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Dynamic regulation of the extracellular matrix in reward memory processes: a question of time

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Substance use disorders are a global health problem with increasing prevalence resulting in significant socioeconomic burden and increased mortality. Converging lines of evidence point to a critical role of brain extracellular matrix (ECM) molecules in the pathophysiology of substance use disorders. An increasing number of preclinical studies highlight the ECM as a promising target for development of novel cessation pharmacotherapies. The brain ECM is dynamically regulated during learning and memory processes, thus the time course of ECM alterations in substance use disorders is a critical factor that may impact interpretation of the current studies and development of pharmacological therapies. This review highlights the evidence for the involvement of ECM molecules in reward learning, including drug reward and natural reward such as food, as well as evidence regarding the pathophysiological state of the brain's ECM in substance use disorders and metabolic disorders. We focus on the information regarding time-course and substance specific changes in ECM molecules and how this information can be leveraged for the development of therapeutic strategies.

KEYWORDS

perineuronal net, extracellular matrix, substance use disorder, metabolic disorder, synaptic plasticity

Introduction

Substance use disorders (SUD) are a debilitating group of psychiatric disorders that affect approximately 7% of people in the United States each year (SAMHSA, 2018; Grant et al., 2016). Relapse is a major factor limiting recovery from SUD and points to the strength of memory circuits involved in reward memory processing (Niaura et al., 1988; Carter and Tiffany, 1999; Weiss, 2005; Zironi et al., 2006; Janak and Chaudhri, 2010). Converging evidence from rodent models and human postmortem studies suggest a key role of extracellular matrix (ECM) molecules in the formation and maintenance of reward memories (Brown et al., 2007; Smith et al., 2011, 2015; Xue et al., 2014; Slaker et al., 2015, 2016a; Chioma et al., 2021; Seney et al., 2021; Browne et al., 2023). In addition, ECM abnormalities have been reported in several psychiatric disorders in which dysfunction in memory processing and synaptic regulation are key features, including schizophrenia (Eastwood and Harrison, 2006; Pantazopoulos et al., 2010, 2015; Enwright et al., 2016;

Steuilet et al., 2018), post-traumatic stress disorder (Gogolla et al., 2009), major depressive disorder (MDD) (Riga et al., 2017; Alaiyed et al., 2020; Blanco and Conant, 2021), and bipolar disorder (BD) (Fatemi et al., 2000; Pantazopoulos et al., 2015; Steuilet et al., 2018) – each of which have significant comorbidity with SUD.

Involvement of the ECM in the regulation of reward memories may represent a shared feature across reward processes involved in strengthening memories necessary for survival such as food seeking. Several lines of evidence indicate that food and drugs of abuse activate overlapping brain circuitry (Blum et al., 2012; Volkow et al., 2013a). Furthermore, as the incidence of obesity and metabolic disorders continues to mount in the U.S., there has been an increasing interest in combining habitual overeating and drug abuse within a common diagnostic framework of disorders of addiction (Barry et al., 2009; Alsio et al., 2012; Blum et al., 2012; Baik, 2013; Volkow et al., 2013a,b). Growing evidence supports the involvement of ECM molecules in reward processes involved in high fat, high calorie diets that may contribute to metabolic disorders including obesity. The strength of reward memories contributes to relapse and habit forming, and targeting ECM processes to alleviate reward memory strength represents a promising strategy for the development of new treatments for SUD and obesity (Niaura et al., 1988; Carter and Tiffany, 1999; Lu et al., 2004; Weiss, 2005; Zironi et al., 2006; Janak and Chaudhri, 2010).

A growing number of studies demonstrate a dynamic regulation of the ECM during learning processes, including fear and reward learning (Gogolla et al., 2009; Slaker et al., 2016a). Evidence from over two decades of research indicates that the ECM is regulated by rewarding substances in a complex experience-dependent manner which may impact interpretation of the disease processes in SUD and metabolic disorders as well as treatment strategies. We summarize the current evidence for the involvement of the ECM in reward memory processes, SUD and obesity with an emphasis on how the ECM is modulated in a substance- and time-specific manner.

The brain extracellular matrix

The brain extracellular matrix (ECM) is a network of chondroitin sulfate proteoglycans (CSPGs), heparan sulfate proteoglycans, glycoproteins, hyaluronan, and other molecules including axon guidance and cell adhesion molecules such as semaphorins and integrins (Table 1; Figure 1). In the brain, ECM molecules form several specialized structures including perineuronal nets (PNNs), perisynaptic ECM, perivascular ECM, and axonal coats (Schuster et al., 2001; Bruckner et al., 2008; Bekku et al., 2009; Dours-Zimmermann et al., 2009; Morawski et al., 2010; Baeten and Akassoglou, 2011; Lendvai et al., 2012; Susuki et al., 2013; Thomsen et al., 2017; Pantazopoulos et al., 2022; Tabet et al., 2022; Miguel-Hidalgo, 2023; Figure 1). These ECM structures are involved in a wide range of processes implicated in SUD including stabilization of synapses, axon guidance during neurodevelopment, regulation of diffusion of molecules such as neurotransmitters, ions, and metabolites, neuronal firing rates, receptor trafficking, protection from oxidative stress, and regulation of the blood-brain barrier (Hartig et al., 1999; Ishii and Maeda, 2008; Maeda, 2015). ECM molecules also have broad,

complex roles in neurodevelopmental processes and brain injury [for reviews see Silver and Silver, 2014; Peters and Sherman, 2020; Carulli and Verhaagen, 2021; Fawcett and Kwok, 2022; Siddiqui et al., 2022; Schwartz and Domowicz, 2023]. CSPGs have been the primary focus of preclinical addiction studies and are one of the key proteoglycan families in the central nervous system (CNS). CSPGs are composed of a core protein with a varying number of covalently attached chondroitin sulfated glycosaminoglycan chains consisting of repeated pairs of glucuronic acid (GlcA) and N-acetyl-galactosamine (GalNAc) (Figure 1). The predominant CSPGs within the CNS are aggrecan, brevican, neurocan, phosphacan, neuron-gial antigen 2 (NG2), neuroglycan-C and versican (Milev et al., 1998; Deepa et al., 2006; Giamanco and Matthews, 2012). In addition to the specific functions of the core proteins, the glycosaminoglycan chains can vary in number and length, and are sulfated in various positions, which significantly contributes to the function of CSPGs (Asher et al., 2001; Wang et al., 2008; Maeda, 2010; Karus et al., 2012; Miyata et al., 2012; Alonge et al., 2019). For example, synaptic plasticity is regulated by chondroitin sulfation. CS-4 sulfation inhibits axonal growth (Smith-Thomas et al., 1995; Wang et al., 2008), whereas CS-6 is permissive for axonal growth (Lin et al., 2011; Miyata et al., 2012).

Chondroitin sulfate proteoglycans form several specialized structures in the brain in addition to the diffuse ECM which exists around all cells within the CNS (Figure 1). PNNs represent the most well-studied of these structures. PNNs are composed of highly condensed ternary ECM molecules including CSPGs, hyaluronan, and tenascin and surround the soma, proximal dendrites, and axon initial segments of neurons, typically inhibitory fast-firing interneurons expressing parvalbumin (Figure 2; Hartig et al., 1994, 2022; Adams et al., 2001; Pantazopoulos et al., 2006). PNNs are involved in a broad range of functions including stabilization of synaptic plasticity, protection from oxidative stress, regulation of neuronal firing properties, N-methyl-D-aspartate (NMDA) receptor trafficking, and maintenance of ionic homeostasis (Kalb and Hockfield, 1988; Pizzorusso et al., 2002; Morawski et al., 2004; Sugiyama et al., 2008; Frischknecht et al., 2009; Gogolla et al., 2009; Dityatev et al., 2010; Gundelfinger et al., 2010; Frischknecht and Gundelfinger, 2012; Cabungcal et al., 2013; Wingert and Sorg, 2021). The role of PNNs as stabilizers of synaptic connections places them at the intersection of formation and consolidation of memories. PNNs are commonly labeled using the plant lectin *Wisteria floribunda agglutinin* (WFA), which binds to non-sulfated N-acetylgalactosamine residues at the terminal ends of CSPG saccharide chains (Hartig et al., 1994; Nadanaka et al., 2020). However, PNNs are complex structures with diverse composition, and labeling with antibodies directed against core CSPG proteins, glycoproteins, or specific sulfation motifs detects varying, partially overlapping populations of PNNs (Ajmo et al., 2008; Pantazopoulos et al., 2015; Dauth et al., 2016; Hartig et al., 2022; Scarlett et al., 2022). Several studies have demonstrated that the distribution of ECM molecules, including CSPGs and PNNs in the brain, varies greatly in a brain region and age specific manner (Mauney et al., 2013; Dauth et al., 2016; Ueno et al., 2017, 2018, 2019; Rogers et al., 2018; Mafi et al., 2020; Lupori et al., 2023).

Chondroitin sulfate proteoglycans also form several distinct structures in the brain in addition to PNNs (Figure 1). For example, ECM molecules including CSPGs condense as

TABLE 1 Glossary.

Structural extracellular matrix molecules		
CSPG	Chondroitin sulfate proteoglycans	Aggrecan, brevican, neurocan, phosphacan, or versican core proteins with covalently attached glycosaminoglycan side chains
HSPG	Heparan sulfate proteoglycans	Agrin, syndecan, perican, decorin, or glypican core proteins with covalently attached glycosaminoglycan side chains
	Hyaluronan	Large non-sulfated polysaccharides, linked to proteoglycans via hyaluronan and proteoglycan link proteins (HAPLN)
TN	Tenascins	Link hyaluronan-proteoglycan complexes to each other
PNN	Perineuronal nets	Composites of CSPG, hyaluronan, and tenascins condensed around neurons
GAG	Glycosaminoglycan	Long, negatively-charged, hetero sulfated chains of repeating disaccharide units
	Integrins	Signaling medium between the ECM and intracellular cytoskeleton
SEMA	Semaphorins	Axon guidance and cell morphology/Motility
NrCAM	Neural cell adhesion molecules	Fibronectin, laminin, focal adhesions, and integrins
Endogenous proteases and extracellular matrix remodeling molecules		
MMP	Matrix metalloproteinases	Large family of proteases which degrade a wide range of the ECM such as hyaluronan, CSPGs, HSPGs, collagen, etc.
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs	Degrade specifically proteoglycans
	Cathepsins	Serine, cysteine, or aspartyl proteases which degrade specifically CSPGs
	Plasminogen	A precursor of plasmin, which is a broad range proteolytic enzyme capable of degrading a wide range of ECM proteins
tPA	Tissue plasminogen activator	Converters of plasminogen to its active proteolytic plasmin form
uPA	Urokinase plasminogen activator	
TIMP	Tissue inhibitors of metalloproteinases	Endogenous protease inhibitors that bind MMPs as their substrate
Miscellaneous (non-endogenous)		
	Doxycycline	Broad spectrum matrix metalloproteinase inhibitor
	FN-439	Broad spectrum matrix metalloproteinase and collagenase-1 inhibitor
ChABC	Chondroitinase ABC	Degrades glycosaminoglycan side chains
WFA	Wisteria floribunda agglutinin	Lectin which labels the terminal ends of chondroitin sulfate glycosaminoglycan residues, used in a majority of studies for quantification of perineuronal nets.

perisynaptic ECM aggregates on dendritic spines and contribute to synaptic homeostasis (Schuster et al., 2001). ECM molecules form perinodal structures at nodes of Ranvier along myelinated axons, where they contribute to axonal conductance through regulation of gap junctions by several processes including sodium channel clustering (Bekku et al., 2009; Dours-Zimmermann et al., 2009; Susuki et al., 2013; Pantazopoulos et al., 2022; Miguel-Hidalgo, 2023). CSPGs also interweave within myelin sheaths to form periaxonal aggregates called axonal coats (Bruckner et al., 2008; Morawski et al., 2010; Lendvai et al., 2012; Pantazopoulos et al., 2022). Furthermore, ECM molecules are critically involved in regulation of the blood-brain barrier and immune signaling through perivascular ECM structures (Baeten and Akassoglou, 2011; Thomsen et al., 2017; Tabet et al., 2022).

Recent studies demonstrate that the ECM, once thought to represent a stable component of the brain, is regularly modified in an activity-dependent manner through a complex combination of proteolytic remodeling and ECM recycling

processes (Nagy et al., 2007; Brown et al., 2009; Ganguly et al., 2013; Dankovich and Rizzoli, 2022). Matrix metalloproteinases (MMP), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), and cathepsins are the putative endogenous proteases involved in degradation of ECMs (Page-McCaw et al., 2007; Mohamedi et al., 2020; Tran and Silver, 2021). These proteases are secreted by astrocytes, microglia, and neurons, indicating that individual neurons may, in part, be able to regulate the composition of their own PNNs (Rossier et al., 2015; Nguyen et al., 2020). MMPs, part of the metzincin superfamily, consist of several functional classes including collagenases, stromelysins, and gelatinases, with the gelatinases MMP-2, and MMP-9 and the stromelysin MMP-3 representing the predominant MMPs in the brain [for review see Rivera et al., 2010 and Brzdek et al., 2017]. ADAMTSs also serve as the substrate for tissue inhibitors of metalloproteinases (TIMP) which bind to these proteases and inhibit ECM proteolysis (Brew et al., 2000). Other proteolytic enzymes include tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), which cleave and activate

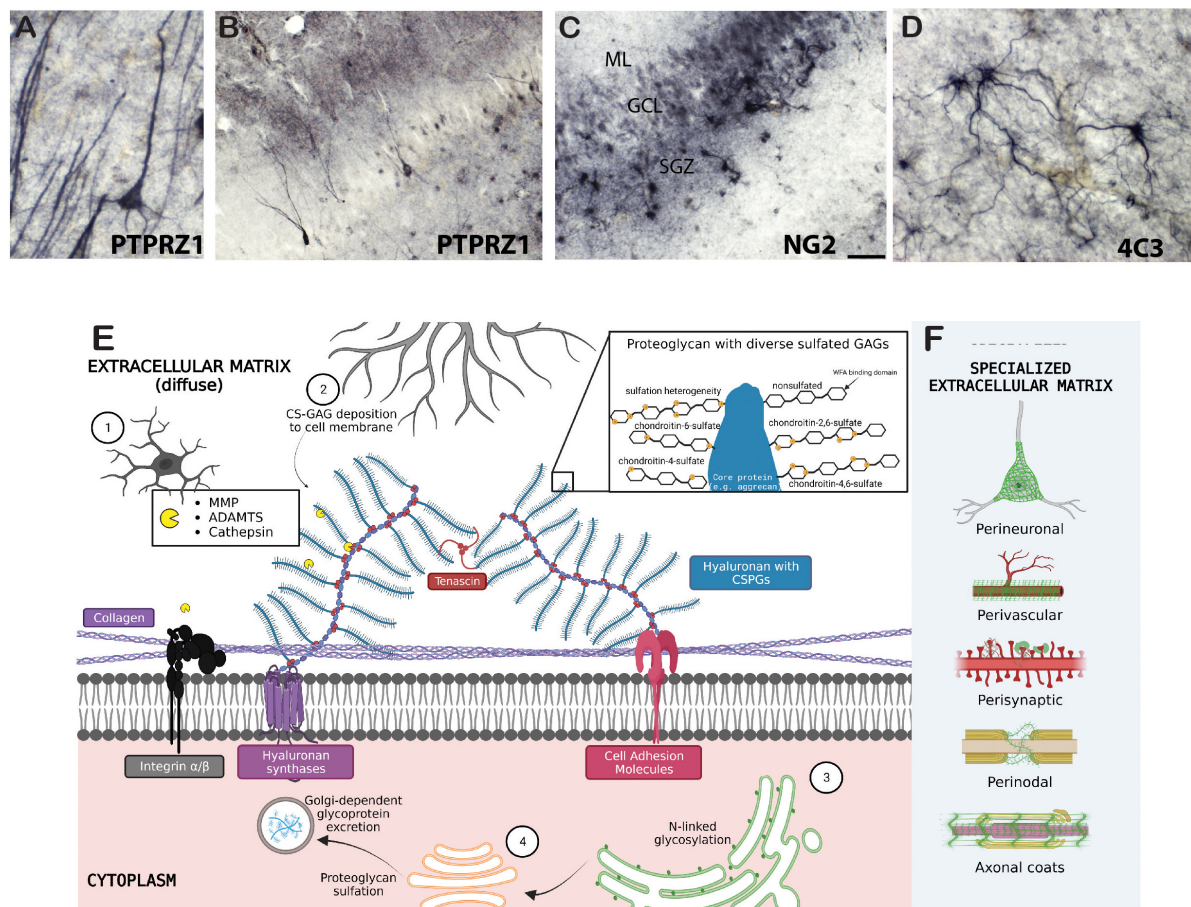


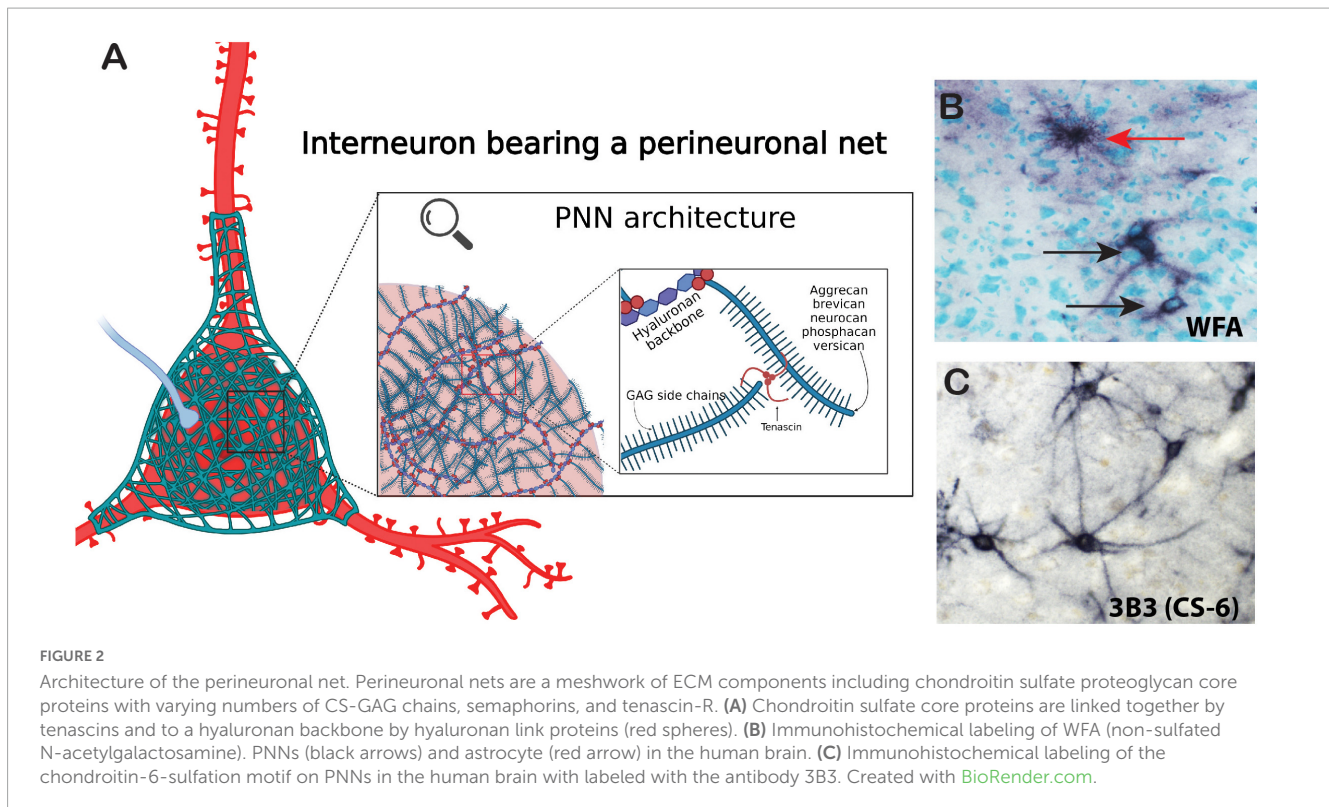
FIGURE 1

Biology of the extracellular matrix. Examples of chondroitin sulfate proteoglycan labeling in several cell types in the human brain include (A,B) immunohistochemical labeling of PTPRZ1 (phosphacan) neurons and glia in the human hippocampus; (C) NG2 labeled glial cells in the human hippocampus; and (D) 4C3 (specific CS sulfation motif) glial cell labeling in the human amygdala. (E) 1, microglia; 2, astrocyte; 3, rough endoplasmic reticulum (ER); 4, Golgi complex. Collagen proteins are tethered to the cell membrane by transmembrane integrins and other cell adhesion molecules. Cell adhesion molecules also attach to hyaluronan and CSPGs, which are attached to other CSPGs via tenascins. CSPGs are cleaved by endogenous proteases secreted by microglia, and are formed by intraneuronal rough-ER and Golgi-dependent processes. Further deposition of CS-glycosaminoglycans (GAGs) on neuron cell membranes is extraneously controlled astrocytes and oligodendrocytes. The zoomed in panel depicts sulfation heterogeneity of CS-GAGs as well as the non-sulfated binding domain of *Wisteria floribunda agglutinin* (WFA) lectin. (F) Specialized ECM structures are illustrated in green. Created with BioRender.com.

plasminogens that can degrade various ECM molecules, including proteoglycans (Saksela, 1985). Endogenous ECM proteases have been reported to modify the ECM during learning, which may facilitate formation of new synapses in response to environmental stimuli (Nagy et al., 2007; Brown et al., 2009; Ganguly et al., 2013). Recent studies have also demonstrated that ECM molecules, including PNNs, are modified in a diurnal manner, which may contribute to memory consolidation processes (Harkness et al., 2019; Pantazopoulos et al., 2020; Gisabella et al., 2021). Taken together, these studies suggest that the ECM is modified in a time-dependent manner which may impact interpretation of studies regarding the role of the ECM in SUD and the development of therapeutic strategies targeting the ECM. Within this context, we review the current literature regarding the involvement of the ECM in reward learning, including drugs of abuse and natural rewards such as high fat diet, and the current evidence for ECM pathology in SUD with an emphasis on time-course dependent findings.

Dynamic extracellular matrix regulation by drugs of abuse

A number of studies have investigated the role of the ECM in animal models and human studies of SUD. Investigations have spanned an array of brain regions, including the prefrontal cortex (PFC) (Goldstein and Volkow, 2011), nucleus accumbens (NAc) (Quintero, 2013), ventral tegmental area (VTA) (Oliva and Wanat, 2016), hippocampus (Kutlu and Gould, 2016), amygdala (Warlow et al., 2017), cerebellum (Moulton et al., 2014), and hypothalamus (Zhang et al., 2020). Together, these brain regions are involved in regulating the rewarding and reinforcing effects of drugs, withdrawal symptoms, and the integration of memories of the rewarding effect of the drug and the associated context. Importantly, several studies cited throughout this review have varying definitions of the terms “acute” and “chronic.” For the purpose of this review, we define acute drug exposures as less than a period of 24-h (<2 h



for “immediate”), and chronic drug exposure as greater than 3 consecutive daily sessions.

Psychostimulants

Stimulant drugs such as cocaine and methamphetamine produce profound effects on CNS function including euphoria and increased motor activity/endurance (Nestler, 2005; Vazquez-Sanroman et al., 2015). Overuse of stimulant drugs can progress to the development of SUD and can also contribute to other serious conditions including psychosis, mood disorders, anxiety, and sleep/circadian rhythm dysfunction (American Psychiatric Association, 2013). Comorbidity of stimulant use with these disorders greatly complicates clinical interpretations and interventions for SUD as well as the comorbid conditions. Currently, there are no FDA-approved cessation pharmacotherapies for stimulant use disorder. Substantial evidence exists for a key role of the ECM in the formation and maintenance of stimulant use disorder endophenotypes (e.g., pervasive memories surrounding stimulant intoxication, withdrawal, and maintained use) (Table 2; Slaker et al., 2016a).

Acute stimulant exposure

An intriguing collection of studies have examined the acute response of ECM molecules to psychostimulant drugs. Integrins serve as a tether for cell membrane-bound condensed ECM and also are involved in cytoskeleton signaling cascades that create a bidirectional interplay of the local ECM and intraneuronal signaling pathways, sometimes serving as the substrate for MMPs (French-Constant and Colognato, 2004; Mezu-Ndubuisi and

Maheshwari, 2021; Samuel et al., 2023). Temporally, $\beta 1$ -integrin protein levels in the NAc of mice are significantly decreased 30 min after a cocaine injection, but not at zero or 120 min (Wiggins et al., 2009). Conditional knockdown of $\beta 3$ integrins in the mouse NAc during cocaine self-administration training prevents cue-induced cocaine seeking and transient excitatory synaptic potentiation (Garcia-Keller et al., 2019), suggesting that the acute increase of β -integrins may be involved in formation of cocaine associated memories. Activating endogenous ECM proteases, such as MMPs, using tPA increases cue-induced cocaine seeking (Garcia-Keller et al., 2019). In line with this, lentivirus-mediated upregulation of uPA (another endogenous MMP activator) in rats potentiates cocaine place preference acquisition (Bahi et al., 2008). Interestingly, knockdown of $\beta 3$ -integrin ameliorates the effect of tPA-induced seeking (Garcia-Keller et al., 2019). Decreased integrin during reward learning may not only inhibit the consolidation of cocaine-associated cues, but also the functions of neurons that are typically ensheathed by PNNs. Another study in rats measured hippocampal MMP protein levels 3 h following nicotine place preference conditioning, demonstrating relatively mild increases of MMP-2 and -9 during the early training sessions, and a much greater nicotine-induced MMP-9 upregulation during later conditioning sessions (Natarajan et al., 2013). Importantly, nicotine acts through mechanisms which are distinct from other psychostimulants of abuse (i.e., cholinergic stimulation of mesolimbic dopamine) and its effects as a reinforcer rely heavily on learning the cues paired with its administration (McClernon et al., 2016). Thus, progressively increased MMP induction over the course of nicotine CPP training may reflect contextual learning mechanisms induced by nicotine.

TABLE 2 Effects of psychostimulants on the ECM.

Treatment	Species	Brain area	Preharvest interval	ECM effect	Manipulation	Behavioral effect	References
Acute psychostimulant exposure							
Experimenter-administered cocaine	Mouse	NAc	30 min	↓ β 1-integrin	NA	NA	Wiggins et al., 2009
Cocaine IVSA	Mouse	NA	NA	NA NA	Heterozygous β 3-integrin deficiency	↓ Cue-induced cocaine seeking ↓ Enhancement of cue-induced cocaine seeking by MMP-9	Garcia-Keller et al., 2019
Cocaine CPP	Rat	NAc	NA	NA	Intra-NAc lentivirus upregulation of uPA	↑ CPP	Bahi et al., 2008
		NA	NA	NA	Inhibition of uPA with doxycycline	↓ Enhancement of CPP	
Nicotine conditioned place preference	Rat	HPC and PFC	3 h	↑ MMP-2 and MMP-9	NA	NA	Natarajan et al., 2013
Cocaine CPP and locomotor activity recordings	Mouse	NA	NA	NA	Heterozygous reelin deficiency	↑ Cocaine-induced hyperlocomotion No effect on CPP	de Guglielmo et al., 2022
Experimenter-administered meth	Mouse	NA	NA	NA	Heterozygous reelin deficiency	No effect on meth-induced hyperlocomotion	Hume et al., 2020
Single cocaine injection	Rat	IL and PL PFC	2 h or 24 h	2 h: ↓ PNNs not apposing PVB neurons	NA	NA	Slaker et al., 2018
Single cocaine injection	Mouse	Amygdala, NAc, putamen	30 min	↑ tPA activity in amygdala	Homozygous tPA KO	Cocaine induces anxiolysis in tPA KO mice	Maiya et al., 2009
Single cocaine injection	Rat	HPC, NAc	1 day	↑ <i>Sema3a</i> in hippocampus ↓ <i>Sema3a</i> in NAc	NA	NA	Bahi and Dreyer, 2005
Chronic psychostimulant exposure							
Cocaine use disorder	Human	HPC	Postmortem	↓ MMP-9 protein ↑ β 1-laminin and β 6-integrin mRNA	NA	NA	Mash et al., 2007
Experimenter-administered cocaine	Rat	IL and PL PFC	5 days: 2 h or 24 h	2 h: ↑ PNNs apposing PVB neurons 24 h: No effect	NA	NA	Slaker et al., 2018
Experimenter-administered cocaine (7 days)	Mouse	Deep cerebellar medial nucleus	24 h after last cocaine	↑ strong-type PNN labeling	NA	NA	Vazquez-Sanroman et al., 2015
Cocaine CPP	Rat	Cerebellum (lobule VIII of vermis)	8 cocaine pairings: 1.5 h after test (25.5 h after last cocaine)	NA	Intra-cerebellar chABC prior to CPP	No effect on CPP acquisition	Guarque-Chabrera et al., 2022
Cocaine CPP short-term memory (cue exposure)	Rat	Cerebellum, lobule VIII of vermis (LVIII)	6 days after last cocaine	NA	Intra-LVIII chABC prior to retest	↓ Cocaine short-term memory	Guarque-Chabrera et al., 2022

(Continued)

TABLE 2 (Continued)

Treatment	Species	Brain area	Preharvest interval	ECM effect	Manipulation	Behavioral effect	References
		Deep cerebellar nuclei (DCN)			Intra-DCN chABC prior to retest		
Stable nicotine IVSA	Rat	VTA and OFC	45 min after last session 72 h after last session	45 min: ↓ PNNs apposing PVB neurons in VTA, OFC 72 h: ↓ PNNs apposing PVB neurons in VTA, no effect in OFC	NA	NA	Vazquez-Sanroman et al., 2017
Chronic (15 days) cocaine injections	Rat	HPC, NAc, VTA	24 h after last cocaine	↑ <i>Sema</i> mRNA in HPC, NAc, and VTA	NA	NA	Bahi and Dreyer, 2005
Cocaine RST from forced abstinence	Rat	HPC, VTA, NAc	24 h after last cocaine	↑ <i>Sema3a</i> in HPC ↓ <i>Sema3a</i> in NAc	NA	NA	Bahi and Dreyer, 2005
Chronic (13 days) cocaine and meth injections	Mouse	LH	Unknown	↑ HS disaccharide and sulfation content	NA	NA	Chen et al., 2017
Chronic (7 days) cocaine injections	Mouse	NAc	3 weeks since last cocaine	↑ β1-integrin	NA	NA	Wiggins et al., 2009
Cocaine CPP	Rat	PL PFC	24 h	↑ PNNs apposing c-Fos neurons	NA	NA	Slaker et al., 2015
Chronic (5 days) meth injections	Rat	PFC, NAc, striatum, and VTA	2 h	↑ <i>Timp2</i> in PFC, NAc, and striatum	D1R and D2R antagonism	↓ Meth-induced <i>Timp</i> induction	Mizoguchi et al., 2007
Cocaine CPP RST	Rat	PFC and HPC	1, 3, 24 h	↑ MMP-9 and -2 in PFC at all timepoints, no changes in HPC	NA	NA	Brown et al., 2008
Cocaine CPP	Rat	PL PFC	24 h	↓ PNNs apposing c-Fos neurons in chABC animals	Intra-PL chABC before acquisition	↓ CPP	Slaker et al., 2015
Cocaine CPP RST	Rat	PL PFC	1 h	↓ PNNs apposing c-Fos neurons in chABC animals	Intra-PL chABC before memory reactivation	↓ CPP	Slaker et al., 2015
Cocaine EXT	Rat	PL PFC	~14 days	No effect on PNNs apposing cFos neurons in chABC animals	Intra-PL chABC before extinction	No effect	Slaker et al., 2015
Cocaine IVSA RST	Rat	NAc	15 min after RST	↑ MMP-9 by cues for cocaine	NA	NA	Smith et al., 2014
Cocaine IVSA RST	Rat	NAc	15 min after RST	NA	FAK inhibitor	↓ Reinstatement of cocaine IVSA	Garcia-Keller et al., 2020
Meth cue exposure during abstinence	Rat	NAc	30 min after cued relapse	Increased MMP-2,9 by meth cues	NA	NA	Lewandowski et al., 2023
Cocaine CPP and IVSA	Rat	LH	NA	NA	Intra-LH chABC injection before behavior	↓ CPP and IVSA	Blacktop et al., 2017

Acute (top) and chronic (bottom) effects of cocaine, methamphetamine, and nicotine on ECM molecules. Preharvest interval denotes the time between the most recent drug exposure and euthanasia. CPP, conditioned place preference; IVSA, intravenous drug self-administration; RST, reinstatement; NAc, nucleus accumbens; HPC, hippocampus; PFC, prefrontal cortex; IL, infralimbic; PL, prelimbic; VTA, ventral tegmental area; LH, lateral hypothalamus; OFC, orbitofrontal cortex; MMP, matrix metalloproteinase; chABC, chondroitinase ABC; PNN, perineuronal net; PVB, parvalbumin; SEMA, semaphorin; TIMP, tissue inhibitor of metalloproteinase; tPA, tissue plasminogen activator; HS, heparan sulfate; D1R/D2R, dopamine 1 and 2 receptors; FAK, focal adhesion kinase.

While acute exposure to stimulants appears to upregulate many ECM proteases, PNN fluorescent intensity 2 h after initial cocaine exposure is significantly decreased in the rat PFC coinciding with increased inhibitory glutamic acid decarboxylase- (GAD) 65/67 synaptic puncta on PNN-coated parvalbumin neurons (Slaker et al., 2018). Reduced PNN composition at 2 h corresponds with findings from a prior study which identified increased expression of tPA, an upstream promoter of MMPs (Tsuji et al., 2005), 30 min following a cocaine injection (Maiya et al., 2009). In comparison, differential effects of semaphorin 3a, a related ECM molecule, were observed between the rat hippocampus and NAc (Bahi and Dreyer, 2005). One day after receiving a bolus cocaine injection, expression of semaphorin 3a, a chemorepulsive protein involved in regulating PNN plasticity (Dick et al., 2013; de Winter et al., 2016), is significantly increased in the hippocampus, but decreased in the NAc (Bahi and Dreyer, 2005). Semaphorin 3a binds to the 4,6-sulfated CS in PNNs and decreased semaphorin 3a is associated with enhanced plasticity of neurons surrounded by PNNs (Dick et al., 2013; de Winter et al., 2016), suggesting that PNNs in these regions are differentially regulated by acute cocaine exposure. Further studies regarding brain region-specific changes in PNN components as well as perisynaptic ECM and axonal coats following acute exposure to psychostimulants will provide insight into the specific role of the ECM in synaptic plasticity during psychostimulant use.

Chronic stimulant use

Extracellular matrix molecules have been extensively studied during chronic stimulant models of self-administration, extinction, and reinstatement. Additionally, effects of PNN digestion using the exogenous enzyme chondroitinase ABC (chABC) have been examined at various timepoints across drug administration protocols by several groups [for review see Slaker et al. (2016a)]. Neuroinflammation is a hallmark of chronic stimulant use, and is induced by direct actions of these drugs on microglia resulting in upregulated inflammatory cytokines (Kohno et al., 2019). However, evidence suggests that stimulant use does not result in persistent microgliosis (Narendran et al., 2014). There is a current lack of evidence regarding how neuroinflammation and ECM alterations intersect in the acute vs. chronic phases of stimulant use disorder.

Protracted exposure to cocaine increases the numerical density and intensity of PNNs in several brain regions, such as the PFC (prelimbic/infralimbic cortex) and cerebellum, whereas nicotine decreases numerical densities of PNNs in the VTA and orbitofrontal cortex (Slaker et al., 2015, 2018; Vazquez-Sanroman et al., 2015, 2017; Guarque-Chabrera et al., 2022). Increased expression of several semaphorin genes was reported in the hippocampus, NAc, caudate putamen, and VTA of rats during chronic cocaine exposure and relapse (Bahi and Dreyer, 2005), suggesting that semaphorin expression may contribute to increased PNNs in these regions during chronic cocaine exposure. In addition to changes in PNNs and semaphorins, HSPGs, such as syndecan-3, are altered after prolonged exposure to cocaine and methamphetamine, increasing both in disaccharide content and total sulfation (Chen et al., 2013, 2017). Interestingly, another study reported no significant effect of 5 days of cocaine exposure on sulfation of diffuse CS, HS or hyaluronan (Slaker et al., 2018). The composition and functional properties of HS and CS proteoglycan/GAG families have a great deal of similarity,

both subserving synaptic homeostasis and acting as structural chemorepellent barriers to neuroplasticity (Maeda et al., 2011). β 1-integrin protein levels also undergo a \sim 1.5-fold increase after prolonged withdrawal from chronic cocaine exposure (Wiggins et al., 2009). Further, expression of tissue inhibitors of MMPs (TIMPs) is significantly upregulated following repeated methamphetamine exposures (Mizoguchi et al., 2007) indicating that suppression of MMPs after prolonged stimulant use may reduce PNN degradation and contribute to the reported increases in PNNs following chronic drug use. In comparison, multiple studies converge on upregulation of proteolytic activity, including increased MMP expression, upon re-exposure to either stimulant-associated cues (i.e., stimulus lights in self-administration chambers, drug-paired CPP chambers) or stimulants alone (Brown et al., 2007, 2008; Smith et al., 2014; Garcia-Keller et al., 2020; Lewandowski et al., 2023). Importantly, the increase in inhibitory (GAD-65/67) synaptic puncta in the PFC during acute cocaine exposure is retained throughout chronic exposure (Slaker et al., 2018). Removal of PNNs using chABC in the anterior dorsal lateral hypothalamus, amygdala or PFC inhibits stimulant-induced place preference and reinstatement of stimulant self-administration (Xue et al., 2014; Slaker et al., 2015; Blacktop et al., 2017; Marchant, 2019). A human postmortem study of the hippocampus in subjects with history of cocaine use identified significantly decreased protein levels of the active form of MMP-9, along with a corresponding upregulation of several cell adhesion genes (Mash et al., 2007). Taken together, studies on stimulants suggest a biphasic modification of ECM over the course of stimulant use. MMPs increase during the acute phase of drug exposure, presumably to degrade PNNs to allow the formation of new synaptic connections involved in reward memory encoding. After prolonged use, MMPs decrease in activity which contributes to decreased modification of CSPGs and HSPGs and in turn the reported increase in PNN composition, which may stabilize the newly formed synapses involved in reward memory and contribute to relapse.

Opioids

The significant abuse liability and mortality of opioids has gained attention over the past couple of decades due to the rise in overdose deaths from illicit and synthetic opioid analogs, particularly heroin and fentanyl (Spencer et al., 2022). Prescription opioids are highly effective pain-relieving medicines; however, they can also lead to dependence, resulting in misuse and development of opioid use disorder (OUD). Thus, the development of new prescription opioids, or additives to opioids, that retain analgesic qualities and reduce the risk of dependence is a current research focus (Negus and Freeman, 2018). A majority of heroin users report using opioids for the first time early in life (Jones, 2013), a critical period of brain circuit wiring where ECM molecules are involved in shaping later stage maturation of brain circuits including the formation of PNNs (Pizzorusso et al., 2002; Gogolla et al., 2009; Mauney et al., 2013; O'Connor et al., 2019; Nguyen et al., 2020; Gisabella et al., 2021). Furthermore, several lines of evidence propose a critical role of the ECM in the analgesic and rewarding effects of opioids (Table 3; Krueger et al., 2020; Ray et al., 2022).

TABLE 3 Effects of opioids on the ECM.

Treatment	Species	Brain area	Preharvest interval	ECM effect	Manipulation	Behavioral effect	References
Acute opioid exposure							
Morphine and EM-2 incubation <i>in vitro</i>	MCF-7 breast cancer cell line	NA	3–72 h in culture	Concentration-gradient ↓ of <i>Mmp2</i> and <i>Mmp9</i> by morphine and EM-2	NA	NA	Gach et al., 2011
Heroin IVSA cued RST	Rat	NAc	0 min	Increased MMP-9 puncta around D1R MSNs	MMP-2 and MMP-9 inhibitors	MMP-9 inhibitors decrease cued reinstatement	Chioma et al., 2021
Morphine incubation <i>in vitro</i>	Human brain microvascular endothelial cells	NA	24 h	↓ MMP-2, LAMA-4	NA	NA	Vujic et al., 2022
Chronic opioid exposure							
Heroin IVSA, EXT and RST	Rat	mPFC, NAc, striatum	21 days (EXT) 0 min (RST)	EXT: ↓ TNR and BCAN in NAc, ↓ 145 kDa BCAN in mPFC RST: ↓ TNR in NAc	i.c.v. FN439 injection	Decreased cue-induced heroin RST	Van den Oever et al., 2010
Heroin IVSA RST	Rat	NAc	15 min after RST	↑ MMP-9 by cue exposure	NA	NA	Smith et al., 2014
Escalating morphine and naloxone mediated withdrawal	Rat	Spinal cord (laminae I–VII)	48 h	Significant increase of MMP-9 in morphine treated animals	Intrathecal MMP-9 inhibition	↓ Morphine withdrawal No effect on pain-threshold or morphine-induced analgesia	Liu et al., 2010
Heroin IVSA forced abstinence	Rat	IL-PFC and vOFC	1 day 30 d	1 day: ↑ PNNs in IL and OFC 30 days: No PNN changes compared to controls	NA	NA	Roura-Martinez et al., 2020
Opioid use disorder	Human	DL-PFC and NAc	Postmortem	↑ Differentially expressed transcripts related to CS-GAG biosynthesis in DL-PFC, NAc	NA	NA	Seney et al., 2021
Opioid use disorder	Human	Midbrain	Postmortem (overdose)	↑ IL-4 in opioid overdoses	NA	NA	Wei et al., 2023

Acute (top) and chronic (bottom) effects of opioids on ECM molecules. Preharvest interval denotes the time between the most recent drug exposure and euthanasia. CPP, conditioned place preference; IVSA, intravenous drug self-administration; NAc, nucleus accumbens; HPC, hippocampus; PFC, prefrontal cortex; IL, infralimbic; PL, prelimbic; VTA, ventral tegmental area; LH, lateral hypothalamus; OFC, orbitofrontal cortex; MMP, matrix metalloproteinase; chABC, chondroitinase ABC; PNN, perineuronal net; TNR, tenascin-R; LAMA, laminin; tPA, tissue plasminogen activator; HS, heparan sulfate; D1R/D2R, dopamine 1 and 2 receptors; MSN, medium spiny neuron; IL, interleukin.

Acute opioid exposure

There is extensive evidence suggesting that the ECM in the CNS is altered by pain, Nakamoto et al. (2012); Ishiguro et al. (2014); Tajerian and Clark (2015); Hu et al. (2021); Mascio et al. (2022); Tansley et al. (2022). Together these studies indicate that microglia degrade PNNs in the spinal cord when pain levels are high to disinhibit the spinal cord nociceptive afferents that evoke pain perception. Chronic pain results in an increased abundance of PNNs, possibly to stabilize newly formed synapses involved in the discriminative and emotional aspects of pain (Mascio et al., 2022). There is, however, relatively limited evidence regarding the immediate effects (0 to 2 h) of opioids on the ECM, particularly regarding the potential role of the ECM as it pertains to pain relief processes by opioids in multiple modalities of nociception (e.g., thermal, inflammatory, neuropathic). Studies indicate that acute

administration of morphine dose-dependently decreases MMP-2, MMP-9, and laminin-4 (LAMA-4) expression in both breast cancer and human brain microvascular endothelial cell lines from 3 h up to 72 h (Gach et al., 2011; Vujic et al., 2022). Speculatively, the 3-h timepoint examined in cell lines may capture a period after prior increases in MMP expression, considering that levels of laminins are also decreased. In line with this, MMP-2 and -9 display increased activity around dendritic spines of dopamine 1 (D1) receptor- medium spiny neurons in the rat NAc during heroin reinstatement (Chioma et al., 2021). Rapid proteolytic induction may also reflect opioid activation of interleukin-33 expression and intracellular microglial cascades downstream of the IL1RL1/ST2 receptor involved in memory processing, which would increase expression of several ECM proteases to facilitate synaptic plasticity (Nguyen et al., 2020; Hu et al., 2021). Alternatively, acute decreases

of MMP activity in response to opioids may contribute to their mechanism of analgesia, as acute pain is associated with increased MMP expression and degradation of the ECM (Tansley et al., 2022). Whether effects on the ECM incurred by opioids in the spinal cord and brain are congruent or divergent is yet to be determined. It is possible that opioids have regional effects on the ECM. For example, in the brain, opioids may contribute to synaptic plasticity underlying drug-associated memories, whereas in the spinal cord, opioids may act on the ECM to inhibit excitatory nociceptive afferents. As evidence in this field continues to mount, it will be important for future studies to improve our understanding of the temporal ECM changes in response to opioids and how they interact with the effect of pain on the ECM.

Chronic opioid use

Early work examined ECM molecules in the brain of rats following heroin self-administration (Van den Oever et al., 2010). Acute abstinence from opioids (1 day) is associated with an increased numerical density of PNNs in the PFC. Long-term abstinence, however, (21–30 days), is associated with a decrease in protein levels of the PNN components tenascin-R and brevican in the medial PFC and NAc, but no significant difference in WFA labeled PNN numerical densities compared to control animals (Van den Oever et al., 2010; Roura-Martinez et al., 2020). This suggests that PNN composition may be modified, or the changes in tenascin-R and brevican occur on other ECM structures distinct from PNNs. Alternatively, multiple studies point to upregulation of MMPs in the NAc during cue-induced heroin relapse (Liu et al., 2010; Smith et al., 2014; Chioma et al., 2021). Interestingly, inhibiting PNN degradation during reinstatement with intracerebroventricular FN-439 administration or enhancing PNN degradation during extinction with chABC in the amygdala impairs cue-induced heroin reinstatement (Van den Oever et al., 2010; Xue et al., 2014).

Two recent human postmortem studies provide critical evidence regarding alterations of ECM and neuroimmune gene expression pathways in the brain of people with OUD (Seney et al., 2021; Wei et al., 2023). Transcriptional profiling of the dorsolateral PFC and NAc revealed a shared, significant upregulation of transcripts related to CSPG and GAG biosynthesis in these two brain regions in subjects with OUD (Seney et al., 2021). Notably, pathways involved in cytokine-mediated inflammation and synapse remodeling were also upregulated (Seney et al., 2021). Moreover, a recent postmortem study of the ventral midbrain transcriptome identified significant upregulation of the IL-4 receptor in microglia in individuals who died by opioid overdose, providing further support for neuroinflammation in the brain of people with OUD (Wei et al., 2023). Collectively, studies on the effects of opioids on brain ECM molecules highlight an interplay of the brain's immune system and the ECM in regulating both reward stabilization and analgesia.

Alcohol

Alcohol use disorder (AUD) is the most prevalent form of SUD in the U.S. (American Psychiatric Association, 2013). Chronic, heavy alcohol use results in an array of health issues affecting several organ systems including the brain and

increases mortality risk. A growing number of studies have investigated ECM alterations in response to alcohol early in adolescence, as well as acute, and chronic alcohol use (Table 4; Lasek, 2016).

Acute alcohol exposure

One of the first studies to examine brain levels of ECM molecules in response to drugs of abuse focused on alcohol's effect on MMP-9 in the rat brain during water maze training (Wright et al., 2003). Alcohol administration resulted in reduced MMP-9 activity in the hippocampus and prefrontal cortex. This reduction was evident after 2 days and became progressively more severe after 4 and 6 days of alcohol administration (Wright et al., 2003). The progressive decrease in MMP-9 activity was accompanied by impaired water maze performance, suggesting that alcohol impairs hippocampal learning by downregulating MMP-9 activity (Wright et al., 2003). Furthermore, intracerebroventricular administration of the broad spectrum MMP inhibitor, FN-439, during ethanol withdrawal, was reported to prevent relapse to alcohol self-administration in rats (Smith et al., 2011). Alternatively, a recent study using chronic adenovirus-mediated overexpression of MMP-9 in the hippocampus demonstrated that mice with chronic MMP-9 overexpression had reduced alcohol-induced place preference (Yin et al., 2023). Persistent MMP-9 upregulation also perturbed ethanol-induced increases in NMDA receptor subtypes (Yin et al., 2023). Inhibitory effects of prolonged upregulation of MMP-9 on alcohol place preference points to the importance of temporal specificity of MMP regulation during phases of reward integration. Upregulation of MMPs, when prolonged, may cause aberrant synaptogenesis that inhibits the normal synaptic refinement and GABAergic (i.e., parvalbumin) modulatory processes which aid in reward memory precision and consolidation (Beroun et al., 2019).

While no studies have examined PNNs after acute exposure to alcohol (i.e., <24 h), exposure to alcohol for one week does not significantly alter the fluorescent intensity of PNNs, or mRNA expression of the PNN components aggrecan, brevican, and phosphacan (Chen et al., 2015). Lack of changes in CSPG levels at this timepoint may indicate that ECM remodeling occurs earlier than 2 days, and at 7 days ECM remodeling remains in an interim phase where neither MMPs nor PNNs/their components are significantly altered.

Chronic alcohol use

Several studies have investigated how chronic alcohol exposure regulates the structure of the ECM. Adolescent exposure to alcohol in mice results in increased densities of PNNs and increased immunoreactivity of brevican and neurocan in the orbitofrontal cortex (OFC) that is sustained into adulthood (Coleman et al., 2014; Dannenhoffer et al., 2022). In adult rats, 6 weeks of alcohol self-administration significantly increases the intensity of WFA-labeled PNNs and mRNA levels of aggrecan, brevican, and phosphacan in the insula (Chen et al., 2015). A set of experiments from the same group used cocktails of quinine, an aversive and bitter additive, with alcohol to investigate whether the ECM regulates aversion-resistant drinking (Chen and Lasek, 2020). Ablating PNNs in the insula with chABC 3 days prior to the onset of alcohol self-administration rendered animals more sensitive to aversive

TABLE 4 Effects of alcohol on the ECM.

Treatment	Species	Brain area	Preharvest interval	ECM effect	Manipulation	Behavioral effect	References
Acute alcohol exposure							
Daily exposure	Rat	HPC, PFC cerebellum	2, 4, and 6 days	Progressive MMP-9 ↓	Morris water maze	↓ Performance in animals with low <i>Mmp9</i>	Wright et al., 2003
EtOH vapor induced-alcohol SA escalation	Rat	NA	NA	NA	i.c.v. FN-439 during withdrawal	No escalation of self-administration	Smith et al., 2011
CPP	Mouse	HPC	NA	NA	Adenovirus MMP-9 upregulation before CPP training	↓ Place preference	Yin et al., 2023
DID (1 wk)	Mouse	Insula	20 h	No effect on PNNs, ACAN BCAN, or PCAN	NA	NA	Chen et al., 2015
Chronic alcohol exposure							
Adolescent intermittent alcohol exposure	Mouse	OFC	73 d	↑ PNN, BCAN, and NCAN IR	Barnes maze reversal learning	Normal adolescent performance, ↓ adult performance	Coleman et al., 2014
Adolescent intermittent alcohol exposure	Rat	Striatum, OFC, and mPFC	26–30 days	↑ PNN number and PNN apposing PVB	NA	NA	Dannenhoffer et al., 2022
DID (6 weeks)	Mouse	Insula	20 h	↑ PNN intensity, ACAN, BCAN, and PCAN	NA	NA	Chen et al., 2015
Two-bottle choice: quinine-alcohol (4 days)	Mouse	Insula	NA	NA	Intra-insula chABC injection before two-bottle choice	↑ Aversion to quinine-adulterated alcohol	Chen and Lasek, 2020
Alcohol use disorder	Human	Blood	GWAS	↑ Frequency of -1562C/T polymorphism on MMP-9	NA	NA	Samochowicz et al., 2010
Alcohol use disorder	Human	Blood	GWAS	Single nucleotide polymorphisms on TNN and TNR genes	NA	NA	Zuo et al., 2012

Acute (top) and chronic (bottom) effects of alcohol on ECM molecules. Preharvest interval denotes the time between the most recent drug exposure and euthanasia. SA, self-administration; CPP, conditioned place preference; DID, 4-day drinking in the dark; HPC, hippocampus; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; MMP, matrix metalloproteinase; PNN, perineuronal net; ACAN, aggrecan; BCAN, brevican; PCAN, phosphacan; chABC, chondroitinase ABC; TNN, tenascin-N; TNR, tenascin-R; IR, immunoreactivity.

quinine cocktails (Chen and Lasek, 2020). As the insula is part of the gustatory cortex, increased PNNs in this area may contribute to integration of the non-pharmacologically relevant aspects of alcohol into the memory trace (i.e., bitter taste). In comparison, the ECM neural cell adhesion molecules (NrCAMs) may be involved in the contextual aspects of alcohol reward circuits. NrCAM knockout mice display reduced alcohol place preference (Ishiguro et al., 2014), and pharmacological inhibition of this signaling pathway via systemic administration of prolyl-leucyl-glycinamide also impaired alcohol place preference, suggesting a potential ECM-based therapeutic approach for alleviating context-induced relapse. Chronic alcohol consumption is also associated with increased neuroinflammation, such as heightened recruitment of several pro-inflammatory cytokines that are known to impact the ECM (Kelley and Dantzer, 2011; Lowe et al., 2020; Xiong et al., 2022). Genetic studies of AUD identified associations of genes encoding ECM molecules with increased risk of AUD. Two genome-wide association studies implicate genetic polymorphisms of several ECM genes including tenascin-N and -R and MMP-9 with AUD (Samochowicz et al., 2010; Zuo et al., 2012), suggesting that ECM molecules may be involved in the susceptibility for developing AUD.

Psychoplastogens

Psychoplastogens encompass a variety of chemical classes (e.g., dissociatives, psychedelics) which produce profound, long-lasting effects on neural plasticity with single exposures (Ly et al., 2018; Ballentine et al., 2022). This feature of psychoplastogens has made them attractive candidates as potential treatments for SUD and MDD in controlled, clinical settings in combination with psychotherapy, such as cognitive behavioral therapy (CBT) (Carhart-Harris et al., 2012; Talin and Sanabria, 2017; Rieser et al., 2022; Slosower et al., 2023).

Ketamine, an NMDA receptor antagonist originally used as an anesthetic, has psychotomimetic effects including hallucinations (Powers et al., 2015). It is also used recreationally and can lead to SUD (Strous et al., 2022). Chronic recreational use reportedly results in structural gray and white matter alterations and memory impairment (Strous et al., 2022). Several studies, including clinical trials, provide support for the use of low dose ketamine administration for treatment-resistant depression (Zarate et al., 2006; Phillips et al., 2019; Can et al., 2021), which is often comorbid with SUD (Shin and Kim, 2020). Repeated exposure to ketamine at anesthetic doses results in decreased composition

of PNNs via microglia-mediated proteolytic ECM degradation which promotes synapse plasticity (Venturino and Siegert, 2021; Venturino et al., 2021). Further, ketamine and phencyclidine (PCP) administration alter expression of a number of ECM genes, including the collagen type IX alpha 2 chain, NrCAM-1, decorin, and heparan sulfate 6-O-sulfotransferase, in the striatum between one and 8 h following administration (Oommen et al., 2023), suggesting that effects on the ECM are much broader than reported PNN composition changes.

The conventional serotonergic psychedelics, lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), and psilocybin, are suggested to have potentially rapid antidepressant effects with a relatively limited side effect profile (Carhart-Harris et al., 2016; Rucker et al., 2016). In the rat PFC, both *in vivo* and *in vitro*, LSD, DMT, and the substituted amphetamine psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) promote neurogenesis, spinogenesis and synaptogenesis (Ly et al., 2018). Furthermore, the synaptic changes induced by psychedelics may be long term. For example, the reported increase in dendritic remodeling detected within 24 h was reported to last for at least 1 month following a single dose of psilocybin (Shao et al., 2021). To date, there are no studies of how these compounds regulate the ECM. Acute administration of DOI produces robust transcriptional responses by recruiting multiple cell types including glia, and significantly increases expression of parvalbumin and somatostatin in activated neuronal ensembles (Martin and Nichols, 2016). In line with this, both psilocybin and ketamine upregulate parvalbumin expression in neurons expressing the immediate early gene *cFos* (Davoudian et al., 2023). Upregulated somatostatin, a neurotransmitter expressed by a subset of interneurons ensheathed by PNNs (Willis et al., 2022), may potentially alleviate molecular alterations in the case of SUD, as our recent study identified decreased hippocampal somatostatin expression in subjects with SUD (Valeri et al., 2022). Taken together, we speculate that psychedelic drugs may have similar actions on the ECM as psychostimulant drugs, mediating rapid and sustained ECM disassembly upon administration. However, serotonergic psychedelics are not reinforcing, and therefore likely do not carry risk of addiction (Nichols, 2016). Several studies suggest that psychedelics combined with CBT may be promising candidates for improving SUD outcomes and preventing relapse, as they may promote plasticity of brain circuits involved in reward and goal-directed behavior (DiVito and Leger, 2020), potentially in part through ECM remodeling.

Obesity and metabolic disorders

Obesity is a global health problem that impacts virtually all aspects of health and results in a significant personal and societal burden (Main et al., 2010). Obesity also increases the risk of a range of diseases, including metabolic disorders, which encompasses cardiovascular disease, diabetes mellitus, and hypertension (Colditz et al., 1995; Calle et al., 2003; GBD 2015 Obesity Collaborators et al., 2017). Several psychiatric disorders associated with increased risk of SUD share comorbidity with metabolic disorders (Luppino et al., 2010; Jimenez et al., 2019; Trevino-Alvarez et al., 2023). For example, MDD is often comorbid with type 2 diabetes (T2D), and

several lines of evidence point to a core metabolic pathology across mood disorders (Fagiolini et al., 2002; Dona et al., 2020; Norwitz et al., 2020). Additionally, conditions associated with metabolic disorders such as painful diabetic neuropathy are commonly managed with opioid medications, which pose a risk of addiction (Callaghan et al., 2012; Jensen et al., 2021). In addition, many people with T2D (over 40%) also have a comorbid SUD (Wu et al., 2018; Feldman et al., 2019). The brain regions primarily responsible for food-seeking behaviors include the hypothalamus (e.g., arcuate nucleus, median eminence, lateral hypothalamus), hippocampus (Martin and Davidson, 2014; Parent et al., 2014), and PFC (Garcia-Garcia et al., 2014). Obesogenic diets have been reported to result in inflammation and alterations in synaptic plasticity and blood-brain barrier regulation, all of which are regulated in part by the ECM (Gustafson et al., 2007; Guillemot-Legris and Muccioli, 2017; Matikainen-Ankney and Kravitz, 2018; Brown and Sorg, 2023).

Several studies support a key role of PNNs in the arcuate nucleus in obesity and metabolic disorders (Table 5). Formation of PNNs in the arcuate nucleus coincides with the closure of the critical period of agouti-related peptide neuron maturation in this region, in a leptin-dependent manner (Mirzadeh et al., 2019). Furthermore, Zucker diabetic fatty rats, which carry spontaneous missense mutations of the leptin receptor gene causing hyperglycemia and rapid development of T2D, have significantly reduced PNNs and altered sulfation of CSPGs in the arcuate nucleus (Alonge et al., 2020). These effects on PNNs are reversed by intracerebroventricular injections of fibroblast growth factor 1, which induces sustained diabetes remission in Zucker rats (Scarlett et al., 2016; Alonge et al., 2020).

Several studies also report ECM alterations in several brain areas outside of the hypothalamus in preclinical models of obesity (Table 5). For example, chronic (3 weeks) exposure to a high-diet in adult male rats decreased the fluorescent intensity of PNNs labeled with WFA in the prelimbic and orbitofrontal cortices, an effect that was not contingent on weight gain (Dingess et al., 2018). In a report from the same group, Sprague-Dawley rats which were bred either prone to obesity or resistant to obesity had differential responses a high-fat diet in the OFC, with decreases in PNN intensity in obese-prone rats and increased PNN intensity in obese-resistant rats (Dingess et al., 2020). Chronic exposure (5 weeks) to a high-fat/high-sugar diet decreased PNN density in the CA1 field of the hippocampus of adult male mice, along with corresponding increases in adiposity and abundance of activated microglia (Reichelt et al., 2021). However, no changes were observed in PNNs in the PFC in the same animals (Reichelt et al., 2021). Although high-fat/high-sugar diet formulations induce changes in PNNs in the PFC, sugar alone does not appear to have any effect on PNNs (Slaker et al., 2016b; Roura-Martinez et al., 2020). Data regarding short term effects of feeding and specific diets on the ECM is greatly limited. A recent study suggests that PNN composition in the median eminence of the hypothalamus is decreased during fasting but PNNs increase after a brief feeding following the fasting period (Kohnke et al., 2021).

A relatively limited set of studies have investigated sexual dimorphic effects of diet on the ECM. In contrast to the data in males, both outbred and obese-prone female rats exhibit an increase in PNN intensity in the infralimbic cortex following a high fat diet, whereas obese-resistant females show a decrease in PNN intensity (Dingess et al., 2020). In contrast, in the arcuate nucleus,

TABLE 5 Involvement of the ECM in diet and metabolism.

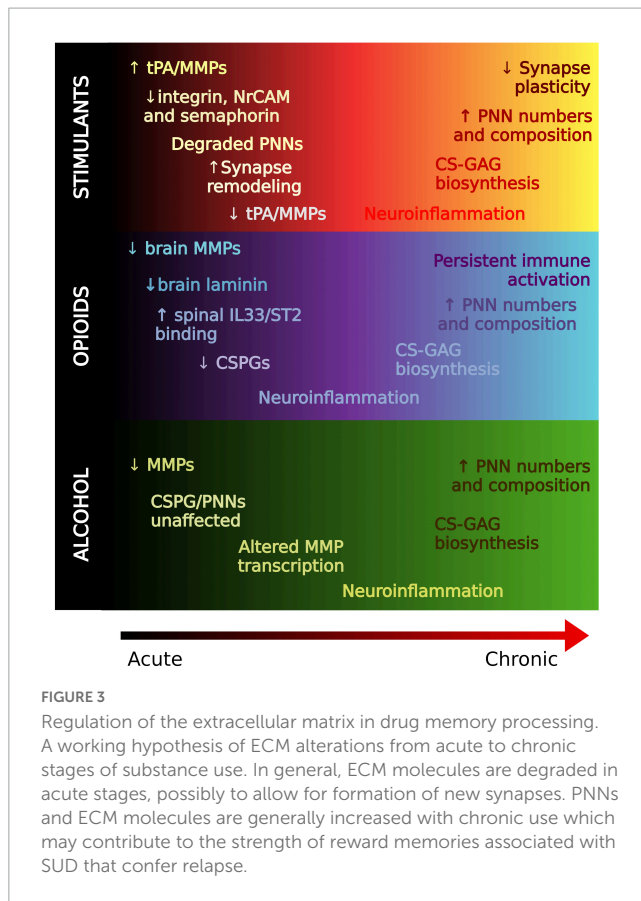
Manipulation	Species	Brain area	ECM response	Treatment	Response	References
Leptin deficiency (ob/ob)	Mouse	Arcuate nucleus (ARC)	↓ PNN apposition on AgRP	Leptin supplement	Rescued PNN abundance	Mirzadeh et al., 2019
ZDF and high-fat diet	Rat	ARC	↓ PNNs Altered CS/DS sulfation	Fibroblast growth factor-1 i.c.v. injection	Rescued PNN abundance and sulfation	Alonge et al., 2020
HFD	Rat	PL-PFC IL-PFC OFC	↓ PNN intensity, but not number No changes ↓ PNN intensity and number	NA	NA	Dingess et al., 2018
Obesity-prone male rats (normal diet vs. HFD)	Rat	PL-PFC IL-PFC OFC	↓ PNN intensity and PVB apposition No changes ↓ PNN intensity number, and PVB apposition	NA	NA	Dingess et al., 2020
Obesity-prone female rats (normal diet vs. HFD)	Rat	PL-PFC IL-PFC OFC	No changes ↑ PNN intensity, number and PVB apposition ↓ PNN intensity	NA	NA	Dingess et al., 2020
Obesity-resistant male rats (normal diet vs. HFD)	Rat	PL-PFC IL-PFC OFC	No changes ↓ PNN intensity No changes	NA	NA	Dingess et al., 2020
Obesity-resistant female rats (normal diet vs. HFD)	Rat	PL-PFC IL-PFC OFC	No changes ↓ PNN intensity No changes	NA	NA	Dingess et al., 2020
HF-HSD	Mouse	PL-PFC IL-PFC OFC HPC	↑ active microglia ↑ active microglia ↑ active microglia ↓ PNNs and ↑ active microglia	NA	NA	Reichelt et al., 2021
Sucrose self-administration	Rat	PL-, IL-PFC, and OFC	No changes	NA	NA	Slaker et al., 2016b
Overnight fast and 1 h re-feed (ob/ob)	Mouse	ARC and ME	↑ PNN intensity in ME following re-feed	MBH chABC injection	↓ Food intake 48 – 96 h post chABC	Kohnke et al., 2021
Male HFD	Mouse	ARC and TE	No changes in TE	Castration	↓ PNN intensity in ARC	Zhang et al., 2021
Female HFD	Mouse	ARC and TE	↑ PNN intensity in TE	Ovariectomy	↓ PNN intensity in ARC	Zhang et al., 2021

Acute (top) and chronic (bottom) effects of cocaine, methamphetamine, and nicotine on ECM molecules. Preharvest interval denotes the time between the most recent drug exposure and euthanasia. ZDF, Zucker diabetic fatty rat; HFD, high fat diet; HF-HSD, high fat-high sugar diet; OP, obesity-prone; OR, obesity-resistant; ARC, arcuate nucleus; ME, median eminence; TE, terete hypothalamic nucleus; HPC, hippocampus; PFC, prefrontal cortex; IL, infralimbic; PL, prelimbic; OFC, orbitofrontal cortex; PNN, perineuronal net; AgRP, agouti-related protein; PVB, parvalbumin; CS, chondroitin sulfate; DS, dermatan sulfate.

sex hormones have been shown to affect the ECM independent of dietary manipulation (Zhang et al., 2021).

Obesity as well as T2D contribute to neuroinflammation (Miller and Spencer, 2014; Van Dyken and Lacoste, 2018). Brain-wide decreases of PNNs in male subjects exposed to a chronic high-fat diet is in line with heightened inflammatory activity from microglia and potential proteolysis of ECM. There is likely

deep complexity between multiple factors that correspond with diet-induced differences in the architecture of the ECM, such as genetic predisposition, age, and sex. Future studies examining these relationships and how they interact in comorbid conditions will provide key insight into the involvement of the ECM in metabolic disorders and how this information can be leveraged for therapeutic strategies. As mentioned previously, metabolic



dysfunction is a characteristic of some psychiatric disorders, such as MDD and BD. The ketogenic (low carb) diet is rapidly gaining support as a treatment for psychiatric disorders including mood disorders, autism spectrum disorder, and schizophrenia (Brietzke et al., 2018; Campbell and Campbell, 2020; Sarnyai and Palmer, 2020; Danan et al., 2022). Intriguingly, the ketogenic diet has been shown to alter the ECM by downregulating gene expression of fibrinogen, but upregulating myelin basic protein expression in the rat hippocampus (Noh et al., 2004).

Current challenges and future directions

Despite the growing evidence for a key role of ECM molecules in substance use disorders, there are several knowledge gaps that limit the development of ECM-based pharmacotherapies. First, as indicated in this review, despite the growing number of studies, there is a lack of sufficient information regarding the temporal ECM changes in specific brain regions for specific substances. In addition, despite evidence for WFA labeled PNN alterations, there is a lack of information regarding changes in PNN composition and specific ECM structures such as perisynaptic ECM, axonal coats and/or perivascular ECM. Moreover, few studies thus far have examined the role of the ECM in neurodevelopmental factors prior to the onset of SUD that can contribute to risk of SUD, including genetic factors, chronic stress, exposure to a culture of drug use, traumatic experiences, and socio-economic status. Future studies

on the ECM that consider such etiological factors would provide critical insight into the role of the ECM in enhanced risk to SUDs.

Furthermore, the vast majority of current evidence is largely based on animal model studies, there is currently a lack of information regarding these ECM structures in the brain of individuals with SUD. Human postmortem studies may provide critical information that can support preclinical studies and guide development of therapeutic strategies. Polysubstance use disorder is the most common clinical presentation of SUD, thus preclinical studies of polysubstance use may provide key insight into potential interactions of various drugs of abuse on the ECM and allow for development of more translatable therapeutic strategies. In terms of developing or repurposing drugs for ECM based treatments of SUD, the current evidence suggests that MMP inhibitors such as doxycycline may inhibit ECM degradation and formation of reward memories associated with initial drug exposure. In comparison, short-term upregulation of MMPs may represent an effective strategy to treat chronic SUD, especially in combination with CBT. Temporary removal of PNNs may allow for reorganization or weakening of reward associated synapses, and may prevent feedforward modulation of neuronal ensembles by parvalbumin, thus creating more glutamatergic noise and less coherence of the neurons that are associated with drug memories (Brown and Sorg, 2023). Furthermore, several lines of evidence indicate that inhibiting MMP activity may be useful in preventing relapse following a period of abstinence. The development of pharmacotherapies with selectivity for brain ECM structures which can be delivered systemically, provide temporal control, and limit potential off-target side effects remains a major challenge for ECM-based therapeutic strategies.

Regarding the role of the ECM in metabolic disorders, a limitation of rodent models of T2D (e.g., the Zucker rat) is the relatively abrupt development of hyperglycemia, which is not characteristic of the gradual human disease progression (Oltman et al., 2005; Hinder et al., 2018). As rodent models of T2D evolve, examining the role of the ECM in the progression from prediabetic-like states to T2D may provide evidence for temporal ECM alterations that can guide preventative and treatment strategies. As previously mentioned, many individuals with mood disorders often suffer from metabolic disorders and eating disorders, such as binge-eating disorder. In this context, there is currently a lack of evidence providing a link between mood dysregulation, HFD, and the ECM. Studies focused on these associations may enhance our understanding of potential ECM-based precipitating factors for metabolic disorders.

Concluding remarks

Current evidence suggests that the ECM is at the intersection of synaptic regulation and neuroimmune responses to drug reward and food reward. Synaptic regulation and inflammation are hallmarks of the neuroadaptations induced by both SUD and metabolic disorders (Cui et al., 2014; Hao et al., 2016). These processes may impact overlapping neuroanatomical circuits and cellular mechanisms. Food is essential for survival, and

evolutionarily conserved processes may promote strengthening of brain circuits involved in integrating environmental cues associated with biologically relevant rewards such as food, especially food that is high in fat and calories. In comparison, drugs of abuse are not necessary for survival, and initial exposure to drugs most commonly occurs after the closure of critical periods of plasticity associated with maturation of PNNs. Therefore, enhanced PNNs by chronic drug (unnatural) reward may be the result of synaptic reorganization occurring later in development, recruiting additional ECM components to stabilize synapses that participate in integration of novel, potent reward experiences engaging brain circuits that are normally involved in regulating memories for experiences that are necessary for survival. Intriguingly, a similar temporal relationship of PNN alterations was reported in the rat hippocampus across stages of social defeat stress (Riga et al., 2017), suggesting that this temporal regulation of PNNs may be a shared mechanism underlying memory processing across positive and negative experiences. Decreased PNNs in obesity and metabolic disorders may instead reflect increased neuroinflammation associated with these conditions.

In summary, ECM molecules may represent key contributors to the pathogenesis of SUD and metabolic disorders. Acute exposure to substances of abuse render PNNs unstable through the activity of endogenous proteases, and chronic exposure generally increases PNNs and ECM molecules (Figure 3). Pathologically, SUD is an ingrained memory trace that maladaptively triggers activation of brain circuits that recurrently promote relapse. Thus, enhanced PNNs may reflect an inflexibility of memory systems pertaining to reward-associated stimuli which perpetuates the cycle of relapse and addiction.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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