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Chapter 10

Chondroitin Sulfate Proteoglycan Abnormalities in Schizophrenia

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Abstract

Schizophrenia is a chronic psychiatric illness known to affect approximately 1% of the population. Genetic and early life environmental factors conjure to disrupt distinct neuronal and glial populations in several cortical and subcortical brain regions. The resulting clinical symptoms emerge in late adolescence to early adulthood, preceded by a prodromal syndrome. Recent evidence points to a role for chondroitin sulfate proteoglycans (CSPGs) in the pathophysiology of schizophrenia. Our group has shown large increases of CSPG expression in glial cells accompanied by reductions of perineuronal nets (PNNs) in the medial temporal lobe of subjects with schizophrenia. Similar findings in the prefrontal cortex and olfactory epithelium suggest that CSPG abnormalities may be widespread in this disease. Genetic studies reporting associations of polymorphisms for specific CSPG genes, including *PTPRZ1*, neuroglycan-C and neurocan with schizophrenia, and recent animal studies examining the effects of abnormal CSPG expression or sulfation on brain development and function, lend further support for CSPG abnormalities in this disorder. In this chapter we discuss these findings and their potential relevance to core aspects of the pathophysiology of schizophrenia, such as brain development, myelination and regulation of key neurotransmitter systems including the glutamatergic, GABAergic and dopaminergic systems. We put forth the hypothesis that altered CSPG expression may contribute to a number of critical components of the pathophysiology of schizophrenia, including altered neuronal migration and connectivity, neural circuit plasticity, synaptic regulation, and electrical oscillatory rhythms observed in this disorder.

Introduction

In recent years, significant advances have been made toward our understanding of the pathophysiology of schizophrenia. Although much remains to be done, as a field we have now identified key brain regions, neurotransmitters and cell systems affected in this disorder. Extracellular matrix molecules, and chondroitin sulfate proteoglycans (CSPGs) in particular, have been recently shown to represent novel, and very promising, players in the pathophysiology of schizophrenia. In light of their role in the developing and adult brain, CSPGs bear the potential to link many seemingly unrelated aspects of neuronal and glial disturbances. Here, we provide a brief overview of the clinical and pathophysiological characteristics of this disorder; in this context, we then discuss current evidence for CSPG abnormalities and their potential pathophysiological implications for schizophrenia.

Schizophrenia: an Overview

Schizophrenia is a severe and often disabling psychiatric syndrome, characterized by a complex symptomatology. Positive symptoms, such as hallucinations, delusions, disorganized speech, abnormal psychomotor behavior (agitation, catatonia), are typically accompanied to various degrees by negative symptoms, including restricted affect, avolition, anhedonia and asociality [1]. The clinical onset of schizophrenia typically occurs between 16 to 30 years of age, and is preceded by a prodromal state characterized by social withdrawal, anxiety, irritability, cognitive decline, attention difficulty and unusual thoughts [2-8]. Relapses, increased suicide risk, worsening of positive, cognitive and, particularly, negative symptoms and repeated hospitalizations are observed in the majority of patients over the course of several years. Sustained recovery occurs in approximately 20-35% of people, while the remaining patients show little or no improvement.

Growing evidence supports the view that schizophrenia is a neurodevelopmental disorder, arising from complex genetic vulnerabilities involving large numbers of genes, each with weak effects [9], in combination with environmental factors likely to occur during fetal and early postnatal life. Several candidate vulnerability genes for schizophrenia, including neuregulin [10-12], dysbindin-1, COMT [13-22], and DISC1 [23-30], are known to play a role in brain development, notably neuronal migration through the regulation of cell to cell and cell to matrix interactions [31]. Early exposure to environmental predisposing factors, such as maternal stress and birth complications, contribute to increased vulnerability for schizophrenia. The long-term effects of these factors may be mediated by epigenetic mechanisms, such as histone modification and DNA methylation, both found to be abnormal in schizophrenia [32-45]. Furthermore, the often protracted prodromal period occurs during late postnatal brain development, coinciding with late stage maturation of synaptic connections and axonal myelination. Together with early neurobiological deficits observed in subjects at risk for schizophrenia, this observation suggests a progressive disruption of brain development that may culminate with the clinical onset of the disease [2-8, 46-52].

Postmortem and brain imaging studies have implicated a number of interconnected brain regions in schizophrenia [53-68]. Abnormalities affecting glutamatergic, GABAergic and dopaminergic neurotransmission, as well as distinct neuronal and glial cell types have been

detected in several brain regions, including the hippocampus, entorhinal cortex, amygdala, dorsolateral prefrontal cortex, anterior cingulate gyrus and thalamus. Not surprisingly, the functional roles of these brain regions are highly relevant to the symptomatology and functional impairment observed in schizophrenia. The hippocampus is involved in episodic memory storage and context related cognitive processing [69-73]; the entorhinal cortex gates cortical and subcortical inputs to the hippocampus and participates in sensory integration and memory processing [74-77]; the amygdala plays a key role in the attribution of salience/emotional valence, associative learning, anxiety and stress response [78-92]; the dorsolateral prefrontal cortex is involved in working memory and executive cognitive functions [93-98]; components of the thalamus, such as the mediodorsal nucleus, contribute to associative learning and working memory (Jones E.G. *The thalamus* 2nd edition New York, Cambridge University Press, 2007) [99-103]; the anterior cingulate cortex is involved in the regulation of attention, motivation, and response selection [104-106]. Several neuronal populations within each of these regions are affected in schizophrenia. Distinct populations of inhibitory GABAergic interneurons play a key role in intrinsic information processing and the generation of oscillatory rhythms, which in turn have been found to be altered in schizophrenia [57, 107-120]. Abnormalities affecting glutamate ionotropic and metabotropic receptors have been reported, although a predominant role of NMDA receptors has been long suspected and validated by growing evidence [121-125]. Dopaminergic neurotransmission abnormalities have been detected in the prefrontal cortex, striatum and amygdala [126-130] (Markota et al., manuscript in preparation). More recently, the involvement of glial cells, astrocytes, and oligodendrocytes in particular, in the pathophysiology of schizophrenia has also been reported [131-144]. Astrocytes take an active role in a broad variety of brain functions, including uptake and release of neurotransmitters, integration of synaptic activity and regulation of the blood-brain barrier [145-147]. Oligodendrocytes are the myelinating cells of the CNS. Axon myelination is a key aspect of brain development. It allows fast saltatory nerve conduction and affects axonal transport processes and neuronal functions [148].

In this context, abnormalities affecting extracellular matrix molecules chondroitin sulfate proteoglycans (CSPGs) in schizophrenia represent a novel and unexpected finding in this disorder [149-154]. CSPGs interact with each of the neurotransmitter systems implicated in this disease, and contribute to critical neurodevelopmental functions [155-159]. During early brain developmental stages, CSPGs play critical roles in neuronal migration and axonal guidance [155-159]. Their regulation of neural functions continues during postnatal development and adult life. During late postnatal development, CSPGs contribute to the maturation of perineuronal nets (PNNs), of which they are major components (**Figure 1**). PNNs are specialized extracellular matrix aggregates that envelop subpopulations of neurons and regulate neuronal plasticity, synaptic formation and electrophysiological maturation [160-162]. Interestingly, in a rodent model, PTPRZ1 overexpression resulted in deficits in the GABAergic, glutamatergic, and dopaminergic neurotransmitter systems, as well as delayed maturation of oligodendrocytes and behavioral deficits associated with schizophrenia [163]. We propose that a disruption of CSPG expression may represent a critical factor in the pathophysiology of this disorder, linking together a variety of key neural abnormalities. In this chapter, we discuss current evidence for the involvement of CSPGs in neurodevelopmental aspects of the pathophysiology of schizophrenia, and their potential impact on distinct neural cell populations and neurotransmitter systems.

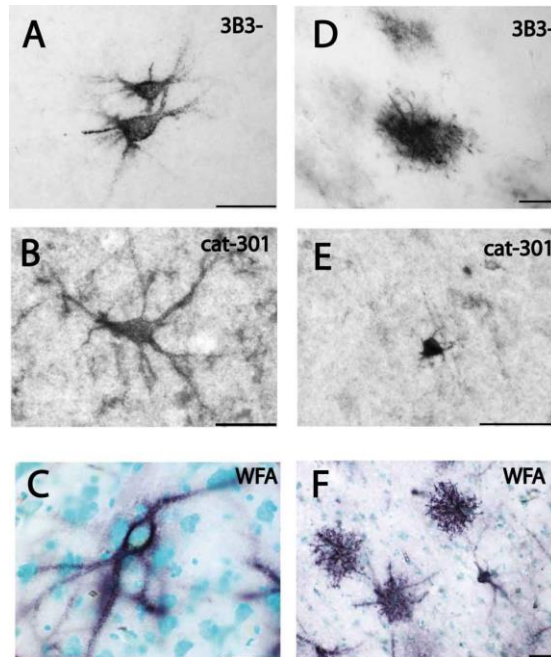
1. Evidence for CSPG Abnormalities in Schizophrenia

Rapidly mounting evidence points to abnormal CSPG expression in schizophrenia. Recent findings from our group have shown marked increases of glial cells expressing CSPGs (419 to 1560 percent) in the amygdala and superficial layers of the entorhinal cortex of subjects with schizophrenia [153] (**Figure 2**). In healthy human subjects, the vast majority of these cells were found to express the astrocytic marker glial fibrillary acidic protein (GFAP), indicating that they correspond to a subpopulation of astrocytes [164]. Numbers of GFAP immunoreactive astrocytes were not increased in subjects with schizophrenia, a finding consistent with previous reports showing that astrocytosis is not present in this disorder [165-168]. Increases of CSPG-positive glial cells were accompanied by significant reductions of CSPG-positive PNNs in the lateral nucleus of the amygdala and in superficial layers of the lateral entorhinal cortex [153]. Therefore, increased CSPG expression in glial cells was accompanied by a more spatially segregated PNN reduction. CSPG-positive glial cell increases and PNN decreases did not correlate with duration of illness and they were not affected by other variables including age, gender, cause of death and treatment with antipsychotic drugs [153]. Therefore, these changes may be present early on in the disease and reflect some of the core aspects of its pathophysiology.

PNN decreases were also found in layers 3 through 5 of the prefrontal cortex [169] and increases of CSPG glia have been reported in layers 2 through 4 of this region in subjects with schizophrenia [152]. Thus, CSPG expression abnormalities in schizophrenia may be widespread, shared by several cortical and subcortical brain regions. Notably, PNNs in the prefrontal cortex of human subjects were shown to continue maturing until late adolescence [169], potentially coinciding with the age of onset of schizophrenia.

CSPG abnormalities were also recently detected in the olfactory epithelium (Pantazopoulos et al., submitted for publication). The olfactory epithelium, located in the nasal cavity, is unique in that neuronal differentiation, migration and axon outgrowth occur robustly throughout life, and are at least in part regulated by CSPGs [170]. Abnormal expression of these molecules observed in postmortem olfactory epithelium of subjects with schizophrenia are consistent with neuronal lineage abnormalities observed in the same subject cohort [171], and suggest that CSPGs may represent a contributing factor. Notably, schizophrenic subjects and first-degree relatives experience deficits in olfactory identification [172-177], possibly due to anomalous connections between olfactory sensory neurons in the olfactory epithelium to the olfactory bulb. Anomalous CSPG expression in the olfactory epithelium may contribute to altered maturation of olfactory sensory neurons and their odor-specific connectivity with the olfactory bulb, ultimately affecting olfactory identification.

Finally, genetic studies have reported associations of polymorphisms for specific CSPG genes including PTPRZ1 [151], neuroglycan-C [150] and neurocan [149] with schizophrenia, suggesting that abnormal CSPG expression may be due, at least in part, to genetic factors. It is worth noting that other extracellular matrix molecules, including semaphorin 3a, and reelin [178-182], have also been found to be affected in schizophrenia, suggesting a broader involvement of the extracellular matrix in this disorder.

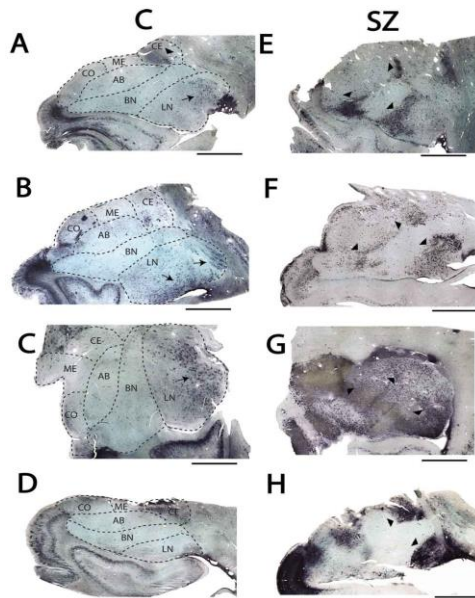


Photomicrographs of PNNs (A-C) and glial cells (D-F) in the normal human amygdala. PNNs and glial cells in A and D, respectively, were detected using antibodies raised against CS isomers containing penultimate 6-sulphated N-Acetyl-galactosamine (3B3; gift from Dr. B. Caterson, Cardiff University, U.K.), while antibodies raised against the aggrecan core protein (cat-301) were using in B and E. CSPGs can also be detected using the lectin *wisteria floribunda agglutinin* (WFA), as shown by PNNs and glial cells depicted in C and F, respectively. Note the difference in size and labeling distribution of CSPG-positive glial cells in D, E, and F, which may reflect different intracellular distribution or expression in distinct cell types. Scale bars = 50 μm .

Figure 1. CSPG-positive PNNs and glial cells in the normal human amygdala.

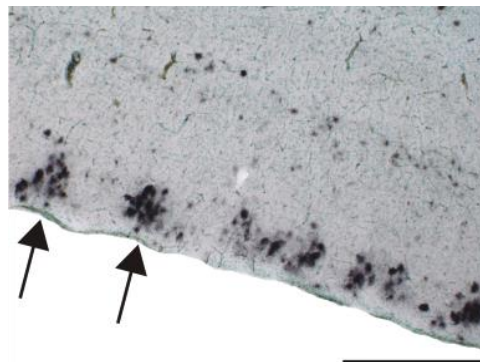
2. Neurodevelopmental Abnormalities in Schizophrenia: Potential Role of CSPG Dysregulation

Pathological evidence for the neurodevelopmental nature of schizophrenia is based in great part on cytoarchitectonic anomalies and heterotopic neuron displacement strongly suggestive of disrupted neuronal migration, reported in several brain regions [183-186, 193-199]. In the entorhinal cortex of subjects with schizophrenia, cytoarchitectonic abnormalities of the superficial layers include invaginations of the surface, decreased neuron density and poorly formed neuronal clusters in layer II with putative displacement of these neurons deeper into layer III [184, 185]. Notably, increases of CSPG-positive glial cells were most pronounced in layer II of the entorhinal cortex of schizophrenic subjects [153], largely overlapping with layer II cell clusters. We put forth that enduring CSPG expression abnormalities in the superficial layers of the entorhinal cortex may contribute to a disruption of neuronal migration and incorrect cell cluster formation in schizophrenia (Figure 3).



High resolution photocomposites depicting sections from the amygdala of four pairs of control (A-D) and schizophrenic subjects (E-H). Sections were stained with the lectin WFA to label CSPGs and counterstained with methyl green. Areas with prevalent CSPG-positive PNN densities are marked with arrows, while those with prevalent CSPG-positive glial cell densities are marked with arrow heads. In subjects with schizophrenia, CSPG-positive glial cells were markedly increased, while CSPG-positive glial cells were decreased. This is reflected by an overall increase of CSPG labeling in subjects with schizophrenia (E-H) with respect to controls, and a shift from PNN to glial CSPG labeling. *Abbreviations:* AB, accessory basal nucleus; BN, basal nucleus; C, control subjects; CE, central nucleus; CO, cortical nucleus; LN, lateral nucleus; ME, medial nucleus; SZ, subjects with schizophrenia. Scale bar = 4 mm.

Figure 2. CSPG expression abnormalities in the amygdala of subjects with schizophrenia.



Photomicrograph showing the superficial layers of the entorhinal cortex in a section stained with WFA from a subject with schizophrenia. Marked increases in the number of CSPG expressing glial cells were observed in clusters within the superficial layer of the entorhinal cortex, corresponding to layer 2 cell islands, known to project to the hippocampus [159]. Cytoarchitectonic abnormalities in this layer have been consistently reported in subjects with schizophrenia [173], suggesting that a disruption of CSPG expression in glial cells in this layer may impact on cell migration in the entorhinal cortex of subjects with schizophrenia. Scale bar, 1 mm.

Figure 3. Increases of CSPG-positive glial cells in the superficial layers of the entorhinal cortex in subjects with schizophrenia.

Heterotopic neuron displacement, and more specifically increase of interstitial white matter neurons, was also detected in the frontal, parietal and temporal cortical lobes, and interpreted as a failure of these neurons to migrate into the cortical grey matter [187-192]. In support of this interpretation, an increase of interneurons expressing somatostatin in the superficial white matter was accompanied by reduced somatostatin mRNA in the gray matter [193]. Notably, in the superior temporal gyrus, an increase of interstitial white matter neurons was accompanied by a reduction of neurons expressing reelin mRNA in layer I and superficial white matter [194], adding further support for the hypothesis that abnormal expression of extracellular matrix molecules, possibly including CSPGs, may contribute to altered neuronal migration in schizophrenia. During early brain developmental stages, CSPGs containing oversulfated CS chains contribute to the guidance of neurons and axons to their proper locations [155, 156]. Chondroitin-4 sulfated (CS-4) CSPGs interact with the secreted membrane protein semaphorin 3a to guide the migration of cortical interneurons originating from the ganglionic eminence [195]. Semaphorin 3a has reported to be increased in schizophrenia [178]. This increase was correlated with decreases of reelin and synaptic markers, indicating that increased CSPGs and semaphorin 3a, may contribute to altered neuronal migration in schizophrenia.

Further evidence for the neurodevelopmental nature of this disorder originates from imaging and postmortem findings consistent with altered connectivity, or ‘mis-wiring’, in schizophrenia. Some of these studies are discussed below, in the context of dopaminergic innervation and myelination abnormalities. It is worth to mention here that findings indicating a disruption of axon fasciculation in the entorhinal cortex [196] strongly suggest a disruption of axonal guidance, another key CSPG function [156, 197-209], and overlap in distribution with CSPG-positive glia and PNN abnormalities in schizophrenia [153].

3. Neurotransmitter System Abnormalities in Schizophrenia: Potential Role of CSPG Dysregulation

3.1. GABAergic and Glutamatergic Neurotransmission

Findings showing the involvement of inhibitory, GABAergic, interneurons are among of the most solid in schizophrenia. Reduction of glutamic acid decarboxylase (GAD), the synthesizing enzyme of GABA, decreased numbers of GABAergic interneurons, and in particular interneurons expressing the calcium binding protein parvalbumin (PVB), and decreased PVB terminals have been reported in several brain regions [40, 57, 58, 66, 179, 210-215]. PVB-positive neurons are a subpopulation of GABAergic neurons with distinct fast-firing properties [216-220]. They form dense axo-somatic contacts onto projection neurons [221, 222], and thus have the ability to powerfully inhibit information outflow from the regions affected [223]. In addition, PVB-positive neurons have been shown to generate gamma-oscillatory rhythms, synchronized neural activity thought to provide the temporal structure for learning and information integration and to be disrupted in schizophrenia [107, 111, 113, 216, 224, 117-120]. Altered gamma oscillations in this disorder have been postulated to contribute to cognitive and memory deficits and, speculatively, to disturb

developmental synaptic reorganization processes known to occur during late adolescence [120, 225]. PVB-positive neurons are predominantly associated with PNNs, which contribute to multiple aspects of neuronal activity. First, the formation of PNNs around PVB-positive neurons during late postnatal life represents a key aspect of the maturation of these neurons [162, 226-233]. Increased expression levels of CSPGs, such as aggrecan, coincide with the maturation of electrophysiological properties of neurons [160], while degradation of PNNs by ChABC results in reduced inhibition of excitatory pyramidal cells in the hippocampus [234]. PNN maturation around PVB-positive neurons closes developmental critical periods, establishing an adult, typically restricted, form of plasticity [161, 235, 236]. In particular, in the amygdala, where PNNs were found to be markedly decreased in schizophrenia, PNN maturation contributes to the transition between juvenile and adult forms of emotion-related plasticity, as exemplified by the effects of CSPG digestion on the resilience of fear memory in a rodent model. Notably, fear extinction and context-dependent recall were found to be disrupted in subjects with schizophrenia in conjunction with anomalous amygdala activation [237, 238]. Second, PNNs are postulated to help maintain the ionic homeostasis necessary to support PVB-positive neurons' distinct fast-firing properties [229, 234, 239-241], and to control the availability of glutamatergic ionic receptors to the postsynaptic membrane specialization and the composition of the NMDA receptor subunits, thus powerfully controlling the excitatory synapse maturation and target neuron responsiveness to glutamate neurotransmission [242, 243]. In turn, PNN formation is an activity-dependent process [236, 244-246]. Decreased NMDA receptors may therefore contribute to decreases of PNNs in schizophrenia [211, 247-253]. Third, PNNs have been shown to regulate the sprouting and pruning of synapses, thus controlling powerful mechanisms mediating plasticity. Notably, reductions of synaptic spines and abnormal expression of presynaptic proteins represents one of the most solid findings in schizophrenia [254-264]. Together, these findings raise the possibility that loss of, or failure to develop, PNNs in subjects with schizophrenia may contribute to interneuron-related dysfunction, including anomalous electrophysiological and neurochemical maturation and responsiveness to glutamatergic inputs. In turn, these changes are likely to contribute to abnormal oscillatory rhythms observed in this disorder [117-120].

3.2. Dopaminergic System

Dopamine was one of the first neurotransmitters to be implicated in the pathogenesis of schizophrenia. Initial findings on reserpine, and observations that dopamine D2 receptors are targeted by antipsychotics and symptoms of schizophrenia are improved by dopamine antagonists and exacerbated by dopamine releasing agents, led to the hypothesis that dopaminergic transmission may be altered in schizophrenia [265-272]. Recent views postulate that dopaminergic transmission may be reduced in the prefrontal cortex, while enhanced in the ventral striatum/nucleus accumbens [129, 126-128, 130]. A similar enhancement in the amygdala is supported by recent findings from our group (Markota et al., manuscript in preparation). Consistent with these findings, higher levels of dopamine have been reported in the amygdala, caudate nucleus, and nucleus accumbens in subjects with schizophrenia, [128-130, 273]. While a state of hypodopaminergia in the prefrontal cortex may contribute to impairment of working memory and cognitive functions observed in schizophrenia, enhanced dopaminergic transmission in the ventral striatum and amygdala has

been postulated to disrupt salience attribution and error prediction mechanisms, speculatively contributing to psychotic symptoms [274-279].

CSPG abnormalities may contribute, and/or interact with, dopaminergic abnormalities in several ways. During development, CSPGs have been shown to promote neurite outgrowth of dopaminergic neurons [280] and to guide dopaminergic axons to their target regions [281-284]. Altered CSPG expression in developmental stages may result in abnormal development of dopaminergic innervation in the brain of subjects with schizophrenia. Furthermore, it is conceivable that altered CSPG expression in the extracellular matrix may impact on neurotransmitter diffusibility in the extracellular space [285]. In subjects with schizophrenia, volume diffusion of excess dopamine overflowing from the synaptic space in the striatum and amygdala, postulated on the basis of evidence for hyperdopaminergia in these regions [128-130, 273], may be impacted by extracellular matrix abnormalities which may affect the likelihood of reaching poorly regulated extrasynaptic dopamine D2 receptors [286]. It is also worth noting that PVB-positive neurons represent one of the main targets of dopaminergic innervation in the amygdala [287]. Loss of PNNs in schizophrenia is predicted to profoundly affect their synaptic inputs, presumably including dopaminergic contacts. Finally, it has been reported that degradation of PNNs in the rodent hippocampus results in increased activity of ventral tegmental area dopaminergic neurons [234]. Thus, CSPGs disruption may have an indirect effect on dopaminergic transmission in schizophrenia, affecting intrinsic hippocampal activity and ultimately its impact on dopaminergic neurons in the ventral tegmental area [234].

4. Glial Cell Dysfunction in Schizophrenia: Potential Contributions of CSPGs

4.1. Oligodendrocytes

Myelin abnormalities have been consistently reported in schizophrenia. Together, altered expression of key myelin components such as sphingomyelin, galactocerebrosides, myelin-associated glycoprotein, decreased numbers of oligodendrocytes, altered expression of oligodendrocyte-related genes, reduction of myelin compactness and increased density of concentric lamellar bodies, point to a significant disruption of myelination in this disorder [288-305]. Decreased expression of multiple genes associated with the integrity of the nodes of Ranvier has been reported in subjects with schizophrenia [306, 307]. Finally, typical and atypical antipsychotic drugs, including haloperidol, quetiapine, olanzapine and clozapine, have been shown to promote proliferation of oligodendrocyte progenitor cells and possibly contribute to re-myelination [308-313].

We postulate that a disruption of CSPG expression in schizophrenia may impact on several aspect of the myelination process. Brevican expression in immature oligodendrocytes postnatally coincides with the extension of membrane processes ensheathing axon fibers [314]. Together with tenascin-R and phosphacan, brevican is present at the nodes of Ranvier of large diameter myelinated axons in the adult CNS, where it is thought to control the ECM composition [315]. The CSPG NG2 is expressed in oligodendrocyte progenitor cells. Although these cells are not directly involved in myelination, their number increases during

re-myelination, possibly in response to cytokines and growth factors [316-328]. A disruption of CSPG expression, perhaps including brevican and NG2, may contribute to myelin defects reported in schizophrenia.

4.2. Astrocytes

Astrocytes perform a wide range of functions in the developing and adult brain, including modulation of neuronal maturation and synaptogenesis, regulation of the blood-brain barrier, ion and neurotransmitter buffering, release of neurotransmitters and growth factors and response to brain injury [147, 329]. Importantly, interactions between astrocytes and the extracellular matrix are at the core of several of these functions. Expression of the CSPGs brevican, aggrecan and phosphacan has been shown to regulate glial cell differentiation [330-333]. Conversely, astrocytes are considered to be the organizers of the brain extracellular matrix, and PNNs in particular [334]. More specifically, converging lines of evidence show that astrocyte-derived tenascins and CSPGs play a key role in regulating PNN formation and maintenance as well as fundamental synaptic functions [334].

While it is widely accepted that reactive astrocytosis is not present in schizophrenia [153, 165-168, 335], growing evidence indicates that abnormal astrocyte functions may contribute to the pathophysiology of this disorder. Altered expression and N-glycosylation of the glutamate transporters EAAT1 and EAAT2, expressed by astrocytes, has been reported in schizophrenia [135-137, 139, 336]. Increased levels of the calcium binding protein S100beta have been detected in the blood serum and cerebral spinal fluid of subjects with this disorder [134, 337-342]. S100beta, expressed primarily by astrocytes and some NG2 cells [343, 344], is involved in the proliferation and differentiation, migration, and maturation of astrocytes [338, 345-347]. Marked increases of CSPG positive glial cells in the amygdala and entorhinal cortex of subjects with schizophrenia [153] are consistent with a prominent glial pathology in schizophrenia and point to abnormalities of astrocyte-derived CSPGs as a contributing factor to key aspects of the pathophysiology of this disease, as discussed above.

Conclusion

In summary, schizophrenia is a neurodevelopmental disorder with a complex neuropathology involving several main neurotransmitter systems, neural cell populations and brain regions. CSPGs interact with each of these components and play critical roles in early and late stages of brain development, including neuronal migration, axon guidance, synapse maturation, and myelination, as well as adult functions, such as regulation of neuronal firing properties, regulation of plasticity and NMDA receptor availability at the postsynaptic space. Together, marked abnormalities affecting both CSPG-positive PNNs and glial cells, their distribution patterns in the brain, indirect evidence that these abnormalities may be inherent to the disease, and the relevance that CSPG functions bear to the pathophysiology of this disorder, raise the possibility that their dysregulation may impact on developmental and adult brain functions known to be disrupted in schizophrenia.

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