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The tetrapartite synapse: a key concept in the pathophysiology of schizophrenia

Gabriele Chelini[a,b], **Harry Pantazopoulos**[a,b], **Peter Durning**[a], and **Sabina Berretta**[a,b,c,*]

[a]Translational Neuroscience Laboratory, Mclean Hospital, 115 Mill Street, Belmont, MA, 02478 USA

[b]Dept. of Psychiatry, Harvard Medical School, 25 Shattuck St, Boston, MA, 02115 USA

[c]Program in Neuroscience, Harvard Medical School, 220 Longwood Ave., Boston, MA, 02115 USA

Abstract

Growing evidence points to synaptic pathology as a core component of the pathophysiology of schizophrenia (SZ). Significant reductions of dendritic spine density and altered expression of their structural and molecular components have been reported in several brain regions, suggesting a deficit of synaptic plasticity. Regulation of synaptic plasticity is a complex process, one that requires not only interactions between pre- and post-synaptic terminals, but also glial cells and the extracellular matrix (ECM). Together, these elements are referred to as the 'tetrapartite synapse', an emerging concept supported by accumulating evidence for a role of glial cells and the extracellular matrix in regulating structural and functional aspects of synaptic plasticity. In particular, chondroitin sulfate proteoglycans (CSPGs), one of the main components of the ECM, have been shown to be synthesized predominantly by glial cells, to form organized perisynaptic aggregates known as perineuronal nets (PNNs), and to modulate synaptic signaling and plasticity during postnatal development and adulthood. Notably, recent findings from our group and others have shown marked CSPG abnormalities in several brain regions of people with SZ. These abnormalities were found to affect specialized ECM structures, including PNNs, as well as glial cells expressing the corresponding CSPGs. The purpose of this review is to bring forth the hypothesis that synaptic pathology in SZ arises from a disruption of the interactions between elements of the tetrapartite synapse.

Keywords

Extracellular matrix; Perineuronal nets; Chondroitin sulfate proteoglycans; Astrocytes; NG2 cells; Microglia

*Corresponding author at: McLean Hospital, Mailstop 149, 115 Mill Street, Belmont, MA, 02478, USA.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

1. Introduction

Growing evidence points to synaptic pathology across several brain disorders, including schizophrenia (SZ), bipolar disorder, major depression, autism spectrum disorder and Alzheimer's disease. Research on the underlying mechanisms for this pathology has only very recently begun to make headway, and important questions arise with regard to the potential common denominators of synaptic pathology among these disorders, and their timeframe across lifespan. With regard to the latter, it is important to consider that synaptic remodeling occurs constantly throughout life. During postnatal development, excessive synaptic formation is followed by elimination of less active synapses, a process named synapse pruning [1, 2]. During adult life, synapses are highly dynamic, with constant, experience-driven synaptic growth and elimination. It is plausible to postulate that timeframe-, mechanism- and brain region- specificity underlying synaptic pathology across a spectrum of brain disorders may at least in part contribute to their diverse clinical and pathophysiological manifestations. Within this context, we suggest that the concept of 'tetrapartite synapse' may be a useful starting point for investigating synaptic pathology. We focus on schizophrenia as a notable example.

1.1. The tetrapartite synapse

The chemical synapse has classically been considered as composed of two main elements, i.e. the presynaptic and postsynaptic elements. This concept evolved over the past two decades to include a third element, i.e. the astrocyte, as processes from these cells envelope the synapse and play a key role in regulating its functions [3,4]. The ensemble of pre- and postsynaptic elements and astrocytes has been proposed to form a functional complex referred to as the 'tripartite synapse' [5]. Growing evidence indicates that other populations of glial cells, including NG2 glia and microglia, also play critical roles in regulating synaptic functions and plasticity. Thus, we suggest that distinct populations of glial cells with specific functions may be considered together to represent the third element of tripartite synapse. Yet more recently, the extracellular matrix (ECM) has come to the forefront of neuroscience as an active component of neural functions and, in particular, synaptic regulation. On the basis of this evidence, Dityatev et al., proposed the elegant concept of the 'tetrapartite synapse', composed of pre- and post-synaptic elements, glial processes and ECM, and elegantly documented the interactions between these components [6–8] (Fig. 1). Here, we review evidence supporting the idea that synaptic functions and plasticity result from interactions between all elements of the tetrapartite synapse, and focus on evidence that these interactions are disrupted in SZ.

1.1.1. The tetrapartite synapse: pre- and post-synaptic elements—The brain possesses the extraordinary ability to continuously reshape itself throughout the entire lifespan. This property, defined as plasticity, is based on the highly dynamic properties of synaptic contacts, i.e. the ability to generate new synapses, eliminate them, and alter the electrophysiological, molecular and structural properties of existing ones in response to experience. The mechanisms underlying synaptic plasticity have been the object of intense work and exciting discoveries over the past few decades, focused initially on the interplay between the presynaptic and postsynaptic elements. For example, the discovery that trains of

presynapticaction potentials induce a long-lasting increase in synaptic strength during long term potentiation (LTP) generated intense debate over whether the predominant underlying changes may be related to postsynaptic modification in α-amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid receptors (AMPARs) or altered presynaptic transmitter release [9,10]. Ensuing work demonstrated that these mechanisms include a series of steps, from receptor phosphorylation, to protein synthesis and, eventually, structural changes including growth of new dendritic spines and increased size of pre-existing spines, mediated by changes dendritic spine molecular cytoskeleton, including long-lasting increases in F-actin content within spines and condensation of the post-synaptic density (PSD), a dense aggregate of scaffolding proteins implicated in structural maintenance and signal transduction [11–13]. Similarly, long-term depression (LTD) of synaptic strength results in spine shrinkage and elimination [14–17]. A review of current knowledge on the role of pre- and post-synaptic elements in plasticity is beyond the scope of this manuscript; arguably plastic modifications of these elements may be considered to be the final result of complex, experience-driven mechanisms, and the underlying substrate of learning and memory.

1.1.2. The tetrapartite synapse: role of glial cells

1.1.2.1. Astrocytes: Astrocytic processes envelop the pre- and postsynaptic elements and closely approach the synaptic cleft, thus representing a key component of the synapse [3,18] (Fig. 1). Their robust expression of the high-affinity glutamate transporters EAAT1-EAAT2 allows them to rapidly re-uptake excess of glutamate released from the presynaptic terminals, thus restricting excitatory transmission [19]. In turn, astrocytes actively contribute to synaptic transmission and plasticity. Although electrically silent, they respond to presynaptic activation with G-protein-mediated Ca2 signals, triggering the release of ‘gliotransmitters’, including glutamate, ATP, and GABA, which modulate local synaptic transmission [20–25]. Astrocyte-derived glutamate facilitates NMDA receptor activation on the postsynaptic sites, enhancing the probability of triggering LTP [26]. Moreover, stimuli inducing synaptic LTP rapidly induce structural remodeling of astrocytic processes enwrapping synapses, resulting in changes in their ability to modulate synaptic transmission [27]. Together, these considerations compellingly point to astrocytes as key active mediators of synaptic plasticity.

1.1.2.2. NG2 cells: In the early nineties, a novel population of cells was identified by their expression of the CSP GNG2, platelet-derived growth factor α receptors (PDGFαR), and O4 sulfatide (O4) [28–30]. These cells are abundant in the white and gray matter, and have been shown to represent the main source of mature oligodendrocytes in the mature brain, earning the name of oligodendrocyte precursor cells [31]. However, morphological features of NG2 cells closely resemble those of mature astrocytes, while their molecular signature is quite distinct [29,32,33]. Further studies showed that NG2 cells represent a distinct matureglial type with unique properties. Indeed, a growing body of evidence indicates that NG2 cell express voltage-gated ion channels and ligand-gated ionotropic neurotransmitter receptors, typically found in neurons but not in glial cells; this peculiar pattern of molecular expression endows them with a unique electrophysiological profile [34]. They are the only glial cell type capable of receiving synaptic GABAergic and glutamatergic contacts from neurons, and to respond to excitatory inputs with excitatory postsynaptic currents and activity-dependent

modifications analogous to LTP at excitatory synapses, although with some notable differences [35–37]. Electron microscopy studies demonstrated that NG2 cell processes often encapsulate neuronal cell bodies and contact synapses [38]. Potential effects of NG2 cells on synaptic transmission are suggested by experiments showing that downregulation of NG2 expression results in altered subunit composition of AMPA receptors and marked reduction of NMDA-dependent LTP [39]. The full range of NG2 cell functions is only partially understood, and is likely to be age-, stage- and brain region-specific; however, plastic responses of these cells to excitatory neurotransmission and their intimate contacts with synaptic complexes strongly suggest that they play a significant role in the regulation of synaptic functions and plasticity [34,40–43].

1.1.2.3 Microglia: Microglial cells serve diverse roles during brain development and adulthood, from regulation of synaptic pruning and plasticity to removal of apoptotic cells and debris, and immune responses, representing primary sources of immune response factors such as cytokines (see 44). Notably, these seemingly unrelated functions may in fact share similar mechanisms, as growing evidence indicates that immune factors play important roles in the regulation of synaptic plasticity [45]. Microglial cells express an impressive variety of receptors, including not only immune receptors, such as pattern-recognition receptors that allow them to recognize pathogen-associated molecular patterns and tissue damage–associated molecular patterns and chemokine receptors, but also a surprisingly large number of receptors for neurotransmitters and neuropeptides [44]. These two latter categories include ionotropic and metabotropic glutamate receptors, and receptors for GABA, dopamine, catecholamines and acetylcholine, which mediate neural-glia communications. These receptors modulate the release of cytokines and guide microglial processes toward active synapses, where they regulate synaptic structural plasticity [44–46]. In particular, microglia represent a key player in the remodeling, particularly removal, of inactive synapses during brain development and adulthood. Microglia processes are highly dynamic, continually extending, retracting and interacting with synapses, thus as acting like sentinels to assess surrounding synapses and contribute to their remodeling when needed [20–23]. Among the immune-related molecules involved in these mechanisms are several complement factors, which act as signal to microglia to find and engulf pre and post-synaptic elements [47–49]. Complement signaling pathways also mediate microglia-induced long term depression (LTD), involved in brain circuitry optimization, and potentially in memory impairments and synaptic disruptions in neuroinflammation-related brain disorders [50]. Notably, the strongest genetic association observed in SZ involves variation in the Major Histocompatibility Complex locus, shown to arise predominantly from alleles of the complement component 4 (C4) genes [51,52]. Elegant work by Sekar et al. recently showed that these alleles do affect C4 expression and that this factor mediates synapse elimination during postnatal development [52]. In summary, microglial cells play a key role in shaping synaptic connectivity in an activity-dependent manner – the underlying mechanisms involve molecular factors with strong relevant to the pathophysiology of SZ.

1.1.3. The tetrapartite synapse: role of the extracellular matrix—The brain ECM is a complex molecular network that surrounds all cells, occupying approximately a 20% volume fraction of the adult brain [53]. It’s main components include hyaluronan,

proteoglycans, glycoproteins and a variety of posttranslational remodeling proteases, such as matrix metalloproinases (MMPs), ‘a disintegrin and matrix metalloproteases’ (ADAMS), and ‘ADAMS with a thrombospondin domain’ (ADAMTS), which cleave ECM molecules, allowing for highly dynamic functional adaptations [54–58]. As discussed below, organized forms of ECM surround the synapse, fill the synaptic cleft and interact with cell surface receptors (Fig. 1). Converging evidence points to peri-synaptic ECM aggregates as a critical player contributing to synaptic signaling and plasticity.

1.1.3.1. ECM factors regulating synaptic plasticity: Chondroitin sulfate proteoglycans (CSPGs) have been described as the organizers of the ECM, of which they represent a main component [59–64]. These macromolecules consist of core proteins linked to varying numbers of chondroitin sulfate (CS) glycosaminoglycan (GAG) chains. The number and length of GAG chains, and particularly their sulfation patterns (e.g. CS-6, CS-4), are key factors in determining their functions, resulting in highly dynamic structural and functional diversity to these molecules [65–68]. While their functions in the developing and mature brain are highly diversified, mounting evidence indicates that CSPGs play a complex role in developmental and adult regulation of synaptic plasticity. For example, enzymatic CSPG removal in vitro mouse hippocampal slices causes a two-fold decrease in long-term potentiation (LTP) [69]. Overexpression of CS-6 sulfation in mice leads to failure to instate an adult form of restricted plasticity [66]. Altered expression of several CSPGs, such as PTPRZ1, neurocan and brevican, was found to be associated with synaptic remodeling LTP abnormalities and learning impairment [70–75]. Notably, several CSPGs have been shown to actively stabilize dendritic spines, while their removal by enzymatic digestion results in increased spine motility [76–79].

Several other ECM molecules have been found to be involved in the regulation of synaptic plasticity. For instance, genetic or pharmacological removal of the ECM component tenascin-C and thrombospondins 1 and 2 resulted in reduced calcium signaling and impaired LTP in rodents (Evers et al.; Dityatev et al.). Hyaluronan, considered to be the backbone of the ECM and enriched in PNNs and other forms of ECM perisynaptic aggregates, was found to regulate hippocampal synaptic plasticity by modulating postsynaptic L-type Ca2+ channels [80]. Other ECM components have been shown to modulate chemical transmission by acting on glutamate NMDA and AMPA receptors and impacting adaptive synapse modifications. Particularly relevant to several brain disorders, including SZ, is the ECM glycoprotein Reelin. Reelin’s effects are mediated through its main lipoprotein receptors, apolipoprotein E receptor 2 and very-low-density lipoprotein receptor [81,82], as well as through the integrin family and the Src family kinases [82–85]. Reelin is secreted into the ECM, where it regulates the composition of NMDA receptors, controlling the predominance and/or phosphorylation of the NR2 NMDA receptor subunits, augments AMPA responses by increasing the number of AMPA receptors on the postsynaptic membrane, and robustly enhances LTP [85–87]. Reelin powerfully promotes spine remodeling, regulating spine size and stability, and number of synaptic contacts per spine [88–93]. Integrins, known to interact with Reelin and other ECM molecules, regulate AMPA receptor internalization, surface mobility of NMDA receptor subunits, and synaptic dwell time of glycine receptors and their scaffolding molecule gephyrin [94–97]. These mechanisms have been postulated to allow

integrins to play complex roles in synaptic plasticity, including carrying out structural and functional changes that accompany LTP [97–99]. Secreted ECM proteases, such as MMPs, affect excitatory transmission and have extensively been investigated as mediators of synaptic plasticity [100–103]. During development, MMPs play a key role in spine formation and maturation [104–106]. In mature neurons, MMPs and their interactions with integrins, are required for spine volume changes induced by LTP and LTD [107,108]. MMP-9 is transiently released in response to enhanced neuronal activity and impacts both synaptic potentiation and dendritic spine enlargement in a dependent manner [108,109]. Notably, several MMPs have been shown to be represented in WFA-labeled PNNs [110], suggesting a role in regulating their functions. Semaphorins, key components of the ECM, have also been shown to regulate synaptogenesis (Pasterkamp & Giger 2009). For instance, semaphorin 3A, a key component of at least a subpopulation of PNNs, exerts a powerful effect on synapses, possibly through its plexin and neuropilin receptors [106,111–114].

1.1.3.2. ECM perisynaptic aggregates

1.1.3.2.1. Perineuronal nets: In addition to a loosely organized molecular lattice, the ECM forms organized, structured aggregates with distinct molecular composition. PNNs are arguably the most extensively investigated. They tightly surround synaptic contacts on distinct populations of neurons, including GABAergic interneuron populations and GABAergic projection neurons, such as those in the reticular nucleus of the thalamus, central nucleus of the amygdala and Purkinje cells in the cerebellum, as well as subpopulations of cortico-cortical pyramidal cells and spinal cord motor neurons [62,115–121]. PNNs represent key players in the regulation of synaptic connectivity and plasticity [111,122–129]. They mature late in postnatal development, in an activity-dependent manner [130–133]. Their maturation brings to a closure critical periods of development, inducing a profound shift from juvenile forms of plasticity to more restricted mature forms, consolidating successfully established synaptic connectivity and controlling formation of new synapses [76,124,129,134]. Enzymatic CSPG digestion dramatically disrupts PNN integrity, reverting local circuits and learning modalities, from visual perception to emotional learning, to a juvenile state [129,134]. The molecular composition of mature PNNs is thought to be species-, neuron- and brain region-specific, but to include CSPGs, hyaluronan and a variety of glycoproteins described above in relationship to synaptic plasticity regulation. Thus, functions such as modulation of glutamatergic transmission, LTP and LTD and synaptic motility and structural plasticity, demonstrated for these molecules, are inherent to PNNs. In addition, recent evidence shows that PNNs are in themselves dynamically regulated [123]. Fear learning and consolidation in response to pure tones was shown to induce marked PNN changes in the adult auditory cortex [123]. Expression CSPG mRNA and numbers of PNN were increased within hours following fear conditioning and returned to baseline 24 h later. CSPG enzymatic digestion in the auditory cortex impaired fear learning and consolidation, demonstrating that PNNs are necessary for fear learning [123]. Notably, in the amygdala, CSPG digestion also affected fear learning, reinstating juvenile forms of extinction-vulnerable conditioning [129].

1.1.3.2.2. CS-6/Glia clusters: Contrary to what initially thought, PNNs are not unique as forms of organized ECM in the brain. Among other forms, CS-6/Glia clusters, or

DAndelion-like Clock Structure, may be equally relevant to synaptic plasticity [135,136]. CS-6/Glia clusters are detectable in human and rodent brain using antibodies raised against the CS-6 sulfation patterns (Fig. 2). Their morphology may vary across brain regions, but in general they present as round rosettes of diffuse immunolabeling, with an overall diameter of 100–200 μm, often organized in short, dense segments. Several dendrites, and occasionally some neuronal and glial cell bodies are embedded in these clusters, while several glial cells surround them (Chelini et al; unpublished observations) [135,137]. In the mouse brain, CS-6/Glia clusters were found to develop in late postnatal development, suggesting a role in regulation of synaptic connectivity similar to that shown for PNNs [135,137–141]. Increases of CS-6 clusters in response to ketamine treatment suggest that these structures may be responsive to changes of glutamatergic transmission [142]. Although still preliminary, information on CS-6/Glia clusters is consistent with their involvement in synaptic functions, potentially representing segregated microenvironments regulated by predominant expression of CS-6 sulfation. The functional effects of these sulfation patterns are currently poorly understood, but evidence suggests a role for CS-6 sulfation patterns in facilitating plasticity. A switch from CS-6 to CS-4 sulfation patterns during postnatal development, and persistent cortical plasticity induced by CS-6 upregulation, suggest that the former may be more permissive, facilitating plasticity, while CS-4 may represent the mature, less permissive, CSPG form [66] (Fig. 3).

1.2. Synaptic pathology in SZ

Growing evidence overwhelmingly points to synaptic abnormalities as core component of the pathology of SZ. Significant reductions of dendritic spines have been reported in several cortical areas, including prefrontal and auditory cortical areas and the hippocampus [143–147]. Anomalous dendritic spine morphology, expression of PSD proteins, including PSD95 and Homer-1, and associated glutamate signaling pathway proteins have also been reported [148,149]. Altered expression of molecules involved in the actin cytoskeleton strongly suggests that dendritic spines in SZ may reflect structural deficits [150–152]. A recent study shows dramatic changes affecting genes involved in synaptic functions in the amygdala [153], notably one of the main regions shown to have significant ECM abnormalities in this disorder. Decreases of dendritic spines in SZ have been proposed to represent the consequence of overpruning during adolescence [154,155].This hypothesis predicts a loss of large, mature spines in this disorder. Contrary to this expectation, a recent report shows that, at least in the primary auditory cortex, loss of dendritic spines in SZ may predominantly reflect decreases of smaller spines, and potentially be related to the SZ risk gene CACNB4 [154]. These findings are prompting novel hypotheses on the potential causes of synaptic pathology in SZ, and its links to genetic vulnerabilities. Importantly, GWAS data and de novo CNV analyses strongly support the involvement of genes involved in synaptic plasticity, and specifically, encoding for elements of the postsynaptic density, as risk factors for SZ [51,156]. Among these are alleles of the complement component 4 (C4) genes which, as mentioned above, were recently shown to play a key role in synapse elimination during postnatal development [51,52]. Additional genetic loci associated with genetic vulnerability to SZ also include genes encoding for ECM molecules and particularly ECM remodeling proteases [51]. Together, these studies support the possibility that risk genes affecting synaptic functions and ECM may interact with each other and with secondary or

environmental factors to affect elements of the tetrapartite synapse, ultimately resulting in disruption of synaptic functions and plasticity.

2. Methods

Methods briefly described here refer to investigations on postmortem human tissue carried out by our group.

2.1. Human subjects

Tissue blocks containing the regions of interest (e.g. the amygdala) from cohorts of normal control and SZ donors (n = 12–25/group) were used for histochemical, immunocytochemical and qRT-PCR studies. All tissue blocks were obtained from the Harvard Brain Tissue Resource Center (HBTRC), McLean Hospital, Belmont, MA, USA. Diagnoses of SZ and BD were made by two psychiatrists on the basis of retrospective review of medical records, extensive questionnaires concerning social and medical history provided by family members and neuropathological report. Cohorts did not include subjects with evidence for gross and/or macroscopic brain changes, or clinical history, consistent with cerebrovascular accident or other neurological disorders. Subjects with Braak stages III or higher [157] (modified Bielschowsky stain) were not included.

2.2. Tissue processing and data collection

Tissue blocks were dissected from fresh brains, lightly fixed and cryoprotected (for immunohystochemistry (IHC) only), or quickly frozen in liquid nitrogen vapor (for Western blotting and qRT-PCR), then sectioned using a freezing microtome or a cryostat. Specificity of primary antibodies for IHC was tested by immunoblotting and pre-absorption with the corresponding antigen. WFA, and a variety of antibodies raised against CSPG protein cores (e.g. aggrecan), or CSPG CS-6 sulfation patterns (CS56, 3B3) were used to label PNNs and CS-6 clusters. Procedures for protein and mRNA detection and data collection were carried out as reported previously [e.g. 136,158].

2.3. Statistical analysis

Differences between groups relative to the main outcome measures in each of the regions examined were assessed for statistical significance using an ANCOVA stepwise linear regression process. Effect sizes were calculated according Hedges' g. A logarithmic transformation was uniformly applied to all original values because the data were not normally distributed. Age, gender, postmortem time interval, inflammation (classified as positive or negative for inflammatory condition at time of death), hemisphere, cause of death, brain weight, exposure to alcohol, nicotine, electroconvulsive therapy, and lifetime, as well as final six months', exposure to antipsychotic drugs, exposure to selective serotonin reuptake inhibitors classified as positive or negative for exposure, and lithium treatment were tested systematically for their effects on the main outcome measures, and included in the model if they significantly improved the model goodness of-fit (see also 136,158]

3. Results

3.1. ECM pathology in SZ

Human postmortem studies from our group consistently show marked decreases of PNNs in people with SZ [136,138,158–160]. Our first findings showed significant reduction of PNNs labeled with the lectin *Wisteria floribunda* agglutinin (WFA) in the amygdala and entorhinal cortex of subjects with SZ [158]. Similar decreases of WFA-labeled PNNs were also detected in the prefrontal cortex and hippocampus, but not in the visual cortex, consistent with specific involvement of brain regions impacted in SZ [138,159]. Notably, numbers of neurons predominantly associated with WFA-labeled PNNs, i.e. interneurons expressing parvalbumin [161–164], were not decreased in these regions [165–169]. This latter finding supports the idea that PNN decreases do not depend on a corresponding reduction of the neurons they envelope, while at the same time suggest that they may contribute to functional abnormalities affecting these neurons in SZ [169,170]. WFA labels a distal *N*-acetylgalactosamine on the CS chains of a group of CSPGs. Thus, decreases of WFA-labeled PNNs suggest CSPG involvement in SZ. To test the hypothesis that PNN decreases in SZ may not be restricted to WFA-positive PNNs, we focused on aggrecan, one of the main CSPGs in the brain and a major component of a population of PNNs, and on CS-6 sulfation patterns. Our results showed marked decreases of PNNs containing aggrecan and CS-6 sulfation in the amygdala of people with SZ [136]. Decreases of aggrecan-positive and WFA-positive PNNs were detected exclusively in the lateral nucleus of the amygdala; however, only one-third of WFA-positive PNNs also expressed aggrecan, raising the possibility that neuronal populations affected by WFA- and aggrecan-positive PNN loss only partially overlap. Decreases of CS-6 immunoreactive PNNs were much broader, impacting several amygdala nuclei, including the lateral, basal, accessory basal, cortical, and medial nuclei. Together, these findings show that PNN abnormalities in the amygdala of people with SZ include several distinct PNN phenotypes encompassing multiple neuronal populations. Such heterogeneity in PNN phenotypes is consistent with previous findings in several other brain regions [171–173].

Results from these postmortem studies also show complex interactions between PNN decreases and glial cells abnormalities. In the amygdala and entorhinal cortex, WFA-positive PNN decreases were accompanied by a robust increase of WFA-positive astrocytes affecting all amygdala nuclei and entorhinal cortex subregions tested, in contrast to the more restricted PNN changes. We speculate that impaired CSPG secretion in glial cells may be causally linked to WFA-positive PNN decreases. In contrast to results with WFA, aggrecan-positive PNN decreases were accompanied by marked reductions of glial cells expressing this CSPG [136], suggesting decreased aggrecan supply from glial cells. Together, these findings are consistent with the hypothesis that interactions between glial cells and ECM may be disrupted in SZ. This hypothesis is also supported by our findings that CS-6/Glia clusters, labeled with two different CS-6 antibodies (CS56 and 3B3), are markedly decreased in the amygdala of SZ [136]. As mentioned above, CS-6/Glia clusters putatively represent a novel form of structured ECM, postulated to affect dendritic spines. Their decreases may represent a clear example of disruption of the interactions between elements of the tetrapartite synapse, i.e. glial cells, ECM and pre- and post-synaptic elements. Additional evidence for

the involvement of the ECM in SZ comes from findings in the olfactory epithelium, a peripheral sensory organ where neurogenesis and axon growth occur throughout adult life [174–176]. ECM components, and CSPGs in particular, are suspected to play a key role in these functions. Postmortem findings from our group show that cytoplasmic CSPG expression is altered in olfactory receptor neurons, potentially contributing to a disruption of olfactory functions observed in people with SZ [177–185].

4. Discussion

In summary, our findings show consistent ECM abnormalities in people with SZ, including reductions of PNNs, altered CSPG expression in glial cells and reduced numbers of CS-6/Glia clusters. These abnormalities are large in magnitude, robust to confounding factors and shared by several brain regions involved in SZ {[136] Pantazopoulos #1181; [138] Mauney #7280; [158] Pantazopoulos #17815}. Yet, they are restricted in their distribution to specific cortical layers and amygdala nuclei, suggesting specialized mechanisms affecting distinct neuronal populations.

The causative mechanisms underlying ECM abnormalities are not yet well understood. However, support for the contribution of genetic factors can be found in a growing number of studies. A common variation of NCAN, encoding neurocan, a brain-specific CSPG highly represented in the brain, has been reported and replicated in several studies, including a large GWAS with more than 36000 SZ cases [51,186,187]. This latter study also discovered SZ risk factors from several other ECM molecules, including MMP-16 [51]. Several additional studies reported the involvement of other MMPs, of which MMP-9 may be the most notable. For instance, polymorphisms of MMP-9 have been shown to be associated with SZ, although some negative findings have also been reported, and plasma levels of MMP-9 were found to be altered in this disorder [109,188–190]. Together, these findings led to suggestions that MMPs may represent a novel therapeutic target for SZ [190,191]. Notably, dose-dependent MMP-9 activity is crucially modulated by mir-132, a microRNA identified as pivotal for synaptic plasticity and found to be decreased in blood and brain tissue of people with SZ [192–195]. Together, these findings support the hypothesis of aberrant CSPGs processing during activity dependent plasticity, potentially linking CSPGs abnormalities to synaptic pathology in SZ.

4.1. The tetrapartite synapse: role in synaptic pathology in SZ

Converging evidence reviewed here and elsewhere compellingly support the idea that all elements of the tetrapartite synapse may be altered in SZ. Briefly, several molecular factors contributing to presynaptic functions, including synaptic vesicle trafficking, have been found to be disrupted in SZ [196–199]. Similarly, altered expression of PSD proteins, such as PSD95 and Homer-1, and glutamate signaling pathway, as well as proteins molecules involved in the actin cytoskeleton has been reported in people with this disorder [148–152]. Emerging evidence for glial involvement in SZ indicates that all glial populations shown to affect synaptic functions, i.e. astrocytes, NG2 cells and microglia, contribute to the pathophysiology of this disorder [200–209]. Finally, ECM abnormalities in SZ have been

reviewed above, including evidence for altered CSPG expression in glial cells [see also 121,210].

It is plausible to postulate that abnormalities affecting distinct elements of the tetrapartite synapse may be causally related, and/or interact with each and result in synaptic dysfunction. Although the underlying mechanisms are not yet understood, current data raises a number of possible hypotheses. For instance, altered CSPG expression in glial cells and decreased PNNs in the same subjects suggests that decreased availability of PNN molecular components may contribute to PNN abnormalities. ECM molecules bind to neuronal surface receptors (e.g. integrins), which in turn link the postsynaptic density to the actin cytoskeleton on one side, and to the ECM and pre-synaptic terminal of the other side. Through this arrangement, cell adhesion molecules (CAMs)-mediate ECM and PSD signaling may impact the dendritic spine actin network, and thus the spine shape [211–217]. This possibility is supported by evidence that several ECM molecules, including CSPGs and Reelin, known to modulate spine formation, size and stability through ECM receptors, are also implicated in the pathology of SZ [76–79, 88–92, 218]. The potential contribution of decreased Reelin expression to dendritic spine decreases in SZ has long been postulated [93,219]. As reviewed above, ECM proteases such as MMPs, secreted into the ECM by astrocytes and microglia in addition to neurons, have been shown to robustly affect dendritic spine stability [106].

5. Conclusions

We reviewed evidence that each element of the tetrapartite synapse plays a role in synaptic plasticity and is involved in SZ. Several glial populations, including astrocytes, NG2 cells and microglia have been shown to regulate synaptic functions and plasticity. Each of these glial cell populations has been shown to have complex, intimate relationships with the ECM. Several ECM molecules have been shown to have powerful effects on synaptic plasticity, and to be represented in ECM organized perisynaptic structures such as PNNs. Genetic and human postmortem evidence supports the involvement of the ECM in SZ, including loss of PNNs and CS-6/Glia clusters. Synaptic pathology, including loss of dendritic spines and molecular factors involved in spine structural stability and enriched in the PSD, is well established in SZ. We put forth the hypothesis that this pathology results from a disruption of interactions between elements of the tetrapartite synapse. Given the clinical, genetic and pathological heterogeneity of SZ, it is possible that synaptic pathology in specific brain regions may represent a point of convergence, potentially caused by a number of distinct molecular mechanisms in different individuals.

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Abbreviations

ADAMS	a disintegrin and matrix metalloproteases
ADAMTS	ADAMS with a thrombospondin domain
AMPAR	α amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ATP	adenosine trisphosphate
C4	complement component 4
CS	chondroitin sulfate
CSPG	Chondroitin sulfate proteoglycan
EAAT1	excitatory amino acid transporter 1
EAAT2	excitatory amino acid transporter 2
ECM	extracellular matrix
GABA	γ-Aminobutyric acid
GAG	glycosaminoglycan chains
GWAS	genome wide association study
IHC	immunocytochemistry
LTD	long term depression
LTP	long term potentiation
MMP	matrix metalloproinase
NG2	neural/glial antigen 2
NMDA	*N*-methyl-D-aspartate
O4	O4 sulfatide
PDGFαR	platelet-derived growth factor α receptors
PNNs	perineuronal nets
PSD	postsynaptic density
SZ	schizophrenia
WFA	*Wisteria floribunda* agglutinin

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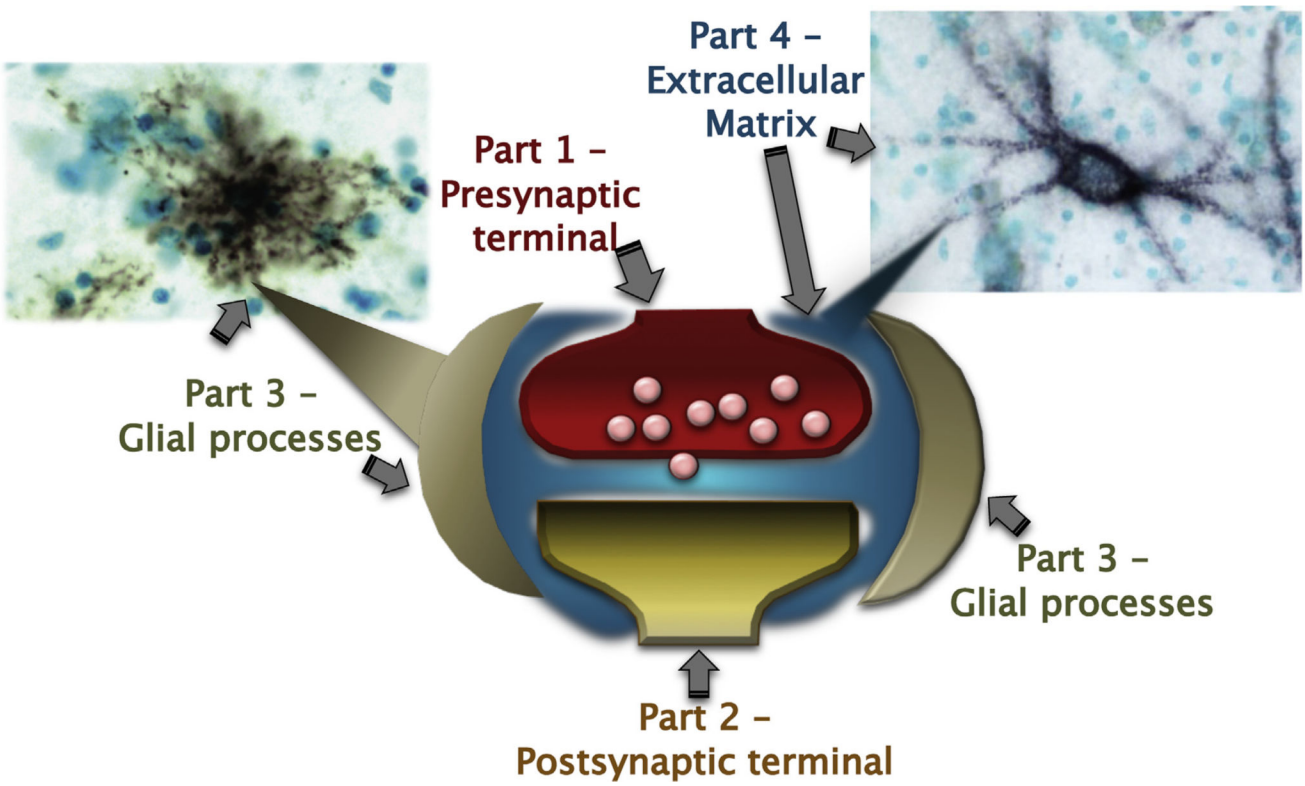

Fig. 1.

Diagramatic representation of the tetrapartite synapse. Elements composing it are the pre- and post-synaptic terminals, astrocytic processes surrounding them and perisynaptic extracellular matrix condensations interposed between these elements.

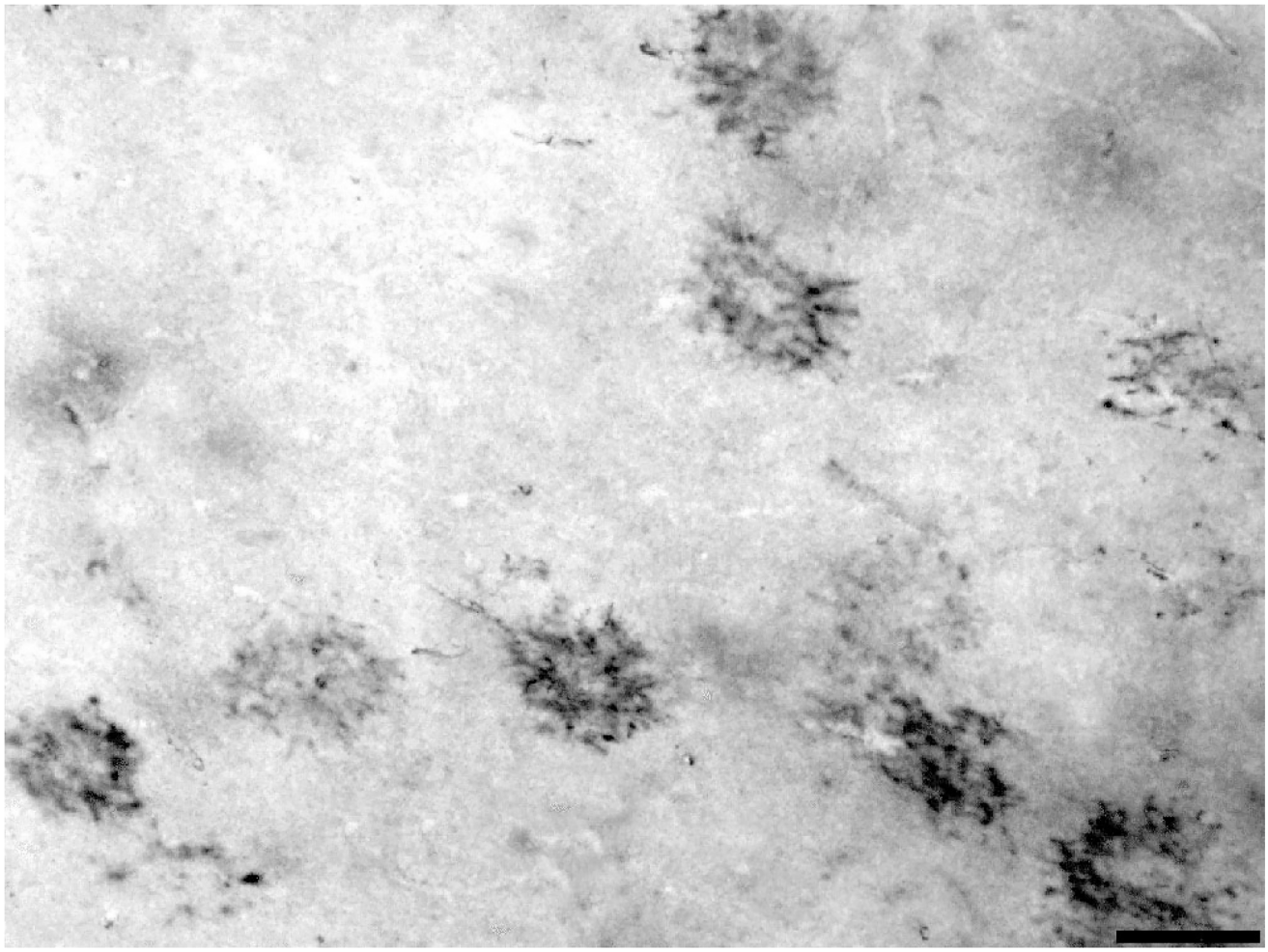

Fig. 2.
CS-6/Glia clusters in the healthy human amygdala, immunolabeled with CS-6 antibody CS56. Scale bar 100 μm.

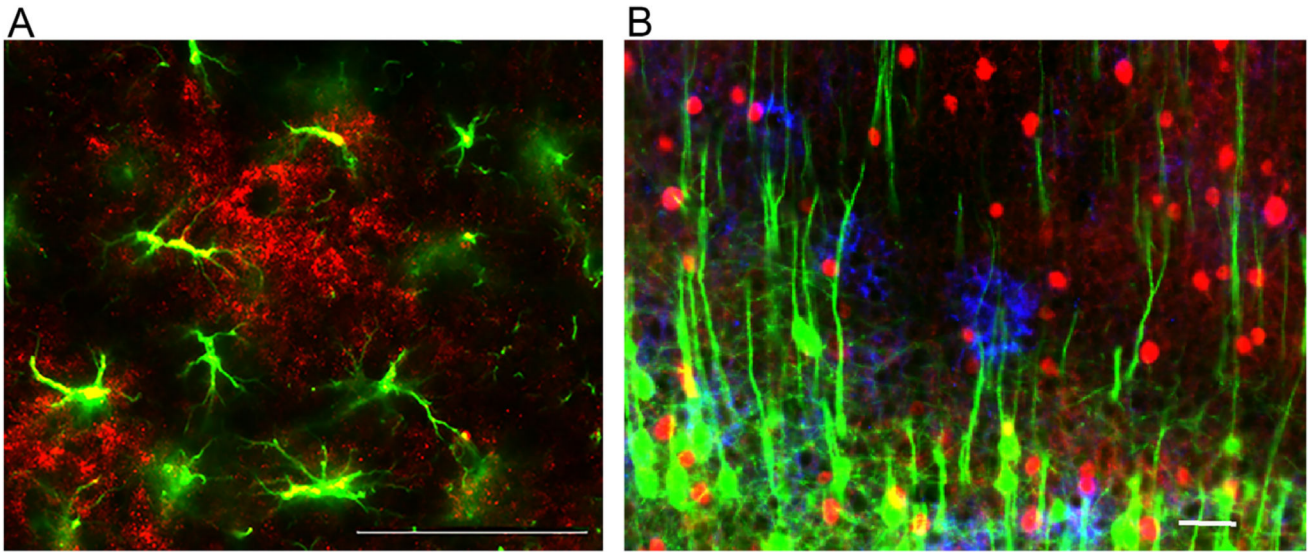

Fig. 3.

(A) Rodent CS-6 cluster (red; immunolabeled with CS56) surrounded by astrocytes (green; immunoreactive for glial fibrillary acidic protein (GFAP). (B) Immunolabeled CS-6/Glia clusters (blue) in the mouse hippocampus. These clusters are crossed by several dendrites arising from projection neurons (green, immunolabeled for Thy1) and are often surrounded by interneurons expressing parvalbumin (red). Scale bar 100 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)