Published in final edited form as:

Neurosci Biobehav Rev. 2014 September ; 45: 85–99. doi:10.1016/j.neubiorev.2014.03.018.

Perineuronal Nets and Schizophrenia: The Importance of Neuronal Coatings

Byron K.Y. Bitanirwe¹ and Tsung-Ung W. Woo^{2,3,4}

¹Systems and Cell Biology of Neurodegeneration, University of Zürich, Switzerland ²Program in Cellular Neuropathology, McLean Hospital, Belmont, Massachusetts, USA ³Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA ⁴Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Abstract

Schizophrenia is a complex brain disorder associated with deficits in synaptic connectivity. The insidious onset of this illness during late adolescence and early adulthood has been reported to be dependent on several key processes of brain development including synaptic refinement, myelination and the physiological maturation of inhibitory neural networks. Interestingly, these events coincide with the appearance of perineuronal nets (PNNs), reticular structures comprised of components of the extracellular matrix that coat a variety of cells in the mammalian brain. Until recently, the functions of the PNN had remained enigmatic, but are now considered to be important in development of the central nervous system, neuronal protection and synaptic plasticity, all elements which have been associated with schizophrenia. Here, we review the emerging evidence linking PNNs to schizophrenia. Future studies aimed at further elucidating the functions of PNNs will provide new insights into the pathophysiology of schizophrenia leading to the identification of novel therapeutic targets with the potential to restore normal synaptic integrity in the brain of patients afflicted by this illness.

Keywords

Perineuronal Nets; Schizophrenia; Neurodevelopment; Parvalbumin; Synaptic Plasticity; Synaptic Connectivity; Neuronal Protection

Introduction

Schizophrenia is a severe and persistent mental disorder associated with a large amount of suffering, discrimination and stigma (Gerlinger et al., 2013; Phelan et al., 1998; Omori et al.,

© 2014 Elsevier Ltd. All rights reserved.

Address of correspondence and reprints: Tsung-Ung W. Woo, M.D., Ph.D., McLean Hospital, Program in Cellular Neuropathology, Mailman Research Center, E303, 115 Mill Street, Belmont, MA 02478, Tel: 617-855-2823, FAX: 617-855-3199, wwoo@hms.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

2014). The symptoms of the disorder can be divided into three broad categories (i.e. positive, negative and cognitive symptoms), which influence a patient's thoughts, speech, perceptions, emotion and behaviors (Schultz et al., 2007). The end result is a brain disorder associated with a life-long course of intellectual, vocational, interpersonal and social impairment. Worldwide, the prevalence for schizophrenia appears to be approximately 1% (Perala et al., 2007), although variation in prevalence and incidence of the illness has been reported according to geographical region and cultural background (Kirkbride et al., 2012; McGrath et al., 2004; McGrath and Susser, 2009; Saha et al., 2005). The combined economic and social costs of this illness are significant and far reaching with schizophrenia comprising roughly 1% of the global burden of disease, a fraction that is considered moderate to high (Lora et al., 2012). Specifically, schizophrenia has been reported to make up more than 7% of the burden attributable to neuropsychiatric disorders as a whole (Whiteford et al., 2013).

While the exact mechanism underlying the pathogenesis of schizophrenia remains shrouded in mystery, the neurodevelopmental theory of schizophrenia (Murray and Lewis, 1987; Weinberger, 1987) has been the dominant paradigm for schizophrenia research over the past two decades. One interpretation of this theory posits that schizophrenia is the behavioral manifestation of a disruption in the developmental trajectory of the brain during early life that underlies the later emergence of psychosis during adulthood, stemming from a combination of small but impactful genetic and environmental factors.

Many candidate vulnerability genes for schizophrenia, including *Disrupted-in-schizophrenia 1*, *Neuregulin 1*, in addition to genes located in the cytogenetic region 22q11, have a well-documented function in regulating neurodevelopmental processes (Bradshaw and Porteous, 2012; Brandon and Sawa, 2011; Harrison and Weinberger, 2005; Karayiorgou et al., 2010; Narayan et al., 2013). Early exposure to environmental predisposing factors, such as infection (Brown, 2012; Brown and Derkits, 2010; Brown and Susser, 2002) or malnutrition before birth (Lumey et al., 2011; Xu et al., 2009), obstetric complications (Cannon et al., 2002; Clarke et al., 2006; Margari et al., 2011; Nicodemus et al., 2008; Suvisaari et al., 2013) and frequent cannabis use during adolescence (Arseneault et al., 2004; Casadio et al., 2011; Henquet et al., 2005; Semple et al., 2005) contribute to increased vulnerability for schizophrenia. Nonetheless, the precise contribution of these prenatal, perinatal and postnatal factors and the ways in which they may interact with one another and with otherwise normal developmental events to result in the expression of the schizophrenia phenotype remains unclear.

A prominent and consistent pathophysiological characteristic that has emerged in schizophrenia involves impaired synaptic connectivity (Stephan et al., 2009) (McGlashan and Hoffman, 2000; Seshadri et al., 2013), a conclusion which has been inferred from multiple imaging and postmortem brain studies (Glantz and Lewis, 1997, 2000; Harrison, 2000; Selemon and Goldman-Rakic, 1999; Whalley et al., 2012). On the basis of these findings, the current consensus is that the symptoms associated with schizophrenia may arise from a malfunctioning synaptic communication within and between brain regions, leading to a functional disruption of the circuitry that underlies many of the cognitive and perceptive functions (Uhlhaas, 2013).

It is thought that this reduced synaptic connectivity stems from disturbances of key events of brain development during late adolescence and early adulthood, including myelogenesis (Bartzokis, 2002; Bartzokis et al., 2003; Benes, 1989) and synaptic pruning (Feinberg, 1982; Keshavan et al., 1994; McGlashan and Hoffman, 2000), a process that ultimately helps sculpt the adolescent brain into its adult form. Other work supporting the neurodevelopmental nature of schizophrenia suggests that its onset is linked to a potential disruption of the physiological maturation of inhibitory neural networks consisting of fast-spiking parvalbumin-positive gamma-aminobutyric acid (GABAergic) interneurons (Gonzalez-Burgos et al., 2010; Gonzalez-Burgos and Lewis, 2008; Lewis et al., 2005; Volk and Lewis, 2002, 2013), which are critical for the integrity of various higher brain functions, such as cognition and perception, via regulation of gamma band neural synchrony (Gonzalez-Burgos and Lewis, 2008; Lewis et al., 2005; Uhlhaas et al., 2009). Disturbances of parvalbumin neurons and gamma synchrony may contribute to aberrant synaptic refinement, hence triggering schizophrenia onset (Woo et al., 2010). Notably, the maturation of parvalbumin neurons and gamma is concurrent with the postnatal developmental formation of perineuronal nets (PNNs) (Mauney et al., 2013).

PNNs represent well-organized components of the extracellular matrix (ECM) that ensheath many mature central nervous system (CNS) neurons and their axons and dendritic processes, but which are excluded from sites of synaptic contact, thereby creating “holes” that give these structures their lattice-like appearance (Alpar et al., 2006; Bruckner et al., 2006; Ojima et al., 1995). Although their role is still not completely understood, PNNs have been implicated in ion homeostasis around highly active neurons (Bruckner et al., 1993; Bruckner et al., 1996a; Bruckner et al., 1996b; Hartig et al., 1999; Hartig et al., 2001; Hobohm et al., 1998) and neuroprotection (Bruckner et al., 1999; Cabungcal et al., 2013; Morawski et al., 2010; Morawski et al., 2012; Morawski et al., 2004; Schuppel et al., 2002). In addition, several studies have indicated that PNNs are important for memory and learning (Bruckner et al., 2000; Bukalo et al., 2001; Gogolla et al., 2009; Lee et al., 2012; Romberg et al., 2013; Saghatelian et al., 2001). Moreover, PNNs appear to function in a multitude of key physiological processes during development, including the closure of the critical period (Bavelier et al., 2010; Friauf, 2000; Galtrey and Fawcett, 2007; Guimaraes et al., 1990; McRae et al., 2007; Miyata et al., 2012; Pizzorusso et al., 2002, 2006; Rauch, 2004) (Nabel and Morishita, 2013; Takesian and Hensch, 2013) as well as synaptic stability and plasticity (Dityatev and Schachner, 2003; Galtrey and Fawcett, 2007; Kwok et al., 2008; Pizzorusso et al., 2002, 2006; Wang and Fawcett, 2012) (Caroni et al., 2012), all factors that have been linked to schizophrenia pathogenesis. Of additional interest is the recent evidence linking genes encoding structural constituents of PNNs and those that regulate their formation to schizophrenia, therefore adding further support to the emerging role of these structures in the pathophysiology of this illness (Buxbaum et al., 2008; Kahler et al., 2011; Muhleisen et al., 2012; So et al., 2009; Takahashi et al., 2011a) (Pietersen et al., 2014a,b) (Ohi et al., 2013) (Ripke et al., 2013).

In this review, we articulate the importance of PNNs in maintaining synaptic integrity and how functional deficits in these structures may contribute to schizophrenia pathogenesis. We begin by summarizing the structure and organization of PNNs, before turning our focus to the unique roles of PNNs in neural and behavioural plasticity. Finally, we discuss how

different mechanisms associated with PNN functions might converge and how perturbations in these functions might contribute to the pathophysiology of schizophrenia.

Discovery of PNNs

PNNs were first described by Camillo Golgi at the end of the 19th century (Bentivoglio and Mazzarello, 2010; Celio et al., 1998)(Vitellaro-Zuccarello et al., 1998)(Golgi, 1898) (Spreafico et al., 1999). However, the opinion of Ramon y Cajal, a key proponent of the neuron doctrine and an influential figure in the realm of neuroanatomy at the time, that PNNs represented a fixation artifact of metallic impregnation abruptly cut short the first period of their investigation (Bentivoglio and Mazzarello, 2010; Celio et al., 1998) (Vitellaro-Zuccarello et al., 1998). Only over the past few decades has a resurgence of interest in the PNN as a structural component of the CNS occurred thanks to the advances in the field of cytochemistry. In this respect, research efforts from pioneers in the field such as Richard and Rene Margolis have not only been able to confirm the existence of PNNs, but have also proven integral in deciphering their chemical nature, thus proving decisively that PNNs consist of condensed proteoglycans (PGs) (Margolis and Margolis, 1993, 1997).

Structural Components of PNNs

Extracellular space, of which the ECM is the principal component, comprises approximately 20% of the brain volume in the adult (Sykova et al., 1998; Sykova and Nicholson, 2008). The components of the ECM are produced intracellularly and secreted from neurons and glial cells to form a dense network of proteins and glycans that occupy the extracellular space (Franco and Muller, 2011; Frantz et al., 2010). Besides providing a structural support system for neural cells by acting as a scaffold and therefore facilitating the organization of these cells into distinct CNS regions, the ECM also represents a source of diverse molecular cues that guide cellular and neuritic growth, activity and survival (Barros et al., 2011; Franco and Muller, 2011). In particular, distinctive differences have been shown to exist between the molecular compositions of neural ECM and ECM from other tissues. Whereas the major constituents of a non-neural ECM are glycosaminoglycan (GAG) sugars, adhesive glycoproteins (laminin and fibronectin) and fibrous proteins (collagen and elastin), the neural ECM, in contrast, is composed of low levels of fibrous proteins, high amount of GAGs (Novak and Kaye, 2000) as well as PGs, specialized glycoproteins that are negatively charged under physiological conditions (Barros et al., 2011; Galtrey and Fawcett, 2007; Margolis and Margolis, 1993; Margolis and Margolis, 1997; Ruoslahti, 1996; Yamaguchi, 2000).

The PNN constitutes a specialized assemblage of ECM molecules expressed in the CNS. The main components are hyaluronan (Figure 1), chondroitin sulfate proteoglycans (CSPGs) (i.e. aggrecan, brevican, neurocan, versican and phosphocan) (Figure 2), tenascins (Figure 3), and link proteins (Kwok et al., 2011; Lau et al., 2013; Soleman et al., 2013; Zimmermann and Dours-Zimmermann, 2008)(Kwok et al., 2012). Through a series of complex interactions, these ECM molecules form large and stable lattice-like structures that rest on the surface of somata, dendrites and axons of neurons (Figure 4). The dynamic assembly and remodeling of PNNs has been associated with the formation of synapses and

connections and thereby neural plasticity (Celio et al., 1998; Kwok et al., 2011; Soleman et al., 2013; Wang and Fawcett, 2012).

Distribution and Development of PNNs in the CNS

A variety of histo- and immunohistochemical staining methods exist to identify PNNs, including the use of plant lecticans *Vicia villosa* agglutinin and *Wisteria Floribunda* agglutinin (WFA), which have high affinity for *N*-acetylglucosamine residues (Bruckner et al., 1993; Bruckner et al., 1996a; Schweizer et al., 1993), the use of colloidal iron hydroxide staining for detection of polyanionic components (Seeger et al., 1994) and monoclonal antibodies to CSPGs (with comparative studies providing evidence indicating species-specific distributions of PNNs) (Atoji et al., 1997; Bruckner et al., 1993; Celio et al., 1998; Nakagawa et al., 1986; Wintergerst et al., 1996)(Cant and Benson, 2006; Deepa et al., 2006; Hartig et al., 2001; Hilbig et al., 2007; Morawski et al., 2009; Morris and Henderson, 2000; Pantazopoulos et al., 2008; Pantazopoulos et al., 2010; Wagoner and Kulesza, 2009). While most studies of PNNs utilize WFA as a marker, PNNs exhibit a high degree of constitutive heterogeneity, and therefore it should be kept in mind that the alteration of a single marker during development or in disease states does not necessarily reflect the alteration or loss of the entire structure.

A large number of animal studies have shown that PNNs are widely distributed in the brain (Bertolotto et al., 1991; Bruckner et al., 1996b; Hockfield et al., 1990)(Dick et al., 2013; Giamanco et al., 2010; Hartig et al., 1994; Hartig et al., 1992; Nakamura et al., 2009; Yasuhara et al., 1994). Similarly, in humans, PNNs have also been found to be present in a variety of brain regions, including entorhinal cortex (Pantazopoulos et al., 2010), amygdala (Pantazopoulos et al., 2008; Pantazopoulos et al., 2010), hippocampus (Lendvai et al., 2013), motor and somatosensory cortex (Hausen et al., 1996), visual cortex (Mauney et al., 2013; Murakami et al., 1994; Seeger et al., 1996) and prefrontal cortex (Mauney et al., 2013).

Consistent with the evidence from animal studies reporting an incremental pattern of PNN expression associated with the postnatal maturation of the CNS (Hensch, 2005a; Miyata et al., 2012; Nabel and Morishita, 2013)(Bavelier et al., 2010; Gogolla et al., 2009; Lee and Sawatari, 2011; Nowicka et al., 2009), we have recently shown that the number of PNNs in the human prefrontal cortex also increases through the peripubertal period until late adolescence and early adulthood (Mauney et al., 2013) (see Figure 5). Formation of PNNs has been found to be activity-dependent. A series of *in vitro* experiments conducted on slices from mouse visual cortex showed that blockage of sodium channels inhibits the formation of PNNs (Dityatev et al., 2007). Interestingly, the same study revealed that blockage of glutamate receptors and presynaptic N- and P/Q-type calcium channels (both implicated in glutamate release) did not affect PNN growth, indicating that neuronal activity is required but that glutamatergic neurotransmission is not essential for PNN development (Dityatev et al., 2007). Other evidence stemming from the visual (Guimaraes et al., 1990; Kind et al., 1995; Lander et al., 1997; Sur et al., 1988), motor (Kalb and Hockfield, 1988, 1990a, b), and somatosensory system (McRae et al., 2007) in animals, as well as in the pallial (cortical) song nuclei (Balmer et al., 2009) in songbirds suggest that PNN expression does not only

revolve around neuronal activity, but rather its expression is dependent on neuronal activity during a maturationally based ‘critical period’, when circuits become particularly sensitive to environmental/activity dependent manipulation (Hensch, 2005b; McRae and Porter, 2012; McRae et al., 2007; Wiesel and Hubel, 1963)(Nabel and Morishita, 2013) (Takesian and Hensch, 2013). The exact mechanisms that govern the ability of neuronal activity to regulate the expression of the PNN remains an open question. Likewise, it is also unknown as to how the adult PNN is able to withstand changes in neuronal activity, making them adequately suited for its role in stabilizing synapses following the advent of neuronal circuitry maturity (Zaremba et al., 1989).

The Role of PNNs in Regulating Plasticity

In recent years, accumulating data suggest that the brain can be surprisingly plastic following synaptic stabilization in the mature organism, with intriguing mechanisms of neurogenesis and synaptogenesis providing novel substrates for brain adaption (Kelsch et al., 2010; Ming and Song, 2011; Song et al., 2005; Bavelier et al., 2010). This is not a new idea per se, and the reader is referred to many more detailed reviews that dissect mechanisms underlying the role of PNN function in CNS plasticity (Dityatev and Schachner, 2003; Galtrey and Fawcett, 2007; Kwok et al., 2011; Wang and Fawcett, 2012). Here we provide a summary of the experimental evidence implicating PNNs in the regulation of synaptic plasticity during critical period development.

The visual system has been the preeminent model of experience-dependent critical period plasticity (Sur et al., 2013). Monocular deprivation in young animals during the critical period leads to a shift in ocular dominance favoring the non-deprived eye; however, in the adult, due to the less plastic nature of the brain, this shift does not occur. To address the role of PNNs in ocular dominance plasticity, Pizzorusso and colleagues used chondroitinase ABC (ChABC) to enzymatically degrade these structures in adult rats (Pizzorusso et al., 2002). Remarkably, this treatment resulted in the reinstatement of ocular dominance plasticity in monocular deprived adult animals (Pizzorusso et al., 2002). In other words, by removing the PNN, synaptic plasticity normally seen only during the critical period was restored (Pizzorusso et al., 2002). Furthermore, when ChABC was applied in adult animals that had undergone monocular deprivation in combination with reverse lid suturing (the previously deprived eye is opened and the non-deprived eye is sutured) during critical period, there was a complete recovery of visual acuity and dendritic spine density (Pizzorusso et al., 2002). Together these findings provide strong support for the notion that PNN formation during development regulates the termination of the critical period in the visual cortex. The mechanism by which PNNs may regulate critical period plasticity in the visual system is not well understood. However, recent evidence has shown the PNN to play a role in the “capture” of the homeodomain transcription factor orthodenticle homeobox 2 (Otx2) from thalamic inputs to visual cortex (Beurdeley et al., 2012). Notably, this homeoprotein signals the maturation of the parvalbumin-containing GABAergic interneurons, which contributes to the opening and possibly also the closure of the critical period (Beurdeley et al., 2012; Miyata et al., 2012; Spatazza et al., 2013; Sugiyama et al., 2008).

The somatosensory system in rodents has also been widely used as a model for studying the formation and plasticity of specific neuronal connections in the brain. By manipulating this system in mice, McRae and co-workers showed that the expression of PNNs in the mouse barrel cortex during development was dependent on appropriate sensory stimulation (McRae et al., 2007). Specifically, sensory deprivation by whisker trimming within the first 30 days of birth was found to decrease the number of aggrecan-positive PNNs around parvalbumin-expressing cells in layer IV of the mouse barrel cortex and prolong the critical period (McRae et al., 2007). Sensory deprivation in adult mice, however, did not alter aggrecan expression, indicating that once established, maintenance of PNNs does not require normal sensory input (McRae et al., 2007). Similarly, sensory deprivation of facial vibrissae in rat barrel cortex has also been found to result in reduced numbers of WFA-labeled PNNs (Nakamura et al., 2009). These observations are reminiscent of the cat visual system, where aggrecan expression decreases after sensory deprivation during development but not in adulthood (Sur et al., 1988).

Converging lines of evidence indicate that the amygdala plays a crucial role in the development and expression of conditioned fear and extinction (Maren et al., 2013; Pare and Duvarci, 2012). Against this background, it was recently reported that PNNs in the amygdala may serve a key role in the developmental regulation of fear extinction (Gogolla et al., 2009). Because the maturation of PNNs in the mouse amygdala was shown to coincide with the end of the developmental period during which extinction induces erasure of fear memories, it was suggested that PNNs prevent extinction from erasing fear. Interestingly, enzymatic degradation of PNNs in the basolateral nucleus of the amygdala of adult mice with ChABC indeed enabled extinction to erase conditioned fear, but only if PNNs were degraded before fear conditioning (Gogolla et al., 2009). This effect was, however, specific for fear memories acquired in the absence of PNNs, as the elimination of PNNs in adult mice that acquired fear with PNNs intact had no effect on extinction. These findings indicate that PNNs are actively involved in protecting the acquisition of fear memories from extinction-induced erasure, allowing extinction memories to coexist with previously acquired fear memories (Gogolla et al., 2009; Quirk et al., 2010).

Recently, a depletion of PNNs in animals following localized digestion with ChABC was shown to result in enhanced object recognition, in addition to a facilitation of long-term depression in the perirhinal cortex, thought to be the major synaptic mechanism underlying object recognition memory (Romberg et al., 2013). Interestingly, an identical prolongation of memory was observed in Ctrl1 (cartilage link protein) knockout mice, in which PNN formation is disrupted (Carulli et al., 2010; Vo et al., 2013). This study also revealed that ChABC induced enhancement of object recognition was reversible. Notably, over the course of 8 weeks, memory gradually returned to control levels, suggesting that reoccurring PNNs gradually restore control plasticity levels (Romberg et al., 2013).

Other evidence implicating PNNs in normal behavior stems from the colocalization of these structures in the striatum (Lee et al., 2012). Indeed, bilateral digestion of striatal PNNs was reported to increase both the width and variability of hind limb gait. Intriguingly, this also resulted in an improvement in the acquisition rate of the Morris water maze, a behavioural test used for assessing spatial and related forms of learning and memory (Morris, 1984).

These findings suggest that PNNs are associated with specific elements of striatal circuits and play a key role in regulating the function of this important structure (Lee et al., 2012).

Finally, the role of PNNs in synaptic and behavioral plasticity appears to extend beyond mammalian species. Evidence from the songbird (*zebra finch*) suggests the functional role of PNNs in vocal plasticity. A study by Balmer and colleagues found the percentage of both total and parvalbumin-positive neurons with PNNs increased with development (Balmer et al., 2009). In the high vocal center, a song area important for sensorimotor integration (During et al., 2013; Wild, 2004), the percentage of parvalbumin neurons with PNNs correlated with song maturity. Notably, shifting the vocal critical period with tutor song deprivation decreased the percentage of neurons that were parvalbumin positive and the relative staining intensity of both parvalbumin and PNNs (Balmer et al., 2009). Because developmental song learning shares key characteristics with sensory critical periods, the songbird system represents an efficient model in which to examine the mechanisms of critical period regulation.

Linking PNNs to Schizophrenia Pathophysiology

Because of the critical function of PNNs in synaptic plasticity, disruption of these structures may contribute to the neuronal circuitry dysfunction associated with neurological and psychiatric diseases (Lau et al., 2013). In this context, a number of studies have shown alterations in PNNs and their constituents to be linked to various brain diseases, such as Alzheimer's disease (Morawski et al., 2010, 2012; Kobayashi et al., 1989; Baig et al., 2005), epilepsy (McRae and Porter, 2012), multiple sclerosis (Gray et al., 2008), prion disease (Guentchev et al., 1999, Franklin et al., 2008) and stroke (Hobohm et al., 2005; Gherardini et al., 2013; Soleman et al., 2012). Recent evidence suggests that PNNs may also be involved in the pathophysiology of schizophrenia. Specifically, a number of human post-mortem brain studies have revealed a disease-specific reduction in the density of PNNs as well as altered expression of genes that regulate PNNs and ECM in key brain structures associated with schizophrenia, including the amygdala, olfactory epithelium, entorhinal cortex, superior temporal cortex and prefrontal cortex (Mauney et al., 2013; Pantazopoulos et al., 2013; Pantazopoulos et al., 2010; Pietersen et al., 2014a, b) (See Figure 6). In this section, we discuss these findings in the context of known and postulated PNN functions and speculate elements of these functions that might play a role in the synaptic pathology associated with this illness.

Ion Homeostasis

Based on their polyanionic character, PNNs provide highly charged structures in the direct microenvironment of neurons that might be involved in local ion homeostasis (Karetko and Skangiel-Kramska, 2009; Morawski et al., 2004). They can thus potentially act as a buffering system for physiologically relevant ions such as calcium, potassium, and sodium around highly active types of neurons (Bruckner et al., 1993; Bruckner et al., 1996b; Hartig et al., 1999), although direct evidence to this effect is still lacking. Even though PNNs have been shown to ensheath a variety of cells in the CNS, they are most commonly associated with the highly metabolically active fast-spiking parvalbumin interneurons (Hartig et al., 1999; Morris and Henderson, 2000; Ojima et al., 1995; Wegner et al., 2003)(Liu et al.,

2013). These neurons express specific potassium channel subunits, such as Kv3.1b, which produce rapidly repolarizing action potentials (Lenz et al., 1994)(Du et al., 1996; Sekirnjak et al., 1997), thus contributing to the fast-spiking phenotype. The firing properties of parvalbumin interneurons participate in establishing the normal gamma oscillations and synchrony of cortical neuronal populations, thought to be a physiological correlate of higher-order information processing in brain (Gray et al., 1992; Singer, 1990; Buzsaki, 2006; Uhlhaas et al., 2008; Uhlhaas and Singer, 2006). In this regard, schizophrenia is associated with deficits in parvalbumin neurons (Bitanirwe et al., 2009; Hashimoto et al., 2003), abnormalities in cortical gamma synchrony (Basar-Eroglu et al., 2007; Cho et al., 2006; Farzan et al., 2010; Grutzner et al., 2013; Kirihaara et al., 2012; Spencer et al., 2008; Sun et al., 2011; Uhlhaas and Singer, 2010; Woo et al., 2010) and in information processing (Braff, 1993; Frith, 1979; Kumari et al., 1999; Perry et al., 2002; Rissling et al., 2012), particularly with dysfunction in working memory and executive function (Goldman-Rakic, 1994; Gonzalez-Burgos et al., 2010; Gonzalez-Burgos and Lewis, 2008; Lewis et al., 2005). Considering that Kv3.1b has a direct effect on the firing of the parvalbumin interneurons (Gan and Kaczmarek, 1998; Lenz et al., 1994; Perney et al., 1992; Weiser et al., 1995), one may speculate that deficits in PNNs may affect local ion homeostasis due to excess potassium extruded by the cell during activity (Bruckner et al., 1993), subsequently resulting in disrupted firing properties of neurons (i.e. neuronal hyperexcitability). In this respect, a variety of evidence exists indicating subtle cortical hyperexcitability in patients with schizophrenia (Daskalakis et al., 2007; Eichhammer et al., 2004; Hoffman et al., 2002; Hoffmann and Cavus, 2002; Spencer et al., 2009; Lakatos et al., 2013). In combination with anomalies in the expression of the Kv3.1b (Yanagi et al., 2013) and other potassium channels (Georgiev et al., 2014; Georgiev et al., 2012), distorted ion homeostasis resulting from PNN deficit could be important in mediating alterations in brain function associated with schizophrenia.

The nodes of Ranvier represent specialized gaps along the length of the axon stemming from an absence of myelin, produced by oligodendrocytes as part of their supportive role to neurons (Bradl and Lassmann, 2010; Wilkins et al., 2003). The myelin sheath reduces current flow across the axonal membrane by providing a layer of high electrical resistance and low capacitance, thereby enabling a fast, saltatory movement of nerve impulses from 'node to node' (Poliak and Peles, 2003). In this context, multiple lines of evidence in schizophrenia, from electrophysiological, genetic analyses, brain imaging and studies in postmortem brains have implicated oligodendrocyte and myelin dysfunction in this disease (Benes, 2000; Hoistad et al., 2009; Takahashi et al., 2011b). Particularly noteworthy are the molecular studies showing a reduction in expression level of multiple genes associated with the integrity of the node of Ranvier (Martins-de-Souza, 2010; Martins-de-Souza et al., 2009; Roussos et al., 2012; Susuki, 2013). Notably, the perinodal-matrix or peridonal net, a PNN-like structure (Dours-Zimmermann et al., 2009; Zimmermann and Dours-Zimmermann, 2008), is commonly associated with the node of Ranvier. This structure functions to create an ion diffusion barrier by acting as a cation buffer at the nodes of Ranvier (Bekku et al., 2010). Given that transgenic animals lacking the CSPG brevican have been reported to exhibit disruptions in the perinodal-net in addition to deficits in nerve conduction (Bekku et al., 2010), it can be conjectured that a disruption in the expression of perinodal-net

components, such as brevican, may contribute to the myelin and electrophysiological deficits observed in schizophrenia.

Neuronal Protection

The potentially neuroprotective function of PNNs might be understood against the background of its molecular interactions with elements associated with neurotoxicity, such as metal ions (Karetko and Skangiel-Kramska, 2009). Because of the polyanionic character of PNNs, it has been suggested that they may provide a system for scavenging and binding redox-active ions, such as iron, copper and zinc, and thus reducing the local oxidative potential in the neuronal microenvironment (Morawski et al., 2004)(Karetko and Skangiel-Kramska, 2009). This may provide some neuroprotection to PNN-associated neurons against oxidative stress. Oxidative stress is a pathophysiological process resulting from an impairment in cellular antioxidant defense mechanisms to counterbalance and control endogenous reactive oxygen species and reactive nitrogen species generated from normal oxidative metabolism or from pro-oxidant environmental exposures (Kohen and Nyska, 2002; Roberts et al., 2009, 2010). Notably, this process has been linked to the pathophysiology of various neurological disorders including schizophrenia (Bitanirwe and Woo, 2011; Do et al., 2009; Yao and Reddy, 2011).

A recent study demonstrated the importance of PNN integrity in reducing the pathophysiological sequelae of oxidative stress (Cabungcal et al., 2013). This study used a mouse model in which disrupted expression of the modifier subunit of glutamate cysteine ligase, the rate-limiting enzyme of glutathione synthesis, elicits elevated oxidative stress (Yang et al., 2002). These animals were challenged with a 6 month chronic oxidative insult using a specific dopamine reuptake inhibitor (GBR12909). The authors found that animals with well formed PNNs (viz. high levels of WFA-labeling) were protected against chronic redox dysregulation. Furthermore, PNN deficit within these mice preferentially affected parvalbumin-containing inhibitory interneurons with a concomitant reduction in neural oscillations in the beta and gamma frequency bands (Cabungcal et al., 2013). This study reported that enzymatic degradation of PNNs with ChABC rendered mature parvalbumin cells and fast rhythmic neuronal synchrony more susceptible to oxidative stress. Interestingly, the frequency of gamma band oscillations may actually be increased in mice with a mild PNN deficit (ChABC treatment alone) while the frequency of gamma band oscillations is decreased (compared to controls) once more oxidative stress is placed on the system. In this regard, one potential interpretation of the human PNN postmortem findings could be that the decrease in PNNs observed in patients with schizophrenia may represent a compensation to elevate gamma band oscillation and neuronal synchrony. Consistent with the notion that the expression of PNNs is accompanied by the maturation of the CNS, parvalbumin-containing cells in juvenile mice showed higher susceptibility to oxidative stress compared with adult mice (Cabungcal et al., 2013). Together these findings highlight the possible role of PNNs in protecting the fast-spiking parvalbumin cells against oxidative stress, which in turn prevents the electrophysiological deficits associated with schizophrenia.

The *dopamine hypothesis* of schizophrenia stems from the body of work suggesting that the major antipsychotic drugs act by blocking dopamine D2 receptors and that dopamine-

releasing drugs worsen schizophrenia symptoms (Snyder, 1976). In this context, rats treated with intra-ventral hippocampal ChABC to remove PNNs not only exhibited an increase in dopamine neuron population activity, as shown by a significantly greater firing rate of putative pyramidal neurons throughout the ventral hippocampus, but were also hyper responsive to the locomotor stimulating effects of amphetamine (Shah and Lodge, 2013). In a complimentary set of experiments, the offspring of rat dams exposed to the DNA-alkylating agent methylazoxymethanol acetate had significantly lower levels of the PNN proteins brevican and phosphacan throughout the ventral hippocampus (Shah and Lodge, 2013). Together these data suggest that a loss of hippocampal PNNs is sufficient, in and of itself, to augment hippocampal activity and induce the dopamine system hyperfunction purported to underlie the positive symptoms of schizophrenia (Howes and Kapur, 2009).

Genetic Manipulation of Murine Phosphacan and its Relevance to Schizophrenia

The spatiotemporal expression pattern of phosphacan within the CNS suggests potential roles for this protein in various developmental processes, including cell migration (Maeda et al., 1996), neurite growth (Garwood et al., 2003), synaptogenesis (Haunso et al., 1999), synaptic function (Murai et al., 2002), and myelination (Harroch et al., 2000)(Garwood et al., 2001), all processes that have been postulated to be affected in schizophrenia. Nonetheless, the role of phosphacan in schizophrenia is fragmentary. On the basis of a genetic case-control study that revealed association between the PTPRZ1 gene (which encodes RPTP β also known as phosphacan) and schizophrenia (Buxbaum et al., 2008), postmortem brain analysis and transgenic animal studies were subsequently performed to gain a better insight into the biological relevance of this gene to schizophrenia. Expression of RPTP β at the mRNA level was found to be significantly higher in the dorsolateral prefrontal cortex of patients with schizophrenia (Takahashi et al., 2011a). Given the PNN deficit observed in the prefrontal cortex of patients with schizophrenia (Mauney et al., 2013), increased RPTP β expression could represent a compensatory mechanism to counterbalance the aberrant PNN formation in the brains of patients with this disease. The limitation, however, is that because the finding of increased expression of RPTP β was generated from homogenized brain tissue, it is not possible to determine any cell type-specific changes. Notably, the same study found that transgenic animals overexpressing RPTP β exhibited altered glutamatergic, GABAergic and dopaminergic activity, as well as delayed oligodendrocyte development, which are perhaps more relevant in the schizophrenia context (Takahashi et al., 2011a). Finally, these animals also demonstrated schizophrenia-like behavioral deficits, including reduced sensory motor gating, hyperactivity and working memory impairment, indicating that enhanced RPTP β signaling can contribute to schizophrenia phenotypes (Takahashi et al., 2011a).

Development and Synaptic plasticity

Given that PNNs can modulate neural circuitry functions stemming from developmental plasticity and closure of the critical period (Friauf, 2000; Guimaraes et al., 1990; Pizzorusso et al., 2002, 2006)(Galtrey and Fawcett, 2007)(Rauch, 2004)(McRae et al., 2007)(Takesian and Hensch, 2013) to maintenance of synaptic network stability in adulthood (Dityatev and Schachner, 2003; Kwok et al., 2008)(Pizzorusso et al., 2002, 2006)(Galtrey and Fawcett,

2007)(Caroni et al., 2012), their disturbances can have widespread consequences, depending in part on when and where these disturbances occur.

In light of the fact that PNNs are known to play a role in regulating developmental synaptic pruning in the cerebral cortex and that synaptic pruning deficit has long been speculated to contribute to the onset of schizophrenia (McGlashan and Hoffman, 2000; Feinberg, 1982; Keshavan et al., 1994), we speculate that a deficit in the formation of PNNs that ensheath parvalbumin and pyramidal neurons and their processes could compromise the experience-dependent consolidation of synaptic connectivities and prolonging the termination of synaptic pruning. In this regard, it is noteworthy that a series of elegant experiments by Orlando and colleagues recently found that removal of PNNs in the hippocampus using ChABC resulted in altered spine dynamics via a restriction of $\beta 1$ -integrin activation and signaling at synaptic sites (Orlando et al., 2012). This is an interesting observation in light of the finding of reduction in spine number on layer 3 pyramidal cells in schizophrenia (Glantz and Lewis, 2000; Sweet et al., 2009).

Yet another element that may be linked to schizophrenia pathophysiology is the biophysics of the neural-ECM. Because diffusion in the extracellular space is dependent on the structure and chemical properties of the ECM (Sykova, 2005), it is conceivable that PNN abnormalities in the adult CNS may alter the efficacy of synapses and transmitter release associated with schizophrenia (Earls and Zakharenko, 2013). 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 (Fuxe et al., 2013; Sykova, 2005), a notable example being dopamine (Fuxe et al., 2013).

Finally, Nogo receptor (NgR), which binds myelin-associated proteins that inhibit axonal growth, such as the Nogo proteins, is expressed in PNN-encapsulated neurons (Ye and Miao, 2013) and also binds CSPGs (Dickendesher et al., 2012). Hence, together with PNNs, myelin formation may provide an additional mechanism that progressively restricts synaptic plasticity and thereby stabilize cortical circuitry in the mature brain. Deficit in myelination in schizophrenia may therefore further compromise the stability and integrity of synaptic connectivities. Interestingly, Nogo and NgR have previously been implicated in the pathophysiology schizophrenia (Willi and Schwab, 2013)(Willi et al., 2010)(Tews et al., 2013)(Budel et al., 2008).

Possible Neurobiological Basis of PNN Deficit in Schizophrenia

The mechanisms underlying PNN deficit, which may be a consequence of PNN degradation and/or failure in PNN formation, in schizophrenia are unclear. It is possible that the degradation of the PNN is a consequence of an alteration in proteases 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). Because cleavage of ECM components is part of their normal turnover process, a dysregulation in this process may be a prerequisite for neurological disease. In this context, several observations suggest that the MMPs may be key mediators of PNN degradation. Two

members of this large group of ECM-degrading enzymes have been shown to have direct CSPG-degrading properties in the brain: MMP-2 and MMP-24 (Wang et al., 1999; Zuo et al., 1998), and other evidence (Muir et al., 2002) has shown that MMP-2 and MMP-3 can degrade most of the components of the PNN. In addition, degradation of brevican by ADAMTS has been demonstrated (Mayer et al., 2005). Moreover, ADAMTS-mediated brevican degradation colocalized with areas of synaptic loss in a kainic acid model of acute neuronal toxicity (Yuan et al., 2002). Interestingly, a recent genome-wide association study has identified *MMP16* as a schizophrenia risk gene (Ripke et al., 2013). We have also recently found in laser-captured pyramidal neurons from layer 3 of the superior temporal gyrus of patients with schizophrenia to exhibit alterations in genes that encode both MMPs and ADAMTSs (Pietersen et al., 2014a, b), including *MMP16*, suggesting that a dysregulation in the remodeling of the ECM may represent a genuine component underlying the pathophysiology of the disease (Pietersen et al., 2014a, b) (see Table 1).

An alternative explanation is that the degradation of the PNN is a consequence of microglial activation. For example, degradation of the PNN is a feature of multiple sclerosis (Gray et al., 2008), a neurological condition that shares a similar clinical course, age of onset and immunological profile to patients with schizophrenia (Stevens, 1988). The degradation of the PNN in multiple sclerosis has been attributed to the production of MMPs by cytokines or activated microglia (Gray et al., 2008). In this context, the neuropathology of schizophrenia has been reported to be closely associated with cytokines and microglial activation (Bayer et al., 1999; Brown, 2011; Juckel et al., 2011; Meyer et al., 2009; Monji et al., 2009; Najjar et al., 2013; Radewicz et al., 2000; Vuillermot et al., 2010). Although speculative, these observations suggest that immune dysfunction may be associated with the PNN deficits observed in schizophrenia. Experimental evidence confirming such a link would be necessary to validate this conjecture. In this regard, prenatal exposure to the immunostimulant polyinosinic:polycytidilic acid has been shown to represent a robust experimental model with a well-characterized evolution of pathologic and behavioural changes relevant to schizophrenia (Bitanirwe et al., 2010; Giovanoli et al., 2013; Nyffeler et al., 2006; Richetto et al., 2013; Vuillermot et al., 2010)(Meyer, 2013). The use of such a tool would prove effective in answering the question as to whether an association exists between immune system activation and loss of PNNs.

Conclusions

As the underlying pathology of schizophrenia continues to be unravelled, novel and exciting pieces to the complex puzzle continue to emerge. One such piece of the schizophrenia puzzle involves PNNs, whose location directly on the surface of neurons places them in a unique position to not only modulate neuronal physiology but to also exert a strong influence on synaptic formation, plasticity and stabilization in the brain (Kwok et al., 2008; Kwok et al., 2011; McRae and Porter, 2012; Wang and Fawcett, 2012). These lattice-like structures represent an integral part of the synapse and appear to be specialized to monitor and adapt according to the dynamic changes in the extracellular environment. Changes in the extracellular milieu under pathological conditions may therefore affect and disrupt the structural integrity of PNNs, triggering a 'neurometabolic' cascade of events culminating in neuronal damage and synaptic dysfunction associated with schizophrenia. Therefore, the

normalization of PNN structural integrity may rescue the neurodevelopmental alterations affecting the physiology of neural circuitry in schizophrenia. In this context, a more complete understanding of PNN function in normal conditions and how their functions are altered in schizophrenia will be of importance in terms of providing new insight into the neurobiological underpinnings of this major public health problem. This information will likely lead to an emergence of novel targets for therapeutic intervention aimed at reversing underlying abnormalities in neural plasticity and in the process improve clinical outcomes.

Acknowledgments

This work was supported by Grants MH076060 and MH080272 from the National Institutes of Health (T-U.W.W.). The authors would like to thank Dr. Mayura Meerang and Dr. Stephan Arni for helpful comments and careful reading of the early draft of the manuscript. We also thank the two anonymous reviewers whose comments helped improve the quality of the manuscript. Figures 5 and 6 are reproduced with permission of Springer-Verlag, Heidelberg.

References

- Alpar A, Gartner U, Hartig W, Bruckner G. Distribution of pyramidal cells associated with perineuronal nets in the neocortex of rat. *Brain Res.* 2006; 1120:13–22. [PubMed: 16996045]
- Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry.* 2004; 184:110–117. [PubMed: 14754822]
- Atoji Y, Yamamoto Y, Suzuki Y, Matsui F, Oohira A. Immunohistochemical localization of neurocan in the lower auditory nuclei of the dog. *Hear Res.* 1997; 110:200–208. [PubMed: 9282902]
- Balmer TS, Carels VM, Frisch JL, Nick TA. Modulation of perineuronal nets and parvalbumin with developmental song learning. *J Neurosci.* 2009; 29:12878–12885. [PubMed: 19828802]
- Barros CS, Franco SJ, Muller U. Extracellular matrix: functions in the nervous system. *Cold Spring Harb Perspect Biol.* 2011; 3:a005108. [PubMed: 21123393]
- Bartzokis G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. *Neuropsychopharmacology.* 2002; 27:672–683. [PubMed: 12377404]
- Bartzokis G, Nuechterlein KH, Lu PH, Gitlin M, Rogers S, Mintz J. Dysregulated brain development in adult men with schizophrenia: a magnetic resonance imaging study. *Biol Psychiatry.* 2003; 53:412–421. [PubMed: 12614994]
- Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C. Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol.* 2007; 64:39–45. [PubMed: 16962192]
- Bavelier D, Levi DM, Li RW, Dan Y, Hensch TK. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J Neurosci.* 2010; 30:14964–14971. [PubMed: 21068299]
- Bayer TA, Buslei R, Havas L, Falkai P. Evidence for activation of microglia in patients with psychiatric illnesses. *Neurosci Lett.* 1999; 271:126–128. [PubMed: 10477118]
- Bekku Y, Vargova L, Goto Y, Vorisek I, Dmytrenko L, Narasaki M, Ohtsuka A, Fassler R, Ninomiya Y, Sykova E, Oohashi T. Bral1: its role in diffusion barrier formation and conduction velocity in the CNS. *J Neurosci.* 2010; 30:3113–3123. [PubMed: 20181608]
- Benes FM. Myelination of cortical-hippocampal relays during late adolescence. *Schizophrenia Bulletin.* 1989; 15:585–593. [PubMed: 2623440]
- Benes FM. Emerging principles of altered neural circuitry in schizophrenia. *Brain Res Brain Res Rev.* 2000; 31:251–269. [PubMed: 10719152]
- Bentivoglio M, Mazzarello P. Chapter 12: the anatomical foundations of clinical neurology. *Handb Clin Neurol.* 2010; 95:149–168. [PubMed: 19892115]
- Berg K, Wiseth R, Bjerre K, Brurok H, Gunnes S, Skarra S, Jynge P, Basu S. Oxidative stress and myocardial damage during elective percutaneous coronary interventions and coronary angiography. A comparison of blood-borne isoprostane and troponin release. *Free Radic Res.* 2004; 38:517–525. [PubMed: 15293560]

- Bertolotto A, Rocca G, Canavese G, Migheli A, Schiffer D. Chondroitin sulfate proteoglycan surrounds a subset of human and rat CNS neurons. *J Neurosci Res.* 1991; 29:225–234. [PubMed: 1890701]
- Beurdeley M, Spatazza J, Lee HH, Sugiyama S, Bernard C, Di Nardo AA, Hensch TK, Prochiantz A. Otx2 binding to perineuronal nets persistently regulates plasticity in the mature visual cortex. *J Neurosci.* 2012; 32:9429–37. [PubMed: 22764251]
- Bignami A, Hosley M, Dahl D. Hyaluronic acid and hyaluronic acid-binding proteins in brain extracellular matrix. *Anatomy and embryology.* 1993; 188:419–433. [PubMed: 7508695]
- Bitanirwe BK, Lim MP, Kelley JF, Kaneko T, Woo TU. Glutamatergic deficits and parvalbumin-containing inhibitory neurons in the prefrontal cortex in schizophrenia. *BMC Psychiatry.* 2009; 9:71. [PubMed: 19917116]
- Bitanirwe BK, Peleg-Raibstein D, Mouttet F, Feldon J, Meyer U. Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia. *Neuropsychopharmacology.* 2010; 35:2462–2478. [PubMed: 20736993]
- Bitanirwe BK, Woo TU. Oxidative stress in schizophrenia: an integrated approach. *Neurosci Biobehav Rev.* 2011; 35:878–893. [PubMed: 20974172]
- Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. *Acta Neuropathol.* 2010; 119:37–53. [PubMed: 19847447]
- Bradshaw NJ, Porteous DJ. DISC1-binding proteins in neural development, signalling and schizophrenia. *Neuropharmacology.* 2012; 62:1230–1241. [PubMed: 21195721]
- Braff DL. Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull.* 1993; 19:233–259. [PubMed: 8322034]
- Brandon NJ, Sawa A. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. *Nat Rev Neurosci.* 2011; 12:707–722. [PubMed: 22095064]
- Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol.* 2011; 93:23–58. [PubMed: 20955757]
- Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Dev Neurobiol.* 2012; 72:1272–1276. [PubMed: 22488761]
- Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry.* 2010; 167:261–280. [PubMed: 20123911]
- Brown AS, Susser ES. In utero infection and adult schizophrenia. *Ment Retard Dev Disabil Res Rev.* 2002; 8:51–57. [PubMed: 11921387]
- Bruckner G, Brauer K, Hartig W, Wolff JR, Rickmann MJ, Derouiche A, Delpech B, Girard N, Oertel WH, Reichenbach A. Perineuronal nets provide a polyanionic, glia-associated form of microenvironment around certain neurons in many parts of the rat brain. *Glia.* 1993; 8:183–200. [PubMed: 7693589]
- Bruckner G, Bringmann A, Koppe G, Hartig W, Brauer K. In vivo and in vitro labelling of perineuronal nets in rat brain. *Brain Res.* 1996a; 720:84–92. [PubMed: 8782900]
- Bruckner G, Grosche J, Schmidt S, Hartig W, Margolis RU, Delpech B, Seidenbecher CI, Czaniera R, Schachner M. Postnatal development of perineuronal nets in wild-type mice and in a mutant deficient in tenascin-R. *J Comp Neurol.* 2000; 428:616–629. [PubMed: 11077416]
- Bruckner G, Hartig W, Kacza J, Seeger J, Welt K, Brauer K. Extracellular matrix organization in various regions of rat brain grey matter. *J Neurocytol.* 1996b; 25:333–346. [PubMed: 8818977]
- Bruckner G, Hausen D, Hartig W, Drlicek M, Arendt T, Brauer K. Cortical areas abundant in extracellular matrix chondroitin sulphate proteoglycans are less affected by cytoskeletal changes in Alzheimer's disease. *Neuroscience.* 1999; 92:791–805. [PubMed: 10426522]
- Bruckner G, Szeoke S, Pavlica S, Grosche J, Kacza J. Axon initial segment ensheathed by extracellular matrix in perineuronal nets. *Neuroscience.* 2006; 138:365–375. [PubMed: 16427210]
- Budel S, Padukkavidana T, Liu BP, Feng Z, Hu F, Johnson S, et al. Genetic variants of Nogo-66 receptor with possible association to schizophrenia block myelin inhibition of axon growth. *J Neurosci.* 2008; 28:13161–72. [PubMed: 19052207]
- Bukalo O, Schachner M, Dityatev A. Modification of extracellular matrix by enzymatic removal of chondroitin sulfate and by lack of tenascin-R differentially affects several forms of synaptic plasticity in the hippocampus. *Neuroscience.* 2001; 104:359–369. [PubMed: 11377840]

- Buxbaum JD, Georgieva L, Young JJ, Plescia C, Kajiura Y, Jiang Y, Moskvina V, Norton N, Peirce T, Williams H, Craddock NJ, Carroll L, Corfas G, Davis KL, Owen MJ, Harroch S, Sakurai T, O'Donovan MC. Molecular dissection of NRG1-ERBB4 signaling implicates PTPRZ1 as a potential schizophrenia susceptibility gene. *Mol Psychiatry*. 2008; 13:162–172. [PubMed: 17579610]
- Buzsáki, G. *Rhythms of the Brain*. Oxford University Press; New York: 2006.
- Cabungcal JH, Steullet P, Morishita H, Kraftsik R, Cuenod M, Hensch TK, Do KQ. Perineuronal nets protect fast-spiking interneurons against oxidative stress. *Proc Natl Acad Sci U S A*. 2013; 110:9130–9135. [PubMed: 23671099]
- Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry*. 2002; 159:1080–1092. [PubMed: 12091183]
- Cant NB, Benson CG. Wisteria floribunda lectin is associated with specific cell types in the ventral cochlear nucleus of the gerbil, *Meriones unguiculatus*. *Hear Res*. 2006; 216–217:64–72.
- Caroni P, Donato F, Muller D. Structural plasticity upon learning: regulation and functions. *Nat Rev Neurosci*. 2012; 13:478–90. [PubMed: 22714019]
- Carulli D, Pizzorusso T, Kwok JC, Putignano E, Poli A, Forostyak S, Andrews MR, Deepa SS, Glant TT, Fawcett JW. Animals lacking link protein have attenuated perineuronal nets and persistent plasticity. *Brain*. 2010; 133:2331–47. [PubMed: 20566484]
- Casadio P, Fernandes C, Murray RM, Di Forti M. Cannabis use in young people: the risk for schizophrenia. *Neurosci Biobehav Rev*. 2011; 35:1779–1787. [PubMed: 21530584]
- Celio MR, Spreafico R, De Biasi S, Vitellaro-Zuccarello L. Perineuronal nets: past and present. *Trends Neurosci*. 1998; 21:510–515. [PubMed: 9881847]
- Chiti Z, Knutsen OM, Betmouni S, Greene JR. An integrated, temporal study of the behavioural, electrophysiological and neuropathological consequences of murine prion disease. *Neurobiol Dis*. 2006; 22:363–373. [PubMed: 16431123]
- Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical {gamma} synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci U S A*. 2006; 103:19878–19883. [PubMed: 17170134]
- Clarke MC, Harley M, Cannon M. The role of obstetric events in schizophrenia. *Schizophr Bull*. 2006; 32:3–8. [PubMed: 16306181]
- Daskalakis ZJ, Fitzgerald PB, Christensen BK. The role of cortical inhibition in the pathophysiology and treatment of schizophrenia. *Brain Res Rev*. 2007; 56:427–442. [PubMed: 17980435]
- Deepa SS, Carulli D, Galtrey C, Rhodes K, Fukuda J, Mikami T, Sugahara K, Fawcett JW. Composition of perineuronal net extracellular matrix in rat brain: a different disaccharide composition for the net-associated proteoglycans. *J Biol Chem*. 2006; 281:17789–17800. [PubMed: 16644727]
- Dick G, Tan CL, Alves JN, Ehlert EM, Miller GM, Hsieh-Wilson LC, Sugahara K, Oosterhof A, van Kuppevelt TH, Verhaagen J, Fawcett JW, Kwok JC. Semaphorin 3A binds to the perineuronal nets via chondroitin sulfate type E motifs in rodent brains. *J Biol Chem*. 2013
- Dickendesher TL, Baldwin KT, Mironova YA, Koriyama Y, Raiker SJ, Askew KL, Wood A, Geoffroy CG, Zheng B, Liepmann CD, Katagiri Y, Benowitz LI, Geller HM, Giger RJ. NgR1 and NgR3 are receptors for chondroitin sulfate proteoglycans. *Nat Neurosci*. 2012; 15:703–712. [PubMed: 22406547]
- Dityatev A, Bruckner G, Dityateva G, Grosche J, Kleene R, Schachner M. Activity-dependent formation and functions of chondroitin sulfate-rich extracellular matrix of perineuronal nets. *Dev Neurobiol*. 2007; 67:570–588. [PubMed: 17443809]
- Dityatev A, Schachner M. Extracellular matrix molecules and synaptic plasticity. *Nat Rev Neurosci*. 2003; 4:456–468. [PubMed: 12778118]
- Do KQ, Cabungcal JH, Frank A, Steullet P, Cuenod M. Redox dysregulation, neurodevelopment, and schizophrenia. *Curr Opin Neurobiol*. 2009; 19:220–230. [PubMed: 19481443]
- Dours-Zimmermann MT, Maurer K, Rauch U, Stoffel W, Fassler R, Zimmermann DR. Versican V2 assembles the extracellular matrix surrounding the nodes of ranvier in the CNS. *J Neurosci*. 2009; 29:7731–7742. [PubMed: 19535585]

- Du J, Zhang L, Weiser M, Rudy B, McBain CJ. Developmental expression and functional characterization of the potassium-channel subunit Kv3.1b in parvalbumin-containing interneurons of the rat hippocampus. *J Neurosci*. 1996; 16:506–518. [PubMed: 8551335]
- During DN, Ziegler A, Thompson CK, Faber C, Muller J, Scharff C, Elemans CP. The songbird syrinx morphome: a three-dimensional, high-resolution, interactive morphological map of the zebra finch vocal organ. *BMC Biol*. 2013; 11:1. [PubMed: 23294804]
- Earls LR, Zakharenko SS. *A Synaptic Function Approach to Investigating Complex Psychiatric Diseases*. Neuroscientist. 2013
- Eichhammer P, Wiegand R, Kharraz A, Langguth B, Binder H, Hajak G. Cortical excitability in neuroleptic-naïve first-episode schizophrenic patients. *Schizophr Res*. 2004; 67:253–9. [PubMed: 14984885]
- Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, Daskalakis ZJ. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain*. 2010; 133:1505–1514. [PubMed: 20350936]
- Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982; 17:319–334. [PubMed: 7187776]
- Franco SJ, Muller U. Extracellular matrix functions during neuronal migration and lamination in the mammalian central nervous system. *Dev Neurobiol*. 2011; 71:889–900. [PubMed: 21739613]
- Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. *J Cell Sci*. 2010; 123:4195–4200. [PubMed: 21123617]
- Friauf E. Development of chondroitin sulfate proteoglycans in the central auditory system of rats correlates with acquisition of mature properties. *Audiol Neurotol*. 2000; 5:251–262. [PubMed: 10899695]
- Frith CD. Consciousness, information processing and schizophrenia. *Br J Psychiatry*. 1979; 134:225–235. [PubMed: 509004]
- Fuxe K, Borroto-Escuela DO, Romero-Fernandez W, Zhang WB, Agnati LF. Volume transmission and its different forms in the central nervous system. *Chin J Integr Med*. 2013; 19:323–329. [PubMed: 23674109]
- Galtrey CM, Fawcett JW. The role of chondroitin sulfate proteoglycans in regeneration and plasticity in the central nervous system. *Brain Res Rev*. 2007; 54:1–18. [PubMed: 17222456]
- Gan L, Kaczmarek LK. When, where, and how much? Expression of the Kv3.1 potassium channel in high-frequency firing neurons. *J Neurobiol*. 1998; 37:69–79. [PubMed: 9777733]
- Garwood J, Heck N, Reichardt F, Faissner A. Phosphacan short isoform, a novel non-proteoglycan variant of phosphacan/receptor protein tyrosine phosphatase-beta, interacts with neuronal receptors and promotes neurite outgrowth. *J Biol Chem*. 2003; 278:24164–24173. [PubMed: 12700241]
- Garwood J, Rigato F, Heck N, Faissner A. Tenascin glycoproteins and the complementary ligand DSD-1-PG/phosphacan--structuring the neural extracellular matrix during development and repair. *Restor Neurol Neurosci*. 2001; 19:51–64. [PubMed: 12082229]
- Georgiev D, Arion D, Enwright JF, Kikuchi M, Minabe Y, Corradi JP, Lewis DA, Hashimoto T. Lower Gene Expression for KCNS3 Potassium Channel Subunit in Parvalbumin-Containing Neurons in the Prefrontal Cortex in Schizophrenia. *Am J Psychiatry*. 2014; 171:62–71. [PubMed: 24170294]
- Georgiev D, Gonzalez-Burgos G, Kikuchi M, Minabe Y, Lewis DA, Hashimoto T. Selective expression of KCNS3 potassium channel alpha-subunit in parvalbumin-containing GABA neurons in the human prefrontal cortex. *PLoS ONE*. 2012; 7:e43904. [PubMed: 22937123]
- Gerlinger G, Hauser M, De Hert M, Lacluyse K, Wampers M, Correll CU. Personal stigma in schizophrenia spectrum disorders: a systematic review of prevalence rates, correlates, impact and interventions. *World Psychiatry*. 2013; 12:155–164. [PubMed: 23737425]
- Gherardini L, Gennaro M, Pizzorusso T. Perilesional Treatment with Chondroitinase ABC and Motor Training Promote Functional Recovery After Stroke in Rats. *Cereb Cortex*. 2013 Epub ahead of print.
- Giamanco KA, Morawski M, Matthews RT. Perineuronal net formation and structure in aggrecan knockout mice. *Neuroscience*. 2010; 170:1314–1327. [PubMed: 20732394]

- Giovanoli S, Engler H, Engler A, Richetto J, Voget M, Willi R, Winter C, Riva MA, Mortensen PB, Schedlowski M, Meyer U. Stress in puberty unmasks latent neuropathological consequences of prenatal immune activation in mice. *Science*. 2013; 339:1095–1099. [PubMed: 23449593]
- Glantz LA, Lewis DA. Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia. Regional and diagnostic specificity. *Arch Gen Psychiatry*. 1997; 54:660–669. [PubMed: 9236550]
- Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Archives of General Psychiatry*. 2000; 57:65–73. [PubMed: 10632234]
- Gogolla N, Caroni P, Luthi A, Herry C. Perineuronal nets protect fear memories from erasure. *Science*. 2009; 325:1258–1261. [PubMed: 19729657]
- Goldman-Rakic PS. Working memory dysfunction in schizophrenia. *Journal of Neuropsychiatry & Clinical Neurosciences*. 1994; 6:348–357. [PubMed: 7841806]
- Golgi C. Intorno alla struttura delle cellule nervose. *Boll Soc Med Chir Pavia*. 1898; 13:1–14.
- Gonzalez-Burgos G, Hashimoto T, Lewis DA. Alterations of cortical GABA neurons and network oscillations in schizophrenia. *Curr Psychiatry Rep*. 2010; 12:335–344. [PubMed: 20556669]
- Gonzalez-Burgos G, Lewis DA. GABA neurons and the mechanisms of network oscillations: implications for understanding cortical dysfunction in schizophrenia. *Schizophr Bull*. 2008; 34:944–961. [PubMed: 18586694]
- Gray E, Thomas TL, Betmouni S, Scolding N, Love S. Elevated matrix metalloproteinase-9 and degradation of perineuronal nets in cerebrocortical multiple sclerosis plaques. *J Neuropathol Exp Neurol*. 2008; 67:888–899. [PubMed: 18716555]
- Gray CM, Engel AK, König P, Singer W. Synchronization of oscillatory neuronal responses in cat striate cortex: temporal properties. *Vis Neurosci*. 1992; 8:337–47. [PubMed: 1562569]
- Grutznier C, Wibrall M, Sun L, Rivolta D, Singer W, Maurer K, Uhlhaas PJ. Deficits in high- (>60 Hz) gamma-band oscillations during visual processing in schizophrenia. *Front Hum Neurosci*. 2013; 7:88. [PubMed: 23532620]
- Guimaraes A, Zaremba S, Hockfield S. Molecular and morphological changes in the cat lateral geniculate nucleus and visual cortex induced by visual deprivation are revealed by monoclonal antibodies Cat-304 and Cat-301. *J Neurosci*. 1990; 10:3014–3024. [PubMed: 1697900]
- Harrison PJ. Postmortem studies in schizophrenia. *Dialogues Clin Neurosci*. 2000; 2:349–357. [PubMed: 22033474]
- Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry*. 2005; 10:40–68. image 45. [PubMed: 15263907]
- Harroch S, Palmeri M, Rosenbluth J, Custer A, Okigaki M, Shrager P, Blum M, Buxbaum JD, Schlessinger J. No obvious abnormality in mice deficient in receptor protein tyrosine phosphatase beta. *Mol Cell Biol*. 2000; 20:7706–7715. [PubMed: 11003666]
- Hartig W, Brauer K, Bigl V, Bruckner G. Chondroitin sulfate proteoglycan-immunoreactivity of lectin-labeled perineuronal nets around parvalbumin-containing neurons. *Brain Res*. 1994; 635:307–311. [PubMed: 8173967]
- Hartig W, Brauer K, Bruckner G. Wisteria floribunda agglutinin-labelled nets surround parvalbumin-containing neurons. *Neuroreport*. 1992; 3:869–872. [PubMed: 1421090]
- Hartig W, Derouiche A, Welt K, Brauer K, Grosche J, Mader M, Reichenbach A, Bruckner G. Cortical neurons immunoreactive for the potassium channel Kv3.1b subunit are predominantly surrounded by perineuronal nets presumed as a buffering system for cations. *Brain Res*. 1999; 842:15–29. [PubMed: 10526091]
- Hartig W, Singer A, Grosche J, Brauer K, Ottersen OP, Bruckner G. Perineuronal nets in the rat medial nucleus of the trapezoid body surround neurons immunoreactive for various amino acids, calcium-binding proteins and the potassium channel subunit Kv3.1b. *Brain Res*. 2001; 899:123–133. [PubMed: 11311873]
- Hashimoto T, Volk DW, Eggan SM, Mirnics K, Pierri JN, Sun Z, Sampson AR, Lewis DA. Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J Neurosci*. 2003; 23:6315–6326. [PubMed: 12867516]

- Haunso A, Celio MR, Margolis RK, Menoud PA. Phosphacan immunoreactivity is associated with perineuronal nets around parvalbumin-expressing neurones. *Brain Res.* 1999; 834:219–222. [PubMed: 10407120]
- Hausen D, Bruckner G, Drlicek M, Hartig W, Brauer K, Bigl V. Pyramidal cells ensheathed by perineuronal nets in human motor and somatosensory cortex. *Neuroreport.* 1996; 7:1725–1729. [PubMed: 8905652]
- Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. *Schizophr Bull.* 2005; 31:608–612. [PubMed: 15976013]
- Hensch TK. Critical period mechanisms in developing visual cortex. *Curr Top Dev Biol.* 2005a; 69:215–237. [PubMed: 16243601]
- Hensch TK. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci.* 2005b; 6:877–888. [PubMed: 16261181]
- Quirk GJ, Paré D, Richardson R, Herry C, Monfils MH, Schiller D, Vicentic A. Erasing fear memories with extinction training. *J Neurosci.* 2010; 30:14993–7. [PubMed: 21068303]
- Hilbig H, Nowack S, Boeckler K, Bidmon HJ, Zilles K. Characterization of neuronal subsets surrounded by perineuronal nets in the rhesus auditory brainstem. *J Anat.* 2007; 210:507–517. [PubMed: 17451528]
- Hobohm C, Hartig W, Brauer K, Bruckner G. Low expression of extracellular matrix components in rat brain stem regions containing modulatory aminergic neurons. *J Chem Neuroanat.* 1998; 15:135–142. [PubMed: 9797071]
- Hobohm C, Günther A, Grosche J, Rossner S, Schneider D, Brückner G. Decomposition and long-lasting downregulation of extracellular matrix in perineuronal nets induced by focal cerebral ischemia in rats. *J Neurosci Res.* 2005; 80:539–48. [PubMed: 15806566]
- Hockfield S, Kalb RG, Zaremba S, Fryer H. Expression of neural proteoglycans correlates with the acquisition of mature neuronal properties in the mammalian brain. *Cold Spring Harb Symp Quant Biol.* 1990; 55:505–514. [PubMed: 2132834]
- Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K, Krystal JH. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Arch Gen Psychiatry.* 2003; 60:49–56. [PubMed: 12511172]
- Hoffman RE, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. *Am J Psychiatry.* 2002; 159:1093–1102. [PubMed: 12091184]
- Hoistad M, Segal D, Takahashi N, Sakurai T, Buxbaum JD, Hof PR. Linking white and grey matter in schizophrenia: oligodendrocyte and neuron pathology in the prefrontal cortex. *Front Neuroanat.* 2009; 3:9. [PubMed: 19636386]
- Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull.* 2009; 35:549–562. [PubMed: 19325164]
- Juckel G, Manitz MP, Brune M, Friebe A, Heneka MT, Wolf RJ. Microglial activation in a neuroinflammatory animal model of schizophrenia--a pilot study. *Schizophr Res.* 2011; 131:96–100. [PubMed: 21752601]
- Kahler AK, Djurovic S, Rimol LM, Brown AA, Athanasias L, Jonsson EG, Hansen T, Gustafsson O, Hall H, Giegling I, Muglia P, Cichon S, Rietschel M, Pietiläinen OP, Peltonen L, Bramon E, Collier D, St Clair D, Sigurdsson E, Petursson H, Rujescu D, Melle I, Werge T, Steen VM, Dale AM, Matthews RT, Agartz I, Andreassen OA. Candidate gene analysis of the human natural killer-1 carbohydrate pathway and perineuronal nets in schizophrenia: B3GAT2 is associated with disease risk and cortical surface area. *Biol Psychiatry.* 2011; 69:90–96. [PubMed: 20950796]
- Kalb RG, Hockfield S. Molecular evidence for early activity-dependent development of hamster motor neurons. *J Neurosci.* 1988; 8:2350–2360. [PubMed: 3249230]
- Kalb RG, Hockfield S. Induction of a neuronal proteoglycan by the NMDA receptor in the developing spinal cord. *Science.* 1990a; 250:294–296. [PubMed: 2145629]
- Kalb RG, Hockfield S. Large diameter primary afferent input is required for expression of the Cat-301 proteoglycan on the surface of motor neurons. *Neuroscience.* 1990b; 34:391–401. [PubMed: 2333149]

- Karayiorgou M, Simon TJ, Gogos JA. 22q11.2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nat Rev Neurosci*. 2010; 11:402–416. [PubMed: 20485365]
- Karetko M, Skangiel-Kramska J. Diverse functions of perineuronal nets. *Acta Neurobiol Exp (Wars)*. 2009; 69:564–577. [PubMed: 20048772]
- Kelsch W, Sim S, Lois C. Watching synaptogenesis in the adult brain. *Annu Rev Neurosci*. 2010; 33:131–149. [PubMed: 20572770]
- Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. *J Psychiatr Res*. 1994; 28:239–265. [PubMed: 7932285]
- Kind PC, Beaver CJ, Mitchell DE. Effects of early periods of monocular deprivation and reverse lid suture on the development of Cat-301 immunoreactivity in the dorsal lateral geniculate nucleus (dLGN) of the cat. *J Comp Neurol*. 1995; 359:523–536. [PubMed: 7499545]
- Kirihara K, Rissling AJ, Swerdlow NR, Braff DL, Light GA. Hierarchical organization of gamma and theta oscillatory dynamics in schizophrenia. *Biol Psychiatry*. 2012; 71:873–880. [PubMed: 22361076]
- Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, Murray RM, Jones PB. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. *PLoS One*. 2012; 7:e31660. [PubMed: 22457710]
- Kohen R, Nyska A. Oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. *Toxicol Pathol*. 2002; 30:620–650. [PubMed: 12512863]
- Kumari V, Soni W, Sharma T. Normalization of information processing deficits in schizophrenia with clozapine. *Am J Psychiatry*. 1999; 156:1046–1051. [PubMed: 10401450]
- Kwok JC, Afshari F, Garcia-Alias G, Fawcett JW. Proteoglycans in the central nervous system: plasticity, regeneration and their stimulation with chondroitinase ABC. *Restorative neurology and neuroscience*. 2008; 26:131–145. [PubMed: 18820407]
- Kwok JC, Dick G, Wang D, Fawcett JW. Extracellular matrix and perineuronal nets in CNS repair. *Dev Neurobiol*. 2011; 71:1073–1089. [PubMed: 21898855]
- Lakatos P, Schroeder CE, Leitman DI, Javitt DC. Predictive suppression of cortical excitability and its deficit in schizophrenia. *J Neurosci*. 2013; 33:11692–702. [PubMed: 23843536]
- Lander C, Kind P, Maleski M, Hockfield S. A family of activity-dependent neuronal cell-surface chondroitin sulfate proteoglycans in cat visual cortex. *J Neurosci*. 1997; 17:1928–1939. [PubMed: 9045722]
- Lau LW, Cua R, Keough MB, Haylock-Jacobs S, Yong VW. Pathophysiology of the brain extracellular matrix: a new target for remyelination. *Nat Rev Neurosci*. 2013
- Lee H, Leamey CA, Sawatari A. Perineuronal nets play a role in regulating striatal function in the mouse. *PLoS One*. 2012; 7:e32747. [PubMed: 22427872]
- Lee H, Sawatari A. Medium spiny neurons of the neostriatal matrix exhibit specific, stereotyped changes in dendritic arborization during a critical developmental period in mice. *Eur J Neurosci*. 2011; 34:1345–1354. [PubMed: 21995728]
- Lendvai D, Morawski M, Nagyessy L, Gati G, Jager C, Baksa G, Glasz T, Attems J, Tanila H, Arendt T, Harkany T, Alpar A. Neurochemical mapping of the human hippocampus reveals perisynaptic matrix around functional synapses in Alzheimer's disease. *Acta Neuropathol*. 2013; 125:215–229. [PubMed: 22961619]
- Lenz S, Perney TM, Qin Y, Robbins E, Chesselet MF. GABA-ergic interneurons of the striatum express the Shaw-like potassium channel Kv3.1. *Synapse*. 1994; 18:55–66. [PubMed: 7825124]
- Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci*. 2005; 6:312–324. [PubMed: 15803162]
- Liu H, Xu H, Yu T, Yao J, Zhao C, Yin ZQ. Expression of perineuronal nets, parvalbumin and protein tyrosine phosphatase σ in the rat visual cortex during development and after BFD. *Curr Eye Res*. 2013; 38:1083–94. [PubMed: 23718120]
- Lora A, Kohn R, Levav I, McBain R, Morris J, Saxena S. Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income countries. *Bull World Health Organ*. 2012; 90:47–54. 54A–54B. [PubMed: 22271964]

- Lumey LH, Stein AD, Susser E. Prenatal famine and adult health. *Annu Rev Public Health*. 2011; 32:237–262. [PubMed: 21219171]
- Maeda N, Nishiwaki T, Shintani T, Hamanaka H, Noda M. 6B4 proteoglycan/phosphacan, an extracellular variant of receptor-like protein-tyrosine phosphatase zeta/RPTPbeta, binds pleiotrophin/heparin-binding growth-associated molecule (HB-GAM). *J Biol Chem*. 1996; 271:21446–21452. [PubMed: 8702927]
- Maren S, Phan KL, Liberzon I. The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nat Rev Neurosci*. 2013; 14:417–28. [PubMed: 23635870]
- Margari F, Petruzzelli MG, Lecce PA, Todarello O, De Giacomo A, Lucarelli E, Martinelli D, Margari L. Familial liability, obstetric complications and childhood development abnormalities in early onset schizophrenia: a case control study. *BMC Psychiatry*. 2011; 11:60. [PubMed: 21492438]
- Margolis RK, Margolis RU. Nervous tissue proteoglycans. *Experientia*. 1993; 49:429–446. [PubMed: 8500598]
- Margolis RU, Margolis RK. Chondroitin sulfate proteoglycans as mediators of axon growth and pathfinding. *Cell Tissue Res*. 1997; 290:343–348. [PubMed: 9321696]
- Martins-de-Souza D. Proteome and transcriptome analysis suggests oligodendrocyte dysfunction in schizophrenia. *J Psychiatr Res*. 2010; 44:149–156. [PubMed: 19699489]
- Martins-de-Souza D, Gattaz WF, Schmitt A, Maccarrone G, Hunyadi-Gulyas E, Eberlin MN, Souza GH, Marangoni S, Novello JC, Turck CW, Dias-Neto E. Proteomic analysis of dorsolateral prefrontal cortex indicates the involvement of cytoskeleton, oligodendrocyte, energy metabolism and new potential markers in schizophrenia. *J Psychiatr Res*. 2009; 43:978–986. [PubMed: 19110265]
- Mataga N, Mizuguchi Y, Hensch TK. Experience-dependent pruning of dendritic spines in visual cortex by tissue plasminogen activator. *Neuron*. 2004; 44:1031–1041. [PubMed: 15603745]
- Mataga N, Nagai N, Hensch TK. Permissive proteolytic activity for visual cortical plasticity. *Proc Natl Acad Sci U S A*. 2002; 99:7717–7721. [PubMed: 12032349]
- Mauney SA, Athanas KM, Pantazopoulos H, Shaskan N, Passeri E, Berretta S, Woo TU. Developmental pattern of perineuronal nets in the human prefrontal cortex and their deficit in schizophrenia. *Biol Psychiatry*. 2013; 74:427–435. [PubMed: 23790226]
- Mayer J, Hamel MG, Gottschall PE. Evidence for proteolytic cleavage of brevican by the ADAMTSs in the dentate gyrus after excitotoxic lesion of the mouse entorhinal cortex. *BMC Neurosci*. 2005; 6:52. [PubMed: 16122387]
- McGlashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry*. 2000; 57:637–648. [PubMed: 10891034]
- McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med*. 2004; 2:13. [PubMed: 15115547]
- McGrath JJ, Susser ES. New directions in the epidemiology of schizophrenia. *Med J Aust*. 2009; 190:S7–9. [PubMed: 19220176]
- McRae PA, Porter BE. The perineuronal net component of the extracellular matrix in plasticity and epilepsy. *Neurochem Int*. 2012; 61:963–972. [PubMed: 22954428]
- McRae PA, Rocco MM, Kelly G, Brumberg JC, Matthews RT. Sensory deprivation alters aggrecan and perineuronal net expression in the mouse barrel cortex. *J Neurosci*. 2007; 27:5405–5413. [PubMed: 17507562]
- Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophr Bull*. 2009; 35:959–972. [PubMed: 18408229]
- Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron*. 2011; 70:687–702. [PubMed: 21609825]
- Miyata S, Komatsu Y, Yoshimura Y, Taya C, Kitagawa H. Persistent cortical plasticity by upregulation of chondroitin 6-sulfation. *Nat Neurosci*. 2012; 15:414–422. S411–412. [PubMed: 22246436]
- Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. *Psychiatry Clin Neurosci*. 2009; 63:257–265. [PubMed: 19579286]

- Morawski M, Alpar A, Bruckner G, Fiedler A, Jager C, Gati G, Stieler JT, Arendt T. Chondroitin sulfate proteoglycan-based extracellular matrix in chicken (*Gallus domesticus*) brain. *Brain Res.* 2009; 1275:10–23. [PubMed: 19269276]
- Morawski M, Bruckner G, Jager C, Seeger G, Arendt T. Neurons associated with aggrecan-based perineuronal nets are protected against tau pathology in subcortical regions in Alzheimer's disease. *Neuroscience.* 2010; 169:1347–1363. [PubMed: 20497908]
- Morawski M, Bruckner G, Jager C, Seeger G, Matthews RT, Arendt T. Involvement of perineuronal and perisynaptic extracellular matrix in Alzheimer's disease neuropathology. *Brain Pathol.* 2012; 22:547–561. [PubMed: 22126211]
- Morawski M, Bruckner MK, Riederer P, Bruckner G, Arendt T. Perineuronal nets potentially protect against oxidative stress. *Exp Neurol.* 2004; 188:309–315. [PubMed: 15246831]
- Morris NP, Henderson Z. Perineuronal nets ensheath fast spiking, parvalbumin-immunoreactive neurons in the medial septum/diagonal band complex. *Eur J Neurosci.* 2000; 12:828–838. [PubMed: 10762312]
- Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. *J Neurosci Methods.* 1984; 11:47–60. [PubMed: 6471907]
- Muhleisen TW, Mattheisen M, Strohmaier J, Degenhardt F, Priebe L, Schultz CC, Breuer R, Meier S, Hoffmann P, Rivandeneira F, Hofman A, Uitterlinden AG, Moebus S, Gieger C, Emeny R, Ladwig KH, Wichmann HE, Schwarz M, Kammerer-Ciernioch J, Schlosser RG, Nenadic I, Sauer H, Mossner R, Maier W, Rujescu D, Lange C, Ophoff RA, Schulze TG, Rietschel M, Nothen MM, Cichon S. Association between schizophrenia and common variation in neurocan (NCAN), a genetic risk factor for bipolar disorder. *Schizophr Res.* 2012; 138:69–73. [PubMed: 22497794]
- Muir EM, Adcock KH, Morgenstern DA, Clayton R, von Stillfried N, Rhodes K, Ellis C, Fawcett JW, Rogers JH. Matrix metalloproteases and their inhibitors are produced by overlapping populations of activated astrocytes. *Brain Res Mol Brain Res.* 2002; 100:103–117. [PubMed: 12008026]
- Murai KK, Misner D, Ranscht B. Contactin supports synaptic plasticity associated with hippocampal long-term depression but not potentiation. *Curr Biol.* 2002; 12:181–190. [PubMed: 11839269]
- Murakami T, Ohtsuka A, Taguchi T. Neurons with intensely negatively charged extracellular matrix in the human visual cortex. *Archives of histology and cytology.* 1994; 57:509–522. [PubMed: 7734178]
- Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *Br Med J (Clin Res Ed).* 1987; 295:681–682.
- Nabel EM, Morishita H. Regulating critical period plasticity: insight from the visual system to fear circuitry for therapeutic interventions. *Frontiers in psychiatry.* 2013; 4:146. [PubMed: 24273519]
- Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflammation.* 2013; 10:43. [PubMed: 23547920]
- Nakagawa F, Schulte BA, Spicer SS. Selective cytochemical demonstration of glycoconjugate-containing terminal N-acetylgalactosamine on some brain neurons. *J Comp Neurol.* 1986; 243:280–290. [PubMed: 3944281]
- Nakamura M, Nakano K, Morita S, Nakashima T, Oohira A, Miyata S. Expression of chondroitin sulfate proteoglycans in barrel field of mouse and rat somatosensory cortex. *Brain Res.* 2009; 1252:117–129. [PubMed: 19056358]
- Narayan S, Nakajima K, Sawa A. DISC1: A Key Lead in Studying Cortical Development and Associated Brain Disorders. *Neuroscientist.* 2013; 19:451–464. [PubMed: 23300216]
- Nicodemus KK, Marengo S, Batten AJ, Vakkalanka R, Egan MF, Straub RE, Weinberger DR. Serious obstetric complications interact with hypoxia-regulated/vascular-expression genes to influence schizophrenia risk. *Mol Psychiatry.* 2008; 13:873–877. [PubMed: 18195713]
- Novak U, Kaye AH. Extracellular matrix and the brain: components and function. *J Clin Neurosci.* 2000; 7:280–290. [PubMed: 10938601]
- Nowicka D, Soulsby S, Skangiel-Kramska J, Glazewski S. Parvalbumin-containing neurons, perineuronal nets and experience-dependent plasticity in murine barrel cortex. *Eur J Neurosci.* 2009; 30:2053–2063. [PubMed: 20128844]

- Nyffeler M, Meyer U, Yee BK, Feldon J, Knuesel I. Maternal immune activation during pregnancy increases limbic GABAA receptor immunoreactivity in the adult offspring: implications for schizophrenia. *Neuroscience*. 2006; 143:51–62. [PubMed: 17045750]
- Ohi K, Hashimoto R, Yamamori H, Yasuda Y, Fujimoto M, Umeda-Yano S, Fukunaga M, Watanabe Y, Iwase M, Kazui H, Takeda M. The impact of the genome-wide supported variant in the cyclin M2 gene on gray matter morphology in schizophrenia. *Behavioral and brain functions: BBF*. 2013; 9:40. [PubMed: 24160291]
- Ojima H, Kuroda M, Ohyama J, Kishi K. Two classes of cortical neurones labelled with Vicia villosa lectin in the guinea-pig. *Neuroreport*. 1995; 6:617–620. [PubMed: 7605912]
- Omori Y, Mori C, White AH. Self-Stigma in Schizophrenia: A Concept Analysis. *Nurs Forum*. 2014 Epub ahead of print.
- Pantazopoulos H, Boyer-Boiteau A, Holbrook EH, Jang W, Hahn CG, Arnold SE, Berretta S. Proteoglycan abnormalities in olfactory epithelium tissue from subjects diagnosed with schizophrenia. *Schizophr Res*. 2013; 150:366–372. [PubMed: 24035561]
- Pantazopoulos H, Murray EA, Berretta S. Total number, distribution, and phenotype of cells expressing chondroitin sulfate proteoglycans in the normal human amygdala. *Brain Res*. 2008; 1207:84–95. [PubMed: 18374308]
- Pantazopoulos H, Woo TUW, Lim MP, Lange N, Berretta S. Extracellular matrix-glia abnormalities in the amygdala and entorhinal cortex of subjects diagnosed with schizophrenia. *Arch Gen Psychiatry*. 2010; 67:155–166. [PubMed: 20124115]
- Pare D, Duvarci S. Amygdala microcircuits mediating fear expression and extinction. *Curr Opin Neurobiol*. 2012; 22:717–23. [PubMed: 22424846]
- Perala J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsa E, Pirkola S, Partonen T, Tuulio-Henriksson A, Hintikka J, Kieseppa T, Harkanen T, Koskinen S, Lonnqvist J. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry*. 2007; 64:19–28. [PubMed: 17199051]
- Perney TM, Marshall J, Martin KA, Hockfield S, Kaczmarek LK. Expression of the mRNAs for the Kv3.1 potassium channel gene in the adult and developing rat brain. *J Neurophysiol*. 1992; 68:756–766. [PubMed: 1432046]
- Perry W, Feifel D, Minassian A, Bhattacharjie I, Braff DL. Information processing deficits in acutely psychotic schizophrenia patients medicated and unmedicated at the time of admission. *Am J Psychiatry*. 2002; 159:1375–1381. [PubMed: 12153831]
- Phelan JC, Bromet EJ, Link BG. Psychiatric illness and family stigma. *Schizophr Bull*. 1998; 24:115–126. [PubMed: 9502550]
- Pietersen CY, Mauney SA, Kim SS, Lim MP, Rooney RJ, Goldstein JM, Petryshen TL, Seidman LJ, Shenton ME, McCarley RW, Sonntag KC, Woo TUW. Molecular profiles of parvalbumin-immunoreactive neurons in the superior temporal cortex in schizophrenia. *Journal of neurogenetics*. 2014a In press.
- Pietersen CY, Mauney SA, Kim SS, Lim MP, Rooney RJ, Goldstein JM, Petryshen TL, Seidman LJ, Shenton ME, McCarley RW, Sonntag KC, Woo TUW. Molecular profiles of pyramidal neurons in the superior temporal cortex in schizophrenia. *Journal of neurogenetics*. 2014b In press.
- Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L. Reactivation of ocular dominance plasticity in the adult visual cortex. *Science*. 2002; 298:1248–1251. [PubMed: 12424383]
- Pizzorusso T, Medini P, Landi S, Baldini S, Berardi N, Maffei L. Structural and functional recovery from early monocular deprivation in adult rats. *Proc Natl Acad Sci U S A*. 2006; 103:8517–22. [PubMed: 16709670]
- Poliak S, Peles E. The local differentiation of myelinated axons at nodes of Ranvier. *Nat Rev Neurosci*. 2003; 4:968–980. [PubMed: 14682359]
- Radewicz K, Garey LJ, Gentleman SM, Reynolds R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. *J Neuropathol Exp Neurol*. 2000; 59:137–150. [PubMed: 10749103]
- Rauch U. Extracellular matrix components associated with remodeling processes in brain. *Cellular and molecular life sciences: CMLS*. 2004; 61:2031–2045. [PubMed: 15316653]

- Richetto J, Calabrese F, Meyer U, Riva MA. Prenatal versus postnatal maternal factors in the development of infection-induced working memory impairments in mice. *Brain Behav Immun*. 2013
- Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kähler AK, Akterin S, Bergen SE, Collins AL, Crowley JJ, Fromer M, Kim Y, Lee SH, Magnusson PK, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet*. 2013; 45:1150–9. [PubMed: 23974872]
- Rissling AJ, Braff DL, Swerdlow NR, Helleman G, Rassovsky Y, Sprock J, Pela M, Light GA. Disentangling early sensory information processing deficits in schizophrenia. *Clin Neurophysiol*. 2012; 123:1942–1949. [PubMed: 22608970]
- Roberts RA, Smith RA, Safe S, Szabo C, Tjalkens RB, Robertson FM. Toxicological and pathophysiological roles of reactive oxygen and nitrogen species. *Toxicology*. 2010; 276:85–94. [PubMed: 20643181]
- Roberts RA, Laskin DL, Smith CV, Robertson FM, Allen EM, Doorn JA, Slikker W. Nitrate and oxidative stress in toxicology and disease. *Toxicol Sci*. 2009; 112:4–16. [PubMed: 19656995]
- Romberg C, Yang S, Melani R, Andrews MR, Horner AE, Spillantini MG, Bussey TJ, Fawcett JW, Pizzorusso T, Saksida LM. Depletion of perineuronal nets enhances recognition memory and long-term depression in the perirhinal cortex. *J Neurosci*. 2013; 33:7057–7065. [PubMed: 23595763]
- Roussos P, Katsel P, Davis KL, Bitsios P, Giakoumaki SG, Jogia J, Rozsnyai K, Collier D, Frangou S, Siever LJ, Haroutunian V. Molecular and genetic evidence for abnormalities in the nodes of Ranvier in schizophrenia. *Arch Gen Psychiatry*. 2012; 69:7–15. [PubMed: 21893642]
- Ruoslahti E. Brain extracellular matrix. *Glycobiology*. 1996; 6:489–492. [PubMed: 8877368]
- Saghatelyan AK, Dityatev A, Schmidt S, Schuster T, Bartsch U, Schachner M. Reduced perisomatic inhibition, increased excitatory transmission, and impaired long-term potentiation in mice deficient for the extracellular matrix glycoprotein tenascin-R. *Mol Cell Neurosci*. 2001; 17:226–240. [PubMed: 11161481]
- Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005; 2:e141. [PubMed: 15916472]
- Schultz SH, North SW, Shields CG. Schizophrenia: a review. *Am Fam Physician*. 2007; 75:1821–1829. [PubMed: 17619525]
- Schuppel K, Brauer K, Hartig W, Grosche J, Earley B, Leonard BE, Bruckner G. Perineuronal nets of extracellular matrix around hippocampal interneurons resist destruction by activated microglia in trimethyltin-treated rats. *Brain Res*. 2002; 958:448–453. [PubMed: 12470883]
- Schwarzacher SW, Vuksic M, Haas CA, Burbach GJ, Sloviter RS, Deller T. Neuronal hyperactivity induces astrocytic expression of neurocan in the adult rat hippocampus. *Glia*. 2006; 53:704–714. [PubMed: 16498620]
- Schweizer M, Streit WJ, Muller CM. Postnatal development and localization of an N-acetylgalactosamine containing glycoconjugate associated with nonpyramidal neurons in cat visual cortex. *J Comp Neurol*. 1993; 329:313–327. [PubMed: 7681454]
- Seeger G, Brauer K, Hartig W, Bruckner G. Mapping of perineuronal nets in the rat brain stained by colloidal iron hydroxide histochemistry and lectin cytochemistry. *Neuroscience*. 1994; 58:371–388. [PubMed: 7512240]
- Seeger G, Luth HJ, Winkelmann E, Brauer K. Distribution patterns of Wisteria floribunda agglutinin binding sites and parvalbumin-immunoreactive neurons in the human visual cortex: a double-labelling study. *Journal für Hirnforschung*. 1996; 37:351–366. [PubMed: 8872558]
- Sekirnjak C, Martone ME, Weiser M, Deerinck T, Bueno E, Rudy B, Ellisman M. Subcellular localization of the K⁺ channel subunit Kv3.1b in selected rat CNS neurons. *Brain Res*. 1997; 766:173–187. [PubMed: 9359601]
- Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry*. 1999; 45:17–25. [PubMed: 9894571]
- Sample DM, McIntosh AM, Lawrie SM. Cannabis as a risk factor for psychosis: systematic review. *J Psychopharmacol*. 2005; 19:187–194. [PubMed: 15871146]
- Seshadri S, Zeledon M, Sawa A. Synapse-specific contributions in the cortical pathology of schizophrenia. *Neurobiol Dis*. 2013; 53:26–35. [PubMed: 23336981]

- Shah A, Lodge DJ. A loss of hippocampal perineuronal nets produces deficits in dopamine system function: relevance to the positive symptoms of schizophrenia. *Transl Psychiatry*. 2013; 3:e215. [PubMed: 23321812]
- Singer W. The formation of cooperative cell assemblies in the visual cortex. *J Exp Biol*. 1990; 153:177–97. [PubMed: 2280220]
- Snyder SH. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. *Am J Psychiatry*. 1976; 133:197–202. [PubMed: 1251927]
- So HC, Chen EY, Sham PC. Genetics of schizophrenia spectrum disorders: looking back and peering ahead. *Ann Acad Med Singapore*. 2009; 38:436–434. [PubMed: 19521646]
- Soleman S, Filippov M, Dityatev A, Fawcett J. Targeting the neural extracellular matrix in neurological disorders. *Neuroscience*. 2013
- Soleman S, Yip PK, Duricki DA, Moon LD. Delayed treatment with chondroitinase ABC promotes sensorimotor recovery and plasticity after stroke in aged rats. *Brain*. 2012; 135:1210–23. [PubMed: 22396394]
- Song H, Kempermann G, Overstreet Wadiche L, Zhao C, Schinder AF, Bischofberger J. New neurons in the adult mammalian brain: synaptogenesis and functional integration. *J Neurosci*. 2005; 25:10366–10368. [PubMed: 16280573]
- Spatazza J, Lee HH, Di Nardo AA, Tibaldi L, Joliot A, Hensch TK, Prochiantz A. Choroid-plexus-derived Otx2 homeoprotein constrains adult cortical plasticity. *Cell Rep*. 2013; 3:1815–23. [PubMed: 23770240]
- Spencer KM, Niznikiewicz MA, Shenton ME, McCarley RW. Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol Psychiatry*. 2008; 63:744–747. [PubMed: 18083143]
- Spencer KM, Niznikiewicz MA, Nestor PG, Shenton ME, McCarley RW. Left auditory cortex gamma synchronization and auditory hallucination symptoms in schizophrenia. *BMC Neurosci*. 2009; 10:85. [PubMed: 19619324]
- Spreafico R, De Biasi S, Vitellaro-Zuccarello L. The perineuronal net: a weapon for a challenge. *J Hist Neurosci*. 1999; 8:179–185. [PubMed: 11624299]
- Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull*. 2009; 35:509–527. [PubMed: 19155345]
- Stevens JR. Schizophrenia and multiple sclerosis. *Schizophr Bull*. 1988; 14:231–241. [PubMed: 3059470]
- Sugiyama S, Di Nardo AA, Aizawa S, Matsuo I, Volovitch M, Prochiantz A, Hensch TK. Experience-dependent transfer of Otx2 homeoprotein into the visual cortex activates postnatal plasticity. *Cell*. 2008; 134:508–20. [PubMed: 18692473]
- Sun Y, Farzan F, Barr MS, Kirihara K, Fitzgerald PB, Light GA, Daskalakis ZJ. gamma oscillations in schizophrenia: mechanisms and clinical significance. *Brain Res*. 2011; 1413:98–114. [PubMed: 21840506]
- Sur M, Frost DO, Hockfield S. Expression of a surface-associated antigen on Y-cells in the cat lateral geniculate nucleus is regulated by visual experience. *J Neurosci*. 1988; 8:874–882. [PubMed: 3346725]
- Sur M, Nagakura I, Chen N, Sugihara H. Mechanisms of plasticity in the developing and adult visual cortex. *Prog Brain Res*. 2013; 207:243–254. [PubMed: 24309257]
- Susuki K. Node of Ranvier disruption as a cause of neurological diseases. *ASN Neuro*. 2013; 5
- Suvisaari JM, Taxell-Lassas V, Pankakoski M, Haukka JK, Lonnqvist JK, Hakkinen LT. Obstetric complications as risk factors for schizophrenia spectrum psychoses in offspring of mothers with psychotic disorder. *Schizophr Bull*. 2013; 39:1056–1066. [PubMed: 23002182]
- Sweet RA, Henteleff RA, Zhang W, Sampson AR, Lewis DA. Reduced dendritic spine density in auditory cortex of subjects with schizophrenia. *Neuropsychopharmacology*. 2009; 34:374–389. [PubMed: 18463626]
- Sykova E. Glia and volume transmission during physiological and pathological states. *J Neural Transm*. 2005; 112:137–147. [PubMed: 15599612]
- Sykova E, Mazel T, Simonova Z. Diffusion constraints and neuron-glia interaction during aging. *Experimental gerontology*. 1998; 33:837–851. [PubMed: 9951627]

- Sykova E, Nicholson C. Diffusion in brain extracellular space. *Physiol Rev.* 2008; 88:1277–1340. [PubMed: 18923183]
- Takahashi N, Sakurai T, Bozdagi-Gunal O, Dorr NP, Moy J, Krug L, Gama-Sosa M, Elder GA, Koch RJ, Walker RH, Hof PR, Davis KL, Buxbaum JD. Increased expression of receptor phosphotyrosine phosphatase-beta/zeta is associated with molecular, cellular, behavioral and cognitive schizophrenia phenotypes. *Transl Psychiatry.* 2011a; 1:e8. [PubMed: 22832403]
- Takahashi N, Sakurai T, Davis KL, Buxbaum JD. Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. *Prog Neurobiol.* 2011b; 93:13–24. [PubMed: 20950668]
- Takesian AE, Hensch TK. Balancing plasticity/stability across brain development. *Prog Brain Res.* 2013; 207:3–34. [PubMed: 24309249]
- Tews B, Schonig K, Arzt ME, Clementi S, Rioult-Pedotti MS, Zemmar A, et al. Synthetic microRNA-mediated downregulation of Nogo-A in transgenic rats reveals its role as regulator of synaptic plasticity and cognitive function. *Proc Natl Acad Sci U S A.* 2013; 110:6583–8. [PubMed: 23576723]
- Uhlhaas PJ. Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia. *Curr Opin Neurobiol.* 2013; 23:283–290. [PubMed: 23228430]
- Uhlhaas PJ, Roux F, Singer W, Haenschel C, Sireteanu R, Rodriguez E. The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. *Proc Natl Acad Sci U S A.* 2009; 106:9866–9871. [PubMed: 19478071]
- Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci.* 2010; 11:100–113. [PubMed: 20087360]
- Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron.* 2006; 52:155–68. [PubMed: 17015233]
- Uhlhaas PJ, Haenschel C, Nikoli D, Singer W. The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. *Schizophr Bull.* 2008; 34:927–43. [PubMed: 18562344]
- Vo T, Carulli D, Ehlert EM, Kwok JC, Dick G, Mecollari V, Moloney EB, Neufeld G, de Winter F, Fawcett JW, Verhaagen J. The chemorepulsive axon guidance protein semaphorin3A is a constituent of perineuronal nets in the adult rodent brain. *Mol Cell Neurosci.* 2013; 56:186–200. [PubMed: 23665579]
- Volk DW, Lewis DA. Impaired prefrontal inhibition in schizophrenia: relevance for cognitive dysfunction. *Physiol Behav.* 2002; 77:501–505. [PubMed: 12526990]
- Volk DW, Lewis DA. Prenatal ontogeny as a susceptibility period for cortical GABA neuron disturbances in schizophrenia. *Neuroscience.* 2013; 248C:154–164. [PubMed: 23769891]
- Vuillermot S, Weber L, Feldon J, Meyer U. A longitudinal examination of the neurodevelopmental impact of prenatal immune activation in mice reveals primary defects in dopaminergic development relevant to schizophrenia. *J Neurosci.* 2010; 30:1270–1287. [PubMed: 20107055]
- Wagoner JL, Kulesza RJ Jr. Topographical and cellular distribution of perineuronal nets in the human cochlear nucleus. *Hear Res.* 2009; 254:42–53. [PubMed: 19383535]
- Wang D, Fawcett J. The perineuronal net and the control of CNS plasticity. *Cell Tissue Res.* 2012; 349:147–160. [PubMed: 22437874]
- Wang X, Yi J, Lei J, Pei D. Expression, purification and characterization of recombinant mouse MT5-MMP protein products. *FEBS Lett.* 1999; 462:261–266. [PubMed: 10622708]
- Wegner F, Hartig W, Bringmann A, Grosche J, Wohlfarth K, Zuschratter W, Bruckner G. Diffuse perineuronal nets and modified pyramidal cells immunoreactive for glutamate and the GABA(A) receptor alpha1 subunit form a unique entity in rat cerebral cortex. *Exp Neurol.* 2003; 184:705–714. [PubMed: 14769362]
- Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry.* 1987; 44:660–669. [PubMed: 3606332]
- Weiser M, Bueno E, Sekirnjak C, Martone ME, Baker H, Hillman D, Chen S, Thornhill W, Ellisman M, Rudy B. The potassium channel subunit KV3.1b is localized to somatic and axonal membranes of specific populations of CNS neurons. *J Neurosci.* 1995; 15:4298–4314. [PubMed: 7790912]

- Whalley HC, Papmeyer M, Sprooten E, Lawrie SM, Sussmann JE, McIntosh AM. Review of functional magnetic resonance imaging studies comparing bipolar disorder and schizophrenia. *Bipolar Disord.* 2012; 14:411–431. [PubMed: 22631622]
- Wiesel TN, Hubel DH. Single-Cell Responses in Striate Cortex of Kittens Deprived of Vision in One Eye. *J Neurophysiol.* 1963; 26:1003–1017. [PubMed: 14084161]
- Wild JM. Functional neuroanatomy of the sensorimotor control of singing. *Ann N Y Acad Sci.* 2004; 1016:438–462. [PubMed: 15313789]
- Wilkins A, Majed H, Layfield R, Compston A, Chandran S. Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J Neurosci.* 2003; 23:4967–4974. [PubMed: 12832519]
- Willi R, Schwab ME. Nogo and Nogo receptor: relevance to schizophrenia? *Neurobiol Dis.* 2013; 54:150–157. [PubMed: 23369871]
- Willi R, Weinmann O, Winter C, Klein J, Sohr R, Schnell L, et al. Constitutive genetic deletion of the growth regulator Nogo-A induces schizophrenia-related endophenotypes. *J Neurosci.* 2010; 30:556–67. [PubMed: 20071518]
- Wintergerst ES, Vogt Weisenhorn DM, Rathjen FG, Riederer BM, Lambert S, Celio MR. Temporal and spatial appearance of the membrane cytoskeleton and perineuronal nets in the rat neocortex. *Neurosci Lett.* 1996; 209:173–176. [PubMed: 8736638]
- Woo TU, Spencer K, McCarley RW. Gamma oscillation deficits and the onset and early progression of schizophrenia. *Harv Rev Psychiatry.* 2010; 18:173–189. [PubMed: 20415633]
- Xu MQ, Sun WS, Liu BX, Feng GY, Yu L, Yang L, He G, Sham P, Susser E, St Clair D, He L. Prenatal malnutrition and adult schizophrenia: further evidence from the 1959–1961 Chinese famine. *Schizophr Bull.* 2009; 35:568–576. [PubMed: 19155344]
- Yamaguchi Y. Lecticans: organizers of the brain extracellular matrix. *Cellular and molecular life sciences: CMLS.* 2000; 57:276–289. [PubMed: 10766023]
- Yanagi M, Joho RH, Southcott SA, Shukla AA, Ghose S, Tamminga CA. Kv3.1-containing K channels are reduced in untreated schizophrenia and normalized with antipsychotic drugs. *Mol Psychiatry.* 2013
- Yang Y, Dieter MZ, Chen Y, Shertzer HG, Nebert DW, Dalton TP. Initial characterization of the glutamate-cysteine ligase modifier subunit Gclm(–/–) knockout mouse. Novel model system for a severely compromised oxidative stress response. *J Biol Chem.* 2002; 277:49446–49452. [PubMed: 12384496]
- Yao JK, Reddy R. Oxidative stress in schizophrenia: pathogenetic and therapeutic implications. *Antioxid Redox Signal.* 2011; 15:1999–2002. [PubMed: 21194354]
- Yasuhara O, Akiyama H, McGeer EG, McGeer PL. Immunohistochemical localization of hyaluronic acid in rat and human brain. *Brain Res.* 1994; 635:269–282. [PubMed: 8173963]
- Ye Q, Miao QL. Experience-dependent development of perineuronal nets and chondroitin sulfate proteoglycan receptors in mouse visual cortex. *Matrix Biol.* 2013
- Yuan W, Matthews RT, Sandy JD, Gottschall PE. Association between protease-specific proteolytic cleavage of brevican and synaptic loss in the dentate gyrus of kainate-treated rats. *Neuroscience.* 2002; 114:1091–1101. [PubMed: 12379262]
- Zaremba S, Guimaraes A, Kalb RG, Hockfield S. Characterization of an activity-dependent, neuronal surface proteoglycan identified with monoclonal antibody Cat-301. *Neuron.* 1989; 2:1207–1219. [PubMed: 2624746]
- Zimmermann DR, Dours-Zimmermann MT. Extracellular matrix of the central nervous system: from neglect to challenge. *Histochem Cell Biol.* 2008; 130:635–653. [PubMed: 18696101]
- Zuo J, Ferguson TA, Hernandez YJ, Stetler-Stevenson WG, Muir D. Neuronal matrix metalloproteinase-2 degrades and inactivates a neurite-inhibiting chondroitin sulfate proteoglycan. *J Neurosci.* 1998; 18:5203–5211. [PubMed: 9651203]

Highlights

- Deficits in PNNs impair key brain maturational processes linked to schizophrenia
- Constituent elements of the PNN are dysregulated in patients with schizophrenia
- Poor structural integrity of PNNs may underlie the neural deficits in schizophrenia
- Restoring the integrity of PNNs may help rescue neurodevelopmental abnormalities

Figure 1.
Chemical structure of Hyaulronan

Figure 2.
Structures of the Lectican family of chondroitin sulfate proteoglycans

Figure 3.
Domain structure of Tenascin-C and -R: Two key components of the perineuronal net

Figure 4. Schematic of perineuronal net organization through interactions with hyaluronan, link protein, tenascins and chondroitin sulfate proteoglycans

Figure 5. Postnatal development of perineuronal nets in the human prefrontal cortex

A. Photomicrographs demonstrating the increase in perineuronal nets (PNNs) in the prefrontal cortex during postnatal development. **B.** Linear regression analysis indicates statistically significant effect of age on PNN density in the entire prefrontal cortex ($R^2=0.45$, $p=0.0017$) and in layer 3 ($R^2=0.49$, $p=0.0008$), suggesting that the density of PNNs in the prefrontal cortex undergoes a prolonged course of progressive increase during postnatal development through adolescence and early adulthood. However, the nonlinear hyperbolic regression models appear to be a better fit of the data ($R^2=0.71$ and 0.76 for the entire prefrontal cortex and layer 3, respectively); these models suggest that PNN density increases during postnatal development with the most pronounced changes occurring around the peri-pubertal period. These findings were derived from postmortem human brains from 19 healthy control subjects obtained from the National Institute of Child and Human Development Brain and Tissue Bank at the University of Maryland in Baltimore, MD. Reproduced with permission of Springer-Verlag, Heidelberg.

Figure 6. Densities of perineuronal nets in the prefrontal cortex in subjects with schizophrenia
A. Representative photomicrographs showing the distribution of perineuronal nets (PNNs) in the prefrontal cortex in a schizophrenia (right) and a normal control (left) subjects. Scale bar=100 μ m. **B.** Photomicrograph showing a WFA-labeled PNN. Scale bar=20 μ m. **C.** WFA-labeled PNNs are significantly decreased in layers 3 (70%) and 5 (76%) in subjects with schizophrenia (SZ; N=16). Bar graphs represent the mean and upper 95% confidence interval by cortical layer. Layer 1 is not shown because no PNNs were found in that layer. There are no significant differences in PNN densities between subjects with bipolar disorder (N=15) and normal control (N=16) subjects. p value, F ratio: *(0.016, 6.49); *(0.028, 5.36); *** (0.042, 4.51). These findings were derived from postmortem human brains obtained from the Harvard Brain Tissue Resource Center in Belmont, MA. Reproduced with permission of Springer-Verlag, Heidelberg.

Table 1

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

Gene title	Gene symbol	Direction of change
aggrecan	ACAN	Down
ADAM metalloproteinase with thrombospondin type 1 motif, 1	ADAMTS1	Up
ADAM metalloproteinase with thrombospondin type 1 motif, 6	ADAMTS6	Up
hyaluronan and proteoglycan link protein 1	HAPLN1	Down
leucine proline-enriched proteoglycan (leprecan) 1	LEPRE1	Down
lumican	LUM	Down
matrix metalloproteinase 16 (membrane-inserted)	MMP16	Down
matrix metalloproteinase 25	MMP25	Down
matrix metalloproteinase 24 (membrane-inserted)	MMP24	Up
sperm adhesion molecule 1 (PH-20 hyaluronidase, zona pellucida binding)	SPAM1	Up
sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 3	SPOCK3	Up
spodin 1, extracellular matrix protein	SPON1	Up
versican	VCAN	Down