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Weaving a Net of Neurobiological Mechanisms in Schizophrenia and Unraveling the Underlying Pathophysiology

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Abstract

Perineuronal nets (PNNs) are enigmatic structures composed of extracellular matrix molecules that encapsulate the soma, dendrites, and axon segments of neurons in a lattice-like fashion. Although the majority of PNNs condense around parvalbumin-expressing GABA(γ-aminobutyric acid)ergic interneurons, some glutamatergic pyramidal cells in the brain are also surrounded by PNNs. Experimental findings suggest pivotal roles of PNNs in the regulation of synaptic formation and function. There has also been an increasing body of evidence linking PNN abnormalities to schizophrenia. Interestingly, the number of PNNs progressively increases during postnatal development until plateauing around the period of late adolescence and early adulthood, which temporally coincides with the age of onset of schizophrenia. Given the established role of PNNs in modulating developmental plasticity, the PNN represents a possible candidate for altering the onset and progression of schizophrenia. Similarly, the reported function of PNNs in regulating the trafficking of glutamate receptors places them in a critical position to modulate synaptic pathology, considered a cardinal feature of schizophrenia. Here we discuss the physiological role of PNNs in neural function, synaptic assembly and plasticity in addition to how they interface with circuit/system mechanisms of cognition. An integrated understanding of these neurobiological processes should provide a better basis to elucidate how PNN abnormalities influence brain function and contribute to the pathogenesis of neurodevelopmental disorders such as schizophrenia.

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Keywords

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Schizophrenia is a multi-factorial disorder of neurodevelopmental origin (1-4) thought to arise from a complex interaction between genetic and environmental factors (5-11). The onset of schizophrenia occurs during late adolescence or early adulthood, when brain circuitry involving the prefrontal cortex and hippocampus, in addition to other limbic regions, undergoes maturation (2-4). The pathophysiologic features of schizophrenia stem from a variety of aberrant neurobiological underpinnings that ultimately impinge on synaptic plasticity and synaptic connectivity (12-14), including anomalies in cortical myelogenesis (13) and synaptic pruning (12, 15), altered glutamatergic signalling (16-18) and reduced neuropil (19) in conjunction with atypical development of cortical inhibitory circuits (14, 20, 21), dopaminergic pathways (22) and perineuronal nets (PNNs) (23-31).

The PNN is a reticular structure of the neural extracellular matrix (ECM) found surrounding many neurons in the central nervous system (CNS) (32-34). The developmental pattern of increasing PNN formation corresponds to the ending of the “critical period”, a time window of postnatal life which is critical for experience-dependent formation of synaptic connections and wiring of functionally related neuronal pathways that underlie sensory, motor, cognitive, social, and language abilities (35), deficits in which have been linked to schizophrenia (36). Interestingly, experimental disruption of PNNs in the adult brain can reopen critical periods, and therefore, the PNN is generally considered to play a role in restricting synaptic plasticity (37). More recent work has expanded the list of functions attributed to PNNs within the CNS (**Table 1**), with potential significance to neuropathogenesis.

Within this review we focus on the neurobiological functions of PNNs and their putative basis in schizophrenia pathophysiology. In addition, we expound on the emerging hypothesis linking a dysfunctional orthodenticle homeobox 2 (OTX2)-PNN interaction to the cognitive and cortical plasticity deficits associated with schizophrenia. We conclude by touching on how these observations may provide a neurobiological framework for the conceptualization of a molecular targeted intervention against this extremely debilitating condition.

Characteristics of PNNs: Molecular Heterogeneity, Distribution and Developmental Expression

PNNs are enriched in complex sugars called glycosaminoglycans (GAGs) and constitute a highly organized structure comprised of hyaluronan, link proteins, tenascin-R (TN-R) as well as chondriotin sulfate proteoglycans (CSPGs) - primarily the lectican family (aggrecan, brevican, neurocan and versican) and phosphocan (38-40). The possibility of simultaneously co-staining for various markers of the PNN has revealed a molecular heterogeneity of PNNs in distinct interneuronal subpopulations as indicated by different staining intensities of these markers in the cerebral cortex, subcortical forebrain and brainstem (41, 42). On the basis

that PNNs exhibit a high degree of constitutive heterogeneity, it should be kept in mind that the alteration of a single marker during development or in disease states may not necessarily reflect the alteration or loss of the entire structure.

Previous research conducted across a variety of animal species (i.e., rhesus monkey (43, 44), bison (45), dog (46), gerbil (47), guinea pig (48), zebra finch (49), rat (38), and mouse (25, 50-56)) has shown PNNs to be widely distributed in the brain. Similarly, in humans, PNNs have been found to be present in a variety of brain regions, including entorhinal cortex (28), amygdala (28, 29, 57), hippocampus (58), motor and somatosensory cortex (59), visual cortex (27) and prefrontal cortex (27), all regions (bar the visual cortex) which have been reported to be affected in schizophrenia (60).

Experimental evidence from animal studies suggests a progressive increase in PNN expression to be associated with the postnatal maturation of the CNS (35, 51, 61-63). Consistent with the animal findings, a recent study using human postmortem brain tissue revealed that the number of PNNs in the prefrontal cortex also increases through the peripubertal period until late adolescence and early adulthood (27), which interestingly is considered the peak period of risk for onset of schizophrenia (2, 64). Indeed, notable findings from the visual (65), motor (66), and somatosensory system (67) in animals, as well as in the pallial (cortical) song nuclei (49) in songbirds suggests that PNN expression is dependent on neuronal activity during the critical period.

Although the majority of PNNs condense around the fast-spiking parvalbumin-expressing GABA(γ-aminobutyric acid)ergic interneurons, some pyramidal cells are also surrounded by PNNs (68, 69). The presence of PNNs around parvalbumin interneurons is of particular significance in the context of critical period plasticity. This period of plasticity seems to be triggered by a shift in the excitatory/inhibitory balance associated with the maturation of parvalbumin interneurons (35, 70), whose functional disturbances have been strongly linked to schizophrenia [25]. It is of note that parvalbumin interneurons control the initiation and termination of the developmental critical periods with termination being dependent on the formation of PNNs (35, 37, 71). In this context, the recent evidence showing the PNN to play a role in the “capture” of the homeodomain transcription factor OTX2 is of particular interest (71, 72). The presence of a short motif within the OTX2 sequence (RKQRRERTTFTRAQL), which partially overlaps with the first helix of the homeodomain, possesses consensus traits of a GAG-binding domain (73) and is a requisite for the specific recognition of OTX2 by parvalbumin interneurons that are surrounded by PNNs (71). The sulfation pattern of PNNs represents another important factor in OTX2 binding (61). Importantly, secretion of OTX2 from choroid plexus epithelial cells has been shown to signal the maturation of the parvalbumin interneurons and the subsequent regulation of critical period plasticity (71, 74). Therefore, PNNs do not only serve as “molecular brakes” that limit morphological and physiological plasticity, but also as “receptors” which function to control the availability of molecular factors (e.g., OTX2) that regulate plasticity and modulate parvalbumin cell function in order to influence the opening and possibly also the closure of the critical period (61, 71, 72, 74, 75).

The Role of the PNN in the Modulation of Cognitive Function

Given that PNN-encapsulated neurons are prevalent throughout the limbic system (28, 29, 76) and PNNs are capable of modulating receptors (i.e., α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA receptors) known to be integral for learning and memory (77), these structures have been considered to play an important role in memory formation (54), which may include emotional memory (51, 55) in addition to reward-related memory (50, 78). In fact, it has been reported that PNNs are involved in long-term potentiation (LTP) and long-term depression (LTD) in hippocampal slices, as these physiological events are impaired following enzymatic degradation of CSPGs, or removal of TN-R (79, 80). Moreover, PNNs seem to be important for the maturation and stabilization of synapses (65, 81), key developmental processes that are altered in schizophrenia (12-14), suggesting that PNNs also serve a specialized role for normal neurophysiological development.

The presence of PNNs in the striatum (52), olfactory pathway (38, 76), basal ganglia (82), cerebellum (83), thalamus (56), visual cortex (27), insular cortex (50), high vocal center (49), orbital cortex (53), central auditory pathway (43, 84, 85), and spinal cord (86) suggests that the regulatory effects of PNNs are involved in a wide range of brain functions, including motor coordination, olfaction, procedural learning, voluntary motor movement, arousal state, vision, integration of cognitive, affective, sensory and autonomic information, vocal development, mediating decision making, processing of auditory stimuli, and nociception, respectively. Indeed, depletion or alterations in the molecular composition of PNNs induced by enzyme degradation (such as chondroitinase ABC, ChABC), by knock-out methods, or by clinical disease processes are associated with anomalies in sensory perception (67), impaired vision (71) as well as altered gait (52). Conversely and perhaps surprisingly, global disruption of PNNs has been shown to significantly improve spatial learning (52), cognitive flexibility (87), recognition memory (54) and extinction training (51, 55). The neurobiological mechanism underlying these cognitive changes involves the PNNs that surround parvalbumin interneurons. In this regard, an increase in the number of inhibitory synapses impinging on parvalbumin interneurons has been associated with memory acquisition (88). This increase in inhibitory synapses on parvalbumin interneurons decreases their production of GABA and thereby increases cortical excitability. Interestingly, treatment with ChABC has been shown to induce a similar effect by increasing the number of inhibitory interneurons associated with parvalbumin interneurons (88). Taken together, these observations suggest that depletion of PNNs can increase the number of synaptic connections and plasticity, facilitating cognitive ability by altering the rules of underlying, experience-driven synaptic plasticity.

The neuronal surface is compartmentalized by PNNs, with these structures serving as lateral diffusion barriers for AMPA receptors and limiting synaptic exchange (89). Research evidence indicates that desensitized synaptic AMPA receptors can be exchanged for naïve receptors during high frequency firing, thereby increasing synaptic fidelity (33, 89, 90). Given that AMPA receptors are the main transducers of rapid excitatory transmission in the mammalian CNS, trafficking of these receptors is important for effective synaptic efficiency (via LTP and LTD) and subsequent memory formation (91). Thus, the role of PNNs in regulating the trafficking of AMPA receptors is critical for optimal brain health and function.

On the Potential Importance of the PNN in Schizophrenia

In this section, we describe postmortem and preclinical studies that may shed light on the role that PNNs may play in schizophrenia (23, 24, 26).

PNN Regulation of Synaptic Functions

Based on the observations that PNNs enwrap the somatodendritic axis and proximal dendrites of neurons, it has been suggested that PNNs play a role in the regulation of synaptic functions (33). Therefore, PNN disruption could affect the activity of intrinsic circuitry and consequent information outflow. Recent evidence stemming from a rodent model is consistent with this possibility. In this study, PNN degradation by ChABC restricted to the ventral hippocampus resulted in an increased activity of pyramidal neurons, postulated to result from disruption of GABAergic neuronal activity following PNN loss (30). Interestingly, evidence from postmortem studies suggest that a similar disruption of inhibitory activity may occur in subjects with schizophrenia in brain regions that have been reported to exhibit PNN abnormalities, including the amygdala, entorhinal cortex and prefrontal cortex (27-29). Along these lines, deficits in PNN structure within the prefrontal cortex may affect neuronal network oscillations in the gamma frequency band (30-80 Hz), which are mediated by parvalbumin-expressing neurons and have been shown to be involved in higher cognitive functions such as feature binding, attention, and working memory (92-94). The research findings showing that PNNs play a role in the regulation of glutamate receptor trafficking (89) could be of pathological significance in terms of the generation and maintenance of gamma band oscillations. In this regard, if confirmed at the translational level, the reduction of NMDA receptor mRNA expression in parvalbumin-expressing neurons reported in the prefrontal cortex of subjects with schizophrenia (95) may represent a potential pathological sequalae linked to PNN functional impairment. Notably, deficits in PNN function could affect the lateral diffusion of glutamate receptors within the plasma membrane, as well as receptor clustering within the synapse which coupled together may lead to deficits in synaptic regulation and plasticity (89). Direct testing of this hypothesis may be possible via fluorescence recovery after photobleaching using appropriate animal models.

Neuroprotection

Emerging evidence has shown PNNs to play a neuroprotective role in the CNS under oxidative stress, which may ensue from reduced levels of glutathione, an important antioxidant in the brain that has been reported to be decreased in schizophrenia patients (96). Components of the PNN, such as aggrecan, Tn-R, and link proteins may represent the basis for the neuroprotective status of these structures (97). However, PNNs may in turn be vulnerable to oxidative stress, as shown in mice with a genetic redox dysregulation (25). Against this background, a recent study by Morishita and colleagues has provided evidence of a prolonged period of brain plasticity in young adult mice under conditions of parvalbumin cell-specific glutathione dysregulation *in vivo* (98). Given that PNNs play a key role in balancing plasticity and stability of cortical circuits via parvalbumin cells (99), the authors of this study suggest that a redox-sensitive failure to maintain parvalbumin cells

enwrapped by PNNs can result in mistimed developmental trajectories of brain plasticity which may contribute, in part, to the etiology of schizophrenia (100).

In keeping with the theme of oxidative stress, downstream effects of oxidative damage on neurons have been shown to involve specific gene promoters resulting in gene silencing (101). The mechanism of transcriptional regulation is likely epigenetic; specifically, it may be mediated through dysregulation of histone acetylation by histone deacetylase 2 (HDAC2). The chromatin modulating function of HDAC2 can be negatively regulated following a post-translational process called S-nitrosylation. Notably, HDAC2 nitrosylation has been shown to have a role in regulating both cortical development and memory formation (102, 103). Neuronal nitric oxide synthase, an enzyme that provides a major source of nitric oxide in neurons, is highly expressed specifically in the parvalbumin interneurons in the adult mouse cortex (104) and has been demonstrated to have positive effects on neuronal plasticity (105) as well as learning and memory (102). In this respect, nitric oxide has been linked to schizophrenia pathogenesis (100). An interesting hypothesis that therefore waits to be tested is whether negative regulation of HDAC2 by nitric oxide and its effect on transcription may modulate the activity of inhibitory circuits in a manner that prolongs windows of critical period plasticity resulting in long-term neurodevelopmental sequalae relevant to schizophrenia.

Development and Synaptic Plasticity

Given that PNNs are known to play a functional role in the regulation of developmental synaptic pruning in the cerebral cortex and that a synaptic pruning deficit has long been speculated to contribute to the onset of schizophrenia (12, 15), a deficit in the formation of PNNs could very well compromise the experience-dependent consolidation of synaptic connectivities, resulting in a protraction of the synaptic pruning process. In this regard, site-specific digestion of CSPGs in the hippocampus of animals using ChABC was shown to induce altered spine dynamics via a restriction of β1-integrin activation and signaling at synaptic sites (106). These findings are notable based on the evidence that dendritic spine density on pyramidal cells is decreased in schizophrenia (107-109). Interestingly, unpublished observations from our laboratory have shown that the proportion of pyramidal neurons surrounded by PNNs is decreased by 25-60% in layers III and V of the prefrontal cortex of subjects with schizophrenia. Of note are the neuropathological findings of decreased spine density and dendritic branching of these pyramidal neurons (107, 109-111).

The recent evidence showing that Semaphorin 3A (Sema3A) localizes to PNNs is of interest from a neurodevelopmental standpoint of schizophrenia. Sema3A is a potent regulator of neurite growth (112) and cell migration (113) in the developing nervous system, and it has strong effects on synapse dynamics (114). A disulfated chondroitin sulfate-E motif in the CSPGs is responsible for binding of Sema3A to PNNs (115). The observation that Sema3A is present on PNNs, coupled with the established role of PNNs in controlling plasticity, suggests that PNNs may exert their effect partly through Sema3A. Interestingly, evidence from both genetic and postmortem studies link Sema3A and its receptor family to schizophrenia. Notably, genome-wide association studies (GWAS) have identified variants within the semaphorin receptor component plexinA2 gene and the Sema3D gene to

influence susceptibility to schizophrenia (116, 117). In a separate study, Eastwood and colleagues reported an increase of Sema3A mRNA expression in the cerebellum of schizophrenia subjects together with a decrease in the expression of synaptophysin and reelin, both of which are important for synaptic formation and maintenance, and have independently been linked to schizophrenia (118). In view of these observations future studies applying both *in vitro* and *in vivo* approaches to assess whether more of the molecules that guide axons during development bind to PNNs in the adult CNS and whether they have effects on synapse dynamics will be of key importance.

If we now turn our focus to non-cell-autonomous factors, specifically OTX2, several issues can be raised. A very general issue is the identification of the transfer mechanisms of this homeoprotein in the context of cerebral function. Although present in the extracellular space throughout the cortex, OTX2 is only internalized by parvalbumin interneurons after activity-dependent PNN assembly (75). Considering the role of OTX2 in maintaining the non-plastic state of the adult brain, it can be speculated that changes in the levels of this homeoprotein would interfere with downstream molecular pathways regulated by OTX2 within parvalbumin-expressing interneurons which could subsequently result in the brain retaining the “juvenile-like state” of plasticity characteristic of schizophrenia (14, 26, 71, 98). In order to answer this vital question, studies evaluating the main source of OTX2 using both appropriate animal models of schizophrenia and patients with schizophrenia will be crucial. In addition, it will also be important to evaluate the regional and developmental expression of OTX2 expression in both animals and humans in order to shed light as to when and where the changes in the expression of this homeoprotein occur during ontogeny. Moreover, investigation of the target genes and proteins of OTX2 will reveal further insights into the mechanisms linking experience, GABAergic circuit maturation, and critical period plasticity in the context of neurodevelopmental disorders such as schizophrenia. In this regard, a major endogenous source of OTX2 has been identified as the choroid plexus (74, 119, 120) that lines the ventricles, which incidentally have commonly been found to be enlarged in patients with schizophrenia (121).

Another interesting element that may be linked to schizophrenia pathophysiology is the biophysics of the ECM. Given that diffusion in the extracellular space is dependent on the structure and chemical properties of the ECM (122), it is conceivable that PNN abnormalities in the adult CNS may alter the efficacy of synapses and transmitter release associated with schizophrenia (123). Such changes could affect the efficacy of signal transmission at synapses by altering neuronal synchronization and neuron-glia communication but also by affecting synaptic and extrasynaptic volume transmission (122, 124, 125), notable examples include dopamine and glutamate (124, 125).

Finally, the Nogo receptor (NgR), which binds myelin-associated proteins (i.e., Nogo proteins) and has an inhibitory effect on neurite growth, is expressed in PNN-encapsulated neurons (126). Notably, this receptor has also been shown to bind CSPGs (127). Therefore, myelin formation in tandem with PNN structural integrity, may provide an additional mechanism that progressively restricts synaptic plasticity with a subsequent effect on stabilizing cortical circuitry in the mature brain. Myelin dysfunction may therefore further

compromise the stability and integrity of synaptic connectivities. Interestingly, both Nogo and NgR have been linked to the pathogenesis of schizophrenia (128).

Potential Causes of PNN Abnormalities

The pathological mechanism(s) governing a PNN deficit in terms of the various schizophrenia hypotheses remains an open question (see Table 4). It is possible that this deficit could result from an alteration in proteinases involved in regulating the dynamic nature of the ECM. Two families of endogenous, extracellular metalloproteinases cleave ECM components: matrix metalloproteinase (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs). The cleavage of ECM components is part of their normal turnover process, but a dysregulation in this process may represent a prerequisite for neurological disease (129, 130). Interestingly, a recent GWAS has identified MMP-16 as a schizophrenia risk gene (131) and MMP-9 has also been implicated in this disorder (132). Towards this end, evidence from a recent study revealed that pyramidal neurons from layer III of the superior temporal gyrus of patients with schizophrenia exhibit alterations in the expression of many genes that encode both MMPs and ADAMTSs, including MMP16 (**Table 2**) (133). In a complementary study that used the same cohort of schizophrenia subjects, it was shown that genes which encode ADAMTS in addition to several key components of the PNN, including aggrecan, hyaluronan and laminin, were differentially expressed in parvalbumin-expressing interneurons (**Table 3**) (134). More recently, an extracellular increase in the level of clusterin (apolipoprotein-J) in the prefrontal cortex of patients with schizophrenia was reported (135). Although the pathological basis for this increase in clusterin remains unknown, given that enzymatic activity MMP-9 has been shown to be inhibited by clusterin (136), an increased expression of clusterin expression may represent a compensatory mechanism to promote the integrity of PNNs (135). Taken together, these observations suggest that a dysregulation in the remodeling of the ECM may represent a genuine component underlying the pathophysiology of the disease.

Along these lines, an impressive study utilizing a single-cell reverse transcriptase multiplex polymerase chain reaction approach identified various clusters of parvalbumin cells that display distinct electrophysiological profiles and exhibit different expression profiles in a subset of genes (137). Among these clusters were a subset of cells that expressed both parvalbumin and somatostatin and a subset of cells which expressed parvalbumin in conjunction with three metalloproteinases (Adamts8, Adamts15 and neprylsin). Notably, *Wisteria floribunda* agglutinin staining of PNNs revealed the subset of parvalbumin interneurons which expressed metalloproteinases to be surrounded by PNNs, as opposed to the parvalbumin interneurons that co-expressed somatostatin and interneurons that solely expressed somatostatin (137). The authors of this study suggest that somatostatin-expressing interneurons and the parvalbumin interneurons which co-express somatostatin are not protected by PNNs and may represent distinct classes of the interneurons that are highly susceptible to developmental insults, such as oxidative stress (137).

Microglia activation represents an intriguing pathological mechanism for PNN deficits observed in schizophrenia. In this respect, degradation of the PNN has been reported to be a

feature of multiple sclerosis (138). The loss of PNNs in multiple sclerosis has been attributed to the production of MMP-9 by activated microglia (138) and, of interest, the upregulation of MMP-9 may be a key event that links oxidative stress to inflammation (139). In the same vein, the neuropathology of schizophrenia has been reported to be closely associated with cytokines and microglial activation (9). It is thus of note that the inflammatory response can provide a source of free radicals with the capacity to modify proteins, lipids, and nucleic acids (i.e., oxidative stress) that are potentially toxic for neurons and PNNs (140). Due to the positive feedback loops formed in such a mechanism, the disease state could self-sustain and persist, resulting in the progressive PNN deficits.

Conclusion and Perspectives

As the function of the PNN in the CNS continues to become unravelled, increasing evidence indicates that this structure not only plays an important role in neurophysiology and neuroplasticity but that PNN abnormalities can contribute to pathophysiological damage of the CNS, as observed in schizophrenia. The potential importance of the PNN in schizophrenia is highlighted by the neuropathological evidence demonstrating that this structure is altered in postmortem brain of these patients. The abnormalities of PNNs may stem from complex interactions of genetic vulnerabilities of genes encoding for CSPGs and metalloproteinases with environmental factors, which may subsequently interfere with postnatal neuronal maturation, protection from oxidative stress, synaptic regulation and plasticity of distinct interneuronal populations, potentially accounting for molecular and functional anomalies of neural circuitry (**Figure 1**) (24). Together, these pathological sequalae may culminate in the disruption of cognitive and emotional processing associated with schizophrenia.

Gaps in our knowledge remain as to whether PNNs serve similar functions for inhibitory and excitatory cells or subsets of these cells. Future studies aimed at identifying the functions and molecular and physiological parameters that differentiate the cells that have nets from those that do not will therefore be of key importance. In this context, it will be essential to identify and examine which CSPG members or other classes of ECM molecules are directly affected in schizophrenia and whether they are equally affected in different subset of interneurons and pyramidal cells. With this in mind, the use of gene set enrichment analysis to evaluate PNN genes and PNN interacting genes in the context of key genetic and environmental aspects that have been linked to schizophrenia through appropriate animal models, will prove integral in terms of elucidating if a clear biological distinction exists in terms of the PNN deficits observed in schizophrenia.

There remain significant challenges to rescuing the aberrant connectional and synaptic assembly associated with schizophrenia. Nonetheless, it could be speculated that therapeutic strategies which modulate the maturation and circuit integration of parvalbumin interneurons and PNNs via factors such as OTX2 (72, 74, 98), brain-derived neurotrophic factor (141), glial-derived neurotropic factor (142), neuregulin-1 (143) and neuronal pentraxins (144) may offer a fresh therapeutic landscape for cognitive interventions targeting brain plasticity in schizophrenia.

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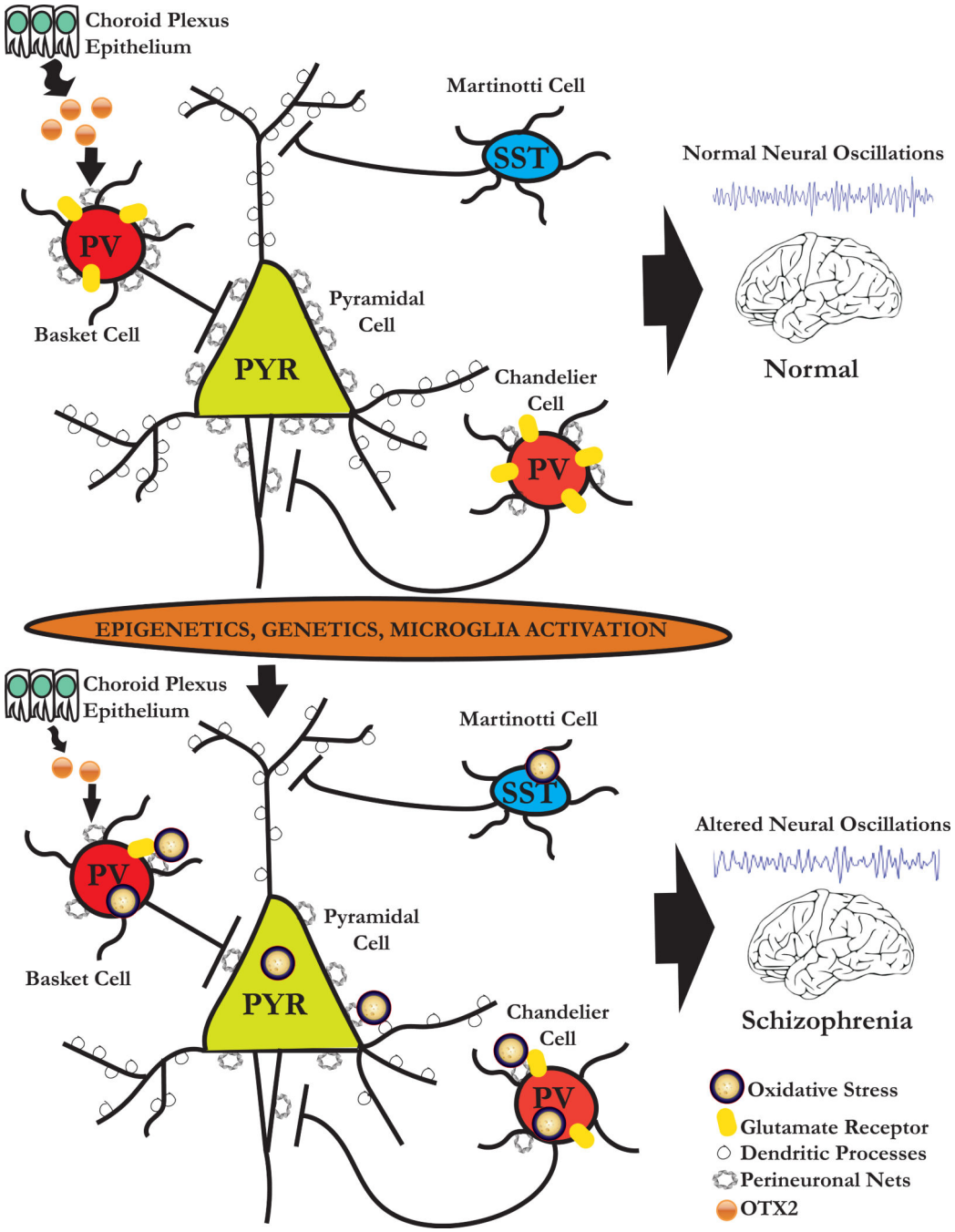

Figure 1.

Schematic diagram of the potential neurobiological mechanisms associated with circuitry dysfunction in schizophrenia. During normal postnatal development, progressive increase in inhibitory inputs to pyramidal (PYR) neurons furnished by parvalbumin (PV) and somatostatin (SST) interneurons enables PYR neuronal circuits to oscillate in gamma and theta band frequencies, respectively. Epigenetic and genetic susceptibility in addition to microglia activation can provide a source of free radicals with the capacity to modify proteins, lipids, and nucleic acids (i.e., oxidative stress) that reduce N-Methyl-D-Aspartate

(NMDA) receptor activity and which are potentially toxic for neurons and perineuronal nets (PNNs). The reduction in PNNs results in a deficit of OTX2 internalization into PV interneurons. As a consequence, PV-bearing PNNs are impaired, as manifested by alterations of local oscillations and distant synchronization. Because PNNs are protective of neurons from oxidative stress, PNN deficits may render them more vulnerable to oxidative injury. These cellular and molecular changes may alter the timing of critical periods.

Table 1

Summary of functions of perineuronal nets in the central nervous system

Function influenced by PNNs	References
Cognitive Functions	
Audition	(85, 87)
Learning and Memory	(41, 51, 52, 54, 80)
Motor Coordination	(52)
Nociception	(86)
Olfaction	(38, 76)
Vision	(71)
Vocal Development	(49)
Neurophysiological/Cell Biological Functions	
Critical Period Regulation	(37, 61, 62, 67)
Glutamate Receptor Trafficking	(33, 89)
Intercellular Transport of molecules	(71)
Ion Homeostasis	(145-147)
Neuroprotection	(148, 149)
Membrane Compartmentalization	(89)
Regulation of γ-Oscillations	(25)
Synaptic stability and Plasticity	(32, 37, 150)

Table 2

Differentially expressed genes associated with extracellular matrix in pyramidal neurons in schizophrenia

Gene Title	Gene Symbol	Direction of Change
Aggrecan	ACAN	Down
ADAM metallopeptidase with thrombospondin type 1 motif, 1	ADAMTS1	Up
ADAM metallopeptidase with thrombospondin type 1 motif, 1	ADAMTS8	Down
Hyaluronan and proteoglycan link protein 1	HAPLN1	Down
Leucine proline-enriched proteoglycan (leprecan) 1	LEPRE1	Down
Lumican	LUM	Down
Matrix metallopeptidase 16 (membrane-inserted)	MMP16	Down
Matrix metallopeptidase 24 (membrane-inserted)	MMP24	Up
Matrix metallopeptidase 25	MMP25	Down
Sperm adhesion molecule 1	SPAM1	Up
Sparc/osteonectin, cwcv and kazal-like domains proteoglycan 3	SPOCK3	Up
Spondin 1, extracellular matrix protein	SPON1	Up
Versican	VCAN	Down

*** Reproduced from (23)**

Table 3

Differentially expressed genes associated with extracellular matrix in parvalbumin-containing neurons in schizophrenia

Gene Title	Gene Symbol	Direction of Change
Aggrecan	ACAN	Up
ADAM metallopeptidase domain 7	ADAM7	Up
ADAM metallopeptidase with thrombospondin type 1 motif, 6	ADAMTS6	Up
Hyaluronan binding protein 4	HABP4	Up
Laminin, beta 1	LAMB1	Down

Table 4

The possible link between PNN deficits and prominent schizophrenia hypotheses

Neuropathological Hypothesis	Contributory effect of PNN
Dopamine	Unknown
Glutamate	Anomalies in trafficking of glutamatergic receptors
GABA	Impairment in the maturation of parvalbumin interneurons/inhibitory circuitry
Immune Dysregulation	Compromised PNNs mediated by MMPs
Myelination	Interaction with PNN via Nogo
Oxidative Stress	Compromised antioxidant defense system on the surface of neurons
Neurodevelopment	Temporal anomalies in the onset and closure of critical periods
Reduced Neuropil	Deficits in the stabilization and formation of synapses
Synaptic Connectivity	Deficits in the stabilization of synapses
Synaptic Prunning	Deficits in the formation of synapses