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Extracellular matrix remodeling in neurological diseases

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ABSTRACT

The neural extracellular matrix (ECM) in the central nervous system (CNS) exists in multiple forms, including perineuronal nets (PNNs), perisynaptic ECM within tetrapartite chemical synapses, and periaxonal coats. Together with the diffuse interstitial ECM, these components regulate synaptic stability, plasticity and network excitability. Recent research highlights the crucial roles of ECM in shaping memory engrams and cognitive flexibility, positioning ECM as a promising therapeutic target for cognitive interventions. Mechanistically, ECM remodeling is driven by multiple factors, including neuronal activity, neuromodulation and neuroinflammation. ECM remodeling is a shared hallmark across multiple CNS diseases, yet it manifests in condition-specific patterns, from robust scar/fibrosis formation in trauma and stroke, to more subtle and distributed but functionally significant ECM changes in chronic disorders, such as diffuse microvascular matrix accumulation in cerebral small vessel disease (CSVD), PNN thickening in metabolic disease, and ECM entanglement with misfolded proteins in neurodegeneration. Multiple ECM-targeting treatments have shown efficacy in preclinical models of CNS diseases and provide attractive options for further optimization, repositioning and clinical development. Innovative technologies such as vital, super-resolution and whole-brain perineuronal net imaging, proximity ligation assays, and ECM multi-omics are emerging as options to provide deeper insights into ECM composition and dynamics, paving the way for novel therapeutic strategies to restore ECM integrity and brain functions and use ECM proteins and glycoepitopes as potential biomarkers for diagnosis and therapeutic monitoring.

Key points

- ECM in the CNS regulates neuronal excitability and synaptic, neural network and cognitive functions as well as vascular permeability and immune cell trafficking.
- Degradation or excessive accumulation of neural ECM in neurological disorders depends on the disease type, progression stage, brain region, neuronal activity and neuroinflammatory status.
- To prevent ECM degradation, inhibitors to metalloproteinases and hyaluronidases have been employed.
- To counter the detrimental effects of excessive ECM accumulation, glycosidases, proteinases, inhibitors of ECM synthesis and receptors proved to be beneficial in multiple models of neurological diseases.
- ECM-targeting therapies restrain the spread of proteinopathies, modulate glial activation, and promote metabolic, synaptic, vascular and cognitive functions.
- Emerging technologies such as glycan profiling, spatial ECM mapping, and detection of proteolytic modifications, are advancing the discovery of potential ECM biomarkers and therapeutic targets.

Introduction

The extracellular matrix (ECM) has attracted significant attention in recent years due to its multifaceted roles across diverse tissues and conditions. The neural ECM, whether interstitial or associated with diverse cells in the nervous system, is distinct from somatic ECM due to the low concentration of fibrous proteins and a high abundance and diversity of glycoproteins, glycosaminoglycans and their corresponding proteoglycans contained within neural ECM[1].

Neural ECM plays critical roles throughout life, from guiding cell proliferation, migration and axon pathfinding during embryonic development, to shaping neural circuitries in neonates and adolescents, regulating the diffusion of Ca^{2+} ions, growth factors and neurotransmitters across synapses, excitation/inhibition balance, synchronization of neuronal activity, and memory and cognition. While research into neural ECM has expanded across many physiological pathways and disease conditions, this review aims to provide an updated unifying view on remodeling and targeting of different ECM forms in neurological diseases. Other reviews are available on the role of neural ECM in substance use and stress disorders [2], gliomas [3], multiple sclerosis [4], and neuropathic pain [5]. At the end, we highlight technological advancements opening new perspectives to characterize ECM heterogeneity and dynamics in health and disease, and develop new therapeutic treatments and biomarkers.

ECM structure and function in health

The ECM is a complex network of structural proteins, such as collagens, proteoglycans, and glycoproteins, that provides mechanical support and biochemical cues to cells. This *bona fide* ECM, also known as the core matrisome, together with ECM-associated molecules including ECM-modifying enzymes (*e.g.* metalloproteinases), regulators, and growth factors, orchestrates the assembly, remodeling, and modulation of ECM functions[6,7]. Many comprehensive reviews have explored this topic[6], this review will focus specifically on *bona fide* ECM molecules within the CNS that influence key brain functions.

ECM forms in the CNS

Neural ECM in early development. The mammalian nervous system originates from neuroectoderm during early embryonic development, where the diffuse interstitial ECM regulates cellular proliferation, differentiation, migration, spatial organization as well as the diffusion of morphogens and growth factors. Early ECM components, including fibronectin, chondroitin and heparan sulfate proteoglycans (CSPGs and HSPGs), and hyaluronan (HA)[8], maintain intercellular space and facilitate efficient diffusion of morphogens and signaling molecules. Many neural morphogens from families such as Wnt, hedgehogs, and semaphorins binds to the neural ECMs to establish a concentration gradient essential for morphogenesis[9-11] and neural patterning. Enzymatic digestion of

neural ECM leads to developmental defects, including cortical plate misfolding and aberrant neuronal migration[12,13].

As the CNS matures, structural stability becomes essential to preserve established synapses, maintain reliable neuronal firing, and protect against inadvertent penetration of drugs and toxins. To achieve this, the neural ECM evolves to become more organized, forming specialized assemblies like perineuronal nets (PNNs), periaxonal, perisynaptic and vascular forms of ECM (Figure 1), which are anatomical stable but yet remain adjustable[14]. ECM molecules, together with interacting proteins, are secreted in an activity-dependent fashion by neurons, glia and vascular cells, forming distinct molecular meshworks around diverse cellular subtypes and subcellular domains of neural cells.

Perineuronal nets. PNNs are specialized ECM structures associated with somatodendritic domain of some neurons whose distribution is highly variable and region-specific[15]. They predominantly surround parvalbumin-expressing inhibitory neurons in the cortex, hippocampus and cerebellum, with sparse occurrence around excitatory pyramidal neurons. PNN architecture consists of long-chain HA anchored to the neuronal surface to which CSPGs from the lectican family (including aggrecan, brevican, neurocan and versican), hyaluronan and proteoglycan link proteins (HAPLNs) and tenascin-R are bound[14] (Figure 1A). Variabilities of PNNs arises from differences in HA chain length, lectican composition, and also the associated PNN binding molecules such as semaphorin 3A and orthodenticle homeobox[16,17].

PNN maturation marks the closure of the critical period, a developmental window characterized by heightened plasticity for circuit establishment and re-organization. Towards its end in postnatal development, PNNs condense around neurons forming distinct holes where synapses localise[18], stabilizing connectivity while limiting further structural remodeling. This process involves chondroitin sulfate (CS) chains in CSPGs, which undergo sulfation changes and signal through CSPG receptors such as protein tyrosine phosphatases PTPσ, PTPδ, and LAR and downstream RhoA - Rho kinase (ROCK) - cofilin pathway to restrict synapse dynamics[19-21,22].

PNN molecules, including brevican, neurocan and tenascin-R, govern the excitability of PV-positive PNN interneurons by shaping excitatory synaptic input and inhibitory output[23-25]. Moreover, PNNs aids astroglial clearance of glutamate and potassium, preventing glutamate spillover and maintain synapse precision[26]. Experimental removal of PNNs with a bacterial enzyme chondroitinase ABC (ChABC) shifts PV-expressing cells towards a more juvenile, disinhibited state[27], reducing GABAergic inhibition. Network consequences include elevated spontaneous activity, impaired evoked gamma oscillations, increased high-frequency ripple-like oscillatory activity, and reduced coherent theta oscillations necessary for integration of multisensory information and memory recall[27,28].

Behaviorally, ECM perturbations enhances cognitive flexibility[28,29], improving reversal learning[30,31], accelerating extinction and increasing memory erasure susceptibility [32,33] while destabilizing spatial representation[34,35]. Recent findings shows that PNN maturation

makes memory engrams less redundant, supports pattern separation and memory precision[35], promotes efficient sparse coding at the cost of reduced adaptability[35]. Thus, ECM-enabled stability ensures accurate memory but limits flexibility, whereas reducing ECM constraints enhances plasticity but risks representational instability.

Periaxonal coats. Perinodal ECM at the nodes of Ranvier and the ECM at the axon initial segment (AIS) are considered specialized, condensed forms of periaxonal ECM, which form molecular scaffolds that stabilize axonal domains, cluster ion channels and limit ion diffusion[36], and ensure reliable action potential initiation and saltatory conduction while permitting regulated plasticity[37,38]. These meshworks comprise of similar molecular composition as PNNs, with HA, lectican (e.g., brevican and versican), HAPLNs (e.g., HAPLN2/Bral1) and tenascin-R, interacting with axonal membrane proteins to maintain excitability and conduction fidelity.

Perisynaptic ECM. Synapses on excitatory neurons are embedded into the perisynaptic ECM that has similar composition as PNN but less dense. Perisynaptic ECM restrains lateral diffusion of AMPA receptors and other transmembrane molecules, which affects short-term synaptic plasticity[39]. Expression of neurocan, brevican and versican, along with tyrosine-phosphorylation of NMDA receptors by integrin ligands, and the activity of ECM glycoprotein reelin, contribute to the induction of long-term synaptic potentiation underlying learning and memory[40]. HA and tenascin-C have been shown to mediate gain-of-function of L-type voltage-gated Ca^{2+} channels[41], further supporting synaptic strengthening. The activity-dependent release of glial CS56-glycoepitope-immunopositive lecticans near stimulated synapses is accompanied by a decrease in synaptic size as well as expression of ARC protein[42], suggesting a role in promoting heterosynaptic long-term depression to constrain structural spine plasticity[43]. These mechanisms contribute to synaptic plasticity and reinforce the concept of a tetrapartite synapse, comprising of pre- and post-synaptic terminals, astrocyte endfeet and the surrounding neural ECM[43].

Interstitial ECM. The interstitial ECM in the CNS is a diffuse ECM network that fills spaces between neurons, glia, and vasculature. While its molecular composition includes hyaluronan, CSPGs and heparan sulfate proteoglycans, glycoproteins such as tenascins and thrombospondins, and a minor fraction of fibrous proteins, it is distinct from highly organized ECM structures that crosslinking proteins such as HAPLNs are absent as shown by fluorescently tagged HAPLN-1 mice and also biochemical characterization[44,45]. Functionally, the interstitial ECM provides structural support, regulates ion and neurotransmitter homeostasis and diffusion, influences cell migration and differentiation, facilitates synaptic plasticity, and contributes to interstitial fluid clearance, thereby maintaining CNS integrity and signaling balance (Deepa et al., 2006; Dityatev & Schachner, 2006).

Vascular ECM. Apart from the CNS parenchyma, neural vasculature is also enriched in ECM components (Figure 1B). Similar to basement membrane in somatic tissues, the

multimeric laminin harbors multiple domains for interaction with HSPGs (perlecan and agrin), type IV collagen, integrins and nidogen, maintaining the integrity of the basement membrane. Basement-membrane ECM participates in blood–brain barrier function, neurovascular coupling, and perivascular (glymphatic) clearance, with implications for cognition and dementia risk when perturbed (e.g., cerebral amyloid angiopathy). Moreover, ECM molecules such as HSPGs are assembled into a thin, hydrogel-like layers lining the luminal surface of blood vessels, called endothelial glycocalyx. The meshwork and selective molecular interaction regulate vascular permeability, inflammation and immune cell trafficking, and protection of vessel wall [46].

Below we focus predominantly on the ECM of PNNs and vascular ECM, for which most data have been gathered, but also discuss remodeling of perisynaptic, periaxonal and interstitial ECM, when relevant. The role of secreted extracellular synaptic organizers accumulating in the synaptic cleft (Fig. 1A) is discussed elsewhere[47].

Mechanisms of physiological ECM remodeling

PNN formation is activity-dependent[48] and delayed by sensory depletion, such as monocular deprivation or whisker trimming in the visual cortex and barrel cortex, respectively[18,49]. While PNN maturation generally correlates with reduced neuroplasticity[18], multiple mechanisms emerged for spatially and temporally confined (i.e. transient) remodeling of ECM to facilitate adaptive synaptic plasticity under physiological conditions. These are similar to mechanisms of ECM dysregulation in diseased brains, although the scale is much different.

Activity-dependent proteolysis by matrix metalloproteases is central to this process. During homeostatic plasticity, prolonged network inactivation triggers cleavage of brevican by members of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family, ADAMTS4 and 5, at inhibitory as well as excitatory synapses[50]. Similarly, reward-related neuromodulation mediated by D1 dopaminergic receptors induces proteolysis of brevican and aggrecan through the activation of NMDA receptors and protein kinase A signaling[51]. Similarly, activation of 5-HT_7 serotoninergic receptors induces proteolysis of ECM receptor CD44 by MMP-9, stimulating dendritic filopodia/spine formation[52] while neurotrypsin-mediated cleavage of HSPG agrin drives the formation of new spines and boutons[53]. Synaptic activity also supports perisynaptic recycling of ECM molecules via integrins as well as ECM re-glycosylation [54].

Another potent mechanism for ECM remodeling involved neuron–microglia interactions. Activity-dependent release of interleukin IL-33 by neurons activates microglial IL-33 receptors to regulate microglial ECM surveillance, synaptic plasticity and memory consolidation through upregulation of microglial proteases, including ADAMTS4, MMP14 and cathepsin-C, and phagocytosis of aggrecan-enriched ECM[55]. In line with this study, depletion of microglia in young and aged mice elevated ECM proteins around synapses and holes of PNNs in the CA1 area[56,57], confirming their roles in ECM turnover. PNN density also fluctuates in a circadian manner in regions involved in emotional memory

processing, such as hippocampus, with fewer WFA-positive PNNs during sleep, coinciding with the rhythm expression of microglial proteases capable of digesting PNNs[58],[59]. This suggests that remodeling of the ECM during sleep might contribute to the consolidation of new memories.

These mechanisms of ECM remodeling open a brief window for synaptic destabilization and structural plasticity in a defined space, enabling information storage and sensory adaptation. Once new synaptic configurations are formed, there is upregulation in expression of ECM molecules to stabilize them[51].

ECM genes and CNS diseases

Considering the important structural and physiological roles of ECM molecules in the brain, it is not surprising that genetic mutations and polymorphisms in neural ECM-related genes have been increasingly linked to a wide range of neurological and psychiatric disorders. These genes encode structural ECM proteins and enzymes that influence brain development, synaptic plasticity, motor functions and vascular integrity (Table 1).

These findings highlight selected cases where rather rare ECM mutations or more common polymorphisms in ECM-related genes are linked to CNS disorders. While mutations in ECM component themselves are rare, mutations in enzymes that degrade matrisome proteins often result in severe conditions and in some cases are embryonically lethal. This is supported by knockout studies in mice where deletion of genes such as Acan (for aggrecan), Chst11 (carbohydrate sulfotransferase 11) and Hapln1 leads to profound developmental defects. The following sections present the concept that dysregulations of neural ECM is a shared and critical factor in widespread major neurological conditions, closely linked to disease progression and pathophysiology.

ECM remodeling induced by acute CNS insults

Triggers and signaling events following acute CNS insults

Acute CNS injuries (Figure 2), including traumatic brain[75] and spinal cord injuries[76,77] (TBI and SCI), acute seizure disorders (status epilepticus)[78], ischemic stroke[79], and viral encephalitis[80], all provoke a rapid and vigorous pathological cascade. Within minutes to hours, there is sudden neuronal depolarization (e.g. seizures or trauma), immediate hypoxia (stroke), or instantaneous immune activation (trauma, infection). Peak signaling changes, such as excitotoxic calcium influx, HIF-1α upregulation, microglial cytokine release, and bursts of reactive oxygen species (ROS), occur within days[81,82,78,79]. The initial magnitude of neuronal hyperactivity and inflammatory/oxidative responses is extremely high, marked by very large surges in extracellular glutamate and cytokines, but short-lived, tapering as the acute injury is contained. Despite differing triggers, these insults converge on common innate pathways: toll-like receptors (TLRs), purinergic P2X receptors, and even inflammasomes are rapidly activated, inducing transcription factors like NF-κB and AP-1[83,84,85,79]. Stroke-specific signals, notably Hypoxia-Inducible Factor 1,

α subunit (HIF-1α) are prominent if vascular injury occurs, whereas excitatory triggers like seizures rely less on hypoxic pathways. In essence, rapid-onset conditions cause an immediate spike in neuronal hyperactivity, hypoxic stress, inflammation, and oxidative stress, all initiating ECM remodeling programs within days. Acute CNS insults activate a broad range of cell types, triggering a rapid and coordinated release of proteolytic enzymes, a “protease storm”, parallelling the well-known “cytokine storm” (Figure 2).

Neurons play a direct role in ECM modification in acute injury. Excessive cell depolarization and firing lead to release of proteases. For example, in epilepsy, hippocampal neurons (and astrocytes) overexpress MMP-9 following acute seizures in rodent status epilepticus[86,87]. The resulting proteolysis degrades PNNs[88] and induces blood-brain barrier (BBB) leakage [89]. In stroke or trauma, neurons often undergo primary or secondary cell death; thus, their main ECM-related role is releasing DAMPs (damage-associated molecular pathways, such as adenosine triphosphate (ATP) and High Mobility Group Box 1 (HMGB1) upon injury, which activate glia and infiltrating immune cells, further driving ECM remodeling[90,91]. Overall, neurons link hyperexcitation to ECM breakdown both through direct enzyme release and by sending distress signals that activate other cells.

Glial cells, particularly microglia and astrocytes, are pivotal drivers to ECM remodeling across acute conditions. Microglia, the resident immune cells, respond rapidly by releasing proteases and actively phagocytosing cell and matrix debris, including PNNs. They secrete enzymes (like MMPs and cathepsins) that degrade ECM components. Astrocytes also become reactive, initially upregulating ECM-degrading proteases (e.g. MMP-2 and -3) and later producing inhibitory matrix molecules (like CSPGs), contributing to glial scar formation[92]. The relative contributions of microglia versus astrocytes vary by pathologies. In conditions with an intact BBB such as epilepsy, resident glia largely mediate ECM changes because peripheral immune cell entry is limited[93]. In contrast, injuries that compromise the BBB (traumatic brain or spinal injury, severe stroke, encephalitis) also involve endothelial cells and pericytes, contributing to acute ECM breakdown by degrading the basement membrane, leading to edema and hemorrhage[94]. In those severe injuries, recruited peripheral immune cells (neutrophils, monocytes/macrophages) that work alongside glia to dismantle damaged ECM[95,96].

Proteolysis and phagocytosis following acute CNS insults

Overall, acute ECM breakdown by proteases facilitates cellular invasion and debris clean-up; subsequent phagocytosis prevents accumulation of inhibitory debris, thereby setting the stage for either tissue repair or, if dysregulated, chronic maladaptation.

MMP-9 stands out as a ubiquitous and deleterious protease in acute CNS injuries. It is highly expressed in human stroke, TBI, and status epilepticus and is a key driver of BBB disruption and edema in these conditions[97,89,98]. Other ECM-degrading enzymes including

MMP-2, MMP-3, MMP-12, ADAMTS4/5, and various cathepsins target specific ECM components such as gelatins, elastin, CSPGs[99,100,101]. Such protease cocktails causes widespread ECM remodeling within the acute phase (minutes to days), which is double-edged: while matrix clearance is necessary for repair and plasticity, excessive proteolysis leads to BBB leakage, cell detachment, and network dysfunction[102,103].

ECM proteolysis is closely coupled with phagocytosis during acute remodeling. Proteases fragment the ECM, loosening structural barriers and generating debris, which is then cleared by microglia and infiltrating macrophages[104]. This coordinated matrix digestion and debris removal prevents accumulation of growth-inhibitory or pro-inflammatory matrix remnants that could impede recovery. The extent of phagocytic involvement varies by injury severity: large infarcts or infections involve robust macrophage infiltration to remove necrotic debris, whereas epilepsy and milder injuries rely on local microglial and astroglial phagocytosis of specific ECM and synaptic elements[105,98].

Functional impact of ECM remodeling after acute CNS insults

Acute CNS injuries share some common outcomes, including loss of PNNs and perisynaptic ECM, which reduces synaptic inhibition and increases network excitability. Concurrently, degradation of the vascular ECM compromises BBB integrity, contributing to increased permeability and edema[106,107,97]. However, the extent and localization of ECM damage vary by injury type. Severe TBI or SCI and large strokes cause widespread, near-irrevocable ECM loss[108,91]. The lesion core may lose structural matrix completely, leading to cell detachment and BBB rupture with hemorrhage. In contrast, epilepsy exhibits more localized ECM alterations, affecting circuit function without large-scale cell death[109,106].

Degradation of PNNs. In early-stage epilepsy, seizures trigger MMP- and microglia-mediated loss of PNNs in hippocampal networks[110,111], contributing to recurrent seizures by reducing GABAergic inhibition. Direct measurements and extrapolation of data on PNN removal in healthy brains suggest that network hyperactivity after loss of PNNs is related to changes in the number and activity of perisomatic GABAergic synapses[40], impaired clustering of K^+ channels on PV interneurons[25] and impaired Cl^- homeostasis in excitatory neurons. Loss of PNNs makes PV interneurons more susceptible to the oxidative stress[112]. The cognitive decline may be related to impairments in some forms of synaptic plasticity dependent on activity of L-type Ca^{2+} channels[41], fuzzier representation of memory engrams[35], and changes in pattern of oscillations and instability of grid cells[34].

Degradation of periaxonal ECM. The ECM at the nodes of Ranvier and AIS plays a crucial role in stabilizing axonal domains and ensuring proper generation and conduction of action potentials. Interestingly, knockdown of neurocan leads to increased expression of the AIS scaffolding protein ankyrin-G and heightened network activity in vitro[24], implying that intact axonal ECM serves to restrain axonal hyperexcitability. Bral1 or

tenascin-R deficiency, in contrast, reduce the spike conduction velocity despite normal channel clustering, demonstrating that ECM microdomains tune axonal signaling[36,113]. Although dysregulation of ECM at the AIS remains understudied in CNS diseases, its molecular similarity to PNNs and perisynaptic ECM suggests shared vulnerability, which may result in changes in axonal excitability and conduction velocity and critically affect signal timing and network synchronization.

Degradation of perisynaptic ECM. Acute insults trigger extracellular proteases that cleave perisynaptic ECM proteoglycans, loosening perisynaptic matrix around excitatory synapses and enabling structural remodeling. In epilepsy, MMP-9 is enriched at excitatory synapses, rises after seizures, and Mmp9 gene ablation reduces seizure-evoked spine pruning and aberrant synaptogenesis [86]. Additionally, loss of perisynaptic ECM may affect microglia-synapse interactions. Enzymatic digestion of CSs with ChABC shortens interactions between dendritic spines and microglia, promoting spine formation under basal conditions[114,115]. Moreover, ECM loss can also depress astrocytic glutamate uptake, increasing excitability and excitotoxicity [26].

Degradation of vascular ECM. Disrupted vascular ECM occurs in acute injuries like stroke, TBI, and encephalitis due to proteolytic degradation of the vascular ECM molecules[97,94,96]. The resulting extravasation of plasma proteins and fluid further exacerbates neural damage and inflammation.

ECM remodeling in the (sub)chronic stage of CNS diseases

In the subchronic and chronic phases (weeks to years after injury or the initiation of gradually progressive diseases), the cellular drivers of ECM remodeling diverge more markedly by disease types. As acute inflammation resolves, distinct cell populations take over matrix remodeling, shaping long-term tissue architecture (Figure 2).

Signaling events in the (sub)chronic stage after acute CNS insults

Traumatic and ischemic CNS injuries, as well as severe epilepsy or viral encephalitis, enter a chronic phase marked by a robust glial scar response. Within the lesion core, fibroblasts proliferate and deposit a collagenous matrix. These scar-forming stromal cells often “outnumber astrocytes in the injured spinal cord”[116,117]. Reactive astrocytes surrounding lesions reorganize into a dense border separating neural parenchyma from stromal/immune cells and restoring CNS . In the chronic stage, microglia and infiltrating macrophages persist in an activated state, while anti-inflammatory signals increase over time; blocking these worsens lesion outcomes[118,119]. Meanwhile, T lymphocytes may accumulate within fibroblast-rich niches of the scar, producing interferon-γ and other cytokines that sustain a low-grade inflammation[120]. Despite differences in etiology (trauma vs. infection), these injuries share conserved chronic responses: reactive astrocytes and NG2-positive cells forming a protective glial border, perivascular

fibroblast-driven collagen deposition, and persistent microglial activation modulating the lesion microenvironment.

CSVD is characterized by diffuse vascular fibrosis orchestrated by pericytes and vascular fibroblasts, with neurons and glia playing secondary roles[121]. In AD, activated microglia contribute to PNN loss, as they are often found engulfing PNN fragments near amyloid plaques. Experimental microglial depletion preserves PNN integrity despite ongoing Aβ pathology[58,122].

In chronic stages, the inflammatory signaling milieu shifts toward pro-repair or pro-fibrotic cytokine signaling that further modulate ECM outcomes. Transforming Growth Factor (TGF)-β1, for example, is consistently upregulated in many chronic settings, such as in the glial scar borders in TBI/SCI, reactive astrocytes in epilepsy, hypoxic white matter in CSVD, and the obese hypothalamus, promoting the production of fibrotic matrix components and CSPGs[123]. IL-10, an anti-inflammatory cytokine, appears in certain resolution-phase contexts (especially in neonatal injuries), potentially promoting ECM stabilization and reorganization rather than degradation[124]. Th2 cytokines IL-4 and IL-13 arise during remyelination and white-matter repair, encouraging ECM changes that support axon regrowth (for instance, by altering astrocyte ECM secretion)[125]. The balance of these signals determines whether chronic ECM remodeling favors scar formation and persistent inhibition of regeneration (e.g. CSPG-rich astrocytic scars in chronic TBI/SCI; diffuse collagen deposition in CSVD) or regenerative plasticity (e.g. PNN remodeling in AD may permit aberrant sprouting, whereas reformation of new PNNs in chronic epilepsy may constrain maladaptive rewiring[126,117].

Another striking commonality across chronic stages is a shift from protease activity to protease inhibition. For instance, while MMP levels surge in acute injury (e.g., early stroke) and correlate with hemorrhagic risk[97,95], prolonged MMP activity can be harmful, prompting upregulation of tissue inhibitors of MMPs (TIMPs) and serpins by reactive astrocytes and other cells. TIMP-1, in particular, is strongly upregulated around chronic scars, curbing MMP-mediated ECM degradation and stabilizing the scar matrix[127]. In Alzheimer's disease (AD) brains, TIMP-1 is enriched in neuritic senile plaques and neurofibrillary tangles [128], yet CSF levels are reduced. Moreover, the MMP-9/TIMP-1 ratio correlates in AD patients with CSF T-tau, a marker of neurodegeneration [129]. Similarly, reduction in TIMP-3 expression and resulting imbalance in cerebrovascular MMP-9 and TIMP-3 expression is associated with intracerebral hemorrhages in patients with cerebral amyloid angiopathy characterized by the deposition of the amyloid β (Aβ) protein in the cerebral vasculature as commonly found in AD patients [130]. Thus, chronic neurodegenerative lesions often retain active proteases (MMP-2, MMP-9, cathepsins, etc.) regulated by tissue inhibitors[131]. The state of glia and ECM as well as progression of disease depends on the ratio between MMPs and TIMPs. Beyond its canonical MMP-inhibitory function, TIMP-1 also acts in AD as a multifunctional cytokine through

interactions with CD63/β1-integrin and low-density lipoprotein receptor-related protein-1 [132].

Signaling in the chronic stage of gradual-onset CNS diseases

Gradual-onset CNS conditions, exemplified by neurodegenerative diseases (e.g. Alzheimer's and Parkinson's), cerebral small vessel disease and metabolic disorders like obesity, follow a slow, progressive trajectory. Persistent initiating triggers (misfolded proteins, chronic vascular risk factors,]high-fat diet, etc.) cause cumulative low-level activation of innate stress pathways such as TLRs, the receptor for advanced glycation end-products (RAGE), or HIF-1α[133,134,135,136,137]. For example, amyloid-β peptides in Alzheimer's disease chronically activate RAGE and TLR4 signaling on microglia, and saturated fatty acids can chronically stimulate microglial TLR4 in diet-induced obesity models. The end result is a sustained trickle of excitotoxic and inflammatory signals rather than an explosive burst. Indeed, chronic neurodegeneration and metabolic stressors maintain a mild but steady glutamate excess and ongoing microglial activation (sometimes accompanied by slight increases in HIF-1α) that gradually alter the ECM[138,139,140]. The body partially adapts to these slow changes, so any given inflammatory episode is less intense than in an acute injury. Acute conditions often overwhelm compensatory mechanisms, whereas gradual-onset conditions feature an unstable equilibrium where damaging signals and partial compensations coexist over long periods. Also, ECM changes concentrate around plaques/synapses**,** perivascular spaces**,** white matter tracts**,** often as many small foci rather than one dominant scar. The cumulative effect of low-grade, long-duration inflammation can be quite prominent, leading to significant ECM remodeling over time. Understanding these temporal differences is crucial for interventions that either dampen an acute overreaction or interrupt a chronic smoldering injury.

Functional impact of ECM remodeling in (sub)chronic conditions

PNN increase/thickening is observed in some chronic conditions, e.g. after SCI and in obesity, when PNN accumulation is increased in the hypothalamus around AgRP neurons[141]. Excessive PNNs and perisynaptic ECM around synapses on excitatory neurons may act like "too much brake," hindering synaptic plasticity through CSPG-mediated inhibition of β1 integrins[114], direct activation of PTPσ, PTPδ and LAR[19-21], and indirect activation of plexins via PNN-associated semaphorin 3A[16]. These events may result in RhoA-ROCK activation and subsequent reduction of cell surface expression of AMPA receptors [142] and inhibition of actin cytoskeleton remodeling and axonal growth[22]. Activation of PTPσ also leads to tyrosine de-phosphorylation of TrkB receptors inhibiting their activity[143]. Moreover, ECM accumulation may hinder diffusion of soluble factors[144] and lateral diffusion of transmitter receptors[39], and promote activation of mechanosensitive channels, like Piezo1 [145]. In obesity, thickened PNNs physically impede insulin from accessing neurons, contributing to central insulin resistance[141]. This

mechanism may be relevant to synaptic insulin resistance in other brain regions[146]. Overall, maintaining an optimal PNN level appears critical for CNS health: excessive PNNs may restrict regeneration and plasticity, whereas too few nets could lead to network instability. Accordingly, the cognitive outcome of interfering with PNNs depends on the interference approach, the targeted brain region, conditions and the behavioral paradigm, as has been reviewed elsewhere[28,29].

Ectopic PNN formation. It has been observed in parallel to the loss of PNNs in chronic epilepsy [147], where new PNNs form around neurons (like somatostatin-espressing interneurons) that do not usually have them. These aberrant PNNs might paradoxically increase firing from those neurons by reducing membrane capacitance, as seen when normally "net-free" neurons acquire a PNN and adopt fast-spiking properties [147].

Remodeling of periaxonal ECM. In chronic epilepsy models, excitatory neurons have demonstrated AIS shortening, elongation, or shift along the axon as a homeostatic response to hyper- or hypoexcitability[148]. The relevance of these changes to ECM remodeling remains to be studied.

Basement membrane thickening. These are hallmarks of CSVD, diabetes, normal aging, as well as neurodegenerative diseases with vascular components (like cerebral amyloid angiopathy in AD)[149,121]. Specifically, chronic hypoxia and metabolic insults promote excessive deposition of collagen IV, laminin, and perlecan in capillary walls, impairing oxygen and nutrient diffusion from blood to brain, and reducing vessel elasticity and reactivity. These changes result in chronic mild tissue hypoxia and impaired neurovascular coupling, contributing to cognitive slowing and white matter injury. In CSVD, such microvascular fibrosis is a core mechanism of vascular cognitive impairment. Loss of pericytes (as in CADASIL or diabetic angiopathy) often worsens both aspects, without pericyte regulation, basement membrane ECM accumulates abnormally and increases vessel fragility[150,151]. Overall, vascular ECM remodeling, whether through excessive accumulation or enzymatic breakdown, profoundly influences BBB integrity and cerebral perfusion, thereby affecting neuronal health and waste clearance (e.g., impaired clearance of amyloid in AD due to fibrotic vessel walls[152]).

Glial scars. They are typically formed within two weeks after CNS injury and may persist indefinitely[153]. Functionally, the astroglial scar serves two principal effects: Firstly, the scar acts as a physicochemical barrier that isolates the lesion core. and astrocytes and other cells within SCI lesions express multiple axon-growth-supporting molecules[126]. Secondly, the flip side is that the scar, also contains a dense meshwork of CSPGs, tenascins, and small leucine-rich proteoglycans, which potently inhibits axon regeneration and plasticity[21,154, 155]. These molecules, similar to those in PNNs, bind to axonal receptors like PTPσ and NgR activating Rho/ROCK signaling pathways that causes growth cone collapse and axon extension failure[20,21]. Moreover, CSPGs in the astrocytic scar inhibit oligodendrocyte precursor cells from maturation and re-myelinating demyelinated

axons[156]. In stroke, astrocytic scars at the infarct border prevent new axon collaterals from re-entering the infarct zone, limiting spontaneous circuit reorganization. Glial scar formation is relatively unique and a hallmark to acute physical injuries and demyelinating lesions; distinguishing them from chronic neurodegenerative, which typically exhibit diffuse astrogliosis without the structured CSPG-rich barrier[157]. Interestingly, AD exhibits a micro-scarring astrocytic clusters around amyloid plaques[158]. In summary, glial scars demonstrate the trade-off inherent in ECM responses: immediate protection *vs.* long-term inhibition of regeneration and plasticity.

Co-aggregation of pathogenic proteins and ECM molecules. In neurodegenerative diseases characterized by pathological protein aggregates such as amyloid plaques in AD, Lewy bodies in PD, and tau tangles in various tauopathies, the pathogenic proteins often co-aggregate with ECM components[159]. Amyloid-β plaques, for example, are enriched with CSPGs and HSPGs (like agrin, glypican, and aggrecan), which may directly bind amyloid fibrils[160]. Similarly, tau protein aggregates (neurofibrillary tangles) bind extracellular CS and HS, while extracellular α-synuclein (released from dying neurons in PD) adheres to cell-surface HS chains[161]. Functionally, these interactions have opposing functional consequences. On one hand, ECM components may shield protein aggregates from enzymatic degradation[162]. For instance, HSPGs can sterically hinder proteases like neprilysin and insulin-degrading enzyme, which normally degrade Aβ. This protective "sugar coating" prolongs aggregate persistence and potentially exacerbates toxicity. On the other hand, by sequestering misfolded proteins in a matrix, the ECM may limit their diffusion and spread. An amyloid plaque concentrates Aβ in some locations; similarly, tau bound to matrix might not diffuse as freely to seed pathology in distant neurons[159]. In AD patients, ECM involvement overall favors persistence of plaques and tangles, contributing to chronicity, although some ECM components (laminin or collagen) may assist clearance of Aβ deposits[159]. Interestingly, individuals with more robust PNNs may have higher resistance to amyloid/tau pathology. Indeed, brain regions rich in PNNs (like perirhinal cortex) show relative resistance to tau pathology in early AD, suggesting a protective role[163]. This is in line with evidence of neuroprotective features of CSPGs against excitotoxicity, amyloid-ß toxicity, and oxidative stress[112]. In PD, less is known, but it is plausible that extracellular α-synuclein is partly captured by perisynaptic matrix, influencing synapses vulnerability, and modulating microglial activation[159]. Additionally, the chronic presence of aggregates may stiffen the tissue locally and traps inflammatory cells.

Fibrotic ECM. It is observed in chronic SCI, TBI and chronic stroke, often in conjunction with the glial scar[117,164]. Functionally, fibrotic tissue permanently blocks axonal regrowth, even if inhibitory astrocytic signals are overcome, the dense collagen matrix is physically impenetrable to growth cones. On the other hand, the fibrotic scar provides structural stability: it fills the void that would otherwise become a fluid-filled cyst, thereby maintaining a degree of mechanical integrity in the injured CNS[165]. Experiments where fibrotic scar is genetically ablated in mice lead to larger post-injury cavities and worse functional

outcomes, indicating that some fibrosis is beneficial for architecture[116]. However, chronic fibrotic tissue tends to perpetuate inflammation. Collagen-rich ECM, via its embedded proteoglycans/GAGs, binds and sequesters inflammatory cytokines and chemokines, creating a feedback loop that continually attracts macrophages[166,167,168]. Indeed, months after a human SCI, macrophages can still be found embedded in the residual fibrotic scar, reflecting non-resolving inflammation[169,170]. In CSVD and AD, diffuse interstitial and perivascular fibrosis, for example, thickening of vessel walls and perivascular space fibrosis in white matter, fosters chronic glial activation and impairs waste clearance like amyloid clearance in AD[171]. Fibrosis underscores a fundamental trade-off in ECM responses: it increases tissue stability but at the expense of regenerative capacity, and it can serve as a niche for persistent inflammation[172].

In conclusion, ECM remodeling is a central and multifaceted process in CNS pathology. Whether in acute injury or chronic neurodegeneration, changes in the ECM via proteolysis, phagocytosis, deposition, or reorganization, critically influence disease progression and outcomes. ECM can exacerbate damage (e.g. proteases-driven BBB disruption or scar-induced inhibition of regeneration) or mitigate it (e.g. containment via glial scars or excitotoxicity buffering by PNNs). The balance between protective and inhibitory roles of ECM is a defining feature of CNS repair and dysfunction.

Therapeutic targeting of neural ECM

Appreciating mechanisms of ECM remodeling suggests two major avenues for therapeutic interventions to preserve the ECM after acute injury, or modify the ECM to restore neuroplasticity in chronic disorders. There are multiple strategies for targeting the ECM molecules and their metabolizing enzymes and receptors with antibodies, peptides, glycosaminoglycans, and other natural and synthetic compounds[173,174], some of which have been tested in animal models of CNS diseases and reviewed here (Table 1).

Targeting ECM after acute CNS insults

In the acute stage of ischemia, MMP-9 has been identified as aberrantly overactive. Systemic administration of clinically admitted drug minocycline, which reduces microglia activation, and expression and activity of MMP-9 and MMP-2, proved to be neuroprotective in rodent models of stroke[175]. Moreover, minocycline demonstrated efficacy in clinical trials and improved outcomes in acute ischemic stroke patients[176]. Other attractive targets are hyaluronidases HYAL1-2, which are upregulated following ischemia and digest HA. Inhibition with VCPAL, the potent hyaluronidase inhibitor and antioxidant, has shown improved cognitive functions in mice[178].

Epileptic disorders are characterized by a rapid and persistent upregulation of multiple MMPs, including MMP-9. A new dual inhibitor of MMP-2 and MMP-9, IPR-179/ACT-03 has shown a high potency and specificity towards the enzyme [195], and demonstrated a remarkable efficacy in suppressing ictogenesis, reducing seizure frequency and improving cognitive function in rodents[87]. Moreover, one-week treatment with IPR-

179/ACT-03 in mice following the status epilepticus induced by intrahippocampal injection of kainic acid, resulted in reduced frequency of seizures after termination of treatment, suggesting partial suppression of epileptogenesis[87]. Another compound, DP-b99, a zinc and calcium chelator that prevents the activation of multiple MMPs, was efficient in preventing the onset and severity of PTZ-induced seizures in mice[177]. In line with a study showing generation of epileptiform activity after hyaluronidase treatment in vitro[196], the duration and number of seizures were reduced by natural and synthetic inhibitors of hyaluronidases (multi-target flavonoid apigenin and more specific thiocarbamate S3A, respectively)[179,180]. However, translating these findings into clinical applications may require further validation. Some of these molecules such as DP-b99 is currently in trial for stroke and could be applicable for epilepsy.

Targeting neural ECM in (sub)chronic conditions

In SCI, a variety of ECM-targeting strategies have been explored during the (sub)chronic stage to promote axonal regeneration and functional recovery. ChABC, which degrades CS chains on CSPGs, has been shown to enhance motor and sensory recovery by creating a more permissive environment for axonal growth, with numerous preclinical studies reporting significant improvements in locomotor function and sensory perception[182,197]. Particularly noteworthy is the work investigating ChABC's effects in rhesus monkeys following a C7 spinal cord hemisection[181]. It was found that 4 weeks after the injury, multiple injections of ChABC were able to promote corticospinal axon growth and hand function improvement. However, repeated injections are invasive and risky for BBB-compromised SCI patients, limiting clinical translation. On the other hand, another study demonstrated that a single ChABC injection into the phrenic motor pool could induce diaphragm contraction even 1.5 years post-injury[198]. This result provides confidence for potential translation in chronic SCI for short distance plasticity. Despite its therapeutic promise, clinical translation remains challenging due to the short half-life of ChABC and limited diffusion from the lesion site. Currently, multiple strategies for ChABC delivery, including direct infusion, encapsulation via nanoparticles, hydrogels and scaffolds, and sustained expression using viral vectors and stem cells are in development to overcome these challenges[182]. Beyond ChABC, other CS-modulating approaches have shown efficacy. These include small inhibitors of chondroitin/heparan sulfate and hyaluronic acid synthesis, such as xylosides[191] and 4-methyl-umbelliferone[193], CS-E-function blocking antibody[187], CSPG receptor blockers, such as PTPσ and LAR[19,20], and treatments targeting PNN-associated Sema3A[194]. They have promoted regeneration, reduced ECM-mediated inhibition of axonal growth and improved motor function in rodent models of SCI. Additionally, AAV-mediated overexpression of ADAMTS4 has facilitated ECM digestion, and increased axonal regeneration and functional recovery [189]. These treatments collectively overcome ECM-mediated inhibition, promote axonal regrowth and restore locomotor function, key measures in SCI recovery.

Recent studies have shown clear link between obesity and changes in brain ECM composition, particularly in regions regulating hunger and metabolism. In diet-induced obese mice fed a high-fat, high-sugar diet, inflammation drives the accumulation of CSPGs around hunger-regulating neurons expressing agouti-related peptide (AgRP) in the arcuate nucleus of the hypothalamus[141]. This build-up of CSPGs impairs accessibility of insulin to its receptor, drives central insulin resistance, and increases spontaneous firing of AgRP neurons, leading to elevated food intake and weight gain. Enzymatic digestion of PNNs by ChABC injection in the arcuate nucleus caused mice to progressively lose their body weight, partly because of reduced food consumption, and improved other aspects of metabolic health. Deleting the gene that encodes insulin receptors in AgRP neurons largely abolished these beneficial effects of ChABC treatment in obese mice, confirming that accumulation of ECM around these neurons leads to metabolic dysfunction through insulin resistance. Fluorosamine, a small molecule inhibitor of chondroitin/heparan sulfate synthesis, has shown similar promising effects. Intranasal fluorosamine treatment of obese mice for 14 days reduced ECM accumulation and achieved metabolic improvements similar to those observed with intracerebroventricular fluorosamine administration and ChABC treatment[141]. Thus, intranasal administration of this small molecules offers a novel and non-invasive strategy for proof-of-principle animal studies on therapeutic benefits of PNN reduction and, if safe in humans, might be a treatment of choice for short-term administration in conditions (e.g. TBI) requiring transient downregulation of chondroitin sulfates.

In AD, several CSPGs and HSPGs targeted treatments have been tested. Administration of heparin and its mimetics led to enhanced synaptic stability and improvements in cognitive function, particularly memory, by reducing Aβ aggregation and tau pathology in preclinical models[190]. For tauopathies, which are characterized by abnormal tau protein accumulation, digestion of neural ECM with ChABC or targeting chondroitin sulfates with anti-chondroitin-4-sulfate antibody has led to improved cognitive outcomes by abrogating synaptic dysfunction[161,186,188].

In PD, ChABC treatment has shown neuroprotection against partial 6-OHDA lesions in the nigrostriatal tract and promoted axonal growth of transplanted midbrain dopaminergic progenitors and their reinnervation of the striatum[184,185], highlighting its regenerative potential.

In summary, these data suggest that modulation of ECM in the CNS offers a significant therapeutic potential across a range of neurological conditions. The strategies are broadly divided into two major classes, one is to preserve or even enhance the neural ECM to support normal brain functions, while the other focuses on reducing/modifying the neural ECM to enhance neuroplasticity, regeneration, and regain neurological functions. Table 1 provides many examples where one ECM-targeting treatment has been applied to multiple conditions, while others with a similar target have not, suggesting promising opportunities for drug repositioning, at least in preclinical studies.

Interesting emerging therapeutic options are to use the available knowledge on the structure and function of native ECM molecules to design synthetic ECM molecules [199], or, in case of well-confined local injury sites, injectable artificial ECM hydrogels offer a promising route to facilitate CNS regeneration[200].

Considering available data on changes in expression of ECM-remodeling enzymes (Figure 2), combinatorial treatments are highly attractive to preserve normal neural and vascular ECM following injuries, e.g. by inhibiting multiple proteinases (e.g. MMP-2/9 and ADAMTS4/5), or combining inhibitors of proteinases and hyaluronidases, or delivering blocking antibodies to protect specific proteolytic sites on key ECM molecules. Similarly, pairing neural ECM digestion with cell therapies can be instrumental to promote tissue integration and connectivity of transplanted cells[185].

Overall, the discussed research supports the concept that ECM-attenuating drugs could serve as valuable adjuvant therapies in chronic CNS conditions, enabling re-opening of therapeutic window for entraining neural network and their reconfiguration neural network from pathological to normal states.

New technologies for neural ECM analysis

The development of neural ECM research has traditionally been hindered by the lack of tools and methods for interrogating individual glycan entities[201]. The non-template driven synthesis of glycans complicates the use of transgenic or mutational technologies. Additionally, the highly conserved ECM structures across species makes it challenging to raise antibodies with high specificity for effective labelling. Recent technological advancements have, however, provided a suite of powerful tools, offering hope for rapid progress in understanding ECM functions. We have provided a concise summary of these new tools in Figure 3 and Box 1. While these techniques have so far been limitedly used, their adoption in the field offers significant promise for advancing our understanding of CNS glycans.

Future directions and Conclusions

This review highlights the remarkable functionality of neural ECM under physiological conditions, with implications that persistent disease-induced changes in ECM composition can be the core of functional disruptions in neuronal circuits controlling cognitive, metabolic and motor functions. Recent studies provide compelling evidence for this concept.

Also numerous examples of ECM-targeting interventions in various animal models of CNS diseases support the view that this approach can be highly beneficial. However, clinical trials remain very rare, primarily in the stroke and glioblastoma fields. This likely reflects limited specificity and BBB permeability, and other limitations of pharmacological, enzymatic and genetic tools available for neural ECM manipulations and monitoring. For

instance, early broad spectrum MMP inhibitors failed in clinical trials because of a common side effect, musculoskeletal syndrome. However, the most recent generation of MMP inhibitors have desirable selectivity and improved pharmacokinetics, resulting in improved toxicity profiles. Evaluation of selective MMP inhibitors led to the conclusion that MMP-2, MMP-9, MMP-13, and MT1-MMP are not involved in musculoskeletal syndrome and represent attractive targets[220]. There is a FDA-approved MMP inhibitor for periodontal disease, and several MMP are in clinical trials, some are BBB-permeable and have demonstrated efficacy in preclinical studies (Table 1). Another potential matter of concern is that MMPs have many other substrates beyond ECM molecules, such as growth and neurotrophic factors, cytokines and cell adhesion molecule, which are essential for normal brain function [221]. Hence, it is important that treatments targeting these molecules are applied just immediately after the insult and for a short time. Other strategies may be applied to condition time and place of drug action as described below.

ChABC treatment remains the most commonly used approach for experimental digestion of ECM. As discussed, injection of ChABC improves novel object recognition in the model of tauopathy[186]. However, it is unlikely that this or other treatments digesting PNNs are optimal for AD patients in a long run, at least due to neuroprotective functions of PNNs in restricting tau/Aβ uptake [112,159]. Hence, more specific long-term treatments are preferable to interfere with PNN components inhibiting plasticity while preserving neuroprotective ones. On the basis of current knowledge, these can be PTPσ inhibitors and antibodies targeting CS-A (i.e. C4S) and CS-E (i.e. C4,6-S) glycoepitopes. Another related strategy would be the modulation of sulfation patterns in CSPGs, which influence ECM properties and plasticity. Thus, under-investigated chondroitin sulfate sulfotransferases represent an emerging therapeutic target[222].

Another complication is that many key neural ECM molecules, like aggrecan, HA, CS, HS are also synthetized and play important roles outside the CNS. Even within the CNS, the levels of ECM molecules vary strongly across regions and, hence, delivering general ECM inhibitors or stimulators may rescue some neural circuits but disturb others. Thus, we have to address several open questions to advance potential use of ECM manipulation as therapies. They are summarized in Box 2. Obviously, a deeper understanding of the heterogeneity of ECM is needed. This may reveal new specific ECM targets associated with particular cell types and/or brain regions that are affected early in a disease progression. The application of multiomics and other advanced technologies to analyze neural ECM holds great promise to uncover the precise regulatory mechanisms and such new molecular targets, paving for the development of next generation of ECM-based treatments.

Other approaches are to design pro-drugs, which would enter CNS at the damage sites with characteristic activation of vascular endothelial cells and/or BBB leakage, and/or selectively activated in the CNS, either by CNS-specific enzymes and/or under specific inflammatory conditions related to a disease.

Gene therapy approaches may offer valuable alternative tools and examples of beneficial effects of AAV-driven expression of proteins controlling ECM integrity and composition (e.g. ADAMTS4 in Table 1) are of particular interest as the starting points for development of gene therapies. By using AAV serotypes for intravenous delivery to the CNS, engineering therapeutic ECM proteins with improved potency and specificity, and further optimizing the promoters and regulatory elements in 5' untranslated region, it may be possible to achieve precise, cell-type-specific and condition-dependent modifications of neural ECM composition in specific functional circuits. As astrocytes and microglia are increasingly recognized as key regulators of PNN formation and remodeling, cell-type specific AAVs could be designed to therapeutically tune activities of these cell types towards ECM production or degradation.

In line with well-recognized higher diversity and complexity of human glial cells compared to those in rodents [223,224], growing evidence indicates species-specific differences in ECM composition. A quantitative analysis of the hippocampal synaptic proteome revealed higher levels of brevican, neurocan, versican, HAPLN2 and tenascin-R in human samples as compared to rodents[225]. Proteomics of cerebrovascular ECM from mouse and human post-mortem brains revealed that about 70% of proteins were shared in the ECM-enriched fraction across both species [226]. Moreover, significant human/mouse-specific differences in CS disaccharide sulfation were identified using liquid chromatography tandem mass spectrometry[227]. Thus, the development of ECM-targeting treatments would greatly benefit from testing in human *in vitro* systems, such as medial ganglionic eminence or midbrain organoids, which exhibit WFA-positive accumulations of ECM molecules [228,229].

Further development of the field would depend on developing ECM biomarkers for CNS conditions and monitoring the efficacies of ECM targeting therapies, as has been achieved for monitoring of fibrosis using biomarkers reflecting synthesis and degradation of several collagens in diverse somatic diseases[230]. This is inherently complex for neural ECM due to overlapping tissue profiles, limited peripheral detectability, and subtle magnitude of changes. While ECM biomarkers are effective outside the CNS, their large size and glycosylation limit blood-brain barrier permeability. CSF remains the primary source, revealing disease-specific changes in molecules like neurocan and brevican across conditions such as AD, ALS, and vascular dementia[231,232,233]. Gender and composition differences further complicate interpretation[234,235]. ECM-degrading enzymes like MMPs appear across conditions[236,237,238,239,87,240], limiting specificity but suggesting therapeutic potential. Given the limitations of single-molecule markers, combinatorial assays may improve diagnostic accuracy. As most current findings are postmortem, there is an urgent need for in situ tools like PET, MRI, and biofluid assays for early diagnosis and treatment monitoring in clinical settings.

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Display items

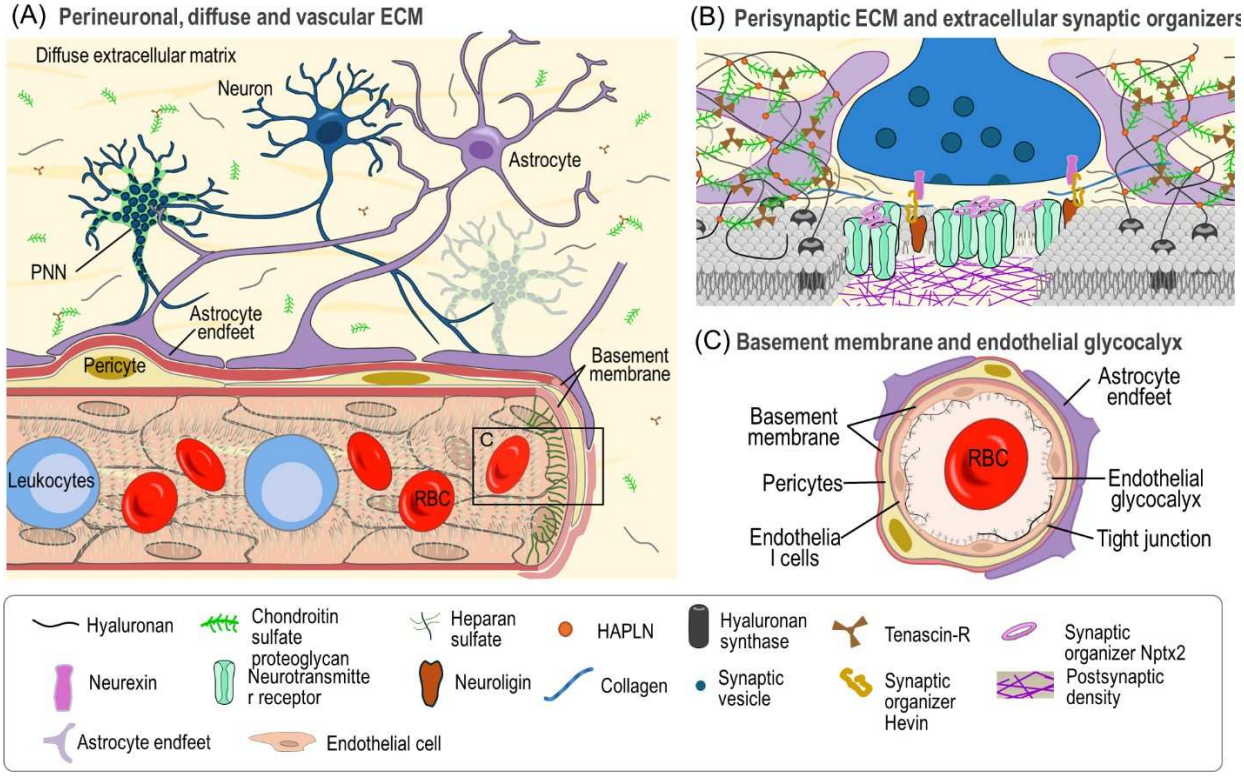

Figure 1. Schematic diagrams showing the different types of extracellular matrix (ECM) in the CNS. (A) PNNs, diffuse ECM, and vascular ECM, including endothelial and astroglial/pericytic basement membranes. (B) Condensed perisynaptic and extracellular synaptic organizers cross-linking synaptic proteins (postsynaptic membrane is omitted to show interactions between transmitter receptors and intracellular scaffold). (C) Cross-sectional illustration of basement membranes and endothelial glycocalyx in the CNS, encased by astrocyte endfeet.

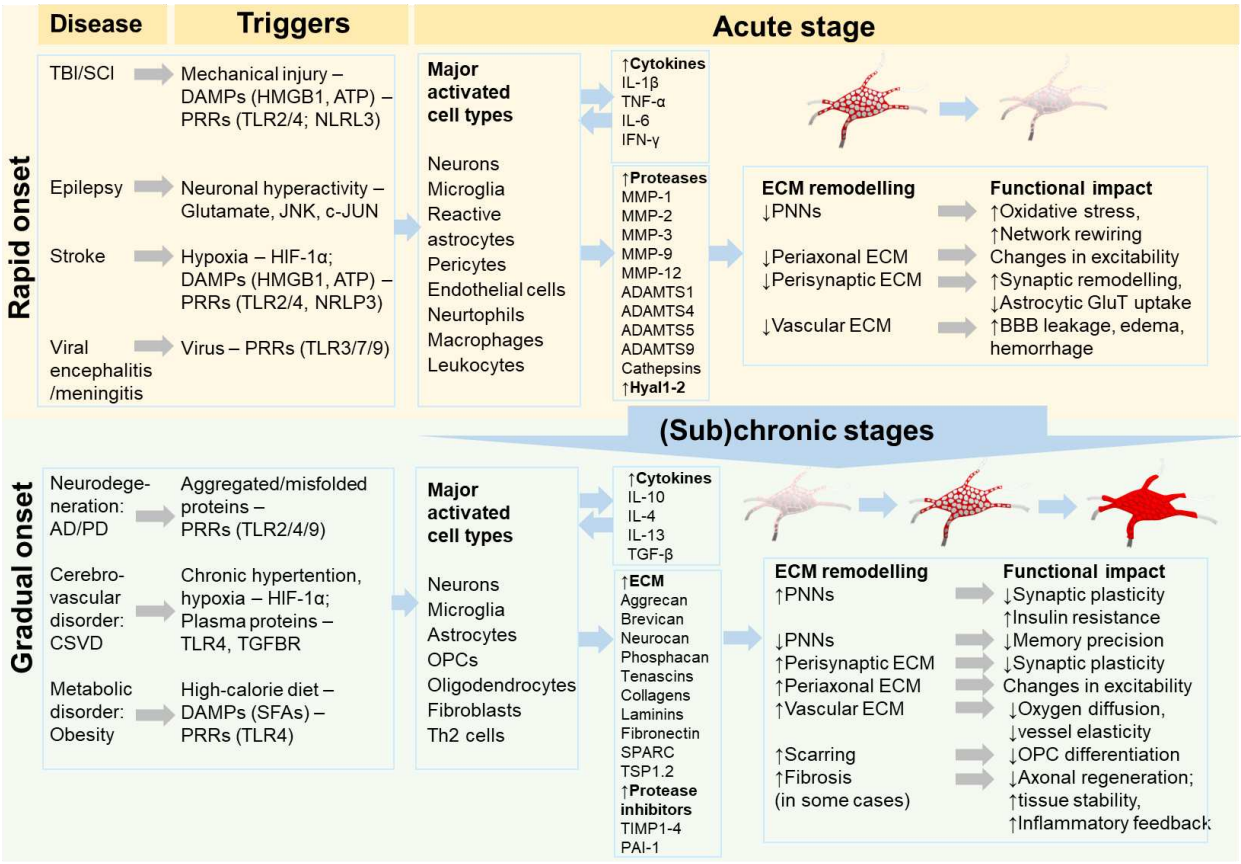

Figure 2. Mechanisms and functional impact of ECM remodeling in CNS diseases. The blue arrows point to link between entire boxes, the grey arrows point to links between specific elements.

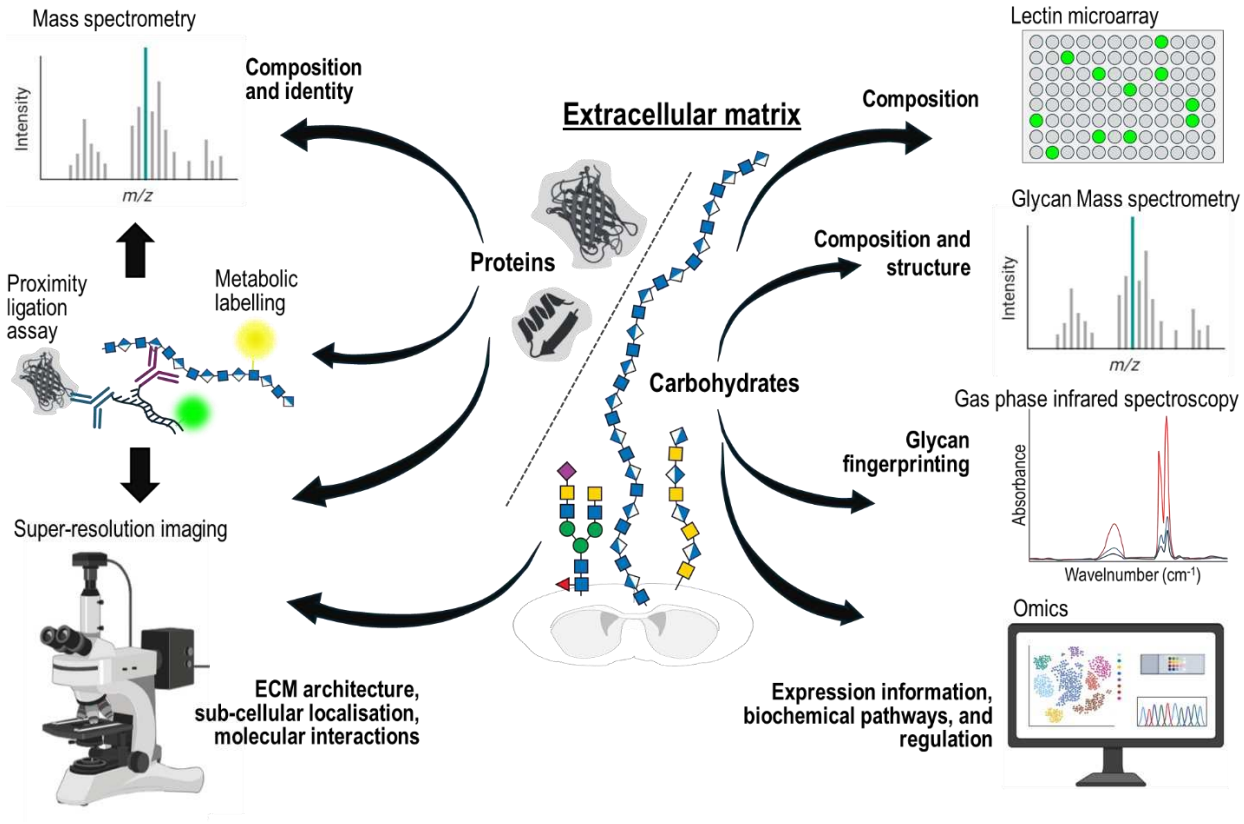

Figure 3. A schematic diagram showing the recent technical development enabling the investigation of ECM composition, structure, fingerprinting, architecture, molecular interactions, biochemical pathways, and their regulations.

Box 1: New technologies for neural ECM analysis

(A) Analysis of glycan structures. Ion mobility mass spectrometry (IM-MS) or MS/MS have provided sensitive glycan characterization based on mass, size and charge[202]. However, their use is constrained by the need for extensive sample preparation and expert interpretation. **Gas-phase infrared spectroscopy** enables highly specificity glycan fingerprinting[203], though limited by low throughput. **Solid-state nanopore analysis** offers sequencing at zeptomole sensitivity for pure synthetic GAG samples[204]. **Lectin microarrays** offer a simple and cost-effective option for profiling glycan composition in unpure biological samples[205] but cross-reactivity limits specificity and may complicate interpretation. **Machine learning** combined with the time of flight secondary ion mass spectrometry (ToF-SIMS) enhances analysis of complex biological samples with high sensitivity[206]. While promising, this approach requires large annotated datasets and computational resources. **Mass spectrometry imaging (MSI)** overcomes spatial resolution limitations in previous technologies, enabling N-glycan mapping down to single-cell resolution[207]. However, its restriction to N-glycans and complex workflows hinder widespread adoption.

(B) Interaction analysis. Superresolution imaging have provided unique opportunities for the study of molecular interactions and ECM architecture at a resolution beyond conventional light microscopy. Techniques like super-resolution SIM have been used to interrogate the importance of molecular interactions in organizing PNN structure and the potential feedback mechanisms in the development of PNN-associated neurons[208]. Using STORM, Sigal et al. has demonstrated the correlation of WFA staining intensity with PNN contiguity and the inverse relation with hole size[209], providing experimental evidence to support the soft-matter-physics theory for PNN pattern formation[210].

(C) Live cell labeling for functional analysis. Metabolic labelling of O-glycans for selective labelling of glycan epitopes has revolutionized the study of biological functions of glycans in live cells[211]. This approach allows the study of *de novo* glycan molecules at different physiological state. When combined with super-resolution imaging, these tools provide important spatial information on distribution of ECM glycans in a biological context[212].

(D) Pathway analysis. Omics technologies provide comprehensive and integrative analysis of biochemical pathways. Combined proteomics and transcriptomics have confirmed PNN molecule expression during development of ventral lateral geniculate nucleus for visual processing[1]. Despite their power, translating omics data into meaningful biological insights remains challenging, largely due to ECM extraction. Protocols must adapt to the lipid-rich CNS environment, yet many extraction methods compromise the native structures of ECM, including glycoproteins, glycolipids and polysaccharides, producing unreliable data. Single-nucleus or single-cell RNAseq offer limited values for ECM analysis, as ECM molecules and proteases are secreted and diffused away from their source cells. Advanced proteomics approaches, such as single-cell laser microdissection (scLM[213]) and proximity-based proteomic techniques [214-216] may overcome these limitations. Another complicating issue is the complex synthesis of glycan molecules, which involve multiple enzymes and proteins, a family of over 200 members[217]. The analysis of omics data for proteins and glycans thus requires further consideration and data integration[218,217,219]. These tools provide a really powerful platform for linking and translating omics technology to predicting glycan capacity of cells.

BOX 2. Open questions

- To what extent does the diversity of cell types in the CNS contribute to the diversity of cell microenvironments associated with these cells? Is this diversity primarily driven by the expression of cell type-specific (trans)membrane ECM-binding proteins or is it more influenced by regional factors, such as cellular composition and functional activity that regulate the concentrations of locally secreted ECM molecules?
- How specific interactions between glycans and lecticans of varying sizes within PNNs do underly their remarkable resistance to endogenous proteases and glycosidases, resulting in exceptional half-life times for some ECM components in the scale of years? In chronic disease states, do alterations in PNN integrity arise primarily through an outside-in mechanism such as enzymatic degradation, or through an inside-out process, where the down-regulated expression of specific ECM components by PNN-embedded cells compromises PNN integrity and renders associated neurons more vulnerable to pathological insults?
- How to manipulate PNNs and neural ECM in a spatiotemporal specific manner to preserve the optimal network function under stable conditions, and safely tune down to adapt to new rules and challenges?
- How can we design treatments that selectively target specific ECM forms in the CNS, preferably only in the functional circuits affected by particular neurological disease? What are the most promising ECM targets?
- How to deal with temporal and spatial heterogeneity of ECM modifications during disease progression, particularly in conditions like cerebral small vessel disease in which multiple small lesions are broadly distributed in the brain and are at different inflammatory stage?
- How to image ECM remodeling in diseased brains in vivo to facilitate disease diagnosis or monitor the efficacy of ECM-targeting therapies?

1461 **Table 1: ECM and related genes associated with CNS disorders.**

Gene	Full name	Genetic modifications	Pathological conditions	Species reported	Clinical manifestations
(1) Core matrisome proteins					
VCAN	Versican (a CSPG)	Autosomal dominant mutation	Cerebral small vessel disease (CSVD)	Human	• Stroke, cognitive decline, white matter lesions [60]
NCAN	Neurocan (a CSPG)	Polymorphism	Bipolar disorder, schizophrenia, Depression	Human	• Mania-like behavior[61]
BCAN	Brevican (a CSPG)	Microdeletion	Episodic falling syndrome	Dogs	• Progressive hypertonicity[62]
COL4A1 COL4A2	Collagen type IV alpha 1 chain or alpha 2 chain	Duplication or Triplication	Familial CSVD	Human	• Ischemic and hemorrhagic strokes, motor impairment, cognitive decline, leukoencephalopathy[62]
RELN	Reelin	Truncation	Schizophrenia, autism spectrum disorder, and Alzheimer's disease	Human	• Cognitive and motor impairment[63]
LGI1	Leucine-rich glioma-inactivated 1	Autosomal dominant mutation	Autosomal dominant lateral temporal epilepsy	Human	• Seizures with auditory features[64]
(2) ECM degrading enzymes in the extracellular space (for local ECM modulation)					
HTRA1	High-Temperature Requirement A serine peptidase 1	Autosomal recessive mutation	CARASIL (an early onset form of CSVD)	Human	• Early-onset subcortical infarcts and vascular degeneration[65]
PRSS12	Serine protease neurotrypsin	Truncation	Mental retardation (ARNSMR)	Human	• Severe cognitive deficits, marked speech delay, and significant learning/memory impairments[66]
MMP3	Matrix metallopeptidase 3	Polymorphism	Multiple Sclerosis (MS)	Human, rodents	• Inflammation and demyelination, compromised BBB[67]
MMP9	Matrix metallopeptidase 9	Polymorphism	Ischemic stroke/PD Neuroprotection in epilepsy and stroke	Human	• Compromised BBB[68]
(3) ECM degrading enzymes in lysosomes (for ECM homeostasis)					
IDUA	Alpha-L-iduronidase	Deficiency due to mutation or deletion	Mucopolysaccharidosis (MPS)-I Hurler Syndrome Scheie Syndrome Hurler-Scheie Syndrome	Human Dogs	• Accumulation of dermatan sulfates and heparan sulfates[69] • Developmental delay and intellectual disability[69,70]
IDS	Iduronate sulfatase	Deficiency due to mutation or deletion	MPS-II Hunter Syndrome	Human	
SGSH	Heparan sulfate sulfatase	Deficiency due to mutation or deletion	MPS-IIIA Sanfilippo syndrome A	Human	• Accumulation of heparan sulfat[71]e or its specific sulfation forms • Motor dysfunction, spasticity, developmental delay and hyperactivity[71]
NAGLU	N-acetylglucosaminidase	Deficiency due to mutation or deletion	MPS-IIIB Sanfilippo syndrome B	Human	
HGSNAT	Heparan-α-glucosaminide N-acetyltransferase	Deficiency due to mutation or deletion	MPS-IIIC Sanfilippo syndrome C	Human	
GNS	N-acetylglucosamine 6-sulfatase	Deficiency due to mutation or deletion	MPS-IIID Sanfilippo syndrome D	Human	
GALNS	Galactosamine-6-sulfate sulfatase	Deficiency due to mutation or deletion	MPS-IVA Morquio syndrome A	Human	• Accumulation of keratan sulfates and chondroitin 6-sulfates • Hydrocephalus[72,73]

ARSB	N-acetylgalactosamine-4-sulfatase	Deficiency due to mutation or deletion	MPS-VI Maroteaux–Lamy syndrome	Human	• Accumulation of chondroitin sulfates, dermatan sulfates, and keratan sulfates • Hydrocephalus, meningeal thickening and ataxia[72]
GUSB	β-glucuronidase	Deficiency due to mutation or deletion	MPS-VII Sly syndrome	Human	• Accumulation of heparan sulfate, dermatan sulfate, chondroitin sulfate • Developmental delay, intellectual disability[74]

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Table 2. Targeting neural ECM in the animal models of CNS diseases.

Note: Most studies were performed in mice. If other animal models were used, this is specified under Conditions.

Target	Treatment	Conditions	Therapeutic effects
Prevention of ECM degradation			
MMP-9	Minocycline, DP-b99, KB-R7785, SB-3CT	Stroke[175,176]	↓infarct size, ↑neuroprotection, ↑ECM protection
	MMP-9 mAb, TIMP-1 ACT-03, DP-b99	Epilepsy in rats and mice[87,177]	↓ictogenesis and epileptogenesis, ↑object recognition, neuroprotection
Hyaluronidase	Hyaluronidase inhibitor VCPAL	Stroke[178]	↓skilled reaching test performance
	Flavonoid apigenin	Epilepsy[179]	↓seizures, ↑neuroprotection
	Flavonoid apigenin, synthetic inhibitor S3	Sheep model of preterm cerebral ischemia[180]	↓duration and number of seizures
Promotion of ECM degradation / Inhibition of ECM signaling			
Chondroitin sulfates	Chondroitinase ABC	SCI in rhesus monkey and rodents[181,182]	↑corticospinal axon growth, number of synapses formed by corticospinal terminals, hand function
		Stroke in rats[183]	↑skilled reaching test performance, number of VGLUT2+ synapses
		PD[184]	Protection against a partial 6-OHDA lesion of the nigrostriatal tract
		PD[185]	↑axonal growth of transplanted DA progenitors and their reinnervation of the striatum
		Tauopathy[186]	↑cognition (object recognition)
		Obesity[141]	↓body weight, fat mass, food intake ↑glycemic control
	CS-E mAb	Brain injury[187]	↑axonal regeneration (optic nerve)
	Cat316 mAb	Tauopathy [188]	↑cognition (object recognition)
ADAMTS4	AAV ADAMTS4	SCI [189]	↑lesion size, sprouting of hindlimb corticospinal tract axons, 5-HT fibers, locomotor recovery
Heparan sulfates	Heparinase, Heparin mimetic F6	AD [190]	↓amyloid burden
		Tauopathy[161]	↓internalization of Tau fibrils
Chondroitin and heparin	Xylosides	SCI[191]	↓ lesion size, ↑locomotor recovery
		Human UVEC[192]	↑angiogenesis

sulfate synthesis	Fluorosamine	Obesity[141]	↓body weight, fat mass, food intake ↑glycemic control
Hyaluronan synthesis	Low dose of 4-methyl-umbelliferone	SCI[193]	↑sprouting of 5-HT fibers into the ventral horn, no functional rescue
CSPG receptors	Inhibitory peptide to PTPσ Inhibitory peptides to PTPσ and LAR	SCI in rats[20] SCI in rats[19]	↑5-HT innervation to the spinal cord, functional recovery of locomotor and urinary systems ↑M2 microglia/macrophages and T regulatory cells, expression of IL-10 and Arginase-1
CSPG binder Sema3A	SM-216289	SCI[194]	↑regeneration and/or preservation of injured axons, Schwann cell-mediated myelination, neuroprotection, angiogenesis, locomotor functional recovery

1467