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Regulation of CNS plasticity through the extracellular matrix

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Abstract

Counter to established dogma, the central nervous system (CNS) has a regeneration capacity and is moderately plastic. Traditionally such changes have been recognised through development, but more recently this has been documented in adult through learning and memory or during the advent of trauma and disease. One of the causes of such plasticity has been related to changes in the extracellular matrix (ECM). This complex scaffold of sugars and proteins in the extracellular space alters functionality of the surrounding tissue through moderation of synaptic connections, neurotransmission, ion diffusion, and modification to the cytoskeleton. Here we discuss the role of the ECM in CNS plasticity in development and the adult. Further, we shall determine how the ECM affects normal neuronal functioning in critical processes such as memory. Finally, we shall assess how the ECM contributes to adverse CNS changes in injury and disease, concentrating on how this matrix may be targeted for therapeutic intervention.

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1. Introduction

The extracellular matrix (ECM) is a complex framework of molecules in the extracellular space which occupies ~20% of the total adult brain volume (Nicholson and Sykova, 1998). It is comprised of secreted proteins and glycans which act to support the functional activity of the surrounding tissue. The ECM is implicated in the modulation of many of the dynamic events in the central nervous system (CNS), including inflammation, myelination, synaptogenesis, plasticity and recently the development of the tetrapartite theory of synaptic signalling has been proposed (Dityatev and Rusakov, 2011). Indeed, the composition and turnover of the ECM affects the rate of local neurotransmission and plasticity through modulating synapse formation, signal transduction, ion diffusion, and cytoskeletal dynamics (Gundelfinger et al., 2010). During development, the ECM facilitates the proliferation and outgrowth of neurons to form functioning synapses (Stranahan et al., 2013). In the adult, its composition is less permissive, and functions more to maintain the proper functioning of the CNS. One of the key extracellular matrix structures pivotal to these functions are the perineuronal nets (PNNs), highly-condensed lattice-like structures that form around specific neurons as one of the last steps of neural development at the end of circuit maturation (Pizzorusso et al., 2002; Yamaguchi, 2000).

There are typically three types of ECM found within the adult brain and spinal cord. These are 1) the standard diffuse ECM which surrounds all cellular structures, 2) the PNNs, and 3) that which is membrane bound. All three types of ECM demonstrate substantial dynamic changes within the CNS and are tightly regulated. This control comes from both de novo synthesis and proteolytic cleavage (Carulli et al., 2006), and thus the ECM is subject to dynamic local and global changes through the course of an individual's lifetime. The focus of this review is the endogenous plasticity exhibited within the CNS which is mediated through the ECM. In this review, our focus is the basic structures of the ECM which influence plasticity, ECM effects on development and maintenance in the adult. Further, we discuss new research detailing the role of the ECM in normal brain functions including neurotransmission, learning and memory and how the ECM may contribute to dysfunction in pathological disease states such CNS injury, schizophrenia, Alzheimer's disease, and addiction. As such, this review shall concentrate on the themes and current information relating to how the ECM affects cellular properties and plasticity as well as how it alters in the progression of disease.

2. CSPGs and ECM in the CNS

The effects of the ECM on cellular properties, plasticity and disease are a direct consequence of its composition. While different types and compartments of ECM have specific properties and components (see PNNs section below), there are over 300 proteins which have been found to comprise the central core of tissue, called the matrisome. In the CNS, this includes glycoproteins (which have numerous functions), chondroitin sulphate and heparan sulphate proteoglycans (Hynes and Naba, 2012). The composition and structure of the ECM varies dynamically through changes in synthesis, breakdown in the extracellular space through enzymes such as matrix metalloproteases (MMPs) and through internalization and breakdown in lysosomes (Freitas-Rodriguez et al., 2017). Of the many molecules that make up the CNS matrix, chondroitin sulphate proteoglycans (CSPGs), have an important role in modulating CNS plasticity and regeneration.

2.1 CSPGs

There are at least 16 different types of CSPGs within the nervous system. Together these macromolecules comprise a key component of the ECM (Herndon and Lander, 1990). Each CSPG consists of a core protein

backbone upon which glycosaminoglycan (GAG) chains of chondroitin sulphate (CS) are attached by a tetrasaccharide linkage, the number varying from one to many depending on the protein core (Fig. 1) (Kjellen and Lindahl, 1991; Silbert and Sugumaran, 2002). The unbranched CS chains are composed of repeating disaccharide units of glucuronic acid (GluA) and N-acetylgalactosamine (GalNAc) that are attached to the core protein through an O-linkage to serine residues (Fig. 2) (Bandtlow and Zimmermann, 2000; Iozzo and Murdoch, 1996). The repeating disaccharide units (up to 25-50 per chain) of the CS-GAGs are responsible for many of the properties of the molecules. Each disaccharide moiety within the CS-GAG chain may be differentially sulphated (Properzi, 2004; Properzi et al., 2003), affecting functionality (reviewed in (Kwok et al., 2008; 2011)). These sulphation patterns change during development and ageing, and also differ between CNS regions and between PNNs and diffuse matrix within the adult CNS and determine the specific binding features of the CS-GAGs with other molecules, and thus the inhibitory properties of specific CSPGs within the ECM (Brown et al., 2012; Dickendesher et al., 2012; Gama et al., 2006). For example, the prevalent CS-GAG disaccharides within the adult mouse brain are CS-A (sulphated at the 4 position) and CS-C (sulphated at the 6 position), although CS-D and CS-E (disulphated 2,6 and 4,6) are also present in lower amounts (Carulli et al., 2006; Maeda et al., 2010). Within a single glycan chain more than one of these sulphation patterns can be present. CS-A, CS-C and CS-E are upregulated following injury (Brown et al., 2012; Gilbert et al., 2005; Lin et al., 2011; Properzi et al., 2005; Wang et al., 2008).

Other than the CS chains, the CSPG core protein can further define the functionality of the CSPG, particularly in the case of neural/glial antigen 2 (NG2) which exists in glycanated and non-glycanated forms (Levine, 2016). Of the many CSPG members, the lecticans/hyalectan family (aggrecan, versican, neurocan and brevican) are the most plentiful in the CNS. The lecticans generally have a link domain through which they can bind to the long hyaluronan (HA) chains that are present throughout the ECM, and at particularly high density on neuronal surface where they are the backbone of the PNNs. The lecticans also have a tenascin-binding domain which is important for the formation of the condensed structure of the PNNs (Brückner et al., 2003; Geissler et al., 2013). The most abundant CSPGs in the CNS are neurocan and brevican, and they are uniquely CNS specific (Seidenbecher et al., 1995; Yamada et al., 1994). Other CSPGs, such as NG2, neuroglycan-C, biglycan, decorin and appican are also present outside the CNS (Asher et al., 2000; Matsui et al., 1998; Oohira et al., 2004).

2.2 How do CSPGs limit growth and plasticity in the CNS?

CSPGs are inhibitory to neuronal outgrowth and extension. Neuronal growth cones become dystrophic upon contact with CSPGs although vesicle formation and membrane turnover continues (Tom et al., 2004). Regeneration or its failure is a balance between inhibitory and permissive molecules in the environment and the intrinsic regenerative state of the axons, with embryonic axons being able to grow in many inhibitory environments that block the growth of mature axons. The sulphation pattern of the CS-GAG chains has a strong influence, with the CS-A form (which is upregulated after injury) being more inhibitory than CS-C (Wang et al., 2008).

While concentrations of the various types of CSPG vary, these macromolecules are typically ubiquitous throughout the CNS. Subsequently, it is important to determine the mechanism through which they act to affect cellular properties and plasticity. The effect of these large macromolecules upon neurons is caused by

interactions with both the protein core and the attached CS-GAG chains (Dou and Levine, 1994; Fidler et al., 1999; Friedlander et al., 1994; Iijima et al., 1991; Lander et al., 1982; Milev et al., 1994; Nakanishi et al., 2006; Oohira et al., 1991; Smith-Thomas et al., 1995). However, the specific mechanism through which they exert these effects has not been fully elucidated but is known to involve multiple processes including microtubule stabilisation (Ertürk et al., 2007; Hellal et al., 2011), the RhoA/ROCK pathway (Borisoff et al., 2003; Conrad et al., 2005; Dubreuil et al., 2003; Dyck et al., 2015; Monnier et al., 2003), epidermal growth factor receptor (Cua et al., 2013; Koprivica, 2005), the Nogo receptor (Dickendesher et al., 2012), integrin signalling (Orlando et al., 2012; Tan et al., 2011), activation of protein kinase A (PKA) (Kuboyama et al., 2013) and the binding to other ECM molecules, such as Semaphorin 3A (Dick et al., 2013; Vo et al., 2013). Recently, CSPG receptors RPTPσ (receptor protein tyrosine phosphatase sigma) and LAR (leukocyte common antigen-related) have been identified (Fry et al., 2010; McLean et al., 2002; Shen et al., 2009; Thompson et al., 2003; Zhou et al., 2014) and shown to mediate inhibition of neuronal regeneration. Whether these receptor-mediated effects and pathways will ultimately converge upon one universal mechanism for CSPGs inhibition on neuronal growth has yet to be determined. However, these data show the extraordinary diversity of effects that CSPGs have upon the cells and cellular properties within the CNS and subsequently the multitude of ways in which regeneration and plasticity may be affected.

2.3 Perineuronal nets (PNNs)

One of the functions of CSPGs within the CNS is as a constituent component of the PNNs which surround the soma and proximal neurites of mainly parvalbumin (PV) expressing inhibitory neurons and are formed at the closure of critical periods (Guimaraes et al., 1990; Matthews et al., 2002). Their major components are CSPGs, HA, tenascin-R and members of the hyaluronan and proteoglycan link proteins (HAPLNs) family (Kwok et al., 2011). Secreted CSPGs bind to the dense pericellular coat of HA produced by HA synthases (Fig. 2) CSPG/HA binding is then stabilised by a HAPLN, which binds both the CSPG (through the Ig region) and HA through conserved cysteine residues (Fig. 2) (Mahoney et al., 2001; Oohashi et al., 2002; Spicer et al., 2003). HAPLNs are essential for PNN development. Indeed, HAPLN deficiency restricts the PNN to a diffuse, immature state and CSPG localisation is diminished (Bekku et al., 2012; Carulli et al., 2010; Kwok et al., 2010). The different HAPLNs may be responsible for distinct CSPG binding, as revealed by knockout studies. In the deep cerebellar nuclei HAPLN4 knockout decreased localisation of neurocan and brevican to the PNN, while leaving aggrecan localisation unaltered (Bekku et al., 2012). Indeed, aggrecan and phosphacan localisation to the PNN is, at least partially, dependent on HAPLN1 expression (Carulli et al., 2010). PNNs typically surround fast-spiking or GABAergic interneurons (Brückner et al., 1993; Härtig et al., 1994) but a form of PNN is also found around other neurons in the CNS, particularly cortical pyramidal neurons (Matthews et al., 2002), and various neurons in the spinal cord (Galtrey et al., 2008). More information on the structure of PNNs can be found in (Miyata and Kitagawa, 2017).

Only a small proportion of CS-GAGs in the adult rodent brain (~2%) are present in the CSPGs composing the PNNs (Deepa et al., 2006). Removal of CS-GAGs (the light green strands in Fig. 2), including those composing the PNNs, using a bacterial enzyme chondroitinase ABC (ChABC) enhances regeneration after spinal cord injury (Bradbury et al., 2002), reactivates ocular dominance plasticity (Pizzorusso et al., 2002; 2006), allows unlearning of fear memory (Gogolla et al., 2009) and enhances novel object recognition memory in an Alzheimer's disease model (Yang et al., 2015). It appears to be these 2% of CS-GAGs present in CSPGs from

the PNNs are the key to the effects on plasticity. Prevention of PNN formation by knockout of link protein (Carulli et al., 2010) or aggrecan (unpublished results) has the same effect as ChABC treatment. As such, the CSPGs in the PNN have been shown to regulate the local plasticity of the neuron they surround. Please refer to section 3 and 4 in this article for more detail on this enzyme and its effects.

The traditionally recognised role for PNNs within the CNS is that of neuroprotection (Brückner et al., 1993). The polyanionic nature of the CSPGs and HA in the PNNs shields the neurons from neurotoxic molecules such as potassium or glutamate (Brückner et al., 1993; Choi and Rothman, 1990; Morris and Henderson, 2000) and oxidative stress (Cabungcal et al., 2013). In addition, PNNs optimise the local environment to ensure efficient functioning of the neurons. Indeed, the PNN can affect the ionic balance across the neuronal membrane and, in particular, chloride gradient/transport which can then determine the polarity of the $GABA_A$ receptor mediated response. Apart from chloride transporters, the charge carried by the proteoglycans of the ECM can control transmembrane chloride flux and the extracellular chloride concentration (Glykys et al., 2014). Interestingly, PNN formation in neonates can be altered by reducing synaptic input to motoneurons (Kalb and Hockfield, 1994). The formation of this structure occurs at the same time as the tripartite synapse (Pyka et al., 2011). Collectively, these data are indicative of the PNNs function in the protection and mediation of typical neuronal function. Due to the importance of the ECM and PNNs in cellular properties and plasticity, the question remains whether they perform the same functions for all the cells they surround and in all areas of the CNS. While their basic function is largely known, recent evidence suggests that the specific components of the ECM mediate specific effects upon cellular function and activity. Both these effects will be discussed within the following sections.

3. PNNs in development and in the adult

In the adult CNS, after the end of the critical periods, most forms of plasticity are much reduced. Traditionally, this is thought to be when ECM components become stabilised. However, in the developing juvenile brain, particularly during the critical periods that occur after synaptogenesis is complete (around 4-5 years old in humans), large changes in the pattern of connections driven by external experience are possible, largely due to the differential composition of the ECM. This was classically shown in the visual cortex, where occlusion of one eye during the critical period caused the cortical neurons to favour connections from the non-deprived eye, which would not have happened if the occlusion was performed after the closure of the critical period (Pizzorusso et al., 2002). Interestingly, CS removal in the visual cortex by ChABC injection reactivates the plasticity, allowing remapping of cortical neurons to the deprived eye to take place in the adult visual cortex after critical period closure (Pizzorusso et al., 2006) and illustrating the importance of CS-GAGs in the induction of plasticity within the CNS. The specific window for this period of plasticity and length of the critical period depend on the neuronal systems and are different between species.

Overall the mature CNS lacks the juvenile level of plasticity (Gundelfinger et al., 2010). Although the main decline in plasticity occurs at the closure of critical periods, there is a further continuing decline during the course of normal ageing, one of the consequences of which is progressive cognitive impairment, and loss of the ability to compensate for the effects of neurodegenerative disease (Morrison and Baxter, 2012; Yang et al., 2017). This effect is clearly seen in the diminishing spatial learning and memory of adults and has been

demonstrated across several species (Gallagher and Rapp, 1997; Maurer et al., 2017; Rosenzweig and Barnes, 2003). There is some synapse loss in ageing and much more in Alzheimer's disease, but memory impairment, does not correlate closely with neuronal and synapse loss in aged animals (Burke and Barnes, 2006; Gray and Barnes, 2015; Rapp et al., 2002). The limited plasticity of the mature CNS cannot be understood just in terms of intrinsic changes to the cells but rather that their plastic potential has become latent. Recently, the ECM has been found to inhibit and restrict adult CNS plasticity as removal of this matrix uncovered levels of plasticity previously only seen in young animal (Pizzorusso et al., 2006; Romberg et al., 2013; Stamenkovic et al., 2017; Yang et al., 2015). However, the mechanisms by which the ECM limits plasticity in the CNS are not well characterised. Nonetheless, CSPGs and particularly those CSPGs in PNNs are known to play a key role. Indeed, the role of CSPGs in the control of plasticity has mostly been revealed by using the bacterial enzyme chondroitinase ABC (ChABC) to digest the CS-GAG chains. This treatment can reactivate plasticity in several parts of the CNS, but it digests CSPGs both in and out of PNNs. Further, knockouts of HAPLN1 link protein, tenascin-R and aggrecan all lead to attenuated PNNs, and all have the same effect as ChABC on plasticity, implicating the CSPGs in PNNs in the control of plasticity ((Brückner et al., 1998; Carulli et al., 2010), unpublished results). The HAPLN family, in particular, play an essential role in PNN development as their expression coincides with the closure of the critical period. Indeed, knockdown of HAPLNs delays critical period closure (Carulli et al., 2010; Oohashi et al., 2002; Popelář et al., 2017). In recent years, the development of specific knock outs and antibodies have allowed the mechanisms by which the ECM governs plasticity to be studied in greater resolution, although there is still much work to be done to determine exactly how these individual components affect specific cellular functions.

3.1 CS sulphation changes in development and aging

Formation of ECM components has been shown critical to the initiation of developmental stages. Indeed, CS accumulation is required for starting the critical period as knock out of chondroitin sulfotransferases has been shown to block the onset of this developmental stage (Hou et al., 2017). Interestingly, the accumulation of CS chains in the PNN enables the closing of the critical period, via sequestration of Otx2 (Beurdeley et al., 2012; Hou et al., 2017). This may support GABAergic neuron maturation, further precipitating critical period closure (Ueno et al., 2017b), and mediating specific cellular functions. CS-GAGs have been shown to bind several different proteins which are potential effectors of the PNNs. An example is Semaphorin3A, which binds specifically to PNNs and has strong effects on synapse dynamics and neurite growth. This binding is dependent on the sulphation pattern of the CS chains, with CS-E attracting both Sema3A and Otx2 (Dick et al., 2013; Gama et al., 2006; Sugiyama et al., 2008). The spatial position, not the overall charge of the sulphate groups, on the CS chain determines the binding properties (Gama et al., 2006). A small proportion of CS chains remains unsulphated, 3% in the diffuse ECM and 10% in the PNN fraction, which may give rise to a different functionality (Bertolotto et al., 1996; Deepa et al., 2006; Jenkins and Bachelard, 1988a).

The sulphation pattern of CS has been found to change during embryonic development from a high CS-C (6-sulphates): CS-A (4-sulphates) ratio of 2:1 in early embryonic development to a low 1:1 ratio at birth (Kitagawa et al., 1997). This change could contribute to the development of the PNNs in the critical period (Ueno et al., 2017a). After the critical periods, there is a further change, and the ratio also changes throughout life as the levels of CS-C progressively decrease with an almost complete loss in aged brains (Foscarin et al., 2017; Jenkins and Bachelard, 1988a). Nonetheless, it is important to note this reduction is specific to the PNNs

(Foscarin et al., 2017). This change causes greater inhibition of neurite out-growth in dorsal root ganglion culture, an effect not being observed when younger PNN extracts were used. It is assumed that the increasingly inhibitory PNNs in the aged brain participate in the loss of memory and cognition in the elderly (Foscarin et al., 2017). These data show that specific CS sulphation in the PNNs of aging brains made these structures more inhibitory, decreasing plasticity and, simultaneously, affecting memory formation (see 4.4). These data leads credence to the idea that specific components of the ECM and PNNs will alter when functionality is changed.

3.2 Further changes in age related plasticity

Apart from the PNNs, age-dependent changes are also observed in the diffuse ECM, affecting CNS plasticity and cellular properties. Ageing is associated with increased background inflammation throughout the CNS (Villeda et al., 2011). Sterile inflammation activates astrocytes that then produce HA (Cargill et al., 2012). Reactive astrocytes also produce higher levels of chondroitin 4-sulphate (CS-A) chains due to up-regulated expression of chondroitin 4-sulfotransferase (Wang et al., 2008), causing a more inhibitory environment in the ECM. Further, HA levels in the grey matter ECM also increase with age (Cargill et al., 2012; Jenkins and Bachelard, 1988a; Sherman et al., 2015). This rise may be due to an increase in HA synthase 1 (HAS1; a membrane bound enzyme which facilitates the production of HA) in reactive astroglia or an increase in astroglia numbers. The high level of HA in the aged population is suggestive of a lack of plasticity during aging and impairment of memory and learning (Moon et al., 2014; Solis et al., 2012) indicative of how the ECM effects the progression of neurological decline.

PNNs are dynamic structures, the number and density of which can change in response to external events. for example, behavioural reinforcement can reduce PNN numbers in both the cortex and the cerebellum (Carulli et al., 2013; Pizzorusso et al., 2002). Further, PNNs are also removed as a result of epileptic events (Miyata and Kitagawa, 2016). It is also probable that there are frequent changes in PNNs at the level of individual synapses and dendritic regions, although this has not been proven. As such, PNNs are critical to the development and progression of some neurological diseases. These changes can be caused both by changes in the synthesis of matrix molecules with age, and also through changes in enzymatic degradation. The PNNs are targets of matrix metalloproteinase (MMP)-9 and several other MMPs (Rossier et al., 2015). This pairing has been linked to plasticity as exposure to enriched environment (EE) caused a decrease in PNN staining in the lateral deep cerebellar nucleus, a reduction that is abrogated in MMP-9 knockout (KO) mice (Stamenkovic et al., 2017). Further, MMP-9 and PNNs were found to co-localise after EE exposure, suggesting that MMP-9 secretion is a cause of the decrease in PNN staining. The remodelling of the PNNs by MMP-9 allows dendritic spine modification and greater plasticity by enabling synaptogenesis (Stawarski et al., 2014). MMP-9 expression is upregulated in ageing but no corresponding decrease in PNN staining is observed (Romero et al., 2010; Ueno et al., 2017b). This suggests an upregulation in the expression of MMP-9 does not directly translate into an increase in the MMP activity. However, there are several MMP inhibitors that exist to balance MMP activity and control digestion. Also, recruitment of MMP to the PNNs is dependent on a corresponding increase in tenascin C. Another possibility is due to an increased permeability of the basement membrane, reducing the amount of MMP-9 in the brain (Brkic et al., 2015; Lepelletier et al., 2017). This reduction of functional MMP-9 could then prevent adequate remodelling of the PNNs during learning and may contribute to the thickening of the matrix observed in aged rats (Ueno et al., 2017b).

3.3 Memory and *Alzheimer's Disease* - a role for the ECM

Memory is a form of plasticity. Digestion of CSPGs with ChABC or attenuation of PNNs in HAPLN and aggrecan knockout animals have the same effect on object recognition memory, with a prolongation of memory out beyond 48 hrs compared with less than 12 hrs in normal animals (Romberg et al., 2013). In fear memory, ChABC application to the amygdala restores the juvenile pattern of unlearning (Gogolla et al., 2009), while in the auditory system, hyaluronidase restores agility to learning new patterns (Frischknecht et al., 2009). Because memory changes are seen in transgenics that specifically affect PNNs, these structures are implicated in the control of memory. A probable mechanism is the control of inhibitory synaptic inputs onto PV GABAergic interneurons. Memory events increase the number of these inhibitory synapses, relieving inhibition in the cortical circuits that the PV neurons control. ChABC treatment also allows a greater number of inhibitory synapses to form, so increasing local cortical excitability (Donato et al., 2013). Ageing is the major risk-factor for neurodegenerative diseases such as Alzheimer's disease (AD). Alzheimer's and related conditions are accompanied by the widespread loss of neurons and synapses and also by a general increase in inflammation in the CNS. The inflammation has many consequences, but in the ECM it leads to greater levels of HA in AD brains compared to age matched controls (Jenkins and Bachelard, 1988b), which can reduce neurogenesis and may affect myelination (Hollands et al., 2016; Moon et al., 2014). Inflammation may also change the sulphation pattern of CSPGs, but this has not yet been investigated.

AD is characterised by a loss of memory as a result of neuronal and synaptic dysfunction (Pozueta et al., 2013). It is reasonable to think of AD pathology as a form of CNS lesion in which function might be restored by enhancing plasticity to enable bypass circuits to form around damaged neurons. In order to test this idea, plasticity in a tauopathy and amyloid beta model was stimulated by injection of ChABC into the rodent brain. In both models, memory was restored, using object recognition memory in the tauopathy mice, contextual fear conditioning in the amyloid beta model (Vegh et al., 2014; Yang et al., 2015). ECM digestion restored synaptic transmission as shown by the restoration of long term depression (LTD) in the hippocampus. However, the effect of ChABC on the matrix is temporary, and PNNs return within five weeks, and as this happens memory is again impaired (Yang et al., 2015). Similar restoration of memory occurred when the inhibitory chondroitin 4-sulphate CS-A was specifically targeted using an anti-chondroitin 4-sulphate antibody. Memory loss also occurs in ageing, and during this process there is a change in the sulphation of CSPGs in the PNNs, with a loss of permissive 6-sulphated CS-C and an increase in inhibitory CS-A (Foscarin et al., 2017). It is very likely that this change in the inhibitory properties of the PNNs could be responsible for some of the memory changes in ageing. The mechanism of restoration of memory in neurodegeneration by ChABC is presumably a combination of enabling sprouting to make bypass circuits, and effects on the excitability of cortical circuits due to increased inhibitory inputs to PV interneurons described above.

How might PNNs be involved in memory? Removal or reduction of the PNNs leads to a permissive neuronal profile, allowing synaptogenesis onto PV interneurons and encouraging memory formation (de Vivo et al., 2013; Quattromani et al., 2017; Yang et al., 2017). In the aged brain, the increasing inhibitory nature and numbers of the PNNs keep PV positive interneurons in an inhibitory profile, probably causing a deficit in memory and learning (Donato et al., 2013; Ueno et al., 2017b). This suggests that the cognitive impairment observed in ageing is partly due to a failure to establish new synapses rather than a loss of established synapses and highlights how ECM mediated restrictions on CNS plasticity have key functional effects upon individuals.

Modification of the ECM in the adult could facilitate further learning or help protect from neurodegeneration. However, the mechanism through which the ECM affects cellular properties and restricts plasticity in the juvenile, adult or degenerative state is not yet fully know. Nonetheless, ECM modification holds great promise as a potential tool to modify the neuronal effects of aging.

4. ECM involvement in neuronal excitability and synaptic plasticity

As previously described, ECM surrounds neurones and affects the vital cellular functions of neuronal excitability and synaptic transmission.

4.1 Neuronal excitability

The role of PNNs in modulating activity has been studied both in vitro and in vivo, mainly though the enzymatic removal of CS with ChABC. PNNs both in vivo and in vitro mostly surround PV-positive GABAergic neurons, so most of the findings relate to these cells. In hippocampi cultures from neonate mice (maintained in vitro for 15-19 days), degradation of PNNs around PV positive inhibitory interneurons with the enzyme increased interneuron excitability without affecting the number or distribution of perisomatic GABAergic presynaptic terminals (Dityatev et al., 2007). Conversely blockade of action potentials, transmitter release, Ca^{2+} permeable AMPA subtype of glutamate receptors or L-type Ca^{2+} voltage-gated channels strongly decreased the extracellular accumulation of PNNs components in cultured neurons (Dityatev et al., 2007). These data suggest that, within this region of the brain, there might be a feedback loop through PNNs act to control neuronal excitability. However, these data are contrary to results obtained in vitro on mice cortical slices. ChABC treatment on P70 cortical slices showed a reduced excitability on PV-positive fast-spiking cortical neurons (Balmer, 2016). Similarly, in the visual cortex, removal of PNNs in vivo by ChABC decreased inhibition and increased gamma activity (Lensjo et al., 2017). Indeed, ChABC treatment lowered mean spiking activity of putative inhibitory units (Lensjo et al., 2017). This would suggest that specific neuronal functions are maintained through the occurrence of the PNNs. Moreover, high-frequency gamma oscillations (30–80 Hz) of the cortex are highly correlated with activity in the PV^{+} cells (Cardin et al., 2009). These results are consistent with the findings discussed above in which ChABC treatment allows an increase in inhibitory inputs onto PV GABAergic neurons, decreasing their activity and allowing increased excitability in the cortex (Donato et al., 2013). Finally, in the auditory brainstem where some of the fastest and most precisely firing neurons are housed (Bertolotto et al., 1996; Blosa et al., 2013; Härtig et al., 2001), principal neurons in the medial nucleus of the trapezoid body (MNTB) are able to follow extremely fast afferent stimulation (>1 kHz) with incredible accuracy (Kim et al., 2013). Removal of PNNs with ChABC does not affect the firing ability (of up to 1kHz) of the MNTB neurons but reduce their excitability and the gain of spike output (Balmer, 2016). From what we have said previously, one might expect the sulphation pattern of PNNs to affect their influence on neurons. The overexpression of chondroitin 6-O-sulphate transferase 1 (C6st1), an enzyme which is responsible for the production of chondroitin 6-sulphates, prevents the maturation of some of the electrophysiological properties of PV interneurons (Miyata et al., 2012), and the PNN neurons show greater depolarisation and wider action potentials (Miyata et al., 2012).These data reveal some ways in which the CNS ECM maintains and regulates neuronal function based upon activity and thus affecting cellular properties.

Other than inhibitory neurons, PNNs and ECM changes have also been shown to affect excitatory neurons. For example, in the CA2 region of the hippocampus, PNNs are mostly found surrounding excitatory synapses of pyramidal neurons (Celio, 1993; Costa et al., 2007; Fuxe et al., 1997). However, these intrinsic properties of CA2 pyramidal neurons are not altered in response to PNN degradation (Carstens et al., 2016). Similarly, ChABC treatment does not affect the mean activity of putative excitatory units in vivo in the visual cortex (Lensjo et al., 2017). These data may suggest that PNNs help regulate the functions of glutamatergic neurons, but are not essential for their normal functioning within the CNS. More data is required to refine and develop these points. However, recent evidence has shown that the PNN protein brevican can mediate cellular responses through activity-dependent gating of PV^+ interneurons (Favuzzi et al., 2017). With the GABAergic interneurons, cortical PV^+ (as opposed to the somatostatin$^+$) interneurons facilitate the balance of neuronal activity between excitation and inhibition, particularly through learning (Froemke, 2015) and has been linked to psychiatric disorders (Hu et al., 2014). Favuzzi et al., (2017) demonstrated that the PNN brevican modifies PV^+ interneuron excitability and therefore their synaptic outputs by controlling synaptic AMPA receptor level imput and potassium channel localisation on these PV^+ neurones. Further that activity dynamically regulates PNN brevican levels. As such, it is shown that PNN components are dynamic and can individually help co-ordinate specific responses to experience.

4.2 Synaptic plasticity

Synaptic plasticity is a consequence of de novo formation of synapses or from transient but strictly controlled proteolysis at the synapse (Magnowska et al., 2016). The presence of ECM CSPGs, particularly brevican, on the neuronal surface limits the lateral diffusion of AMPA-type glutamate receptors. Enzymatic removal of HA, the PNN scaffold, increases extra-synaptic receptor diffusion and the exchange of synaptic AMPA receptors (Frischknecht et al., 2009). NMDA-type glutamate receptor function and trafficking are also strongly influenced by components of ECM including reelin, MMPs and integrins (Groc et al., 2006; Shi and Ethell, 2006). These data demonstrate how the ECM affects the specific functionality of CNS cells and their properties.

The ECM within the CNS has been shown to affect plastic changes on the functional properties at the synapse, acting in both the short-term and the long-term. In the presence of bicuculline (a $GABA_A$ receptor antagonist), no significant differences in basal excitatory synaptic transmission or AMPAR/NMDAR ratio was observed after ChABC treatment in CA2 region of hippocampal slices (Carstens et al., 2016). Similarly, treatment with ChABC did not interfere with short term plasticity (Bukalo et al., 2001). By contrast, decreased short-term potentiation and depression was observed in knockout mice for tenascin-R (Bukalo et al., 2001). Alternatively, substantial work has shown similarly important effects of ECM upon long-term synaptic plasticity. Under normal physiological condition, CA1 neurons show a typical long term potentiation (LTP) under a “pairing protocol”, while CA2 neurons do not. However, LTP of excitatory synapses in the CA2 stratum radiatum (SR) can be altered to a level comparable to that induced at CA1 synapses, via ChABC treatment (Carstens et al., 2016). These results are at variance with the ones obtained in CA1 region of hippocampus. In this latter, LTP is similarly reduced in mice knockout for tenascin-R and after treatment with ChABC. However, LTD in KO mice for tenascin-R is normal but impaired after treatment with ChABC (Bukalo et al., 2001). These data show that the local ECM can modulate the plasticity in specific areas of the CNS. The mechanism for this modulation, and precisely why some areas are more affected than others requires further exploration. However, these data clearly demonstrate the importance of the ECM in modulation of CNS functional activity and cellular properties.

5. ECM plasticity in CNS disorders and injury

The component molecules of the ECM alter and reorganise either in response to or in the development of disease and injury. There are many years of evidence showing the importance of ECM upregulation following insult to the CNS, particularly in the formation of the glial scar, and how this may prevent functional recovery over-time. However, recent evidence has shown that downregulation of the ECM is additionally correlated with and probably important in psychiatric disorders including schizophrenia, mood disorders, autism, and addiction. Here we shall discuss how the pathophysiology of the ECM changes in the progression of each of these conditions, highlighting potential ways in which manipulation of the ECM may be therapeutically useful.

5.1 Upregulation of ECM components: injury, stroke, and brain tumours

Over the last two decades, experimental research has shown the effect of ECM upregulation following injury and trauma to the CNS and how, without intervention, this contributes to a reduction of plasticity and failure to functionally recovery.

5.1.1 CNS injury and stroke

Stroke and injury to the CNS cause substantial alterations in the ECM. The trauma leads to the migration of activated astrocytes, oligodendrocyte precursor cells, and microglia into the site of injury and, subsequently, the formation of scar tissue (Asher et al., 2000). This deposition of densely compacted tissue performs a biphasic response to injury where acutely it seals the area, preventing further damage, restricting inflammation, sealing the blood-brain barrier and supporting neurons, but chronically can act as a barrier blocking functional recovery (Anderson et al., 2016; Renault-Mihara et al., 2008; Rolls et al., 2009). Interestingly, formation of the astrocytic scar has been shown to be partly instigated by plastic changes in type I collagen in the fibrotic ECM at the lesion core which acts on astrocytes by integrin binding and N-cadherin, signalling formation of the tissue (Hara et al., 2017). Indeed, recent studies have shown that scar forming reactive astrocytes become quiescent and unreactive a week following spinal cord injury (Hara et al., 2017), indicating the short time window that is required to form this permanent barrier surrounding the site of trauma.

Key molecules in this scar tissue are CSPGs with neurocan, versican, brevican, and NG2 predominating at the site of trauma and (without intervention) remain constant throughout the patient's life (Asher et al., 2000; 2002; Buss et al., 2009; Galtrey and Fawcett, 2007). The high CSPG content in the scar can inhibit axon regeneration, outgrowth, and plasticity (Alilain et al., 2011; Barritt et al., 2006; Borisoff et al., 2003; Bradbury et al., 2002; Dou and Levine, 1994; Fitch and Silver, 2008; Friedlander et al., 1994; Snow et al., 1990; Tang et al., 2003). Davis et al. demonstrated that dorsal root ganglion neurons form dystrophic growth cone formation in areas of CSPG upregulation (Davies et al., 1997; 1999). However, removal of astrocytes in regions of CNS damage can reduce the scarring reaction, but has adverse effects through loss of the ability of astrocytes to control inflammation, stimulate resealing of the blood-brain barrier, protect neurons and other functions (Anderson et al., 2016). Interestingly, while CSPGs have been shown to increase at the site of injury after stroke, they are reduced in the PNNs of the peri-infarct area. This suggests that a local plastic and endogenous response may occur to reactivate activity in the local area of the trauma (Hobohm et al., 2005; Madinier et al., 2014).

As the CSPG rich area can be a significant obstacle against functional regeneration and recovery following injury, it is not surprising that they are a target for treatment strategies. These can be broadly divided into four areas. The first being to target the CSPG, offsetting its effects through the use of monoclonal antibodies to aid functional recovery through an increase in axon conduction and excitement (Tan et al., 2006; Ughrin et al., 2003). However, this is not the only experimental method readily used to reduce CSPG inhibition. The most common method is through the breakdown of CS-GAGs with the application of ChABC (Huang et al., 2003; 2000; Prabhakar et al., 2005; Tkalec et al., 2000; Yamagata et al., 1968). An alternative is to target CSPG glycanation through knockdown of a key enzyme (Grimpe et al., 2005). These CSPG strategies have had substantial success at causing axonal regrowth both in vitro and in vivo, using a variety of animal species, numerous different models and at a variety of time points post injury. The effects can be maximised in combination with rehabilitation strategies that can direct the plasticity (Alilain et al., 2011; Garcia-Alias et al., 2011; Wang et al., 2011). Alternatively, the core proteins of CSPGs can be digested by the endogenously produced disintegrin-like and MMPs with thrombospondin type 1 motif 4 (ADAMTS4) (Apte, 2009; Lemarchant et al., 2014; Tauchi et al., 2012) and matrix MMPs (Larsen et al., 2003; Lemke et al., 2010) to aid recovery following spinal cord injury. Other methods being employed experimentally to reduce the inhibitory CSPGs is to prevent their formation through the use of DNA enzymes (Grimpe, 2004), prevention of enzyme conversion (Nigro et al., 2009), or gene deletions (Takeuchi et al., 2013), although the clinical application of these techniques is limited. Overall, treatments targeting CSPGs after CNS damage have shown very consistent results in a variety of animal models and species. To date the only clinical trial has been in canine spinal cord injury, where ChABC injection enhanced recovery (Jeffery et al., Brain in press), but there have been no clinical trials in human patients; this step is very overdue,

5.1.2 Brain tumours

Similar to injury and trauma, a number of molecules in the ECM are upregulated around brain tumours. This includes increases in tenascin-C (Bellail et al., 2004). Located near blood vessel walls, tenascin-C acts to facilitate angiogenesis in the primary tumour region. It has been shown that targeting drugs to tumours using RNAi against tenascin-C increases the patient's life by 10 weeks in glioblastoma multiforme and 18 weeks in grade III astrocytoma (Wyszko et al., 2008). Similarly, secreted protein acidic and rich in cysteine (SPARC) has been shown to increase in astrocytomas and meningiomas, decreasing cellular growth and increasing cell invasion (Bellail et al., 2004; Rempel et al., 1999; 2001; 1998). Further, it has recently been shown through KO experiments that brevican facilitates the progression and motility of cells in glioma, although has not required to maintain these characteristics perhaps indicating a time dependent effect for the ECM component in tumour progression (Dwyer et al., 2014). Perhaps one of the most highly upregulated ECM molecules in gliomas and meningiomas is HA, and the molecules receptors hyaluronan-mediated motility receptor (RHAMM) and CD44 (Delpech et al., 1993). Recent interest in the role of HA in cancer progression has increased as the high molecular mass hyaluronan produced by the naked mole rat was shown critical for the animal's resistance to cancer development (Tian et al., 2013). However, the effect of increasing HA and its receptors in human brain tumours is to augment cellular migration and thus invasion (Bellail et al., 2004). As a number of malignancies express the HA receptor CD44, it has been used as a target for directed nanoparticle coupled therapies. This has led to increased delivery of paclitaxel to brain tumour cells in a rodent model, increasing life expectancy (Mittapalli et al., 2013). While the mechanism is unclear, the upregulation of ECM components in both the brain tumour stroma and parenchyma have been shown to facilitate cellular growth and invasion. However, there is

also great potential to use these upregulated molecules for targeted treatment of the condition and thus to use these plastic changes to extend life expectancy.

5.2 ECM components in psychiatric disorders

Numerous studies have demonstrated alterations in ECM regulation, components, and formation in individuals with CNS disorders. For example, alterations in the expression of reelin have been demonstrated in the numerous areas of the brain associated with patients on the autism spectrum (Fatemi, 2005; Hussman et al., 2011; Weiss et al., 2009). These data suggest that the consequence of abnormalities in ECM formation and maintenance have wide-reaching implications. Here we shall discuss how decreases in ECM components are linked to psychiatric disorders as diverse as addiction, schizophrenia and mood disorders.

5.2.1 Addiction

Modifications of ECM occur during the development of addiction disorders. Cocaine has been shown to induce changes in neural ECM in both human patients and rodent models (Mash et al., 2007; Smith et al., 2014). Interestingly, evidence suggests that PNNs in the prefrontal cortex (PFC) initially decrease during the initial stages of heroin self-administration but are increased with continuing exposure to the drug suggesting that PNNs may be depleted during acquisition of addiction and then increased during consolidation (Van den Oever et al., 2010). Breakdown of PNNs using ChABC enhanced the extinction of morphine- or cocaine-induced conditional place preference and decreased rates of behaviour reinstatement in experimental models of opioid addiction (Slaker et al., 2015; Xue et al., 2014). This may be caused by a reduction in activation of the neurons previously surrounded by the PNN (Slaker et al., 2015). These data were replicated following assessment with heroin self-administration (Xue et al., 2014). Similarly, both mRNA and protein levels of HA, brevican, tenascin-R in the medial pre-frontal cortex decreased following forced removal of self-administered heroin as compared to animals that self-administered saline (Van den Oever et al., 2010). The levels of CSPG recovered following cue-induced reinstatement of drug self-administration. Further, with the reoccurrence of heroin self-administration, the frequency of spontaneous inhibitory postsynaptic currents increased. These data give another example where PNN components or turnover is dynamically mediated by alterations in experience and the environment (Van den Oever et al., 2010). Further, that drug-associated cues correlate to an increase in interneuronal GABAergic activity which may alter with changes in the PNN surrounding these neurons. Xue et al. additionally showed that only animals with ChABC mediated breakdown of PNNs and extinction training showed increased levels of GluR1, GluR2 and BDNF (Xue et al., 2014). This may further indicate that PNN removal facilitates neuronal plasticity but requires additional environmental influence or training to ensure the plasticity evoked can be functionally harnessed. However, it is likely that the plasticity induced by ECM modification alone is not sufficient to induce addictive behaviours, one would require additional environmental cues or behavioural training to develop these traits. Nonetheless, the promising evidence linking such plastic changes to the development of disorders suggests that PNN components may be targets for therapeutic intervention.

5.2.2 Schizophrenia

Schizophrenia is a polygenic disorder which typically is first exhibited at late adolescence/early adulthood, stages at which the amygdala, entorhinal cortex, and PFC (brain areas associated with the disease) mature (Woo, 2014). There is evidence to suggest that errors within brain development facilitate development of the

disorder (Halim et al., 2003; Lewis et al., 2012; Woo, 2014). Essentially, that altered neurotransmission inhibits gamma oscillations in schizophrenic individuals, which are critical for cognitive function (Lewis et al., 2005; Sun et al., 2011; Woo, 2014). ECM components are implicated through their effects on growth, migration and development of neurons and through PNNs.

The majority of evidence linking ECM changes and schizophrenia concern PNNs and reelin. Regions of the brain associated with schizophrenia demonstrate a ~60-75% decrease in PNNs, altered glial CSPG expression, and altered expression of PNN components and metalloproteases (Mauney et al., 2013; Pantazopoulos et al., 2013; 2015; 2010; Pietersen et al., 2014). In addition, the components of PNNs have been shown altered in form or density in schizophrenic individuals. For example, recent genetic analysis has confirmed the correlative link between a neurocan variant in PNNs and altered cortical folding in schizophrenic patients (Muhleisen et al., 2012; Schultz et al., 2014). These data suggest that significant areas of the schizophrenic brain have substantial alterations in ECM. This may increase periods of synaptic instability, reduce pruning, and facilitate neurotransmission by reducing ion buffering in cortical networks facilitating development of the disorder (Mauney et al., 2013; Woo, 2014).

In addition to the evidence concerning PNNs, there is strong evidence to suggest that the development of schizophrenia is associated with reductions in the expression of the ECM component reelin in the hippocampus and PFC (Fatemi et al., 2000; Impagnatiello et al., 1998). This downregulation occurs simultaneously with alterations in GABA metabolism and receptor expression un-associated with changes in GAD67 expression (Impagnatiello et al., 1998; Liu et al., 2001). Reelin is important for the regulation of NMDA subunit expression in synapses (Campo et al., 2009; Iafrati et al., 2014). As such it is possible that glutamatergic input through these reelin modulated receptors may underlie the neuronal GABAergic dysfunction evident within the disorder (Woo, 2014). Collectively, these data show a clear correlation between schizophrenia and events in the ECM. Whether they are causative is not proven, but it is conceivable that the ECM is involved in the formation of schizophrenia and thus there could be possible routes for potential intervention in the disorder. However, the mechanism of PNN involvement and development has yet to be fully elucidated which may limit clinical application of any treatment.

5.2.3 Mood disorders

Major depressive disorder and bipolar disorder have a similar neurobiology and affect similar brain areas including the PFC and hippocampus and are associated with disruption to neurodevelopment and plasticity (Martinowich et al., 2009). As such, the ECM components within these regions have the potential to contribute to the pathology of the disorder. Post-mortem studies have demonstrated reductions in the PNNs across a number of nuclei in the amygdala of depressed patients (Pantazopoulos et al., 2015). Although humans with bipolar disorder and rodent models do not show such trends, they more regularly demonstrate alteration in neurocan (Cichon et al., 2011; Mauney et al., 2013; Zhou et al., 2001). Nonetheless, similar to schizophrenia, decreases in reelin additionally occur in areas of the brain associated with both major depression and bipolar disorder (Fatemi, 2005; Guidotti et al., 2000; Lussier et al., 2011). Further, bipolar disorder has been associated with a variant of the reelin gene (Goes et al., 2010). However, the decrease in ECM components and the development of mood disorders is currently no more than a strong association, possibly indicating that they contribute to the development of the disorder but alone are not causal. To determine this the mechanism of

ECM plasticity and the development of mood disorders must be determined. However, the advent of these changes in patients suggests a potential use of ECM modification as a facilitation to the treatment of these psychological disorders.

6. Conclusion

Both long-standing and emerging evidence shows that the ECM is essential for the normal functioning, cellular properties, and plasticity of the CNS. That its composition and formation are important from development (enabling plasticity and growth within neuro-circuitry) to the adult (where it stabilises the neural networks formed). Indeed, it has been shown that removal of ECM components in the adult can cause an increase in plasticity. However, this system is dynamic, as the activity in the neural circuitry changes, so does the composition of the ECM, facilitating continued learning and optimisation of CNS function. Indeed, through its functions as a buffer and regulating ion diffusion, recent evidence has shown the ECM of the CNS is critical for the formation of memory and learning, fundamental functions of the brain. The data presented here also demonstrate how perturbations in the composition of the ECM is related to numerous disease and disorder states. This includes Alzheimer's disease, stroke, trauma, mood disorders, diseases on the autism spectrum, brain tumour progression, Schizophrenia, and addiction. However, the mechanism of these disease progression and its relationship to changes in the ECM is not often clear, thus it is not known if the alterations in matrix are a causal factor in the initiation or progression of these disorders. It is important to understand this as ECM components in the CNS could be valuable targets for therapeutic intervention in clinical disease states. Indeed, due to the ubiquitous nature of the ECM within the CNS, this matrix hold substantial potential for affecting neuromodulation and plasticity within multiple systems and areas in the brain and spinal cord simultaneously.

7. References

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Figures:

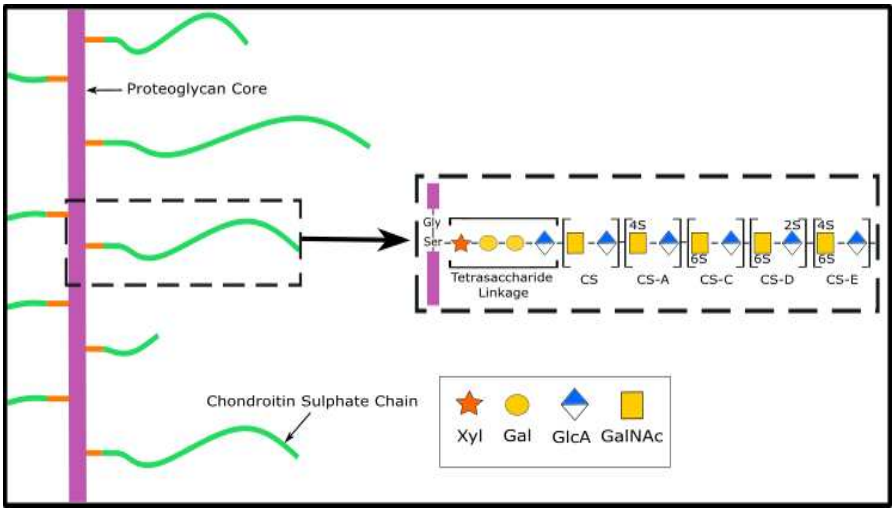

Fig. 1: Schematic of chondroitin sulphate (CS) chain attachment to the proteoglycan core. CS chains are assembled onto proteoglycan cores via a serine attached O-linkage, which must first be assembled. The CS chain is then formed from alternating monosaccharides by a family of different glycosyltransferases. CS chain length can vary between 25-50 disaccharide units. The chains can then be further modified by the addition of sulphate groups onto the disaccharide components creating distinct species. Sulphation on the fourth position or the 6th of N-acteylgalactosamine (GalNAc) produces either monosulphated CS-A or CS-C. GalNAc can be dual sulphated at both positions to create CS-E. CS-C can be further sulphated on the second position of the glucuronic acid (GlcA) residue. Within one CS chain several sulphation patterns can be present.

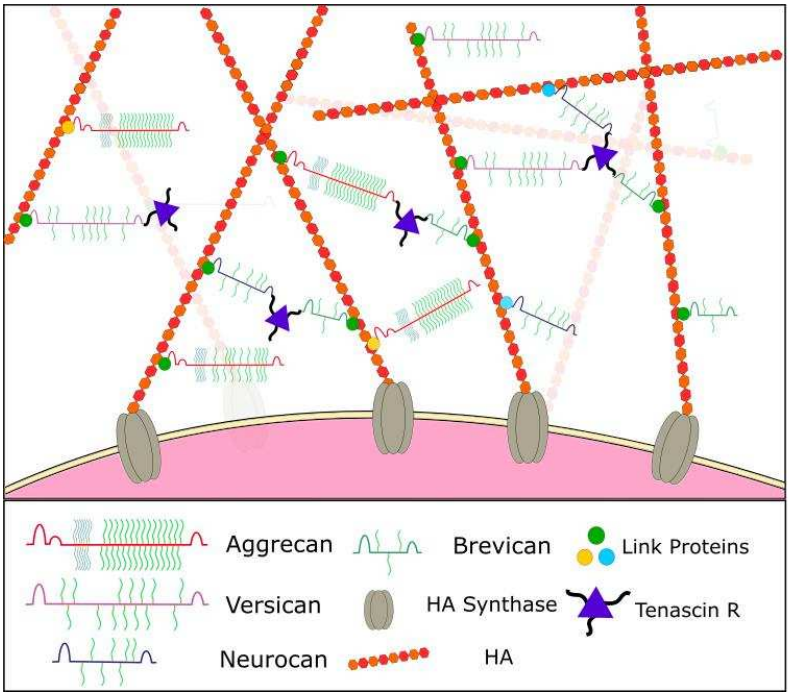

Fig 2: Schematic of the perineuronal net (PNN). The PNN forms a macromolecular structure around the cell and is formed of several components. The backbone of the PNN are the hyaluronan (HA) chains. These large unbranched chains are docked onto the cell surface by their synthase. The HA provide the backbone on which the CSPGs can dock. Their binding to the HA chains is stabilised by the HAPLN family. Tenascin R is then thought to condense the PNN further by acting as a cross-linker between attached CSPGs. Together they form a rich polyanionic environment.