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Review

Dendritic spine alterations in schizophrenia

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HIGHLIGHTS

- Schizophrenia is a neurodevelopment disorder with multiple contributing genes.
- Dendritic impairments, including spine loss, are present in schizophrenia.
- Identification of conserved underlying molecular pathologies is ongoing.

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ABSTRACT

Schizophrenia is a chronic illness affecting approximately 0.5–1% of the world's population. The etiology of schizophrenia is complex, including multiple genes, and contributing environmental effects that adversely impact neurodevelopment. Nevertheless, a final common result, present in many subjects with schizophrenia, is impairment of pyramidal neuron dendritic morphology in multiple regions of the cerebral cortex. In this review, we summarize the evidence of reduced dendritic spine density and other dendritic abnormalities in schizophrenia, evaluate current data that informs the neurodevelopment timing of these impairments, and discuss what is known about possible upstream sources of dendritic spine loss in this illness.

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Abbreviations: BA, Brodmann area; SZ, schizophrenia; C, control; HMW, high molecular weight MAP2 isoforms (MAP2A, MAP2B); MAP2-IR, MAP2 immunoreactivity; CA1,CA2,CA3,CA4, cornu ammonis areas 1–4.

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1. Introduction

Schizophrenia is a chronic illness associated with lifelong debilitation, and reduced quality of life that affects approximately 0.5–1% of the world's population [1]. Schizophrenia is characterized by a variety of symptoms, which can be categorized into positive, negative, and cognitive symptom domains [2,3]. Positive or psychotic symptoms describe the presence of perceptions or behaviors involving distortions of reality, including disorganized thought processes, delusions, and hallucinations. Hallucinations may occur in any sensory modality, but are typically auditory and verbal in nature. Negative symptoms refer to the absence of behaviors which should be present, including alogia (absence of speech), avolition (absence of motivation), anhedonia (inability to experience pleasure), and flattened affect (inability to express emotion). Cognitive symptoms include impairments in memory performance, executive function, attention, as well as poor language and reading ability [4], and impaired social cognition [5].

The age of onset of schizophrenia, defined by the first episode of psychotic symptoms, is typically during the late adolescent to early adult years; generally between 18 and 30 years of age [2]. This might lead to a view of schizophrenia as a disorder of late neurodevelopment. However, prior to the first episode of schizophrenia, there is also evidence for cognitive deficits, and other abnormalities of movement and behavior, suggesting earlier time points in neurodevelopment are affected [6].

A definite cause of schizophrenia has yet to be identified. However, evidence suggests a strong role of genetics in the etiology of schizophrenia. Monozygotic twins demonstrate 45–60% concordance for schizophrenia and the estimate of heritability is about 80% [7]. A number of potential schizophrenia susceptibility genes have been identified, including both common and rare structural variants [8]. These susceptibility loci overlap with those for other disorders of neurodevelopment, including intellectual disability and autism [9]. Importantly, for attempts to model underlying mechanisms, no simple mendelian form of schizophrenia has yet to be identified [8]. The fact that the concordance rate between monozygotic twins is not 100% further suggests that environmental influences contribute to the likelihood of developing schizophrenia. Many environmental risk factors for developing schizophrenia have been identified [10], and include both early neurodevelopmental insults such as prenatal exposure to maternal infection [11] and obstetric complications [12], as well as later insults such as cannabis use in adolescence [13].

Thus, the clinical syndrome of schizophrenia is likely the result of a number of genetic contributions that interact with any of several environmental events to adversely impact the course of neurodevelopment. While this multiplicity of etiologies is daunting, it does not preclude the development of understanding of disease if there are any conserved "downstream" pathologies that could instead serve as a focus for investigation [1]. This review will focus on one such conserved neuropathology of schizophrenia, reduced dendritic spine density in neocortex. Specifically, we will review the evidence of reduced dendritic spine density and other dendritic abnormalities in schizophrenia, evaluate when in neurodevelopment individuals with schizophrenia may separate from typically developing individuals on this parameter, and discuss what is known about possible upstream sources of dendritic spine loss in this illness.

2. Dendritic alterations in schizophrenia

2.1. Reduced dendritic spine density

Reduced density of dendritic spines is one of the most consistently observed neuropathologic alterations in postmortem brain tissue studies of individuals with schizophrenia. Dendritic spine density has been evaluated in 7 separate studies (Table 1) [14–20]. Multiple areas within frontal and temporal neocortex have been evaluated, as have primary visual cortex and the subiculum within the hippocampal formation. Significantly, reduced spine density was found in schizophrenia subjects relative to control subjects in most comparisons. In two other studies of layer 3 pyramidal neurons, one in primary visual cortex and one in prefrontal cortex, spine density was modestly reduced in schizophrenia, approaching but not reaching significance [15,20]. Only in a single study, confined to layers 5 and 6 of Brodmann area (BA) 46, was there no reduction in spine density [16]. The median reported decrease in spine density was 23% (range 6.5–66%). Reduced spine density has been found using Golgi-impregnated tissue to yield an estimate of density of spines per dendritic length [14,15,18,20], using antibody to label the dendritic spine protein, spinophilin [17], and using dual labeling with antibody to spinophilin and the F-actin binding toxin, phalloidin [19]. These latter, immunohistochemical approaches provide an estimate of the density of spines per volume of gray matter rather than per dendritic length. In the one study to estimate spine number, which reflects total number of spines in a region of interest independently of changes in volume of the surrounding gray matter, in deep layer 3 of primary auditory cortex reductions of 19% were found in schizophrenia [19]. Two studies evaluated whether reduced spine density in deep layer 3 of BA 46 was specific for schizophrenia. One found evidence for spine density reductions in bipolar illness, while the other found no evidence of reduction in a group consisting predominantly of major depression with psychotic features [15,20]. Finally, two studies examined whether spine density reductions

Table 1
Studies of dendritic spine density in schizophrenia.

References	Brain regions	*N* of subjects SZ/C	Method	Finding(s)
Garey et al. [14]	BA 10, BA 11, BA 45	13/11	Golgi	66% decrease in layer 3
Garey et al. [14]	BA 38, BA 20, BA 21, BA 22	13/11	Golgi	59% decrease in layer 3
Glantz and Lewis [15]	BA 46	15/15	Golgi	23% decrease in deep layer 3. No significant reduction in superficial layer 3
Glantz and Lewis [15]	BA 17	13/15	Golgi	14% reduction (not significant) in layer 3
Rosoklija et al. [18]	Subiculum	13/8	Golgi	35% decrease
Kolluri et al. [16]	BA 46	14/15	Golgi	No difference in layers 5 and 6.
Sweet et al. [17]	BA 41	15/15	Anti-spinophilin antibody	27% decrease in deep layer 3
Sweet et al. [17]	BA 42	15/15	Anti-spinophilin antibody	22% decrease in deep layer 3
Shelton et al. [19]	BA 41	20/20	Dual label with anti-spinophilin antibody and phalloidin	20% decrease in spine density and spine number in deep layer 3
Konopaske et al. [20]	BA 46	14/19	Golgi	6.5% decrease in spine density and 21.6% decrease in number of spines per dendrite in deep layer 3