortex of diseased subjects (Glantz and Lewis, 1997). Furthermore, prefrontal reduction of synaptophysin and SNAP-25 has been also reported on a different cohort of subjects, suggesting that 'hypofrontality' of schizophrenia arises from abnormalities of synaptic number or structural integrity in prefrontal cortex (Karson et al., 1999). Synaptophysin immunoreactivity was also significantly reduced in both the inner and outer molecular layers of the dentate gyrus, but not in the hilus (Chambers et al., 2005), arguing that the synaptophysin defect affects multiple cortical regions in the schizophrenic brain. Lower phosphorylated Syntaxin 1 (pSTX1) levels has been also reported in the prefrontal cortex of schizophrenia, and reduced pSTX1 levels were associated with reduced binding of STX1 to SNAP-25 and MUNC18 and decreased SNARE complex formation (Castillo et al.). In addition, data-driven gene expression profiling methods also identified a robust, subjects-specific reduction in presynaptic secretory machinery transcripts in the prefrontal cortex (synapsin II, N-ethylmaleimide sensitive factor, synaptotagmin, synaptojanin and synaptobrevin), which could not be attributed to chronic neuroleptic treatment (Mirnics et al., 2000; Mirnics et al., 2001a). Furthermore, in a recent study of genomic convergence analysis of cerebellar cortices shotgun cDNA sequencing identified twenty three genes with altered expression and involvement in presynaptic vesicular transport (Mudge et al., 2008).

The vast majority of the published studies suggest that schizophrenia is characterized by reduced expression of presynaptic transcripts/proteins, however, there have been also a few cohort-specific reports suggesting that presynaptic gene expression might actually increase in some brain regions (Gabriel et al., 1997; Sokolov et al., 2000).

The disease process of schizophrenia is also likely to affect postsynaptic elements. Postsynaptic receptor expression changes have been reported in the monoamine, glutamatergic and GABAergic systems, yet these are more suggestive of functional deficits, and not anatomical deficits of postsynaptic structures. Perhaps most interestingly, several studies suggest that postsynaptic density proteins (e.g. PSD93, PSD95, neurofilament-light and SAP102) are also affected by the disease process (Hahn et al., 2006; Kristiansen et al., ; Meador-Woodruff et al., 2003; Ohnuma et al., 2000). However, the reduced expression of these binding partners of NMDA receptor subunits and mediators of synaptic plasticity has been less consistently replicated across various studies.

## Which synapses are affected in schizophrenia?

Theoretically, any brain disease process can affect inhibitory or excitatory synapses, or both simultaneously. Furthermore, the functional outcome would also depend on the exact cell

type affected and the brain region where the alteration would occur. In schizophrenia, synapse-related deficits appear to be widespread, affecting multiple cortical and subcortical regions, involving both glutamatergic projection neurons and multiple classes of GABA-ergic inhibitory neurons (Hashimoto et al., 2008a; Hashimoto et al., 2008b; Lewis et al., 2005; Lewis and Hashimoto, 2007). However, it appears that the disease process has a differential effect on projection neurons and interneurons: synaptic deficits in projection neurons appear to be both microanatomical and functional, while synaptic deficits in the interneurons are likely to be predominantly functional. Prefrontal cortical projection neurons in schizophrenia show both reduced size (Pierri et al., 2003; Rajkowska et al., 1998; Sweet et al., 2003) and decreased dendritic spine density (Glantz and Lewis, 2000; Hill et al., 2006). In a study of Golgi-impregnated pyramidal neurons of the dorsolateral prefrontal cortex Glantz and colleagues (Glantz and Lewis, 2000) found that deep layer III projection neurons had a dendritic spine decrease of ~20%. In this study, dendritic spine alterations were not observed in superficial cortical layers, other cortical areas, or psychiatry control group treated with antipsychotic medication. On the other hand, perhaps the most intriguing functional synaptic abnormality in schizophrenia is observed in the cortical parvalbumin-containing interneuron subclass, the chandelier cells. Chandelier cells, via their characteristic axon terminals (cartridges) provide potent axon initial segment inhibition to the cortical projection neurons. In the prefrontal cortex of subjects with schizophrenia, GAT1 immunoreactivity appears to be preferentially reduced in the chandelier cell cartridges in a treatment-independent fashion (Lewis). However, at the present it is believed that reduced GAT1 immunoreactivity is part of molecular reorganization at the axon initial segment, and not a result of chandelier cartridge pruning (Pierri et al., 1999). Still, at the current time we have to consider the possibility that interneuron dendritic trees or axon terminals also undergo structural remodeling as part of the diseases process.

## The relationship of synaptic changes to other molecular deficits

In addition to altered expression of multiple single-genes, the molecular pathophysiology of schizophrenia encompasses synaptic, oligodendroglial, mitochondrial and immune system disturbances (Mirnics et al., 2006). The exact relationship between these disturbances is poorly understood, but it is very likely that the deficits are intertwined, perhaps even causally related (Mirnics et al., 2001a). For example, synaptic activity requires energy, and reduction in neuropil might lead to reduced energy requirements (Middleton et al., 2002). As a result, adaptation takes place, and the transcripts/proteins of the energy metabolism pathway are downregulated. However, the opposite might also hold true: if a neuronal metabolism is impaired, the affected cells might not be able to support an extensive arborization. Similarly, in an attempt to compensate for inefficient presynaptic release during development, postsynaptic changes may follow, including (but not limited to) down-regulation of regulator of G-protein signaling 4 (RGS4) (Mirnics et al., 2001b). Such a reduction will give rise to increased duration of signaling through a number of different G-protein coupled receptors, attempting to compensate for reduced input from the presynaptic structures. Unfortunately, such adaptational events may not be effective, and they can even have a further detrimental effect on the function of the postsynaptic cell, resulting in further desynchronization and accelerated pruning (Mirnics et al., 2001a).

## Developmental time course of synaptic deficits in schizophrenia

Unfortunately, human postmortem studies offer very limited insight into the time course by which the synaptic alterations develop in schizophrenia. As synapse development and pruning are dynamic processes following a complex trajectory, genetic-environmental influences can alter synapse development through a wide time window that encompasses prenatal development to the onset of the disease (Lewis and Levitt, 2002). Importantly, the

clinical symptoms of the disease might develop many years after the adverse genetic or environmental influences. Within this context, there are two possible mechanisms by which this can occur: less synapse production or overpruning. If synapse developmental trajectory is suppressed at the time of insult, fewer synapses are generated, but the reduced number of synapses is still sufficient to maintain almost normal function during the “pre-pruning” period. However, in late adolescence/early adulthood, when normal developmental pruning occurs, the number of synapses fall below a “psychosis threshold”, arising to symptoms of the disease. Alternatively, one can envision that synapse generation during development is unimpaired, but the pruning mechanisms are accelerated, perhaps due to eliminating and increased number of inefficiently functioning synapses. Thus, the synapse loss due to overpruning would also result in reaching “psychosis threshold”, once again leading to the clinical manifestations of the disease.

## Synaptic schizophrenia?

Schizophrenia is a heterogeneous disorder that encompasses different phenotypic manifestations of the disease. Genetic, gene expression and animal model studies unequivocally suggest that the molecular pathophysiology of the disease is complex, perhaps even unique to each patient. While synaptic alterations can be clearly demonstrated in the brain of some subjects with schizophrenia, they are not present in each and every one of the studied postmortem brains. Based on gene expression data in the literature, we argue that schizophrenia can be broadly subclassified at a molecular level as “synaptic” (Mirnics et al., 2001a), “oligodendroglial” (Hakak et al., 2001), “metabolic” (Middleton et al., 2002) or “inflammatory” (Arion et al., 2007). From these categories, it appears that “synaptic” and “oligodendroglial” gene expression phenotypes are the most distinct, non-overlapping, and are not found within the same brains. Yet, this classification doesn't imply homogeneity within the molecular sub-phenotype. Subjects in the “synaptic schizophrenia” subclass could be affected by any number or combination of the genetic or environmental insults and that pattern likely varies between individuals. Simply put, different subjects with schizophrenia within this sub-class have different, subject-specific synaptic deficits, but they all converge at a functional level to affect synaptic transmission between neurons.

In summary, anatomical and functional synaptic disturbances are most likely a strong contributing factor to the development, pathology and possibly symptomatology of schizophrenia. However, the synaptic disturbances might be unique to each patient. The genetic predisposition to the disease will be different, it might affect different cell types (interneurons and projection neurons) or different cellular compartments (axonal arborization and dendritic tree). Importantly, synaptic disturbances in schizophrenia cannot be studied and understood as an independent disease hallmark, but only as a part of a complex network of events. Development, glial-neural interaction, changes in energy homeostasis, diverse genetic predisposition, neuroimmune processes and environmental influences all can tip the delicate homeostatic balance of the synaptic morphology and connectivity in a uniquely individual fashion, thus contributing to the emergence of the various symptoms of this devastating disorder.

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## REFERENCES


Andreasen NC, Olsen SA, Dennert JW, Smith MR. Ventricular enlargement in schizophrenia: relationship to positive and negative symptoms. Am J Psychiatry. 1982; 139:297–302. [PubMed: 7058942]

Arion D, Unger T, Lewis DA, Levitt P, Mirnics K. Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. Biol Psychiatry. 2007; 62:711–21. [PubMed: 17568569]

Arnold SE, Trojanowski JQ. Recent advances in defining the neuropathology of schizophrenia. Acta Neuropathol. 1996; 92:217–31. [PubMed: 8870823]

Bourgeois JP, Rakic P. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci. 1993; 13:2801–20. [PubMed: 8331373]

Browning MD, Dudek EM, Rapier JL, Leonard S, Freedman R. Significant reductions in synapsin but not synaptophysin specific activity in the brains of some schizophrenics. Biol Psychiatry. 1993; 34:529–35. [PubMed: 8274580]

Carpenter WT, Buchanan RW. Schizophrenia. New England Journal of Medicine. 1994; 330:681–690. [PubMed: 8107719]

Castillo MA, Ghose S, Tamminga CA, Ulery-Reynolds PG. Deficits in syntaxin 1 phosphorylation in schizophrenia prefrontal cortex. Biol Psychiatry. 67:208–16. [PubMed: 19748077]

Chambers JS, Thomas D, Saland L, Neve RL, Perrone-Bizzozero NI. Growth-associated protein 43 (GAP-43) and synaptophysin alterations in the dentate gyrus of patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:283–90. [PubMed: 15694236]

Eckenhoff MF, Rakic P. A quantitative analysis of synaptogenesis in the molecular layer of the dentate gyrus in the rhesus monkey. Brain Res Dev Brain Res. 1991; 64:129–35.

Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 1982; 17:319–34. [PubMed: 7187776]

Gabriel SM, Haroutunian V, Powchik P, Honer WG, Davidson M, Davies P, Davis KL. Increased concentrations of presynaptic proteins in the cingulate cortex of subjects with schizophrenia. Arch Gen Psychiatry. 1997; 54:559–66. [PubMed: 9193197]

Glantz LA, Lewis DA. Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia. Regional and diagnostic specificity. Arch Gen Psychiatry. 1997; 54:660–9. [PubMed: 9236550]

Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry. 2000; 57:65–73. [PubMed: 10632234]

Hahn CG, Wang HY, Cho DS, Talbot K, Gur RE, Berrettini WH, Bakshi K, Kamins J, Borgmann-Winter KE, Siegel SJ, Gallop RJ, Arnold SE. Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. Nat Med. 2006; 12:824–8. [PubMed: 16767099]

Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, Fienberg AA. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A. 2001; 98:4746–51. [PubMed: 11296301]

Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain. 1999; 122(Pt 4):593–624.

Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry. 2005; 10:40–68. image 5. [PubMed: 15263907]

Hashimoto T, Arion D, Unger T, Maldonado-Aviles JG, Morris HM, Volk DW, Mirnics K, Lewis DA. Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. Mol Psychiatry. 2008a; 13:147–61. [PubMed: 17471287]

Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. Am J Psychiatry. 2008b; 165:479–89. [PubMed: 18281411]

Hill JJ, Hashimoto T, Lewis DA. Molecular mechanisms contributing to dendritic spine alterations in the prefrontal cortex of subjects with schizophrenia. Mol Psychiatry. 2006; 11:557–66. [PubMed: 16402129]

Hof PR, Schmitz C. The quantitative neuropathology of schizophrenia. Acta Neuropathol. 2009; 117:345–6. [PubMed: 19247680]

Hoffman RE, Dobscha SK. Cortical pruning and the development of schizophrenia: a computer model. Schizophr Bull. 1989; 15:477–90. [PubMed: 2814376]

Horvath S, Mirnics K. Breaking the gene barrier in schizophrenia. Nat Med. 2009; 15:488–90. [PubMed: 19424205]

Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res. 1979; 163:195–205. [PubMed: 427544]

Huttenlocher PR, De Courten C, Garey LJ, Van der Loos H. Synaptic development in human cerebral cortex. Int J Neurol. 1982; 16-17:144–54.

Huttenlocher PR, de Courten C. The development of synapses in striate cortex of man. Hum Neurobiol. 1987; 6:1–9. [PubMed: 3583840]

Innocenti GM. Exuberant development of connections, and its possible permissive role in cortical evolution. Trends Neurosci. 1995; 18:397–402. [PubMed: 7482805]

Iritani S. Neuropathology of schizophrenia: a mini review. Neuropathology. 2007; 27:604–8. [PubMed: 18021384]

Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL. Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. Arch Gen Psychiatry. 1991; 48:881–90. [PubMed: 1929757]

Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 1976; 2:924–6. [PubMed: 62160]

Karson CN, Mrak RE, Schluterman KO, Sturner WQ, Sheng JG, Griffin WS. Alterations in synaptic proteins and their encoding mRNAs in prefrontal cortex in schizophrenia: a possible neurochemical basis for 'hypofrontality'. Mol Psychiatry. 1999; 4:39–45. [PubMed: 10089007]

Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J Psychiatr Res. 1994; 28:239–65. [PubMed: 7932285]

Kristiansen LV, Patel SA, Haroutunian V, Meador-Woodruff JH. Expression of the NR2B-NMDA receptor subunit and its Tbr-1/CINAP regulatory proteins in postmortem brain suggest altered receptor processing in schizophrenia. Synapse. 64:495–502. [PubMed: 20175224]

Kung L, Conley R, Chute DJ, Smialek J, Roberts RC. Synaptic changes in the striatum of schizophrenic cases: a controlled postmortem ultrastructural study. Synapse. 1998; 28:125–39. [PubMed: 9450513]

Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry. 1998; 172:110–20. [PubMed: 9519062]

Lewis DA. The chandelier neuron in schizophrenia. Dev Neurobiol. 71:118–27. [PubMed: 21154915]

Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci. 2002; 25:409–32. [PubMed: 12052915]

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci. 2005; 6:312–24. [PubMed: 15803162]

Lewis DA, Hashimoto T. Deciphering the disease process of schizophrenia: the contribution of cortical GABA neurons. Int Rev Neurobiol. 2007; 78:109–31. [PubMed: 17349859]

Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol. 2000; 12:501–27. [PubMed: 11014750]

Maser JD, Keith SJ. CT scans and schizophrenia--report on a workshop. Schizophr Bull. 1983; 9:265–83. [PubMed: 6867633]

Mata I, Perez-Iglesias R, Roiz-Santianez R, Tordesillas-Gutierrez D, Gonzalez-Mandly A, Vazquez-Barquero JL, Crespo-Facorro B. A neuregulin 1 variant is associated with increased lateral ventricle volume in patients with first-episode schizophrenia. Biol Psychiatry. 2009; 65:535–40. [PubMed: 19058791]

McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry. 2000; 57:637–48. [PubMed: 10891034]

Meador-Woodruff JH, Clinton SM, Beneyto M, McCullumsmith RE. Molecular abnormalities of the glutamate synapse in the thalamus in schizophrenia. Ann N Y Acad Sci. 2003; 1003:75–93. [PubMed: 14684436]

Middleton FA, Mirnics K, Pierri JN, Lewis DA, Levitt P. Gene expression profiling reveals alterations of specific metabolic pathways in schizophrenia. J Neurosci. 2002; 22:2718–29. [PubMed: 11923437]

Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. Neuron. 2000; 28:53–67. [PubMed: 11086983]

Mirnics K, Middleton FA, Lewis DA, Levitt P. Analysis of complex brain disorders with gene expression microarrays: schizophrenia as a disease of the synapse. Trends Neurosci. 2001a; 24:479–86. [PubMed: 11476888]

Mirnics K, Middleton FA, Stanwood GD, Lewis DA, Levitt P. Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. Mol Psychiatry. 2001b; 6:293–301. [PubMed: 11326297]

Mirnics K, Levitt P, Lewis DA. Critical appraisal of DNA microarrays in psychiatric genomics. Biol Psychiatry. 2006; 60:163–76. [PubMed: 16616896]

Mudge J, Miller NA, Khrebtukova I, Lindquist IE, May GD, Huntley JJ, Luo S, Zhang L, van Velkinburgh JC, Farmer AD, Lewis S, Beavis WD, Schilkey FD, Virk SM, Black CF, Myers MK, Mader LC, Langley RJ, Utsey JP, Kim RW, Roberts RC, Khalsa SK, Garcia M, Ambriz-Griffith V, Harlan R, Czika W, Martin S, Wolfinger RD, Perrone-Bizzozero NI, Schroth GP, Kingsmore SF. Genomic convergence analysis of schizophrenia: mRNA sequencing reveals altered synaptic vesicular transport in post-mortem cerebellum. PLoS One. 2008; 3:e3625. [PubMed: 18985160]

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: a meta-analytic study. Arch Gen Psychiatry. 1998; 55:433–40. [PubMed: 9596046]

Niemann K, Hammers A, Coenen VA, Thron A, Klosterkotter J. Evidence of a smaller left hippocampus and left temporal horn in both patients with first episode schizophrenia and normal control subjects. Psychiatry Res. 2000; 99:93–110. [PubMed: 10963985]

Ohnuma T, Kato H, Arai H, Faull RL, McKenna PJ, Emson PC. Gene expression of PSD95 in prefrontal cortex and hippocampus in schizophrenia. Neuroreport. 2000; 11:3133–7. [PubMed: 11043537]

Okasha A, Madkour O. Cortical and central atrophy in chronic schizophrenia. A controlled study. Acta Psychiatr Scand. 1982; 65:29–34. [PubMed: 7187173]

Pierri JN, Chaudry AS, Woo TU, Lewis DA. Alterations in chandelier neuron axon terminals in the prefrontal cortex of schizophrenic subjects. Am J Psychiatry. 1999; 156:1709–19. [PubMed: 10553733]

Pierri JN, Volk CL, Auh S, Sampson A, Lewis DA. Somal size of prefrontal cortical pyramidal neurons in schizophrenia: differential effects across neuronal subpopulations. Biol Psychiatry. 2003; 54:111–20. [PubMed: 12873800]

Prasad KM, Almasy L, Gur RC, Gur RE, Pogue-Geile M, Chowdari KV, Talkowski ME, Nimgaonkar VL. RGS4 Polymorphisms Associated With Variability of Cognitive Performance in a Family-Based Schizophrenia Sample. Schizophr Bull. 2009

Rajkowska G, Selemon LD, Goldman-Rakic PS. Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. Arch Gen Psychiatry. 1998; 55:215–24. [PubMed: 9510215]

Rakic P, Bourgeois JP, Goldman-Rakic PS. Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. Prog Brain Res. 1994; 102:227–43. [PubMed: 7800815]

Roberts RC, Conley R, Kung L, Peretti FJ, Chute DJ. Reduced striatal spine size in schizophrenia: a postmortem ultrastructural study. Neuroreport. 1996; 7:1214–8. [PubMed: 8817535]

Roe AW, Pallas SL, Hahm JO, Sur M. A map of visual space induced in primary auditory cortex. Science. 1990; 250:818–20. [PubMed: 2237432]

Sokolov BP, Tcherepanov AA, Haroutunian V, Davis KL. Levels of mRNAs encoding synaptic vesicle and synaptic plasma membrane proteins in the temporal cortex of elderly schizophrenic patients. Biol Psychiatry. 2000; 48:184–96. [PubMed: 10924661]

Stryker MP, Harris WA. Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex. J Neurosci. 1986; 6:2117–33. [PubMed: 3746403]

Sweet RA, Pierri JN, Auh S, Sampson AR, Lewis DA. Reduced pyramidal cell somal volume in auditory association cortex of subjects with schizophrenia. Neuropsychopharmacology. 2003; 28:599–609. [PubMed: 12629543]

Takacs J, Hamori J. Developmental dynamics of Purkinje cells and dendritic spines in rat cerebellar cortex. J Neurosci Res. 1994; 38:515–30. [PubMed: 7815471]

Van Horn JD, McManus IC. Ventricular enlargement in schizophrenia. A meta-analysis of studies of the ventricle:brain ratio (VBR). Br J Psychiatry. 1992; 160:687–97. [PubMed: 1534268]

Vita A, De Peri L, Silenzi C, Dieci M. Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. Schizophr Res. 2006; 82:75–88. [PubMed: 16377156]

Weinberger DR, Torrey EF, Neophytides AN, Wyatt RJ. Lateral cerebral ventricular enlargement in chronic schizophrenia. Arch Gen Psychiatry. 1979; 36:735–9. [PubMed: 36863]