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REVIEW

From molecules to behavior: Implications for perineuronal net remodeling in learning and memory

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Abstract

Perineuronal nets (PNNs) are condensed extracellular matrix (ECM) structures found throughout the central nervous system that regulate plasticity. They consist of a heterogeneous mix of ECM components that form lattice-like structures enwrapping the cell body and proximal dendrites of particular neurons. During development, accumulating research has shown that the closure of various critical periods of plasticity is strongly linked to experience-driven PNN formation and maturation. PNNs provide an interface for synaptic contacts within the holes of the structure, generally promoting synaptic stabilization and restricting the formation of new synaptic connections in the adult brain. In this way, they impact both synaptic structure and function, ultimately influencing higher cognitive processes. PNNs are highly plastic structures, changing their composition and distribution throughout life and in response to various experiences and memory disorders, thus serving as a substrate for experience- and disease-dependent cognitive function. In this review, we delve into the proposed mechanisms by which PNNs shape plasticity and memory function, highlighting the potential impact of their structural components, overall architecture, and dynamic remodeling on functional outcomes in health and disease.

KEYWORDS
cognition, extracellular matrix, memory, perineuronal nets, remodeling enzyme

1 | INTRODUCTION

While it is often forgotten, the space between neurons and glia is not empty but is composed of the extracellular matrix (ECM), accounting for an astonishing 20% of the brain's total volume (Nicholson et al., 2000). This heterogeneous network of proteins and complex sugars is present in several different forms, including the basement membrane that coats the cerebral vasculature, the interstitial matrix (often referred to as the "loose" ECM) that is diffusely distributed throughout the brain parenchyma, and

Abbreviations: AD, Alzheimer's disease; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; C4S, chondroitin-4-sulfate; C6S, chondroitin-6-sulfate; ChABC, chondroitinase ABC; CNS, central nervous system; CSF1R, colony-stimulating factor 1 receptor; CS-GAG, chondroitin sulfate chains; CSPG, chondroitin sulfate proteoglycan; ECM, extracellular matrix; GAG, glycosaminoglycan; GalNAc, N-acetylgalactosamine; GlcA, glucuronic acid; HA, hyaluronan; HAPLN, hyaluronan and proteoglycan binding link protein; HAS, hyaluronan synthase; HLS, hibernation-like state; HYase, hyaluronidase; IL33, interleukin-33; LTD, long-term depression; LTP, long-term potentiation; MMP, matrix metalloproteinase; Nptx2, neuronal pentraxin; NPY, neuropeptide Y; Otx2, orthodenticle homeobox 2; PNN, perineuronal net; PTPσ, protein tyrosine phosphatase; PV, parvalbumin; RPTPζ1, receptor protein tyrosine phosphatase ζ1; Sema3a, semaphorin 3a; SWR, sharp wave ripple; TnC, tenascin-C; TnR, tenascin-R; tPA, tissue-type plasminogen activator; VGAT, vesicular GABA transporter; VGLUT, vesicular glutamate transporter; WFA, *Wisteria floribunda agglutinin*.

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the specialized aggregated structures called perineuronal nets (PNNs) that surround some neurons (Fawcett et al., 2019; Sorg et al., 2016). These various forms of ECM support a wide range of processes, playing prominent roles in circuit formation during development as well as providing a substrate for experience-dependent plasticity throughout adulthood.

PNNs are condensed, lattice-like extracellular structures that cover the cell body, proximal dendrites, and axon initial segments of certain neuronal populations (Fawcett et al., 2019; Sorg et al., 2016). These protective PNN coatings embed and surround synapses (Fawcett et al., 2022; Sigal et al., 2019; Tewari et al., 2023), where they promote synaptic stabilization and limit brain plasticity (Fawcett et al., 2022; Sorg et al., 2016). They consist mainly of chondroitin sulfate proteoglycans (CSPGs) held together by various link proteins to a hyaluronan (HA) backbone, which is anchored to the membranes of the neurons they ensheath (Figure 1) (Fawcett et al., 2019; Sorg et al., 2016). While PNNs are dispersed throughout almost all parts of the mammalian central nervous system (CNS), they are notably abundant in brain areas that support cognitive function, such as the cerebral cortex, striatum, amygdala, hippocampus, and cerebellum (Carstens et al., 2016; Lupori et al., 2023; Morikawa et al., 2017). Within cortical regions, PNNs are almost exclusively found coating fast-spiking, GABAergic parvalbumin (PV)+inhibitory interneurons (Lupori et al., 2023); however, in certain subcortical regions, such as within the amygdala and hippocampal CA2 area, they can also be found coating excitatory pyramidal cells (Carstens et al., 2016; Morikawa et al., 2017).

Despite being popularized by Camillo Golgi over a 100 years ago, PNNs were dismissed by many neuroscientists at the time as mere staining artifacts, rather than real structures (Celio et al., 1998). However, there is a growing appreciation for PNNs as active participants in regulating brain plasticity, including synaptic structure and signaling, as well as shaping cognitive function. Modifications to the mesh-like structure of PNNs as well as the presence of many PNN-associated signaling molecules give rise to a unique and diverse PNN structure whose role goes beyond a mere scaffold. In this review, we will focus on the role of PNNs in synaptic plasticity and cognitive function, speculating on how their structural components, as well as the cellular and signaling processes that participate in PNN remodeling, ultimately impact their functional outcome.

2 | PNN COMPOSITION

Multiple ECM components assemble to form a diverse PNN structure that affects the overall function of the PNN. Although their basic composition is similar, all populations of PNNs are not identical (Deepa et al., 2006; Lupori et al., 2023). The quantities and precise makeup of PNN components vary from development to adulthood (Carulli et al., 2010), displaying heterogeneity within the specific neuronal subpopulations they surround (Dauth et al., 2016) and across different brain regions (Dauth et al., 2016; Lupori et al., 2023; Ueno et al., 2018, 2019). In order to understand how PNNs impact brain function, it is crucial to consider the role of each component within the structure and how their manipulation reveals their unique contribution to PNN formation and function. In its basic form, PNNs are made up of (1) a HA backbone tethered to the neuronal membrane, (2) CSPGs, (3) link proteins that stabilize the overall structure, and (4) tenascin glycoproteins that hold the CSPGs together (Figure 1). Of note, the most common PNN marker is the plant-based lectin *Wisteria floribunda agglutinin* (WFA), which binds to residues on the CSPG glycosaminoglycan (GAG) chains (Nadanaka et al., 2020). In this review, we will refer to PNNs as structures that are identified with WFA labeling unless otherwise noted.

2.1 | HA and PNN anchorage to the membrane

The backbone of PNNs is composed of extracellular linear chains of HA, which are negatively charged molecules consisting of N-acetylglucosamine and glucuronic acid (GlcA) that bind to CSPGs (Fawcett et al., 2019; Sorg et al., 2016). HA synthesis is mediated by three transmembrane enzymes called hyaluronan synthases (HAS)—HAS1, HAS2, and HAS3 (Weigel, 2015). These enzymes are responsible for producing HA at the neuronal membrane to be deposited into the extracellular space (Weigel, 2015). At least one of these enzymes is expressed in all PNN-positive neurons, although their expression is different depending on the developmental time window and brain region (Deepa et al., 2006; Galtrey et al., 2008). Enzymatic degradation of HA with hyaluronidase (HYase) has been shown to completely abolish the PNN structure both ex vivo (Sun et al., 2018) and in vivo (Deepa et al., 2006; Happel et al., 2014), demonstrating the necessity of this component to PNNs.

Although several receptors, including CD44, receptor for hyaluronan-mediated motility (RHAMM), and lymphatic vessel endothelial hyaluronan receptor-1 (LYVE1), have high affinity for HA (Toole, 2004), evidence suggests that these receptors are not required for HA anchorage into the neuronal membrane during PNN formation (Carulli et al., 2006). Instead, in addition to synthesizing and extruding HA into the extracellular space, HAS proteins themselves anchor HA to the membrane (Kwok et al., 2010). Another proposed anchoring protein is the transmembrane protein tyrosine phosphatase (PTPσ), a receptor for CSPGs. In vitro knockout of PTPσ has been shown to prevent CSPG-mediated inhibition of neuronal outgrowth, suggesting that PTPσ facilitates the actions of CSPGs (Shen et al., 2009). However, it remains unknown the extent to which PTPσ contributes to the overall integrity of the PNN structure.

2.2 | Chondroitin sulfate proteoglycans

The group of CSPGs includes the lectican family, of which aggrecan, brevican, versican, and neurocan are the most common in the CNS, as well as the receptor protein tyrosine phosphatase ζ1 (RPTPζ1)/phosphacan. These CSPGs play critical roles in the structure and function of PNNs. All lecticans have an N-terminal G1 globular

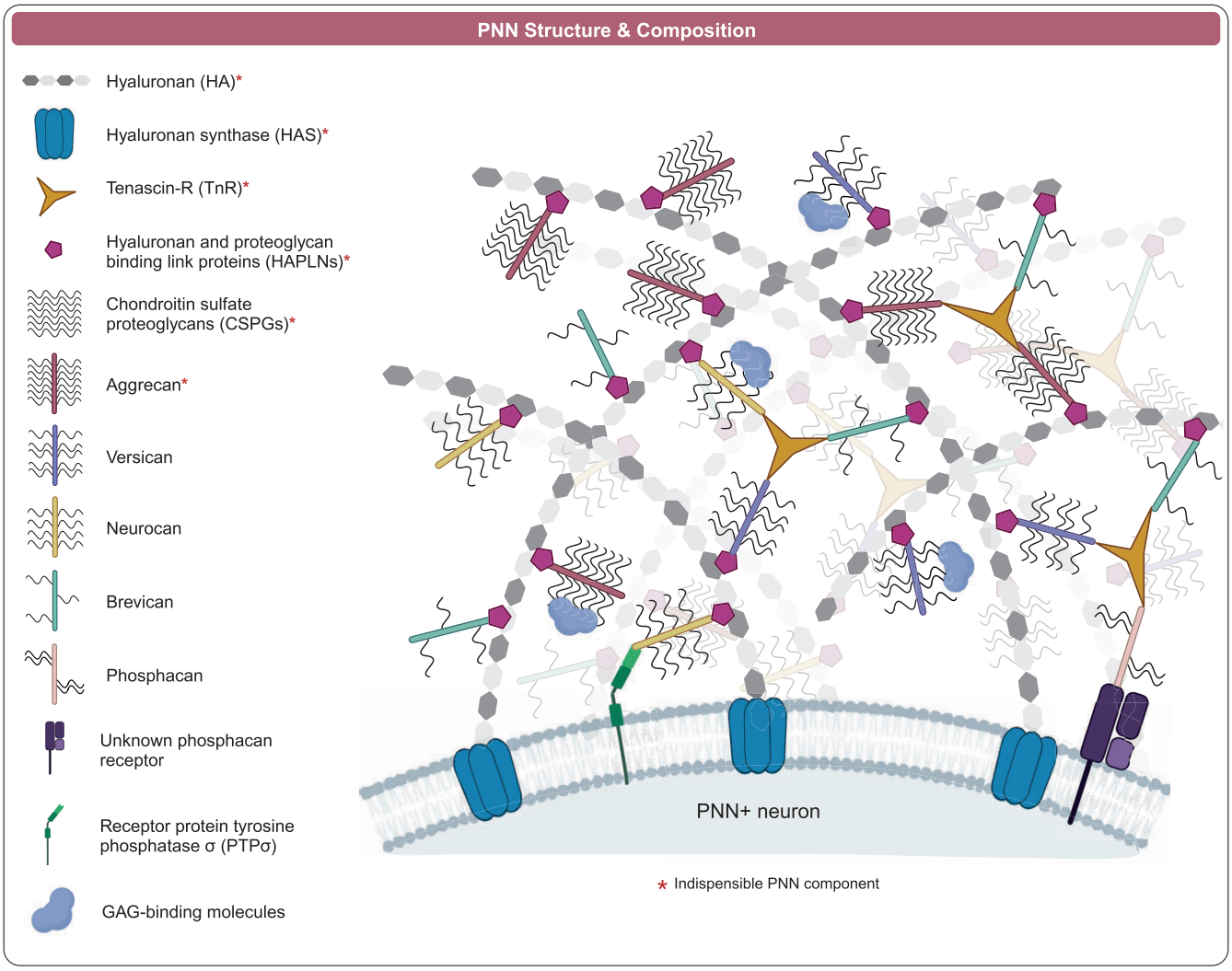

FIGURE 1 Overview of the structure and composition of perineuronal nets (PNNs). Many different extracellular matrix components organize together to form the mesh-like structure of PNNs. Hyaluronan (HA) serves as the backbone of the PNNs, and is tethered to the surface of the neuronal membrane via hyaluronan synthase (HAS). The chondroitin sulfate proteoglycans (CSPGs) (i.e., aggrecan, versican, neurocan, brevican, and phosphacan) attach to the HA backbone via the links proteins (HAPLNs), which are then joined together by the tenascin glycoproteins (TnR). Additional stabilization arises from binding of CSPGs with other membrane-bound receptors (e.g., protein tyrosine phosphatase and an unknown phosphacan receptor). CSPGs differ in their number of glycosaminoglycan (GAG) chains and bind molecules such as inhibitory molecules, cytokines, and growth factors. Many of these components are essential for the PNN to assemble, including aggrecan, TnR, HAPLN, and HAS, while the absence of other PNN components results in more nuanced structural PNN abnormalities. Figure was created using BioRender.com.

domain and a C-terminal G3 globular domain which bind to HA and tenascin glycoproteins, respectively (Fawcett et al., 2019; Lundell et al., 2004). The N- and C-terminal domains are highly conserved among the lectican family and thus utilize the same linking proteins for their crosslinking (Brissett & Perkins, 1998; Yamaguchi, 2000). However, the central domain length differs between lectican proteins (Yamaguchi, 2000) and is heavily post-translationally modified by the attachment of many complex GAG chains. Aggrecan, versican, neurocan, and brevican have approximately 120, 20, 7, and 3 GAG attachment sites, respectively (Yamaguchi, 2000). This leads to substantial diversity between the CSPGs, which has been identified within and between many brain regions (Dauth et al., 2016) and across development (Lipachev et al., 2019).

Manipulations of the specific lectican components of PNNs, both in vitro and in vivo, have helped us to understand their distinct roles in the PNN structure. Overall, aggrecan appears to be the most abundant CSPG within PNN populations (Dauth et al., 2016) and is also indispensable for the structure of PNNs. While genetic knockout of aggrecan is lethal at birth in mice, Giamanco et al. used organotypic cell culture from embryonic aggrecan knockout mouse brains to show that PNNs do not form with aggrecan deficiency (Giamanco et al., 2010). More recent studies have developed conditional knockout mice to target brain- and neuronal-specific aggrecan expression and found that loss of aggrecan ablates the PNN structure (Rowlands et al., 2018; Tewari et al., 2023), indicating that aggrecan is a limiting component for PNN formation. Mice lacking brevican or neurocan

by genetic knockout do not exhibit overall changes in the number of their PNNs (Brakebusch et al., 2002), suggesting that, unlike aggrecan, PNNs still form in their absence. At the ultrastructural level, the PNNs of brevican knockout mice appear to be more diffuse, which implies that PNN integrity is compromised (Brakebusch et al., 2002). Similarly, recent work from the auditory brainstem has shown that neurocan alters the fine structure of PNNs by regulating the quantity of various PNN molecules (Schmidt et al., 2020). Loss of versican isoform V2 does not cause PNN structural abnormalities or alterations in other PNN components in the cerebellum and brainstem (Dours-Zimmermann et al., 2009). In addition to the lecticans, work has shown that loss of CSPG RPTPζ1/phosphacan also causes PNN malformations. Mice and in vitro cultures lacking RPTPζ1 lose the typical PNN mesh-like integrity and instead express punctate and discontinuous signals of WFA and aggrecan (Eill et al., 2020). This may be because phosphacan—the soluble form of RPTPζ1—through its binding to TnR, stabilizes the PNN structure. Interestingly, phosphacan does not bind to HA but has been shown to anchor directly to the neuronal membrane (Eill et al., 2020), although the putative membrane receptor for this remains completely unknown. These findings overall highlight the importance of each of these CSPGs to the PNN structure.

The addition of GAG chains to the central domain of the lecticans adds substantial complexity to the structure of PNNs. These CSPGs exhibit varying glycosylation patterns, both between different CSPGs and within individual glycoforms (Miyata et al., 2018; Ueno et al., 2018). Knockout of one of the enzymes responsible for the elongation of GAG chains, N-acetylgalactosaminyltransferase-1/ChGn-1, has been shown to result in fewer and shorter GAG chains associated with PNNs in the cortex (Hou et al., 2017; Miyata et al., 2018). Studies using Cat-315 and Cat-316 antibodies, which target the initial and end fragments of the GAG chains, respectively, as well as WFA labeling, which binds along the length of the GAG chains (Nadanaka et al., 2020), have revealed spatial variations in aggrecan distribution based on specific glycosylation modifications. This includes some aggrecan+ PNN populations expressing some combination of the aforementioned markers as well as populations expressing none of these markers (Ueno et al., 2018). It is possible that aggrecan+ PNN populations that are negative for these various glycosylation markers may represent PNN populations that lack specific GAG chains and/or GAG chain residues. While this suggests region- and cell-type specific expression of distinct aggrecan glycoforms (Miyata et al., 2018; Ueno et al., 2018), it remains unknown how individual CSPG glycoforms contribute to the structural properties of PNNs through these different lengths and compositions of the GAG chains.

The majority of the GAG chains are chondroitin sulfate chains (CS-GAG), consisting of repeating disaccharide units of N-acetylgalactosamine and GlcA (GalNAc-GlcA) that are modified by sulfation. The GalNAc units are sulfated at the carbon 4 and 6 positions and can occur in the single or the di-sulfation pattern. In general, chondroitin-6-sulfate (C6S) is considered to be more supportive of neuroplasticity, while chondroitin-4-sulfate (C4S) is more restrictive (Yang et al., 2017). These patterns change dramatically across brain development and aging. At birth, 18% of the CS is C6S, while 60% is C4S. After development, the amount of C6S decreases to 2%, while the amount of C4S increases to 91% (Deepa et al., 2006; Kitagawa et al., 1997). Most of the remaining C6S is removed in the aged brain so that the major sulfation pattern is C4S (Fawcett et al., 2022; Foscarin et al., 2017). GAG chains are highly negatively charged molecules, and their sulfation pattern influences the overall negative charge of the PNN (Benito-Arenas et al., 2018), which then impacts their ability to buffer and maintain local physiological concentrations of cations (Burket et al., 2021; Härtig et al., 1999). PNN sulfation also affects the binding affinity of positively charged regulatory molecules such as inhibitory molecules (Dick et al., 2013; Nadanaka et al., 2020), inflammatory cytokines (Rogers et al., 2011), and growth factors (Deepa et al., 2002; Rogers et al., 2011). Indeed, over-expression of C6S prevents the binding of orthodenticle homeobox 2 (Otx2) and impairs PNN formation, resulting in a more diffuse PNN structure and persistent plasticity in the adult brain (Miyata et al., 2012). Although CS sulfation patterns are not well studied in the context of PNNs, certain motifs may promote a unique PNN environment by sequestering selective and varying amounts of ions and regulatory molecules, carrying significant implications for the overall biological function of PNNs.

2.3 | Link proteins

The stabilizing components of PNNs are the hyaluronan and proteoglycan binding link proteins (HALPNs), which bind the HA backbone to the CSPGs N-terminal domain. Among the three HAPLNs abundant in the CNS, only HAPLN1/Crtl1 and HAPLN4/Bral2 are localized within PNN structures. HAPLN1 binds to all CSPGs, while HAPLN4 binds selectively to brevican (Bekku et al., 2012; Nojima et al., 2021), suggesting micro-organization of different CSPGs by specific HAPLN proteins. Evidence suggests that link proteins orchestrate the formation of the PNN structure. Several key PNN components, such as HA and CSPGs, are expressed during embryonic and postnatal periods well before PNNs are formed (Carulli et al., 2010; Miyata & Kitagawa, 2016). Temporal and spatial distribution analyses of PNN components have shown that link proteins are expressed in PNN+ neurons around the same time of PNN development (Carulli et al., 2010). Work by Kwok et al. (2010) examined this premise with a non-neuronal cell model (human embryonic kidney 293T cells) that do not normally form PNN structures. While over-expression of HAS3 results in the formation of an aggrecan-trapping diffuse matrix, it does not form a condensed structure, whereas HAS3 and HAPLN1 over-expression is sufficient to form a PNN-like structure. Knockout of HAPLN1 significantly reduces PNN formation throughout the entire brain (Carulli et al., 2010). Yet, CSPG abundance and sulfation patterns do not change but remain in a diffuse form, further supporting the notion that link proteins play critical roles in organizing PNN components into a condensed structure. Similarly, the loss of HAPLN4 also leads to attenuated PNNs,

mainly in the brainstem and cerebellum (Bekku et al., 2012). Overall, HAPLN proteins are indispensable for PNN structure and their loss prevents PNN formation.

2.4 | Tenascins glycoproteins

Another vital joining element of PNNs is the tenascin glycoproteins that link the various lecticans' C-terminal domains to each other (Lundell et al., 2004). In the brain, there are two main forms of tenascin: tenascin-R (TnR) and tenascin-C (TnC), which oligomerize into either trimeric or hexameric structures, respectively. Since they have a unique multidomain structure, tenascins can interact with a variety of ECM molecules, making them critical regulators of the diverse organization and function of PNNs. In addition to their structural differences, tenascins also exhibit expression pattern variations throughout development. For instance, TnC is predominantly expressed early in brain development (Bartsch, 1996), while TnR expression increases throughout postnatal development, coinciding with the formation and condensation of PNNs around neurons in cortical and subcortical regions (Brückner et al., 2000). In vivo studies have demonstrated that genetic knockout of TnC does not affect the morphology of PNNs, although the intensity of PNNs is lower than wildtypes (Irintchev et al., 2005; Stamenković et al., 2017). On the other hand, TnR has been shown as an indispensable constituent of the typical PNN structure. Knockout of TnR disrupts the mesh-like structure of PNNs and causes the formation of punctate signals around neurons (Brückner et al., 2000; Haunsø et al., 2000). TnR affects the expression of other PNN components, such that TnR knockout diminishes the expression of brevican, neurocan, and HA (Brückner et al., 2000), while double knockout of TnR and PV diminishes the expression of neurocan and phosphacan (Haunsø et al., 2000). Additionally, TnR is thought to stabilize the PNN structure through aggrecan clustering, as exogenous addition of TnR protein or anti-aggrecan antibody (which mimics tenascin crosslinking of aggrecan) rescues PNN appearance in in vitro cultures that lack TnR (Morawski et al., 2014). Taken together, these findings suggest the crucial role of tenascins in PNN homeostasis with TnR being required for the formation of the mesh-like morphology of PNNs.

3 | PNNs AND PLASTICITY

Research has focused on the role of PNNs in regulating plasticity from development to adulthood, encompassing their formation, maturation, and contribution to the transition from developmental-like plasticity to an adult-like state (Figure 2). PNNs form close interactions with synapses, which together with the pre- and postsynaptic neuron and glia, are now acknowledged as essential components of the "tetrapartite" synapse (reviewed by Song & Dityatev, 2018). In general, PNNs provide a protective coating around neurons, limiting their neuroplasticity and stabilizing synaptic connections. However, PNNs also facilitate plasticity in some circumstances, such as during learning and memory formation. The holes interlaced in the PNN structure provide a substrate for synaptic contacts and promote both neuronal and nonneuronal interactions. PNNs influence synaptic structure and neuronal physiology by acting as a physical barrier, providing binding sites for various molecules, preventing the lateral mobility of receptors and exchange of desensitized receptors, and localizing ions (Figure 2).

3.1 | PNN formation from development to adulthood

The formation of PNNs and their binding of specific signaling molecules is influenced by sensory and experience-dependent neural activity. Through this interaction, PNNs effectively regulate plasticity during both development and adulthood. The formation of PNNs has a delayed developmental trajectory that is closely linked to the maturation of the nervous system. During rodent brain development, PNNs appear at different ages across different brain regions, and by and large, their assembly coincides with the closure of critical periods of plasticity, a developmental window characterized by the establishment and strengthening of neural circuits in an activity- and experience-dependent manner (Figure 2a). Following their initial granular-like appearance, PNNs gradually undergo a process of arborization and condensation that can take several weeks to complete, and they restrict plasticity once fully mature, thereafter marking the timepoint when plasticity is diminished or altogether absent.

The maturation of PNNs in response to neural activity is essential for neural development to reach completion. A pioneering study from the visual cortex of rats showed that at the beginning of the critical period, PNNs sparsely surround neurons and their density progressively increases until it reaches adult levels, marking the end of the critical period (Pizzorusso et al., 2002). Rearing rats in darkness from birth prevents the condensation of PNNs and prolongs the window of ocular dominance plasticity into adulthood. Acclimating visually-deprived adult rats to a normal light/dark cycle restores control-like levels of PNNs and terminates ocular dominance plasticity (Pizzorusso et al., 2002). Normally, ocular dominance cannot be shifted after monocular deprivation in adult rats, but a shift occurs towards the non-deprived eye upon PNN degradation with chondroitinase ABC (ChABC) (Pizzorusso et al., 2002), an enzyme that cleaves PNN components. This suggests that PNNs restrict visual critical periods. In support of this, knockout of several PNN components causes the persistence of juvenile-like visual plasticity into adulthood (Carulli et al., 2010; Rowlands et al., 2018). Several signaling molecules are sequestered in the mesh-like structure of PNNs, including Otx2, semaphorin 3a (Sema3a), and neuronal pentraxin 2 (Nptx2), which facilitate the maturation of PV interneurons and their accumulation of PNNs during visual critical period closure (Fawcett et al., 2022; Sorg et al., 2016). Outside of the visual system, sensory deprivation has also been shown to restrict PNN assembly and perturb normal PNN development in the rodent auditory (Myers et al., 2012) and somatosensory (McRae et al., 2007; Ueno et al.,

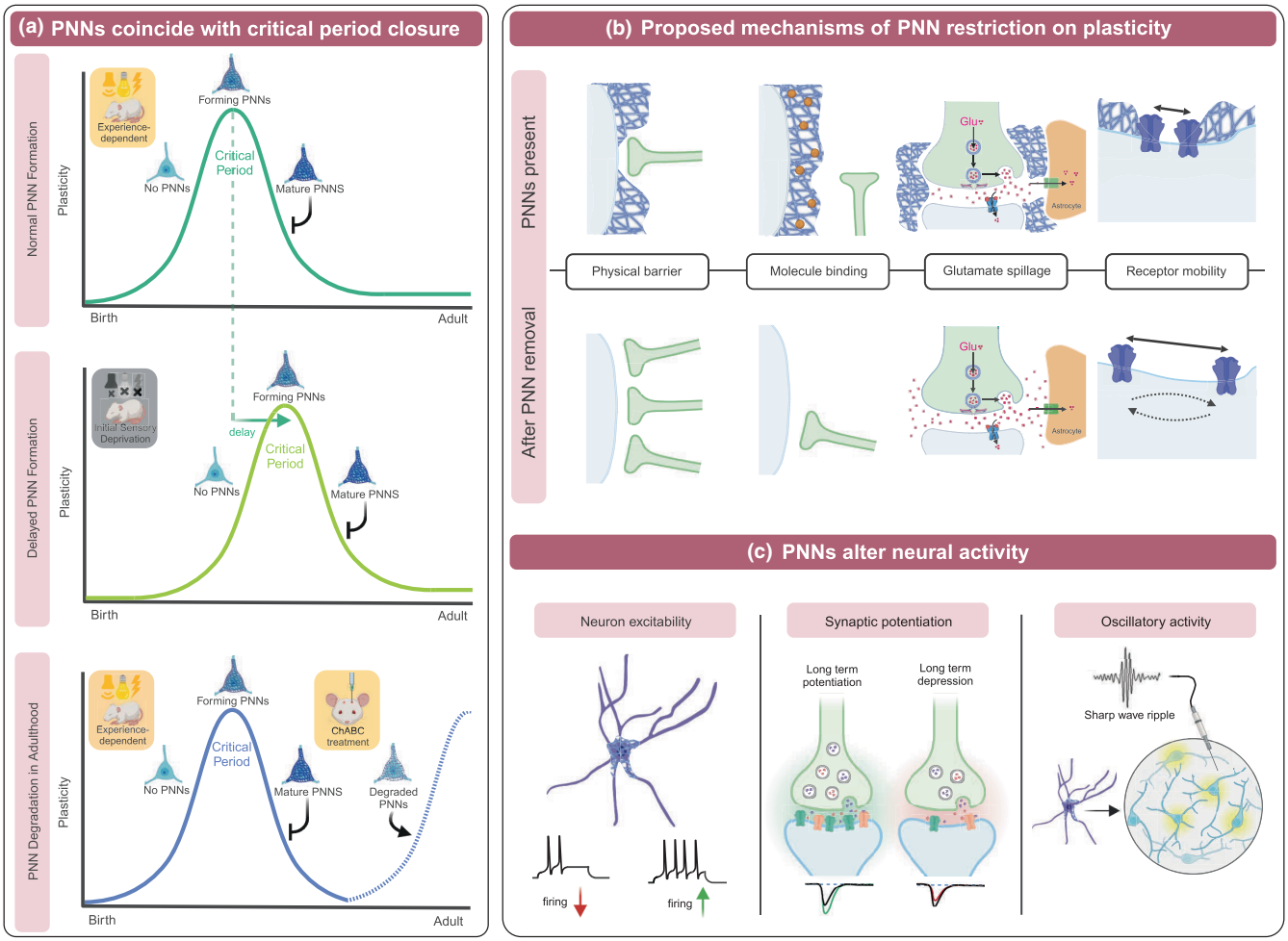

FIGURE 2 Influence of perineuronal nets (PNNs) on plasticity. (a) PNN formation and maturation marks the end of various critical periods of plasticity. Initially, higher plasticity levels are associated with little to no PNNs, whereas, in adulthood, reduced plasticity levels are linked to complete PNN maturation. A shift in normal PNN formation occurs when restricting neuronal activity through sensory deprivation early in development and depleting PNNs in adults reinstates juvenile-like levels of plasticity. (b) The proposed mechanisms governing PNN-mediated neuronal plasticity restriction include: creating a physical barrier to prevent incoming neuronal contacts while stabilizing existing neuronal contacts, providing binding sites for inhibitory molecules, growth factors, and cytokines that direct neuronal contacts, preventing glutamate spillage to precisely control neuronal firing, and limiting receptor mobility and preventing desensitized receptor exchange to tightly regulate neuronal firing. (c) Moreover, PNNs alter neuronal activity by modulating the intrinsic firing properties of neurons, facilitating synaptic potentiation, and influencing network-level oscillatory activity. The figure was created using BioRender.com.

2017) systems. This repository of studies has laid the groundwork of evidence that PNN formation and their binding of inhibitory molecules hinders experience-dependent plasticity during development.

While not as widely studied, there are also changes in PNN expression that coincide with the sensitive periods of different aspects of learning. In the zebra finch song nucleus HVC, a structure that integrates sensorimotor information, the number of PNN+ PV interneurons is linked to song maturity. PNN formation increases during the critical period of song learning, but rearing finches without a song tutor during this time decreases PV interneurons surrounded by PNNs (Balmer et al., 2009; Cornez et al., 2018). In adulthood, spatial and fear learning has been shown to influence the expression of PNNs and their components. While learning the location of the hidden platform in the Morris Water Maze test, adult mice have a transient reduction in the proportion of PV interneurons expressing brevican that then returns to baseline after completion of spatial training (Favuzzi et al., 2017). An increase in the number of PNN+ cells as well as mRNA levels of key proteoglycan components has been identified in the auditory cortex soon after fear conditioning, but not at later times (Banerjee et al., 2017). The transient changes in PNN expression induced by learning in adulthood may represent more plastic-like states, similar to those seen in development.

Consistent with the extensive sensory development literature, evidence suggests that PNNs form in response to neural activity. In hippocampal cultures, PNNs are observed to accumulate around active synapses; however, blocking neuronal spiking, neurotransmitter release, and important sources of calcium influx (i.e., GluR2-lacking AMPA receptors and L-type Ca2+ channels) all decrease PNN formation (Dityatev et al., 2007). In adulthood, recent in vivo studies have highlighted the effects of dynamic neuronal activity on PNN

formation and disassembly. Chemogenetic inhibition of PV interneurons or excitatory neurons decreases PNN intensity around inhibitory interneurons in the cortex, while chemogenetic activation does not affect PNN expression (Devienne et al., 2021). Conversely, chronic inhibition or excitation of hippocampal CA2 pyramidal cells with chemogenetics increases and decreases PNNs, respectively (Carstens et al., 2021). The inverse regulatory effect on PNNs in the CA2 compared to the cortex may reflect differences in the PNN-enwrapped neuronal cell type in these brain regions, i.e., excitatory pyramidal cells in the CA2 versus inhibitory interneurons in the cortex, although this has not been explored. The state of heightened neuronal activity induced by epileptic seizures also decreases PNNs in the cortex and hippocampus (Carstens et al., 2021; Tewari et al., 2018), although certain PNN components, including many CSPGs, appear to be upregulated post-seizure (reviewed by Chaunsali et al., 2021). These studies suggest that neurons are able to modulate PNN aggregation in an activity-dependent manner throughout life.

3.2 | PNNs and synapse formation and stability

The ECM surrounds all synapses, which are either embedded in the loose ECM or the condensed ECM of PNNs. On an ultrastructural level, the PNN coating is interrupted by holes that create space for synapses to form (Sigal et al., 2019). Neurons can come into contact with one another within the perforations, but these contacts are restricted within the solid framework of the PNNs. Excitatory and inhibitory synaptic markers have been identified in PNN holes surrounding PV interneurons (Sigal et al., 2019; Tewari et al., 2023) with approximately 90% of PNN holes holding synaptic inputs and 70% of these also carrying astrocytic processes (Tewari et al., 2023). On PV interneurons, spinogenesis is higher in dendritic segments with sparsely developed PNNs compared to dendritic segments with a higher abundance of PNNs (Foggetti et al., 2019). These studies collectively provide observational evidence for the structural interactions between PNNs and synapses.

The mesh-like structure of PNNs acts like a physical barrier that directs the neuronal contacts made. Indeed, evidence indicates that PNN manipulations alter synaptogenesis and synapse stability. In a cell-insert co-culture system of hippocampal neurons and cortical astrocytes, degradation of formed PNN-like structures using ChABC or HYase increases the number of structurally intact synapses as shown by the co-localization of key presynaptic and postsynaptic proteins (Pyka et al., 2011). The increased formation of synapses is also observed in co-cultures of neurons and astrocytes from mice devoid of various key PNN components (i.e., TnC, TnR, brevican, neurocan) (Geissler et al., 2013). Axon sprouting increases at sites of ChABC injection in intact and denervated regions of the spinal cord (Barritt et al., 2006; García-Alías et al., 2009) as well as in the cerebellum, but axon sprouting is reverted to its previous levels once PNNs reform (Corvetti & Rossi, 2005). Time-lapse imaging of dendritic spines has shown that ChABC treatment increases dendritic spine motility and spine head protrusion density in hippocampal slice cultures (Orlando et al., 2012) and in the visual cortex (De Vivo et al., 2013), although there is no change in overall spine density or length (De Vivo et al., 2013). This suggests that PNN removal allows for new synapse formation while destabilizing existing synaptic connections. In the hippocampus, treatment with ChABC increases the turnover of synapses and inhibitory synaptic puncta marked by gephyrin on PV dendrites (Donato et al., 2013). Conversely, ChABC treatment decreases inhibitory presynaptic vesicular GABA transporter (VGAT)+ puncta on PV interneurons in the entorhinal cortex (Christensen et al., 2021) without altering VGAT+ puncta in the somatosensory cortex (Tewari et al., 2023), findings which were also confirmed in mice lacking PNNs by aggrecan knockout (Tewari et al., 2023). Additionally, loss of PNNs results in no notable changes in excitatory vesicular glutamate transporter (VGLUT)1+ or VGLUT2+ puncta (Christensen et al., 2021; Tewari et al., 2023). These findings demonstrate PNN removal-associated changes in certain inhibitory synaptic connections while excitatory synapses remain unaffected. There is also further evidence that the PNN structure itself promotes rather than inhibits synaptic connections. Notably, newly formed axons from adult-born neurons in the mouse hippocampus are more likely to be located near PV interneurons with PNNs than those with little to no PNNs (Briones et al., 2021), suggesting that PNNs attract new connections. Taken together, these data suggest that PNNs go beyond just providing a physical barrier, but instead regulate synaptic connections by stabilizing existing synapses, while inhibiting or attracting new connections. This may, in part, be because of the mesh-like structure of the PNNs, which captures repulsive axon guidance molecules—such as Otx2, Sema3a, Nptx2 (Dick et al., 2013; Nadanaka et al., 2020)—as well as many growth factors (Deepa et al., 2002; Rogers et al., 2011) and inflammatory cytokines (Rogers et al., 2011), which may direct connections (Figure 2b).

3.3 | PNNs and neuronal and synapse function

While PNNs surround a subset of excitatory pyramidal cells (Carstens et al., 2016; Morikawa et al., 2017) throughout the brain, they primarily ensheath fast-spiking GABAergic inhibitory interneurons, the majority of which are PV interneurons (Lupori et al., 2023). The assembly of PNNs around these neurons causes functional changes, impacting their electrophysiological properties, and consequently influencing neuronal communication between neurons as well as synchronized neuronal activity (Figure 2c).

PNNs have been shown to specifically alter the electrophysiological properties of PV interneurons (Christensen et al., 2021; Dityatev et al., 2007; Hayani et al., 2018), with minimal observable impact on most excitatory neurons (Dityatev et al., 2007; Khoo et al., 2019; Lensjø et al., 2017). In general, studies have shown that PNNs limit the excitability of PV interneurons. The firing threshold of PV interneurons is consistently reduced upon brevican loss in hippocampal slices (Favuzzi et al., 2017) and in ChABC-treated hippocampal cultures (Dityatev et al., 2007) and slices (Hayani et al., 2018), effects that were absent when ChABC was administered for a shorter period (Hayani et al., 2018). Alternative data suggests that PNN

elimination actually reduces PV interneuron excitability. In ChABC-treated cortical slices, a decrease in cell excitability is evidenced by a delay in cell firing and reduced firing frequency (Balmer, 2016). Consistent with this work, other studies have found a reduction in spiking activity of PV interneurons (Christensen et al., 2021; Lensjø et al., 2017) along with either a decrease (Christensen et al., 2021) or increase in spiking variability often seen during critical periods (Lensjø et al., 2017).

One of the unique abilities of PV interneurons is their ability to fire at high frequencies, which allows them to rapidly control network-level activity. PNNs may regulate these fast-spiking abilities of PV interneurons by governing factors such as cell membrane capacitance, membrane protein expression, and extrasynaptic ion and neurotransmitter homeostasis (Figure 2b). PNN removal caused by tumor-released matrix-degrading enzymes results in an increase in cell membrane capacitance and subsequent decrease in cell firing (Tewari et al., 2018). This effect of capacitance on firing frequency was confirmed in ChABC-treated somatosensory cortical slices (Tewari et al., 2018) and further assessed in computational neuron models (Hanssen et al., 2023), unveiling a novel insulating function of PNNs similar to myelin sheaths. PNNs have also been shown to prevent the lateral mobility of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and exchange of desensitized receptors at the synapse (Frischknecht et al., 2009). Altered AMPA receptor expression and decreased potassium channel clustering in mice deficient for brevican affects excitatory synapses on PV interneurons and contributes to impaired spike frequency (Favuzzi et al., 2017). Regulating the composition and mobility of specific membrane proteins thus allows brevican to influence the intrinsic properties of PV interneurons (Favuzzi et al., 2017). PNNs also act as local buffers to ensure stable extracellular cation levels near the synapse (Härtig et al., 1999) and bind metal cations to maintain nontoxic concentrations (Burket et al., 2021). In this way, they can fulfill critical functions by impeding the diffusion of diverse ions while also sustaining an extracellular reservoir of these molecules. Recent findings demonstrate that PNN loss leads to glutamate spillage into the extrasynaptic space and impairs astrocytic uptake (Tewari et al., 2023). This implies that PNNs help keep released neurotransmitters in place to be cleared by astrocytes and this cooperative activity may enable fast-spiking PV interneurons to manage ion and neurotransmitter fluctuations during rapid firing.

In addition to intrinsic electrophysiological properties of PV interneurons, some evidence suggests PNNs alter the persistence and strength of synaptic communications. Synaptic plasticity events include forms of long-term potentiation (LTP) and long-term depression (LTD), which are thought to help transform fleeting experiences into lasting memories. Studies have shown that enzymatic PNN degradation (Kochlamazashvili et al., 2010; Shi et al., 2019) or removal of specific structural components, including neurocan, brevican, and TnR (Brakebusch et al., 2002; Saghatelyan et al., 2001; Zhou et al., 2001), causes LTP deficits. On the other hand, ChABC-mediated or genetic attenuation of PNNs has been shown to enhance LTD (Khoo et al., 2019; Romberg et al., 2013). PNN removal increases synaptic potentiation in typically resistant excitatory synapses in the CA2 region of the hippocampus (Carstens et al., 2016), indicating that PNNs restrict synaptic plasticity. The emergence of these LTP induction-resistant excitatory synapses corresponds to the formation of PNNs in the CA2 (Carstens et al., 2021). In Mecp2-null mice, a neurodevelopmental model of Rhett syndrome, accelerated PNN maturation has been observed and coincides with early restricted synaptic potentiation, which is reversed with ChABC treatment (Carstens et al., 2021). Inhibitory LTD emerges in the CA2 upon maturation of PNNs and ErbB4 signaling, but degrading PNNs impairs LTD (Domínguez et al., 2019).

On a population level, PNNs have been shown to participate in the generation of rhythmic events that affect memory consolidation and retrieval, such as gamma, theta, and sharp wave ripple (SWR) oscillations (Bocchio et al., 2017; Buzsáki, 2015). Enzymatic digestion of PNNs increases gamma band power (Steullet et al., 2014) and increases theta and gamma power during spontaneous activity (Lensjø et al., 2017). In ChABC-treated anesthetized animals, tail-pinch stimulation induces a decrease in gamma activity that is accompanied by an increase in theta activity (Carceller et al., 2020). A shift in theta peak frequency has also been observed in TnR knockout and ChABC-treated rodents (Christensen et al., 2021; Gurevicius et al., 2004). Another study found that theta power is increased following fear conditioning but PNN removal impairs both theta oscillations and fear memory consolidation (Shi et al., 2019). Degrading PNNs leads to a decrease in the phase alignment between theta oscillations after fear conditioning as well as impairments in memory recall (Thompson et al., 2018). Pretreating mouse hippocampal slices with HYase or ChABC increases SWR events (Sun et al., 2018), showing the important role PNNs play in ex vivo spontaneous ripple events. However, an in vivo study in TnR knockout mice did not find a significant change in the number of SWR events during behavioral states of immobility where these ripple oscillations occur frequently (Gurevicius et al., 2004). Given the importance of these oscillations in regulating memory function, it is possible that PNNs influence cognition areas via their influence on oscillatory activity. PNNs allow for precise firing of PV interneurons which, when dysregulated, may result in an excitatory/inhibitory imbalance, causing noisy synchronized firing activity and ultimately cognitive dysfunction.

4 | PNNs IN LEARNING AND MEMORY

Synaptic connections and their activity are fundamental to the formation and consolidation of memories. The intimate relationship of PNNs with synaptic structure and neuronal function highlights their significant role in cognitive function. Numerous studies have provided compelling support that PNNs shape learning and memory processes in health and disease. This section will discuss evidence suggesting that PNNs are indeed important for normal cognitive functioning and are modulated by specific experiences. Subsequently, their disruption contributes to the development and manifestation of various memory disorders.

TABLE 1 Influence of perineuronal net (PNN) manipulations on cognitive function.

Memory type	Brain region	PNN manipulation	Outcome	References
Fear	Amygdala	ChABC-mediated degradation	↓ Fear memory	Gogolla et al. (2009)
	Hippocampus	ChABC-mediated degradation HYase-mediated degradation	↓ Fear memory	Ramsaran et al. (2023); Kochlamazashvili et al. (2010)
	Prefrontal cortex	ChABC + HYase-mediated degradation	↓ Fear memory	Hylin et al. (2013)
		Aggrecan knockdown	↓ Fear memory	Lavertu-Jolin et al. (2023)
	Visual cortex	ChABC-mediated degradation	↓ Fear memory	Thompson et al. (2018)
	Auditory cortex	ChABC-mediated degradation	↓ Fear memory	Banerjee et al. (2017)
Spatial	Medial prefrontal cortex	ChABC-mediated degradation	↑ Spatial working memory	Anderson et al. (2020)
	Entorhinal cortex	ChABC-mediated degradation	↓ Spatial navigation	Christensen et al. (2021)
Social	CA2 hippocampus	ChABC-mediated degradation	↓ Social memory	Domínguez et al. (2019); Cope et al. (2021)
Object	Whole brain	Aggrecan knockout	↑ Object recognition memory	Rowlands et al. (2018)
		HAPLN1 knockout	↑ Object memory retention ↑ Object memory retention (aged mice)	Romberg et al. (2013); Yang et al. (2021)
	Perirhinal cortex	ChABC-mediated degradation	↑ Object memory retention ↑ Object memory retention (aged mice)	Romberg et al. (2013); Yang et al. (2021)

Abbreviations: ChABC, chondroitinase ABC; HAPLN1, hyaluronan and proteoglycan binding link protein 1; HYase, hyaluronidase.

4.1 | PNN ablation affects memory

To investigate the impact of PNNs on cognitive function, the majority of manipulation studies either degrade PNN structures enzymatically (i.e., ChABC or HYase) or target specific PNN components using genetic or viral knockout techniques. While PNNs have been investigated in a variety of cognitive tests (Table 1) (reviewed by Fawcett et al., 2022), we will focus this section on fear, spatial, social, and object memory.

Studies on PNN manipulations in fear memory circuits, including the amygdala, hippocampus, and prefrontal cortex, are linked to disruptions in the encoding, retention, and recall of memories related to a fear-inducing event. Experiments conducted by Gogolla et al. (2009) supplied evidence that PNNs in the amygdala help fortify the retention of fear memories in adult mice but degradation of PNNs leaves long-term fear memories at risk of erasure. ChABC-treated mice freeze in response to a stimulus paired with a foot shock 1 day after conditioning. When the conditioned stimulus is presented a month following extinction training, the fear memory and associated response are not restored in the treated mice (Gogolla et al., 2009). Recently, there has been interest in understanding the molecular events that contribute to the development of fear memory. In the mouse hippocampal CA1 region, precise memories and the cellular ensembles that make up the memory traces arise after the first postnatal month and rely on the maturation of PNN-enwrapped PV interneurons (Ramsaran et al., 2023). Destabilizing PNNs by viral and enzymatic manipulations in adult mice impairs the allocation of memories to cellular ensembles and thus manufactures imprecise memories associated with contextual fear learning (Ramsaran et al., 2023). Similarly, injecting HYase into the hippocampus impairs contextual fear conditioning and HYase-injected mice show less freezing than their control counterparts (Kochlamazashvili et al., 2010). PNN disruptions in the hippocampus and medial prefrontal cortex also impair memory in trace fear conditioning where the conditioned and unconditioned stimuli are temporally separated (Hylin et al., 2013). A recent study shows that reducing aggrecan in prefrontal cortex PV interneurons limits the spontaneous recovery of fear memories following extinction training (Lavertu-Jolin et al., 2023). PNNs in the visual and auditory cortex have also been recognized as contributors to fear memory processing, contributing to remote (Thompson et al., 2018) and recent (Banerjee et al., 2017) recall of fear memory, respectively.

PNNs appear to be involved in different aspects of spatial memory and navigation, processes dependent on selective firing of place cells of the hippocampus and grid cells of the entorhinal cortex as well as connections with the prefrontal cortex and other related regions. Although not yet investigated in place cell function, PNN removal in the entorhinal cortex alters grid cell function involved in spatial navigation (Christensen et al., 2021). Specifically, it impairs the ability of grid cells to both form stable representations of a new environment and retain stable representations during re-exposure to a familiar environment (Christensen et al., 2021). Impaired spatial learning and cell activity induced by neuropeptide Y (NPY) signaling disruption is associated with increased PNN expression in the hippocampus (Bertocchi et al., 2021). These effects were rescued upon PNN degradation, showing that PNN expression regulated by NPY transmission is essential for maintaining tuned cell activity and facilitating spatial learning abilities (Bertocchi et al., 2021). Additionally, ChABC treatment in the medial prefrontal cortex reveals subtle enhancements in rat performance when they are exposed to one of

four delay conditions of a spatial working memory task (Anderson et al., 2020), implying that PNNs in this region contribute to spatial working memory function in a more nuanced manner. Although the link is not well established, the PNN holes themselves have also been speculated to serve as a resilient molecular substrate for preserving very long-term memories (Tsien, 2013). In a recent study, Ruzicka et al. (2022) investigated the idea that spatial memories are stored in the PNNs following synapse retraction from induction of a hibernation-like state (HLS) in mice. In mice with HLS memory deficits, the removal of hippocampal PNNs, both enzymatically and genetically, does not worsen spatial memory but rather expedites recovery and re-learning in the Morris Water Maze test (Ruzicka et al., 2022). This suggests that hippocampal PNNs are not needed for long-term spatial memory storage.

Studies also show that PNNs have a role in social memory, which encompasses the cognitive and behavioral processes involved in recognizing and interacting with conspecifics. Accumulating evidence indicates that the hippocampal CA2 area and its connecting regions form a unique circuit that is critical for encoding, consolidating, and recalling social memories (Meira et al., 2018). Unlike other parts of the hippocampus, the CA2 region is characterized by a high abundance of PNNs surrounding both excitatory and inhibitory cells, which contributes to the limited synaptic plasticity in this area (Carstens et al., 2016; Domínguez et al., 2019). In direct social interaction tests, mice naturally prefer novel mice and show a decrease in investigation time when repeatedly exposed to the same mouse. Studies indicate that degrading CA2 PNNs using ChABC impairs the ability of mice to recognize familiar mice, as evidenced by their unchanged interaction times with previously encountered mice (Cope et al., 2021; Domínguez et al., 2019). Excessive CA2 PNNs have also been observed in BTBR mice, an inbred wildtype mouse strain with known social deficits, and reducing their PNNs to control-like levels partially rescued their social memory (Cope et al., 2021). Consistent with this, a recent study showed that reduction in the C4S sulfation pattern by elimination of the sulfotransferase gene *chst11* increases CA2 PNNs and causes social memory impairments, which are then rescued by treatment with ChABC (Huang et al., 2023).

Emerging evidence has elucidated the involvement of PNNs in the recognition of objects, which is often measured by the innate rodent ability of discriminating between a novel and familiar object. PNN ablation by brain-wide genetic targeting of the gene encoding aggrecan improves the recognition memory of mice 24 h after object exposure whereas control mice sustain little memory (Rowlands et al., 2018). Several studies have also investigated changes in object memory associated with region-specific PNN manipulations. PNN reductions by ChABC or genetic knockout in the perirhinal cortex, a region associated with object memory processing, extend object memory retention to 24 h (Romberg et al., 2013; Yang et al., 2021) and 48 h (Romberg et al., 2013), time points at which mice normally forget (Yang et al., 2021). This effect on memory retention weakens over time such that PNN-degraded mice perform similarly to control mice (Romberg et al., 2013), indicating that PNN restoration restricts the retention of object-based memories.

In general, PNNs play multifaceted roles in a broad range of memory processes, contributing to the encoding, retention, and recall of memories, although their selective role in these processes appears to be highly dependent on the memory type and brain region. It is worth noting though that many of the current methods used to ablate PNNs (e.g., enzymatic, genetic, or viral disruption) also result in changes to the surrounding loose ECM because they directly modify components, most notably CSPGs, present in both structures (Fawcett et al., 2022). Like PNNs, the loose ECM is closely associated with synapses and the ECM has been shown to impact synaptic plasticity as well as neuronal activity (Fawcett et al., 2022), processes that govern memory function. The current methodology does not allow us to selectively tease apart the unique versus similar roles of aggregated and diffuse ECM structures in memory processes.

4.2 | Experience-dependent regulation of PNNs and cognition

PNNs are highly sensitive to environmental stimuli, suggesting that they may serve as an important substrate for experience-dependent changes. Several rewarding experiences for rodents, such as voluntary physical exercise and environmental enrichment, have been shown to enhance cognition and modulate PNNs. Conversely, experiences that disrupt cognitive function, such as aging and stress, also lead to alterations in PNNs. Here, we will discuss studies that emphasize the dynamic nature of PNNs and their involvement in the regulation of cognitive processes in response to different environmental contexts.

While not yet examined in the context of cognitive function, several studies have investigated the various ways in which rewarding experiences regulate PNNs. The effects of physical exercise on PNNs are mixed. Rodent studies have shown that giving rats or mice free access to a running wheel decreases the number of PNNs in the hippocampus (Briones et al., 2021; Smith et al., 2015). A more recent study revealed that running not only decreases the overall numbers of PNNs, but also disrupts their structure (Evans et al., 2022), indicating that running causes PNN degradation. However, in the spinal cord, running increases PNN expression (Smith et al., 2015), and exercise-based therapies reverse PNN decreases induced by spinal cord injury (Sánchez-Ventura et al., 2021). In the visual cortex, prolonged enrichment from birth extends ocular dominance plasticity into adulthood without affecting PNNs (Greifzu et al., 2014), but providing enrichment in adult and aged rodents correlates with a decrease in PNN density and the reinstatement of ocular plasticity (Sale et al., 2007; Scali et al., 2012). Environmental enrichment does not appear to cause global decreases in PNNs as early-life enrichment increases PNNs in the striatum (Simonetti et al., 2009) and CA2 region of the hippocampus (Carstens et al., 2016). Moreover, environmental enrichment-induced improvements in drug-seeking behavior and recovery from ischemic stroke correlate with increases (Slaker, Barnes, et al., 2016) and decreases (Madinier et al., 2014) in cortical PNNs, respectively, implying that

environmental enrichment rescues PNN effects depending on the disease state.

Aging is a natural process that is often characterized by progressive decline in cognitive function and diminished plasticity (Radulescu et al., 2021). Studies have investigated the effects of aging on PNNs and some have observed an increase in PNNs in the aged brain (Karetko-Sysa et al., 2014; Ueno et al., 2018), while others have reported a decrease (Briones et al., 2021; Gray et al., 2023; Yamada & Jinno, 2013), although these findings are likely region-specific (Ueno et al., 2018, 2019). Despite no significant changes in transcript levels of PNN components, a recent report has shown an increase in the degradation of HA into smaller fragments in the aged brain (Sugitani et al., 2021). This degradation causes disassembly of the HA-aggrecan complex from PNNs, resulting in an increase in the soluble form of aggrecan in the ECM (Sugitani et al., 2021). In the context of spatial memory, aged rats with greater PNNs in the hippocampus perform better on the Morris Water Maze compared to aged rats with less PNNs, although this relationship between PNN coverage and spatial learning is not observed in other age groups (Gray et al., 2023). PNN digestion with ChABC treatment in the perirhinal cortex of aged mice fully restores their 6 h object memory retention to a level comparable to young adult mice, although this effect is not observed 24 h after object exposure (Yang et al., 2021). Aging also causes a change in PNN plasticity, shifting them to a more inhibitory state as characterized by a higher C4S to C6S ratio (Foscarin et al., 2017). Aging-induced increases in C4S-associated PNNs have been shown to negatively impact cognitive function (Yang et al., 2021). On the other hand, increases in C6S levels improve cognitive decline in aged mice, while transgenic loss of C6S causes early cognitive decline in young mice (Yang et al., 2021). These findings suggest that PNN deterioration in the aged brain contributes to worsened cognitive function and manipulations of PNNs may provide a potential therapeutic avenue for aging-induced cognitive decline.

Chronic stress in rodents is typically associated with reduced plasticity and impaired cognitive performance (Laham & Gould, 2022). Various rodent stress paradigms (e.g., social defeat, corticosterone exposure, restraint, and early life stress) have pointed to the profound effects that stress has on PNNs depending on the age at which negative stimuli are experienced and with variations across brain regions. Social defeat-induced persistent stress in adult rats increases PNN+ PV interneurons in the hippocampus and leads to deficits in hippocampal-dependent memory tests (Koskinen et al., 2020; Riga et al., 2017). Treatment of stressed rats with the antidepressant imipramine restores PNNs and memory performance to control-like levels (Riga et al., 2017). Similarly, reducing hippocampal PNNs with ChABC treatment has comparable improvements in cognition of stressed rats (Riga et al., 2017). Chronic exposure to corticosterone increases PNN intensity and reduces gamma rhythms in the hippocampus, effects that are rescued with antidepressant treatment venlafaxine (Alaiyed et al., 2020). In response to chronic restraint stress, PNN coverage increases in the medial prefrontal cortex and thalamus, but PNN density decreases in the hippocampus (Pesarico et al., 2019). A recent study demonstrated that soon after chronic stress the density of hippocampal PNNs are reduced, but are then increased at later time points, coinciding with observed memory impairments (Koskinen et al., 2020). This suggests that the impact of chronic stress on PNN expression is temporally regulated, although variation also likely exists based on the stress paradigm and duration of the stressor. Early life stress models have also been shown to affect PNNs. In the hippocampus, maternal separation and early weaning stress increase PNNs in both male (Murthy et al., 2019) and female (Laham et al., 2022) mice. Infant maltreatment in the scarcity-adversity model of early life stress reduces PNN coverage in the amygdala (Santiago et al., 2018). Developmental degradation of PNNs with a combination of ChABC and HYase recapitulates early life stress-induced increases in innate threat response to predator odor in controls (Santiago et al., 2018). Overall, studies suggest that PNN aberrations may be a contributing factor to stress-induced behavioral abnormalities.

4.3 | PNNs and memory-related disorders

The necessity of PNNs in cognitive function is profoundly evidenced in memory-related disorders, in which PNN disruption is commonly observed. Experimental studies have shown that disrupting PNNs can lead to synaptic and cognitive impairments that resemble the characteristics of certain disorders that affect memory, such as Alzheimer's disease (AD) and drug addiction disorders.

AD is a progressive neurodegenerative disease characterized by the accumulation of amyloid plaques and neurofibrillary tangles, causing severe memory loss and cognitive impairment (Busche & Hyman, 2020). Human post-mortem studies examining AD-associated changes in the expression of PNNs have yielded conflicting results. Some studies have found reduced PNNs (Baig et al., 2005; Crapser et al., 2020), while other evidence suggests that PNNs are not changed (Morawski et al., 2012). Similarly, contradicting results have been produced when investigating PNN abnormalities in mouse models of AD neuropathology, with the majority of studies showing PNN reductions (Crapser et al., 2020; Kudo et al., 2023; Lendvai et al., 2012; Rey et al., 2022). These discrepancies may reflect alterations in specific CSPG PNN components rather than the PNN structure as a whole. Manipulations of PNNs have also been shown to improve memory function in AD mouse models. PNN digestion with a ChABC injection into the perirhinal cortex reverses object recognition memory deficits in two mouse models of tau pathology (Yang et al., 2015). In the amyloid AD mouse model, hippocampal ChABC injections improve contextual memory performance (Végh et al., 2014). Another AD amyloid model shows reduced PNNs in the CA2 of the hippocampus and deficits in social memory, but administering the growth factor neuregulin-1 restores CA2 PNN levels and social memory function (Rey et al., 2022). These studies suggest that disturbances in normal PNN levels may, in part, underlie memory impairments observed in various mouse models of AD.

Interestingly, a spatial pattern has been observed between AD pathology and the presence of PNN-enwrapped cells. For instance, in human AD patients, neurofibrillary tangles are not present near PNN+ neurons (Brückner et al., 1999; Morawski et al., 2012), and hyperphosphorylated tau areas do not overlap with areas rich in PNNs (Brückner et al., 1999). While PNN-associated neurons are seen near regions of amyloid deposition, they are located only in the peripheral zone of plaques but not in the plaque's core (Morawski et al., 2012). These findings have also been recapitulated in mouse models of AD neuropathology (Morawski, Brückner, et al., 2010; Morawski, Pavlica, et al., 2010). Regions without aggrecan+ PNNs are vulnerable to tau pathology while PNN-dense regions exhibit less neurofibrillary changes (Morawski, Brückner, et al., 2010). PNNs in areas with severe tau pathology are largely intact, resisting degradation (Morawski, Brückner, et al., 2010). In dissociated cortical neuronal cultures, neurons lacking PNNs are more vulnerable to the neurotoxicity of Aβ1-42 treatment than mature PNN-associated neurons (Miyata et al., 2007). After ChABC, the neuroprotective effect provided by PNNs is gone and Aβ1-42 kills previously ensheathed neurons (Miyata et al., 2007). Together, PNN-rich areas are less affected by AD pathology and prevent neuronal loss, suggesting a prominent neuroprotective function of PNNs against amyloid and tau pathology.

Drug addiction influences many of the same brain circuits that govern learning and memory, and drug-associated memories are a main contributor to relapse. Drug use or addiction impacts PNNs in several brain regions, including the prefrontal cortex, striatum, amygdala, hippocampus, hypothalamus, and cerebellum, although the effects vary based on the type of drug used (reviewed by Slaker, Blacktop, et al., 2016). In rats curbed from self-administering heroin, protein and mRNA levels of PNN components like brevican, TnR, and HA decrease in the medial prefrontal cortex (Van Den Oever et al., 2010). However, an increase in brevican is noted after heroin re-exposure (Van Den Oever et al., 2010). Increases in PNNs following cocaine exposure have been associated with consolidation of drug-related memories in the cerebellum (Carbó-Gas et al., 2017). Consistent with this, in the medial prefrontal cortex, neurons enveloped by PNNs are primarily activated by cocaine reward memory (Slaker et al., 2015). Degrading PNNs in this region compromises the acquisition of memories associated with cocaine-induced conditioned place preference, but it has no effect on the rate of extinction or reinstatement of conditioned place preference when PNN degradation precedes extinction training (Slaker et al., 2015). In contrast, the removal of PNNs in the amygdala before extinction training effectively erases drug memories and prevents the reinstatement of morphine- or cocaine-induced conditioned place preference (Xue et al., 2014). Adolescent exposure to alcohol, the most common drug of abuse, produces long-lasting increases in PNNs in the prefrontal (Dannenhoffer et al., 2022) and insular cortex (Chen et al., 2015). Disruption of insular cortical PNNs enhances alcohol consumption even when it is made aversive to taste (Martins de Carvalho et al., 2023), suggesting that insular cortical PNNs may play a role in compulsive behavior. The observed changes in PNNs after exposure to different drugs of abuse indicate their potential involvement in the brain's adaptive responses and conditioned memories associated with drug experiences, highlighting the potential value of targeting PNN disruption as an approach to suppress these memories and prevent drug relapse.

5 | MECHANISMS OF PNN REMODELING

PNNs play a crucial role in maintaining the stability of neuronal connections and supporting the formation, maintenance, and recall of memories. However, they are not static structures and undergo dynamic remodeling in response to environmental cues and disease conditions. Remodeling of the abundance and composition of PNNs is essential for enabling modifications in neural circuits, allowing for synaptic plasticity and adaptability to changing demands and experiences. On the other hand, excessive or aberrant remodeling of PNNs can have detrimental effects on synaptic connections and cognitive functions, particularly in the context of certain diseases. Recent work indicates that the modulation of PNNs is tightly controlled by a variety of factors and involves the actions of not only neurons but also glial cells which have been demonstrated to be crucial to this process.

5.1 | Enzymatic remodeling of PNNs

PNNs and their specific components undergo constant remodeling once they are assembled. This process of remodeling PNNs and, more broadly, the ECM is largely performed by numerous metalloproteinases, enzymes that proteolytically cleave their components, most notably lecticans. In this way, metalloproteinases regulate PNN abundance by degrading specific components and, in some cases, lead to a complete disassembly of the PNN structure. The most studied metalloproteinase classes in relation to PNN biology are matrix metalloproteinases (MMPs) and a disintegrin and MMP with thrombospondin motifs (ADAMTSs), which collectively are able to break down all elements of the ECM and PNNs (Shiomi et al., 2010). These enzymes are produced by multiple cell types, including neurons and glia, although the specific cellular contributions have not been well studied. Because their activity is precisely controlled through differential expression, proteolytic activation, and binding of their inhibitors, such as the tissue inhibitors of metalloproteinases (Shiomi et al., 2010), they are able to spatially and temporally control the ECM and PNNs in response to experience and disease.

MMPs belong to a family of zinc-binding endopeptidases and usually act in soluble forms located in the extracellular space. They are produced in an inactive zymogen form and require proteolytic activation (Shiomi et al., 2010). There are 23 members of this family in humans, although only a select few have been researched in regards to PNN component degradation (Bozzelli et al., 2018). MMPs are released in response to experiences that increase neural activity, such as learning and memory (Ganguly et al., 2013) or exposure

to an enriched environment (Foscarin et al., 2011; Stamenković et al., 2017), and presumably "loosen" the ECM to promote plasticity. MMPs cleave numerous ECM constituents, resulting in a modulation of the perisynaptic ECM that consequently induces synaptic changes. Indeed, MMPs regulate both excitatory and inhibitory neuronal transmission in multiple ways (Wiera & Mozrzymas, 2021). Reducing or inhibiting several MMPs (i.e., MMP 3, 7, and 9) also impacts cognitive function, causing impairments in fear and spatial memory (Beroun et al., 2019). While many MMP family members lack extensive study in the PNN context, research has demonstrated MMP9's ability to influence PNN abundance. Genetic reduction or pharmacological inhibition of MMP9 increases PNNs (Wen et al., 2018; Pirbhoy et al., 2020), while higher levels of MMP9 correlate with lower PNNs (Alaiyed et al., 2020; Wen et al., 2018). MMP9 has also been shown to be essential for PNN modulation driven by environmental enrichment. Stamenković et al. (2017) observed that while mice exhibit a decrease in PNNs after environmental enrichment, MMP9 KO mice show an increase in PNN levels. This signifies that MMPs are important regulators of PNN abundance as well as key mediators of PNN remodeling in response to more plastic states.

MMP dysregulation has been reported in many different diseases involving PNN abnormalities and likely contributes to disease pathology. It has been shown that MMP activity mediates PNN loss in a glioma-induced model of epilepsy and reducing this activity increases peritumoral PNNs (Tewari et al., 2018). Moreover, MMP family proteins, MMP3 and MMP13, have been correlated to aggrecan and brevican PNN component degradation in HIV-infected brains, suggesting that they may play a role in the remodeling of these specific components following viral stimuli. MMPs have also been implicated in PNN degradation associated with behavioral and cognitive abnormalities. For instance, MMP9 contributes to PNN degradation around PV interneurons and sensory deficits in the Fmr1 KO model of Fragile X Syndrome (Lovelace et al., 2019; Wen et al., 2018). Knockout of MMP9 in Fmr1 KO mice prevents PNN degradation (Wen et al., 2018) and ameliorates their behavioral abnormalities (Lovelace et al., 2019). Furthermore, in the 5xFAD mouse model of amyloidosis, reduced PNNs are observed (Crapser et al., 2020) along with increased MMP9 levels (Ringland et al., 2021). Inhibition of MMP9 in 5xFAD mice results in an improvement in social memory (Ringland et al., 2021), suggesting that MMPs may contribute to PNN loss and cognitive decline in AD. Overall, MMPs, mainly MMP9, are critical players in multiple pathologies, often driving both structural and cognitive abnormalities.

Several ADAMTS proteins have been observed to cleave many PNN components, including the entire lectican family (Stanton et al., 2011). While there is overlap in the substrates of ADAMTS and MMPs, they differ significantly in substrate specificity and possess unique cleavage sites (Shiomi et al., 2010). Differential sulfation plays a role in modulating ADAMTS5's efficacy in degrading PNN component aggrecan. Specifically, aggrecan enriched with C6S, as found in mice overexpressing chondroitin-6-sulfotransferase, is more efficiently degraded by ADAMTS5 compared to aggrecan from control mice (Miyata & Kitagawa, 2016). Moreover, evidence indicates that the expression and/or activation of ADAMTS proteins is closely associated with neural development. Notably, ADAMTS15 expression has been identified in PV interneurons within the hippocampus and cortex, with its expression showing a negative correlation with PNN maturation during critical periods (Levy et al., 2014). Despite being relatively underexplored, ADAMTS proteins are emerging as significant contributors to PNN remodeling.

Besides MMPs and ADAMTSs, additional enzymes play a role in cleaving PNN components. One such enzyme is tissue-type plasminogen activator (tPA), a serine protease responsible for converting the inactive proenzyme plasminogen into plasmin (Pang et al., 2004). A recent study has suggested direct involvement of tPA in PNN remodeling. Knockout of tPA has been shown to increase PNN density around PV interneurons in the somatosensory cortex (Lépine et al., 2022). Additionally, plasmin activity has been found to facilitate aggrecan degradation directly in vitro (Lépine et al., 2022). In summary, enzymatic remodeling of PNNs is a complex, dynamic, and tightly regulated process involving many different enzymes and their inhibitors, providing a potential opportunity for therapeutic intervention in disease.

5.2 | Glial-specific remodeling of PNNs

In principle, both neurons and glia are capable of producing PNN components and remodeling the overall structure of PNNs. Sequencing studies have shown that astrocytes and neurons express many of the same genes that encode PNN components, including CSPGs and TnR (Anderson et al., 2016; Devienne et al., 2021). Accumulating evidence also suggests that glia, most notably microglia and astrocytes, play central roles in PNN remodeling. They secrete a multitude of enzymes and signaling molecules that actively modulate the structure and composition of PNNs. Glia are highly sensitive to the changes in the neural environment and have been as established as prominent regulators of synaptic numbers and plasticity (reviewed by Sancho et al., 2021). Given that synapses are set within the holes of the PNNs, this makes glia as an ideal intermediary for enabling synaptic refinement by remodeling PNNs in response to different disease and context-specific stimuli (Figure 3).

Emerging research indicates the involvement of microglia, the resident macrophages of the brain, in ECM and PNN remodeling. Global depletion of microglia through pharmacologic inhibition of colony-stimulating factor 1 receptor (CSF1R) robustly increases the abundance of PNNs in the cortex, an effect reversed by microglial repopulation (Liu et al., 2021). PNN accumulation induced by microglial depletion enhances local circuit connectivity to excitatory cells and increases both excitatory and inhibitory cell activity (Liu et al., 2021). In another study, it was observed that CSF1R-mediated microglial ablation increases the accumulation of PNN component brevican around hippocampal synapses and reduces the size of the PNN holes (Strackeljan et al., 2021). This implies that microglia play a role in regulating the finer structure of PNNs rather than simply promoting a general accumulation of PNNs. Pain induced by peripheral

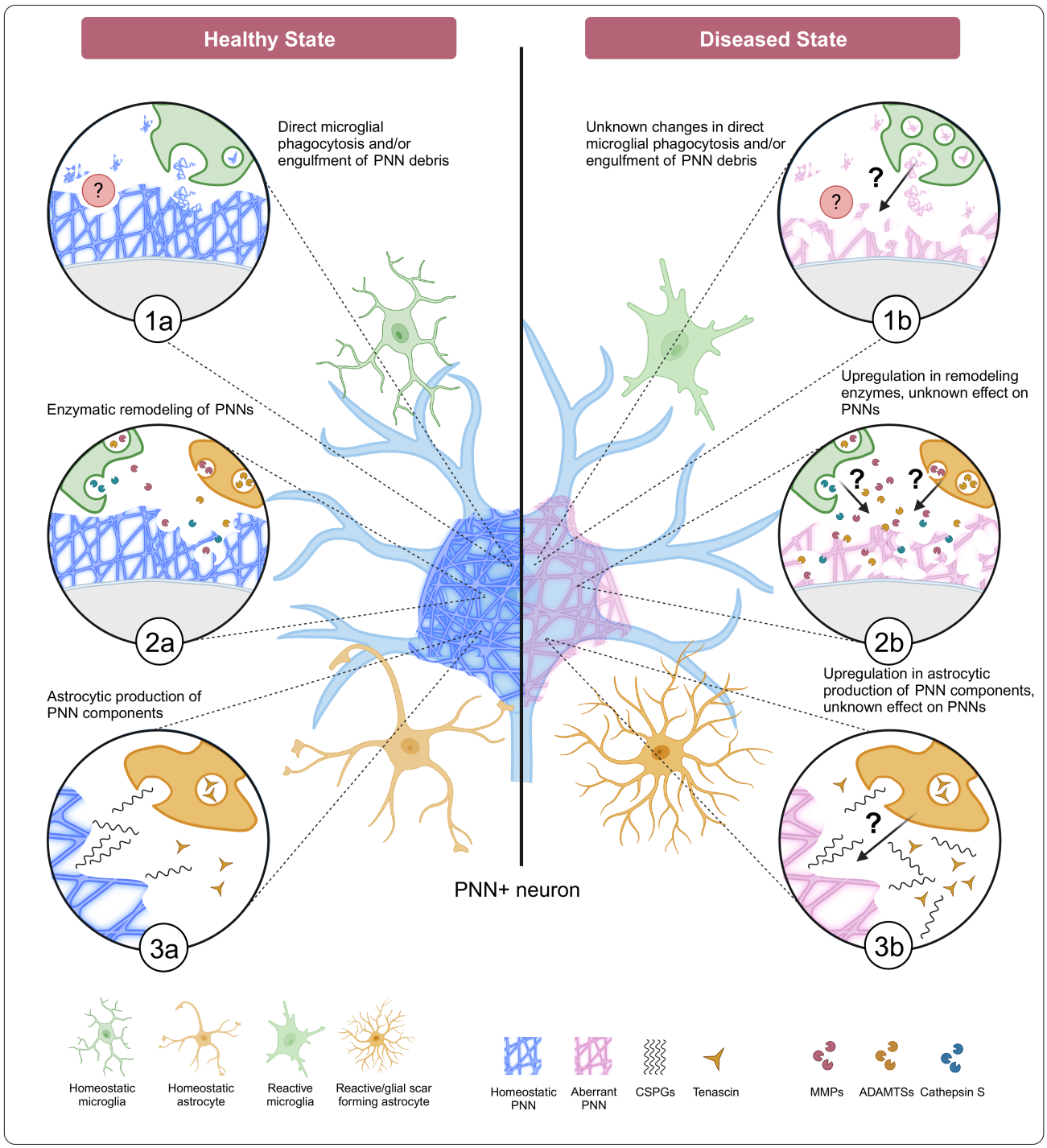

FIGURE 3 Glial remodeling of perineuronal nets (PNNs) in health and disease. The working models for glial regulation of PNN integrity in health and disease states include: (1a) Microglia maintain a healthy abundance of PNNs by directly engulfing PNNs from the neuronal surface and/or engulfing PNN debris after removal from the neuronal surface. (1b) Reactive microglia may alter this homeostatic role (upregulate or downregulate) in disease states, resulting in aberrant PNNs. (2a) Microglia and astrocytes maintain a healthy abundance of PNNs by releasing enzymatic proteases such as MMPs, ADAMTSs, and cathepsins. (2b) Reactive microglia and astrocytes increase their release of enzymatic proteases in disease states, which may result in aberrant PNNs. (3a) Astrocytes produce PNN components, including CSPGs and tenascins, in the healthy brain, (3b) while in disease states, reactive astrocytes upregulate PNN component production, although it is unknown if these components become part of the PNN structure in health and/or disease. ADAMTSs, a disintegrin and metalloproteinase with thrombospondin motifs; CSPGs, chondroitin sulfate proteoglycans; MMPs, matrix metalloproteinases. The figure was created using BioRender.com.

nerve damage has been shown to reduce WFA+, but not aggrecan+, PNNs in the spinal cord (Tansley et al., 2022). Elimination of microglia prevents WFA+ PNN loss but does not alter aggrecan+ PNNs (Tansley et al., 2022), suggesting the microglia remodel some selective elements of the PNN structure to induce pain hypersensitivity. Under the direction of interleukin-33 (IL-33) signaling, microglia are activated to clear the ECM, thereby allowing for new synaptic connections (Nguyen et al., 2020). Decreased IL-33 compromises the amount of aggrecan localized to CD68+ lysosomes within microglia and subsequently causes an amassment of presynaptic ECM, which is associated with fear memory deficits (Nguyen et al., 2020). Further, restoration of IL-33 signaling between neurons and microglia improves fear memory precision associated with aging (Nguyen et al., 2020). In response to anesthetic ketamine, cortical microglia have been shown to increase PNN engulfment through purinergic receptor P2RY12, which detects ATP/ADP levels and initiates a chemotactic response by microglia (Venturino et al., 2021). Disruption of P2RY12 signaling prevents microglia-mediated PNN remodeling (Venturino et al., 2021), implying that neuronal activity dictates microglial removal of PNNs. They further showed that stimulation of microglia by specific light entrainment induces PNN removal (Venturino et al., 2021), suggesting that microglia promote PNN remodeling in response to specific cues. Taken together, the data suggest a crucial homeostatic process wherein microglia regulate the abundance of the ECM and PNNs surrounding synapses, which may provide an additional role for microglia in synaptic remodeling. The mechanisms by which microglia regulate PNNs (i.e., directly via engulfing PNNs from the neuronal surface or enzymatic degradation and/or indirectly via clearing PNN debris after degradation) and, more broadly, the ECM remain an area to be further explored.

Previous work has also speculated that microglia may contribute to PNN loss in various disease contexts. Abnormal PNNs because of microglial reactivity have been observed in many pathological conditions. In mouse models of neurodegenerative disease (e.g., Huntington's disease, AD, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia), microglia facilitate PNN loss, and eliminating microglia ameliorates this effect and disease progression (Arreola et al., 2021; Crapser et al., 2020). It is possible that disease-induced PNN degradation is caused by an overall increase in this newly recognized homeostatic role for microglia in PNN remodeling, or it may be through an intensified or complementary alternative process that removes PNNs through altered secretion of remodeling enzymes or their inhibitors (Figure 3). In addition to proinflammatory cytokines, microglia release a variety of MMPs and ADAMTSs following CNS injury and infection, and dysregulation of microglial MMPs has been implicated in the pathogenesis of cognitive disorders (e.g., AD) (Beroun et al., 2019). While not well studied, PNN loss has been correlated with microglial release of MMP and ADAMTS proteases after viral infection (Medina-Flores et al., 2004; Wegrzyn et al., 2021), suggesting that enzymatic removal of PNNs via microglia is a plausible explanation for reduced PNNs in disease states. Microglial cathepsins are another proposed enzymatic candidate to control PNN abundance. Cathepsins are secreted by microglia following lipopolysaccharide (Ryan et al., 1995) and brain injury (Petanceska et al., 1996) activation. Ex vivo mouse brain slice incubation with cathepsin S has been shown to abolish PNN+ staining, demonstrating its ability to modulate PNNs (Pantazopoulos et al., 2020). Decreased daytime PNNs are negatively correlated with microglial cathepsin S expression, although these diurnal PNN effects were not recapitulated in a more recent study (Barahona et al., 2022). These findings collectively illustrate that microglia, in response to various pathological stimuli, can act on PNNs, often resulting in their degradation, and further highlight the need for future investigation as potential therapeutic interventions for targeting PNN plasticity.

Astrocytes are the most abundant glial cell type in the CNS and play crucial roles in both healthy brain development and adult brain function. A recent study showed that astrocytes increase connexin 30 levels as they mature, triggering the RhoA-ROCK pathway to restrict the production of MMP9 (Ribot et al., 2021). This, in turn, promotes the aggregation of PNNs and the maturation of PV interneurons, facilitating critical period closure in the visual cortex (Ribot et al., 2021). In the brainstem, disrupting neuron-astrocyte fibroblast growth factor 9 signaling triggers early astrocyte maturation, resulting in increased production of astrocytic PNN structural components (Brandebura et al., 2022). Notably, elevated levels of PNN component brevican are associated with enlarged synaptic terminals (Brandebura et al., 2022), suggesting a role for astrocytes in PNN component modulation and synaptic refinement. While astrocytes are capable of producing many of the same PNN components as neurons, it remains unknown the necessity of astrocytes in maintaining PNNs in the adult brain during homeostatic conditions. However, in response to both acute injury and chronic disease, astrocytes undergo a multitude of morphological, molecular, and functional changes that transform them into reactive astrocytes (reviewed by Liddelow & Barres, 2017). Reactive astrocytes have altered expression of PNN remodeling enzymes MMPs and ADAMTS as well as their inhibitors (Demircan et al., 2013; Muir et al., 2002). Furthermore, glial scar-forming reactive astrocytes also deposit various ECM components like CSPGs, which inhibit neuronal recovery and growth (Anderson et al., 2016; Hara et al., 2017; McKeon et al., 1999) (Figure 3). In glioma-associated epilepsy, reactive astrocytes do not show MMP activity near PNN loss (Tewari et al., 2018), suggesting astrocytes are not the primary contributor of PNN degradation. While these studies indicate that reactive astrocytes are active participants in ECM remodeling, their specific role in the context of PNNs remains largely unexplored.

6 | CONCLUDING REMARKS

While largely understudied, there is a growing appreciation for the multifaceted roles PNNs play in regulating brain plasticity

and cognitive function. PNN condensation is associated with developmental time windows of increased plasticity and provides a framework for stabilizing synapses and restricting plasticity in adulthood. The diverse elements that constitute the PNN structure provide a highly organized, but dynamic, substrate for the brain to adapt during disease or experience-related plasticity events that affect cognitive function. PNN remodeling can be beneficial, facilitating the formation of new synaptic connections following certain learning experiences; however, aberrant PNN remodeling can be harmful, contributing to synaptic instability and cognitive dysfunction as observed in various memory disorders. Recognizing the significance of PNNs in regulating plasticity and memory opens up potential avenues for therapeutic intervention for cognitive function. However, much remains unknown about the contributions of the individual PNN components and how changes in the precise composition of the PNN structure ultimately impact their functional outcome. It is possible that remodeling enzymes and/or glia serve as the main effectors of PNN changes in health and disease, influencing cognitive function either positively or negatively through alterations in the structure of PNNs. These pose intriguing areas for further exploration.

AUTHOR CONTRIBUTIONS

Brenda Sanchez: Conceptualization; writing – original draft; writing – review and editing. **Piotr Kraszewski:** Conceptualization; writing – original draft; writing – review and editing. **Sabrina Lee:** Visualization; writing – review and editing. **Elise C. Cope:** Conceptualization; resources; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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