Neuroscience and Biobehavioral Reviews 118 (2020) 65–79

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Incubation of depression: ECM assembly and parvalbumin interneurons after stress

Sabine Spijker (PhD)[a,1,*], Maija-Kreetta Koskinen[a,1], Danai Riga (PhD)[b]

[a] Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit, Amsterdam, the Netherlands

[b] Molecular Neuroplasticity, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

ARTICLE INFO

Keywords:
Hippocampus
Prefrontal cortex
Experience-dependent plasticity
Social defeat stress
Chronic mild/unpredictable stress
Restraint stress
Early life stress
Hyper-excitability
Hypo-excitability

ABSTRACT

The extracellular space is occupied by a complex network of proteins creating a mesh-like assembly known as the extracellular matrix (ECM). ECM assembles into dense net-like structures, perineuronal nets (PNNs), that envelope cell somas and proximal neurites of predominantly parvalbumin$^+$-(PV$^+$) interneurons. ECM regulates cell-to-cell communication, thereby modulating neuronal network function. Accumulating evidence points to the importance of network dysfunction in the pathophysiology of psychiatric diseases, in which stress acts as a major predisposing factor. Here we review stress-induced changes in ECM/PNNs and PV$^+$-interneurons in preclinical models of (or for) depression, with a special focus on social stress. We argue that the direction of these alterations largely depends on stress recency, as well as on stress timing and the brain region under investigation. A biphasic temporal regulation of ECM/PNNs and PV$^+$-interneuron function is typically observed after stress. Understanding the complex mechanisms underlying ECM organization in relation to stress-induced molecular, cellular and network changes is crucial to further decipher the implications of ECM remodeling in the incubation of depressive symptoms.

1. Introduction

Depressive pathologies are amongst the most prevalent psychiatric disorders worldwide, affecting 1 out of 8 Europeans, with higher incidence in women (Malhi and Mann, 2018). Major depressive disorder (MDD), characterized by persistent negative affect and diminished interest in everyday activities (anhedonia), is amongst the most commonly diagnosed mood disorders, and it is considered a recurrent, lifelong condition (Malhi and Mann, 2018). Apart from their anhedonic traits, mood disorders are marked by a variety of somatic symptoms including fatigue, sleep disturbances and changes in appetite. Importantly, depression largely affects the cognitive domain, manifested in indecisiveness, concentration difficulties, intrusive memories (Brewin et al., 2010), over-generalization of autobiographical memories (Williams et al., 2007; Murrough et al., 2011), as well as reduced cognitive flexibility and spatial memory deficits (Murrough et al., 2011; Disner et al., 2011).

While genetic factors might render an individual prone to the development of MDD (Howard et al., 2018; Wray et al., 2018), one of the most well-described triggers of the disease is exposure to severe or chronic stress (Hammen, 2005). Coping well with stress is essential for a healthy, adaptive lifestyle, and traumatic stress triggers a neurobiological cascade that sets the stage for increased vulnerability to psychiatric disorders across the life span (Kloet et al., 2005). Stress exposure initiates a variety of physiological and psychological events that interrupt the homeostatic state of an organism (McEwen et al., 2015). These are predominantly manifested in a “fight or flight” response that has countless evolutionary advantages. Nevertheless, some individuals display excessive stress reactivity, seen at the hormonal, neurochemical and neurocircuitry levels, in erroneous settings, *e.g.*, in absence of a stressful trigger. In addition, stress reactivity in these individuals persists well-beyond the appropriate autonomic response (Franklin et al., 2012), hindering the restoration of homeostatic balance.

Given the importance of the individual stress response on subsequent emergence of pathology (Riga et al., 2017a), and based on a reverse translational approach, rodent models were developed to study the mechanisms underlying stress vulnerability. Different approaches have been adopted leading to behavioral assays that employ non-social (*e.g.*, chronic mild stress, learned helplessness) or social (*e.g.*, maternal deprivation, early-life isolation) stressors for the induction of a

* Corresponding author at: De Boelelaan 1085, 1081 HV, the Netherlands.
E-mail address: s.spijker@vu.nl (S. Spijker).
[1] Equal contribution.

https://doi.org/10.1016/j.neubiorev.2020.07.015
Received 25 October 2019; Received in revised form 6 July 2020; Accepted 15 July 2020
Available online 17 July 2020

depressive-like state. Collectively, these efforts focused on studying the behavioral, molecular and cellular effects of stress in the presence, or shortly after cessation, of the stressor. Less often, studies consider the perpetuating nature of the depressive state, given that in humans mood disorders require months to develop (Lupien et al., 2009).

In this respect, it could be of interest for the depression field to mirror aspects of research on drug addiction, for which, during the last two decades, several models were developed that focused on long-term drug-induced changes (Deroche-Gamonet et al., 2004). Specifically, the concept of 'incubation of drug-craving' has caught attention as it describes time-dependent adaptations that perpetuate drug-seeking behavior (Pickens et al., 2011). Relapse to drug use in humans can occur after prolonged abstinence (Gawin and Kleber, 1986), and both in humans (Wang et al., 2013; Bedi et al., 2011) and rodent models of addiction (Grimm et al., 2001) alike, the likelihood to relapse increases with the passage of time. In addition, similar to preclinical models of depression in which enriched housing (Schloesser et al., 2010) and activity (Duman et al., 2008) can relieve from depressive symptoms, the extent of incubation of drug craving can be diminished by housing conditions (Thiel et al., 2011; Chauvet et al., 2009) and activity (Lynch et al., 2010).

An important question arises then, namely, whether a similar phenomenon occurs following exposure to stress, mediating the "incubation" of depressive-like symptoms. If so, what is the molecular mechanism that could mediate long-term changes and confer vulnerability to depressive symptoms, including the cognitive hallmarks of the disease? An attractive hypothesis is to introduce the extracellular matrix (ECM), a class of molecules that mainly reside outside neurons and glia cells, as the suitable substrate for long-lasting behavioral phenotypes of stress-triggered psychiatric disorders (Dityatev and Schachner, 2003). The ECM is considered a major regulator of experience-dependent plasticity in adulthood (Warren et al., 2018), and has been proposed to physically represent long-term memory maintenance (Tsien, 2013). Previously, we showed that ECM dysregulation mediates the persistence of drug-related memories after prolonged abstinence (den Oever et al., 2010; Lubbers et al., 2016). Importantly, our data indicated that interference with ECM assembly reduces both incubation of drug craving and vulnerability to relapse (den Oever et al., 2010; Lubbers et al., 2016). We propose that the late development of depressive-like symptoms in the weeks and months following exposure to stress, which co-occurs with gradual changes in ECM composition (Riga et al., 2017b; Koskinen et al., 2019), implies a similar phenomenon of "incubation". Here, we will first introduce the organization of the ECM, together with typical preclinical models used to study stress and model depression. After highlighting specific examples where ECM is dysregulated, we will discuss these data in light of the concept of 'incubation of depression symptomatology', in which stress recency is considered.

1.1. Extracellular matrix organization

The extracellular space is occupied by a complex network of proteins, macromolecules such as proteoglycans and glycoproteins, and cell-surface receptors, which combined, create a mesh-like assembly known as the extracellular matrix (ECM). The brain's ECM, rich in lecticans, like chondroitin sulphate proteoglycans (CSPGs), and ECM-tethering molecules including hyaluronic acid (HA) and proteins of the Tenascin family, surrounds both neurons and synapses (Dityatev and Schachner, 2003).

In the adult brain, the CSPGs aggrecan, brevican, neurocan and versican are core components of the ECM. The various CSPGs are attached to HA, the structural backbone of the ECM, *via* link proteins, including hyaluronan and proteoglycan link protein (Hapln1). Furthermore, CSPGs are cross-linked *via* tenascin-R to form stable net-like structures (Yamaguchi, 2000; Deepa et al., 2006). CSPGs carry glycosaminoglycan (GAG) side chains of chondroitin sulfate (CS) that vary in numbers, length and sulfation patterns, and are critical determinants of the functional properties and heterogeneity of these proteoglycans (Miyata et al., 2012; Kwok et al., 2012). ECM components are expressed and secreted both by neurons and glial cells in an activity-dependent manner (Song and Dityatev, 2018). In order to swiftly respond to changing external conditions, the ECM is under tight regulation that enables temporally and spatially precise remodeling, as seen both in long-term changes and in rapid changes upon a physiological challenge (den Oever et al., 2010; Lubbers et al., 2016; Riga et al., 2017b; Koskinen et al., 2019; Slaker et al., 2016). A key player in this process is proteolytic processing of the ECM by metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) that are produced by neurons and astrocytes alike (Stawarski et al., 2014; Beroun et al., 2019).

It has become increasingly evident that the ECM not only provides neurons with biochemical and structural support but critically modulates cell-to-cell communication. First, diffuse ECM encloses synapses, where it actively regulates synaptic transmission. For example, ECM around excitatory synapses regulates lateral mobility of the α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) receptors, thereby altering short-term synaptic plasticity (Frischknecht et al., 2009).

Likewise, brevican regulates AMPA receptor localization in parvalbumin-expressing interneurons (PV^+), modifying interneuron excitability and plasticity (Favuzzi et al., 2017). These studies exemplify how perisynaptic ECM constitutes an integral part of the synaptic machinery, justifying the concept of the tetrapartite synapse (Dityatev and Rusakov, 2011) (Fig. 1, Box 1). Second, ECM assembles into dense aggrecan-based net-like structures, the perineuronal nets (PNNs), that envelope cell somas and proximal neurites (Fig. 1, Box 1). PNN formation is linked to restricted plasticity, as they act as a physical barrier that inhibits formation of novel synaptic contacts onto the surrounding cell, while providing structural support for the existing ones (Hockfield et al., 1990; Nikonenko et al., 2003; Sullivan et al., 2018). Importantly, by embedding numerous molecular cues that can be either inhibitory or permissive, the matrix forms a microenvironment that functions as a hub for signal detection and transmission, thereby actively participating in neuronal communication (van' t Spijker and Kwok, 2017; de Winter et al., 2016).

PNNs often enwrap a specific interneuron subtype, *i.e.* parvalbumin-expressing (PV^+) interneurons (Celio and Blumcke, 1994; Härtig et al., 1992; Celio, 1993), an abundant population of interneurons that typically shows fast-spiking (Hu et al., 2014) properties. PNN presence around other types of neurons, including excitatory cells, has been observed (Nakagawa et al., 1986; Carstens et al., 2016; Morikawa et al., 2017). PV^+-interneurons comprise ~20 % and 40 % of all GABAergic cells in the hippocampus and cortex, respectively (Hu et al., 2014; Rudy et al., 2011). Parvalbumin, a Ca^{2+} binding protein, regulates intracellular Ca^{2+} homeostasis and can, therefore, modulate many aspects of neuronal signaling (Albéri et al., 2013; Collin et al., 2005; Schwaller, 2007). Indeed, parvalbumin expression, measured as intensity of immuno- fluorescence, has been shown to correlate with GABA production (Donato et al., 2013), and it is often taken as a reflection of PV^+ cell activity (Favuzzi et al., 2017; Donato et al., 2013; Hijazi et al., 2019), albeit that this has not always been consistently verified with electrophysiological read-outs. By innervating the soma and axon initial segment, PV^+ basket cells exert powerful inhibitory control over their postsynaptic targets through feedforward and feedback inhibition (Hu et al., 2014). This way, PV^+ cells orchestrate the synchronization of network activity, especially in the theta and gamma frequency, crucial for cognitive processing (Buzsáki and Wang, 2012).

In the visual cortex, PNNs appear onto PV^+ cells at the end of the critical developmental period, marking the maturation of the inhibitory network (Pizzorusso et al., 2002). In a series of elegant experiments, Pizzorusso and colleagues demonstrated that targeting the ECM by chondroitinase ABC (chABC), an enzyme that catalyzes the removal of sulfate side chains of proteoglycans, jumpstarts a critical period-like

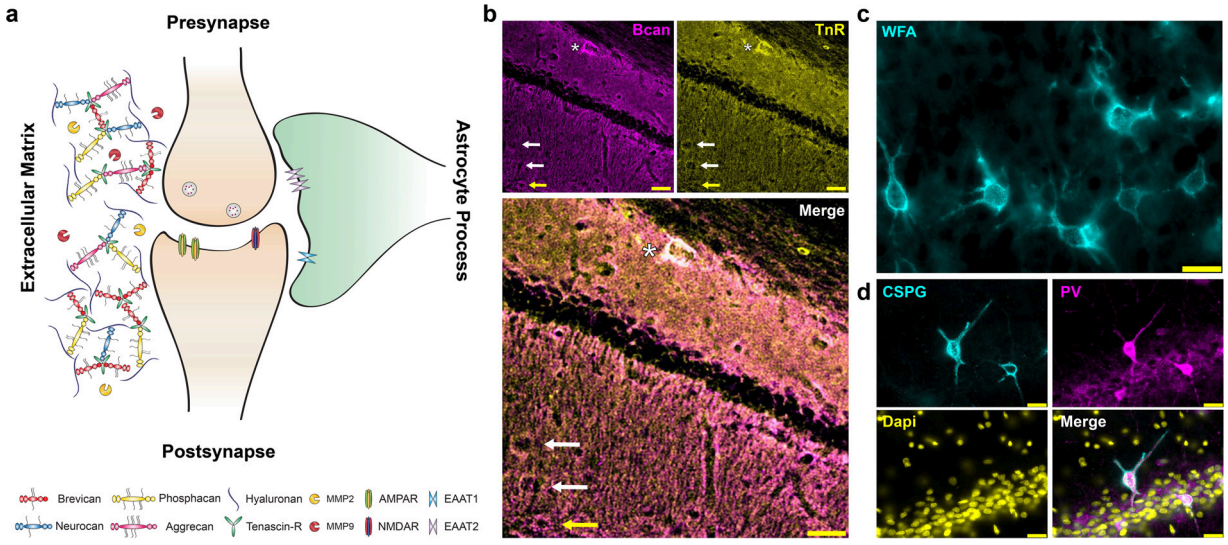

Fig. 1. Brain extracellular matrix (ECM). a) Schematic representation of diffuse perisynaptic ECM, which in the brain is enriched in chondroitin sulphate proteoglycans (CSPGs), in particular brevican, and the ECM-tethering molecule tenascin-R. Together, pre- and post-synaptic terminals, astrocytic processes and perisynaptic ECM form the tetrapartite synapse (Dityatev and Rusakov, 2011). **b**) Example of diffuse brevican and tenascin-R staining at the hippocampus CA1 region of the mouse; yellow and white arrows, indicate minor deposition of each marker respectively. Asterisk denotes a perineuronal net (PNN). **c**) ECM molecules assemble into dense mesh-like structures, the PNNs, which are enriched in aggrecan. Example of WFA-labeled PNNs in the rat prefrontal cortex. **d**) PNNs preferentially surround parvalbumin-expressing (PV^+) interneurons in the hippocampus CA1 region. Example of Cat301-labeled PNNs (CSPG), PV^+ interneurons and nuclei (Dapi) in the CA1 pyramidal layer of the rat. Note that brain region- and species-differences exist in the reactivity of antibodies used to visualize PNNs (Matthews et al., 2002). Scale bars indicate 50 μm (b) and 25 μm (c, d).

plasticity in adulthood. Similar to the visual cortex, in the amygdala the appearance of PNNs coincide with a switch to an adult-like state, after which fear memories become resilient to extinction (Gogolla et al., 2009). In addition, degradation of amygdalar ECM renders acquired fear memories prone to erasure, similar to what observed in juvenile animals. These groundbreaking studies demonstrated the pivotal role of the ECM in controlling plasticity, and are increasingly accompanied by studies showcasing the critical involvement of the ECM in mediating experience-dependent plasticity across brain regions (den Oever et al., 2010; Happel et al., 2014; Banerjee et al., 2017; Xue et al., 2014).

Accumulating evidence points to the involvement of PV^+ network dysfunction, as well as changes in PNN^+-PV^+ interneurons, in the pathophysiology of several psychiatric diseases, in which stress acts as a major predisposing factor (Fogaça and Duman, 2019; Ferguson and

Box 1
Markers of perisynaptic and perineuronal ECM.

Perineuronal ECM – Aggrecan is the most abundant form of lectican giving rise to perisomatic net-like structures, and is enriched in PNNs over perisynaptic ECM. Instrumental in the detection of perineuronal ECM was the generation of monoclonal antibodies raised against the cat spinal cord (McKay and Hockfield, 1982), which turned out to detect mostly aggrecan (Hockfield et al., 1990). Antibodies that are largely based on aggrecan immunodetection, such as Cat-301, are commonly used to visualize PNNs (Hockfield and McKay, 1983; Zaremba et al., 1989), structures that were already identified during the 19th century, as elegantly reviewed by Celio et al. (1998). Wisteria floribunda agglutinin (WFA) is a lectin that labels selectively N-acetylgalactosamines beta 1 (GalNAc beta 1 − 3 Gal) residues of glycoproteins, and in its biotinylated form it is an easy way to label PNNs. However, whereas PNNs are well visualized with WFA in the mouse hippocampus and cortex, this is not the case for the rat, in which WFA recognizes solely cortical PNNs. The reverse is true for Cat-301 staining in rat preparations (Riga et al., 2017b). This suggests brain area- and species-specific compositional changes in PNNs, be it due to differences in glycosylation or in expression of specific ECM proteins. Although multiple glycosylation forms could be detected by the different Cat-antibodies (Matthews et al., 2002) a systematic biochemical characterization of different forms of ECM is yet to be carried out. An overview of specific ECM markers was given by Celio and Blümcke (Celio and Blumcke, 1994).

Perisynaptic ECM – Extracellular matrix surrounding specific synaptic sites (Lenn and Reese, 1966; Atoji et al., 1989) has been shown in the brain using electron microscopy and immunolabelling of specific ECM markers, predominantly brevican (Lendvai et al., 2013; Frischknecht and Seidenbecher, 2012). In addition, individual components of perisynaptic ECM have been detected by biochemically isolating synaptic membranes and the post-synaptic density (Pandya et al., 2017), validating limited expression of aggrecan in this particular form of ECM.

PNN density – In absence of changes in total PV^+ interneuron population, an increase in the number of PNN^+-PV^+ cells, indicates that a larger percentage of interneurons acquire a detectable PNN coating. Alternatively, increased PNN density could indicate a shift in cell-type specificity of PNN engagement, namely a preferential coating of principal cells or non-PV^+ interneurons. When coinciding with a reduction in PV^+ density, an increase in PNN number could indicate specific cell death of PNN-free PV^+ cells; a typical example of this is shown by Cabungcal et al., (Cabungcal et al., 2013a) where an imbalance in redox potential led to specific loss of unprotected PV^+ neurons in the long run.

PNN intensity – As noted above, PNN detection depends on the species and brain region under investigation, and is particularly susceptible to methodological differences, including the antigens used for PNN visualization. For these reasons, the biological significance of changes in PNN intensity should be interpreted with caution. Increased PNN intensity could hint to the presence of more immunoreactive groups available for staining, in turn indicating PNN maturation (Gildawie et al., 2020). Vice versa, decreased PNN intensity could indicate a reduction -or change in the expression ratio- of individual PNN components. Finally, shifts in the distribution of PNN intensities within a particular cell population might be indicative of their physiological output (Donato et al., 2013), *e.g.*, neuronal activity.

Gao, 2018). Post-mortem studies have demonstrated reduced PNN density in the amygdala of patients diagnosed with bipolar disorder (Pantazopoulos et al., 2015), while a variation in the gene encoding for the proteoglycan Neurocan has been identified as a risk factor for the disease (Cichon et al., 2011). Furthermore, widespread reduction in PV^+ neuron density and the ratio of PNN-ensheathed PV^+ neurons is observed throughout the brain of patients with schizophrenia or bipolar disorder, including the entorhinal cortex (Pantazopoulos et al., 2010), dorsolateral PFC (Enwright et al., 2016) and thalamic reticular nucleus (Steullet et al., 2018), suggesting that PNN^+-PV^+ changes are common across brain regions in these psychiatric disorders.

1.2. Stress paradigms in preclinical models

Exposure to physical and psychological stressors has been extensively used to examine both acute and long-term effects of stress on animal physiology and behavior in relation to hallmarks of psychiatric diseases, such as depression (Nestler and Hyman, 2010; Krishnan and Nestler, 2011). Such stressors span from social deprivation in critical periods, *e.g.*, during development and adolescence, to social dominance in adulthood. The type, duration of stress, and timing of stress exposure during the life span (Box 2) all determine the animal's response to stressful stimuli, and as a consequence, how they weigh in on the emergence of pathology.

One of the most widely used paradigms of stress exposure in rodents is the chronic mild stress (CMS) model, consisted of exposure to a series of moderate physical and psychosocial stressors, lasting up to 12 weeks (Willner, 2017). In its many variations, CMS animals are exposed to uncontrollable environmental stressors ranging from food and water deprivation to severe light and temperature changes. A social component is commonly added to the paradigm, where animals are subjected to overcrowded and/or isolated housing conditions.

Other animal paradigms have focused exclusively on social deprivation as a source of stress, in an attempt to model environmental adversity. Limited maternal care or contact with conspecifics during early life have been extensively used, and are linked to severe anxiety and depression-related phenotypes later in adulthood (Pryce et al., 2005; Marco et al., 2015). Deviations in these protocols concern the timing and duration of maternal deprivation or social isolation, with the latter being more detrimental when applied during critical neurodevelopmental periods, such as in early life or adolescence (Box 2).

Finally, one of the most commonly used animal models of social stress is social defeat, which is based on the resident-intruder paradigm (Blanchard et al., 2001; Hollis and Kabbaj, 2014). Social defeat takes advantage of natural hierarchy and dominance/submission dynamics between male rodents, and occurs when a larger territorial male (resident) physically defeats a smaller, submissive conspecific (intruder). Variations in social defeat procedure utilize differences in intensity (*e.g.*, number of episodes, duration of physical contact, repetitions over time) to mimic stress-associated pathological states.

As stated above, the ECM is highly dynamic and responsive to external forces, making it an appropriate substrate for regulation of experience-dependent plasticity. Only in recent years, research identified stress exposure as an effector of ECM (dys)regulation and started tapping into its role in mediating stress-induced psychopathology. In the following sections, we attempted to summarize the accumulating evidence linking stress and ECM, with a special focus on stress-inducing stimuli of social nature. In addition, due to their putative role in shaping plasticity and their distinct relationship with PNNs, we discuss the implications of PV^+ interneuron-mediated alterations following stress.

2. ECM and PV^+ interneuron adaptations following adversity in early life and adolescence

2.1. Deprivation of maternal care

Deprivation of maternal care (Box 2), brought about by multiple maternal separation episodes and/or early weaning, has been implicated in the regulation of ECM both at early time points and later during adulthood. For example, maternal deprivation reduced the number of PNNs and PNN^+-PV^+ interneurons in the prelimbic (PrL) and infralimbic (IL) cortices throughout development, in a sex-independent manner (Gildawie et al., 2020). In addition, maternally separated adolescent male rats exhibited an increase in PNN and PV density in the amygdala, which normalized in adulthood (Gildawie et al., 2020). Furthermore, maternal separation was shown to increase the expression of several ECM core components, including Brevican, Neurocan and Tenascin-R in the hippocampus (HPC) of adult rats (Dimatelis et al., 2013). In accordance, it was recently shown that maternal deprivation and early weaning induced changes in PNN-enwrapped interneurons of the ventral HPC in adult mice (Murthy et al., 2019). These animals, which displayed increased anxiety and altered hippocampal oscillations, showed reduced PV^+ and increased PNN^+-PV^+ cell density in the dentate gyrus (DG). Notably, this was parallel to an increase in extracortical homeoprotein OTX2 in double immunoreactive PNN^+-PV^+ interneurons. During critical developmental periods, OTX2 in the visual cortex is specifically internalized by PV^+ cells, facilitating PNN assembly (Bernard and Prochiantz, 2016; Beurdeley et al., 2012). In turn, PNN maturation further promotes accumulation of the homeoprotein, creating a positive feedback loop that is maintained throughout adulthood, thereby limiting plasticity. The reported OTX2 build-up following maternal deprivation provides a plausible molecular substrate for the regulation of PNNs and PV^+ cell plasticity, driving maladaptations that lead to the observed behavioral deficits. Importantly, OTX2 methylation has been shown to confer increased risk of depression in children with early maltreatment, supporting the translational value of these preclinical findings (Kaufman et al., 2018).

2.2. Social isolation

Accumulating evidence supports changes in ECM expression and PV^+-interneuron vulnerability after stress exposure in adolescence.

Box 2
Rodent early life and adolescence.

Early life – In rodents, ultrasonic vocalization begins right after birth, eliciting an array of maternal behavior that is crucial for the survival of newly born pups. Vocalization intensifies until around postnatal (PN) week 1, when rodents are completely dependent on maternal care (Thiels et al., 1990). Even after eye opening at PN week 2, pups still depend on maternal care. The quality of maternal care is of large influence on the (long-term) physiology and behavior of their offspring (Roy et al., 2001).

Adolescence – The early postnatal period ends about 3–4 weeks postnatally with the completion of weaning and thus independence from the mother. This period is generally viewed as the developmental transition from childhood to adulthood and includes sexual maturation. Although the exact start and end of this period are not precisely defined, it is generally viewed as the range from weaning (PN 3–4 weeks) to adulthood (> PN 8–10 weeks). The period of adolescence can be subdivided into three intervals (Laviola et al., 2003; Adriani et al., 2004) 1) early adolescence (PN day 22–34), 2) mid-adolescence (PN day 35–46), and 3) late adolescence (PN day 47–60), which includes sexual maturation.

Social isolation at early adolescence (Box 2), resulting in increased anxiety and sensorimotor gating deficits, was shown to decrease PV^+ cell density in the rat HPC (Harte et al., 2007), an effect thought to reflect reduced expression of parvalbumin protein and, by extension, altered PV cell activity. In accordance, decreased PNN^+-PV^+ density after prolonged social isolation in young mice coincided with reduced PV-intensity across brain regions, including the cingulate cortex, and hippocampal subregions (Ueno et al., 2017). Likewise, a recent study demonstrated a reduction in the number of PV^+ cells of the ventral hippocampus (vHPC) after a two-month social isolation period, commenced in early adolescence (Deng et al., 2019). Socially isolated mice displayed impaired social recognition (Deng et al., 2019), reflecting deficits in emotional cognition and autobiographic memory as seen in many psychiatric disorders (Gollan et al., 2010; Demenescu et al., 2010; Köhler et al., 2015; Danion et al., 2007). Notably, the authors showed that silencing of vHPC PV^+ cells was sufficient to impair social recognition, mimicking the effects of adolescent isolation. Together, these results reveal a crucial role for the hippocampal PV^+ circuitry in mediating social memory and illustrate network vulnerability to stress exposure during critical developmental periods.

2.3. Chronic mild stress

Application of CMS during early adolescence culminates into severe deficits in ECM assembly. Acute behavioral abnormalities, including depression-like symptoms and social deficits were observed after 10 days of CMS (Ueno et al., 2018). These effects were accompanied by a reduction in WFA immunoreactivity, but not PNN density, in several brain regions, including the stress-susceptible CA1 hippocampal subfield, anterior cingulate (AC) and IL cortex. These results could indicate a change in PNN composition, such as a reduction in expression of individual ECM proteins, triggered during and shortly after stress.

Apart from ECM-related changes, heightened stress-induced vulnerability of the hippocampal PV-circuitry has been demonstrated in adolescence (Gomes et al., 2019). Particularly, 10-day stress exposure (foot shocks in combination with restraint stress) during adolescence arrested the developmental increase in the number of PV^+ and PNN^+-PV^+ cells in the vHPC. These changes appeared and persisted for weeks after the initial stress exposure. Moreover, they were accompanied by increased activity of hippocampal pyramidal cells, suggesting a long-lasting weakening of the local inhibition circuitry. Interestingly, exposure to the same stress paradigm in adulthood did not alter PNN^+-PV^+ density or principal cell activity. In these animals, administration of the mood stabilizer valproate during stress exposure triggered reductions in the number of PV^+ and PNN^+-PV^+ density, similar to what is seen in adolescence. Valproate is proposed to re-open the critical period of increased plasticity in the adult, possibly *via* inhibition of histone deacetylase, thus, the latter results further highlight the susceptibility of the developing hippocampal PNN^+-PV^+ circuitry to stress.

ECM changes are not confined to the HPC, as shown by the effect of CMS in adolescent rats, where duration of stress exposure leads to a biphasic regulation of PNNs density in the medial prefrontal cortex (mPFC) (de A. C. Folha, 2017). In particular, after 7 days of stress exposure, an increase in PNN numbers was reported, which was followed by a decrease after 35 days of stress. This was in contrast to non-stressed controls, that showed a time-dependent gradual increase in mPFC PNNs, highlighting normal brain development. The differential pattern of cortical PNN maturation after stress co-occurred with changes in executive function, namely an initial increase followed by a reduction in working memory performance after chronic stress, mirroring the changes in PNN density. As mentioned above, PNN presence coincides with the closing of the critical neurodevelopmental period guiding experience-dependent plasticity (Pizzorusso et al., 2002), thus it is possible that CMS-induced changes in PNN maturation pattern underlie the behavioral deficits observed. In another study, CMS applied for 2 weeks during adolescence induced severe anxiety-like symptoms in both male and female mice during adulthood (Page and Coutellier, 2018). In male mice, exposure to adolescent stress affected cognitive aspects, resulting in impaired processing of contextual information. In female mice, CMS exposure led to a transient increase in the percentage of PNN-enwrapped PV^+ cells in the IL, which normalized in adulthood, revealing interesting sex-specific differences in stress response.

Together with increased PV expression and PNN density marking the onset and closure of critical periods, respectively (Pizzorusso et al., 2002), these findings indicate that adversity during early postnatal life can alter proper maturation and hardwiring of PV-networks, causing pathology that can endure across lifetime. In support, the role of aberrant PNN^+-PV^+ network maturation as a pathophysiological mechanism underlying schizophrenia has been extensively studied and excellently reviewed elsewhere (Berretta, 2012; Steullet et al., 2017). Early life adversity also serves as a risk factor to other psychiatric diseases, such as anxiety and mood disorders (Syed and Nemeroff, 2017), suggesting that ECM remodeling may represent a global substrate for pathophysiology resulting from early life stress that is sustained into adulthood.

3. ECM and PV^+ interneuron adaptations following stress exposure during adulthood

Due to its robust nature, our lab has exploited the social defeat-induced persistent stress (SDPS) model, a variation of the original resident-intruder protocol, to examine the chronic effects of social stress on affective and cognitive function (Bokhoven et al., 2011; Riga et al., 2015). The SDPS utilizes exposure to short-lived but severe physical stress, in the form of social defeat (5 episodes), mimicking adverse life events that are linked to the emergence of depression in humans. Defeat stress is then followed by exposure to prolonged social isolation ($\geq$8 weeks of single housing) in impoverished environments (non-enriched housing), emulating seclusion, and the lack of social support that depressed patients often experience (Kupferberg et al., 2016). The combination of the two leads to an abiding depressive-like state, characterized by chronic affective and cognitive deficits.

Using SDPS, we recently showed that stress-induced ECM and PNN regulation at the dorsal HPC underlies reduced hippocampal plasticity and accompanying deficits in HPC-dependent spatial memory (Riga et al., 2017b). In particular, using complementary proteomic and biochemical techniques, we observed robust upregulation of synaptic CSPGs and ECM-link proteins, and an ensuing increase in PNN-enwrapped PV^+ interneurons of dHPC CA1, seen up to 12 weeks after the last defeat exposure. These changes were in parallel to reduced maintenance of hippocampal long-term potentiation (LTP), and disturbed hippocampal inhibitory transmission. Single intra-hippocampal administration of chABC restored PNN density in defeated animals, normalized hippocampal plasticity and inhibitory tone and rescued the observed behavioral deficits. Interestingly, it has been shown that adolescent social stress, imposed by repeated alterations in home-cage composition, renders animals prone to late-life hippocampus-dependent cognitive decline (Sterlemann et al., 2010). Particularly, the authors reported that 12 months after social stress, mice displayed impairments in spatial memory, and a concomitant reduction in LTP maintenance. These data mirror the deficits brought by SDPS, substantiating that exposure to social stress during critical developmental periods is characterized by the same neuroadaptations that mediate cognitive deficits seen in adulthood, namely, alterations in hippocampal ECM assembly.

Apart from timing and duration of the stress protocol, recency plays a crucial role in the effects of social stress on ECM organization. We recently reported that the transition from stress to depression is characterized by bidirectional changes in hippocampal ECM composition and PNN density (Koskinen et al., 2019). In particular, we showed that 72 h after the last of five defeat episodes, both perisynaptic and

pericellular hippocampal ECM undergo extensive downregulation, an effect that is accompanied by a severe reduction in HPC-dependent spatial memory performance. Subsequent temporal profiling of ECM remodeling at 2–4 weeks after stress exposure, showed a transient recovery of ECM proteins expression levels, and the number of CA1 PNN^+-PV^+ interneurons. During this period, no memory disturbances could be observed. Finally, at week 8 post-defeat, we reported an increase in the expression of ECM components, in parallel with an increase in the density of PV-associated PNNs and re-occurrence of disrupted memory. Together, these data illustrate the pliability of mature ECM, and how stress infringes its dynamic nature.

A recent study exploited the CMS paradigm in adult mice to assess whether astrocyte-specific alterations mediate the depressogenic effects of stress (Simard et al., 2018). The cortical astroglial translatome was profiled at 24 h following the last of 35 days of exposure to variable mild stressors, which led to despair- and anxiety-like phenotypes. In CMS-exposed mice, stress triggered an increase in transcripts encoding astrocyte-derived ECM components, particularly proteoglycans that are indispensable for the maturation and maintenance of PNNs. These changes at the transcript level were supported by increased PNN density (Simard et al., 2018) in the frontal motor cortex (M2), where no distinction was made for excitatory or inhibitory neurons. Importantly, intra-cortical chABC-assisted degradation of PNNs reversed the depressive-like effects of CMS, confirming the antidepressant potential of ECM remodeling after chronic stress (Riga et al., 2017b).

In contrast to the effects seen above, another study reported a reduction in the expression of cortical ECM components profiled a week after the last of 30 days of CMS (Yu et al., 2020). In particular, young adult rats that were exposed to 30 (but not 10 or 20) days of CMS exhibited depressive-like symptoms, including anhedonia and despair. These behavioral effects were accompanied by a reduction in aggrecan protein expression at the PrL. In addition, the authors showed decreased PrL PNN density in a CMS-vulnerable subpopulation after 20 days of CMS, together with a reduction in neurocan (but not aggrecan) expression. Interestingly, rats selected for a low locomotor response to novelty displayed a similar reduction in cortical PNNs and neurocan expression in absence of stress, and showed vulnerability to the behavioral effects of CMS. The discrepancy between the two studies might lay on methodological differences, *e.g.*, different species, the comparison of mRNA *vs.* protein levels, measures performed on the motor cortex (M2, posterior cingulate cortex) *vs.* PrL, and tissue taken at 24-h *vs.* 7 days after stress cessation. Independently, the observed temporal development in co-occurrence of behavioral and molecular phenotypes resembles that discussed above for the SDPS paradigm, further validating the causal role of ECM changes in the pathophysiology of depression.

Similar to CMS, prolonged physical stress in the form of restraint has been shown to alter cortical and subcortical PV and PNN numbers in adulthood in rat (Pesarico et al., 2019). In particular, 24 h after the last of 10 daily 6-h stress episodes, the number of both PV^+ and PNN-enwrapped cells were increased in the mPFC subregions, while a reduction in PNN density was seen in dHPC CA1. The latter results are in accordance with our own observations (Koskinen et al., 2019), validating that at the short-term, a brief period of stress, independent of its social nature, results in a weakening of hippocampal ECM and PNNs. Together, these results illustrate the dynamic response of the ECM to stress-related challenges, and highlights the impact of experimental conditions, such as brain-region as well as time after stress and duration of stress on the directionality of these adaptations.

4. Genetic factors involving ECM and PV^+ interneuron adaptations that contribute to stress vulnerability

Until very recently, the limited success in achieving genome-wide significance for MDD (Howard et al., 2018; Wray et al., 2018) has been attributed to the relatively low heritability of depression compared with other psychiatric diseases. Several additional reasons have been put forward, including the numerous low-contributing genes to this largely heterogenous disease (Keller and Miller, 2006), as well as the existence of environmental factors that reinforce the genetically-based liability to develop depression (Cattaneo et al., 2018). This sparked a large interest into finding genetic influences contributing to disease symptoms in animal models, using environmental factors such as exposure to (early/social) life stressors.

An example of this where ECM organization is affected comes from a study on GAD67-GFP (Δneo) mice, which lack 50 % of the GABA-producing enzyme (Wang et al., 2018). In these mice, prenatal stress reduced PV^+ and PNN density in the mPFC, as well as the number of double immunoreactive PNN^+-PV^+-interneurons, as measured by both WFA and the PNN-enriched ECM protein, aggrecan. Notably, stress-induced changes in PV^+ and PNN density had functional consequences, as assessed by electrophysiological interrogation of the mPFC. Transgenic mice exposed to prenatal stress displayed a reduced threshold for generation of evoked inhibitory postsynaptic currents (IPSCs) and increased evoked and spontaneous IPSC amplitudes, indicative of altered excitability of the inhibitory cortical network. Importantly, mutation in the G*ad1* gene alone had no effect on cortical PNNs, nor on mPFC inhibitory transmission, arguing in favor of genetic vulnerabilities that promote the detrimental effects of stress on matrix maturation and, in turn, on PV-mediated synaptic plasticity.

Another study revealed an interesting interaction between stress during adolescence and genetic predisposition is related to *Npas4*, which encodes a brain-specific transcription factor critical in inhibitory network regulation (Page et al., 2018). It was shown that CMS stress during adolescence resulted in late-appearing attentional deficit in *Npas4*-deficient mice compared to WT conspecifics. At the cellular level, CMS resulted in increased mPFC PNN^+-PV^+ cell density in WT mice, an effect that was absent in *Npas4*-deficient mice. As WT mice did not display impaired cognitive flexibility following CMS, these findings suggest a protective role of PNNs in the developing cortical GABAergic network, which is required for intact cognitive function later in adulthood. Correspondingly, lack of NPAS4 signaling-mediated maturation of PNNs surrounding inhibitory interneurons might contribute to stress proneness and the accompanied cognitive deficits.

Lastly, genetic deletion of *CD44*, an adhesion molecule that binds to HA, rendered adolescent mice susceptible to stress-induced anxiety- and depression-like symptoms using CMS (Barzilay et al., 2016). In particular, a month-long exposure to variable stressors in *CD44*-deficient mice, led to the emergence of anhedonia and behavioral despair that were accompanied by reduced gene expression of several ECM-associated molecules, an effect also observed, although to a limited extent, in WT mice. Recently, MMP-9-mediated cleavage of CD44 was recognized as an integral part of a signaling cascade that promotes structural remodeling of dendrites, thereby providing a possible molecular substrate involved in stress effects (Bijata et al., 2017).

5. PV^+ network vulnerability to stress

Neuronal networks possess a wide repertoire of homeostatic mechanisms, including adaptations of synaptic strength, changes in excitation–inhibition (E/I) balance, and modulation of intrinsic excitability, to face the continuous environmental challenges placed upon them (Turrigiano, 2011). Recently, it was shown that while the hippocampal network achieves a balanced output in a few days after a challenge of excitatory input, the majority of individual neurons within such a network adapt to a new set-point of neuronal firing to accomplish balanced network output (Slomowitz et al., 2015). The authors suggested that network homeostatic plasticity comes at the cost of plasticity parameters important for working memory. As such, it is of interest to analyze neuronal parameters at the single cell level in the days to weeks after stressful episodes.

An increasing number of studies have demonstrated aberrant

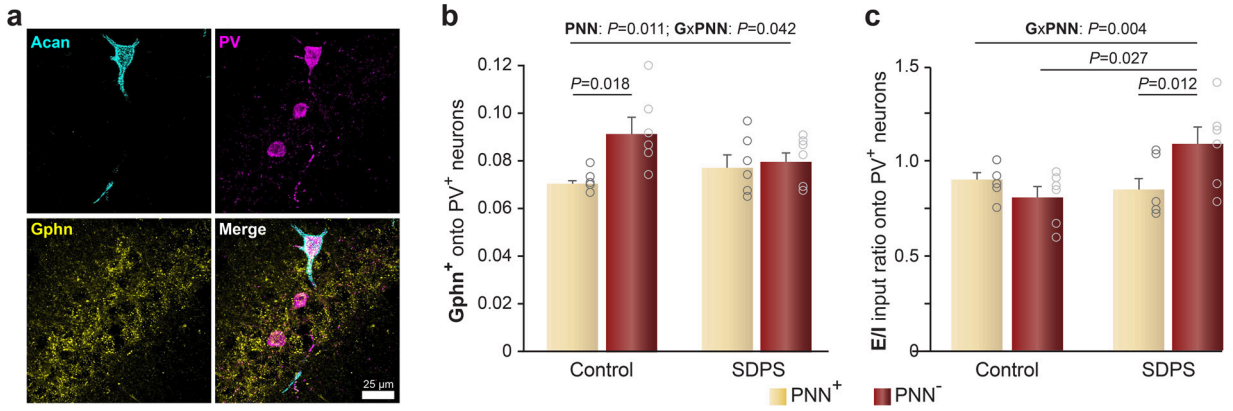

Fig. 2. Alterations in hippocampal PV$^+$ interneuron E/I input ratio long-term after social stress. a) The number of inhibitory inputs onto PNN-coated (PNN$^+$) and PNN-free (PNN$^-$) PV$^+$ interneurons, as indicated by Gephyrin (Gphn), a marker for inhibitory synapses, in control and animals subjected to SDPS (> 8 weeks after the last defeat exposure) was analyzed. Example image of perisomatic Gphn$^+$ puncta onto a PV$^+$ interneuron surrounded by an aggrecan (Acan)-labeled PNN at the hippocampus CA1 region. PNN$^-$ PV$^+$ cells can also be seen. **b)** In control rats, PNN$^+$-PV$^+$ interneurons receive less inhibitory inputs than their PNN$^-$ counterparts, whereas in SDPS animals, an equal number of inhibitory puncta is quantified in both PNN$^+$- and PNN$^-$-PV$^+$ cells. Independently of stress-status we previously observed an increase in excitatory puncta onto PNN$^-$ *vs.* PNN$^+$-PV$^+$ interneurons (Riga et al., 2017b). **c)** Together with the present data, this results in a balanced 'E/I' input ratio across the two PV$^+$ cell subtypes in controls. In contrast, in SDPS animals, this results in an increased E/I input ratio onto PNN$^-$ PV$^+$ interneurons, whereas 'E/I' input ratio for PNN$^+$-PV$^+$ interneurons is similar to that of controls. Note that this is a gross approximation, as excitatory and inhibitory puncta quantification was not carried out on the same PV$^+$ neuron, and this analysis is based on different type of molecular markers (pre- *vs.* post-synaptic) instead of measuring intrinsic electrophysiological properties of PV$^+$ interneurons. *P*-values of repeated measure ANOVA for cell type (PNN$^+$- and PNN$^-$-PV$^+$ cells) with 'Group (G; control *vs.* SPDS)' as between-subject factor, and post-hoc *t*-test are indicated. Scale bar indicates 25 µm.

inhibitory network activity resulting from altered PV$^+$ interneuron function in response to stress. Social defeat stress during mid-adolescence was shown to result into a hyperactive PV$^+$ cell population in the ventral pallidum (VP), a brain region involved in reward behavior (Knowland et al., 2017). Notably, increased intrinsic excitability of long-range projecting PV$^+$ cells and reduced inhibitory drive onto these VP PV$^+$ cells were exclusively present in stress-susceptible mice displaying depressive-like behavior. Furthermore, opto- or chemo-genetic silencing of VP PV$^+$ neurons in a projection-specific manner after stress exposure promoted stress resilience against social withdrawal and behavioral despair, demonstrating a causal link between aberrant PV$^+$ network and depression-like behaviors.

Further evidence for the critical involvement of PV$^+$ circuitry in stress response and in proneness to stress comes from a study employing the learned helplessness paradigm (Perova et al., 2015). In this study, a reduction in the amplitude of miniature excitatory postsynaptic currents (mEPSCs) measured in PrL PV$^+$ neurons was present in stress-susceptible adolescent mice that displayed helplessness, *i.e.*, inability to evade an otherwise escapable aversive stimulus. This weakening of cortical excitatory drive onto PV$^+$ neurons was absent in stress-resilient mice. Importantly, the authors showed that direct suppression of PV$^+$ neuron activity in the PrL during learned helplessness reproduced the effects, that is, promoted depression-like behavior, thereby demonstrating an important pathway by which adaptive behavioral responses are regulated.

Restraint stress during early adolescence was shown to reduce the frequency of action potentials fired by PV$^+$ neurons in response to current injection in the sensory cortex (Chen et al., 2018). Importantly, counteracting reduced PV$^+$ excitability by selective activation of PV$^+$ neurons during stress exposure prevented the emergence of stress-induced sensory deficit. Moreover, after a 3-week exposure to restraint stress in mid-adolescent rats, increased frequency of spontaneous IPSCs was measured in CA1 pyramidal cells, indicative of enhanced inhibitory input onto these cells (Hu et al., 2010). This increase in frequency was accompanied by a failure to generate rhythmic sIPSC in response to PV$^+$ neuron activation. The authors proposed a mechanism in which chronic stress results in sustained activation of PV$^+$-interneurons and excessive GABA release that can compromise the capacity to generate rhythmic oscillations and subsequently affect cognitive function.

Collectively, these data indicate that PV$^+$-mediated inhibition is vulnerable to stress across brain regions, yet with different profiles depending on stress recency and brain region under study. Importantly, PV$^+$-targeted interventions display potential in protecting from stress effects. Although the role of the PNNs were not explored in all these studies, it is tempting to speculate that PNN-related mechanisms contribute to the observed abnormalities and to the therapeutic effects, possibly involving PNN's ability to modulate PV$^+$ cell excitability and synaptic inputs onto these cells (Favuzzi et al., 2017; Dityatev et al., 2007).

Major differences in the trajectory of stress effects exist based on the age at which stress is applied (see discussion). Hence, it is of no surprise that the seemingly contradictory results reported by different labs are most likely due to age effects (stress timing), in addition to analysis of short-lived (Hu et al., 2010) (reduction in PV$^+$ PNN coverage) *vs.* long-term (increased PV$^+$ PNN coverage) (Riga et al., 2017b; Koskinen et al., 2019) effects of stress. We observed decreased CA1 sIPSCs at > 2 months after exposure to social defeat stress applied during adulthood that was accompanied by disturbed HPC-dependent memory function (Riga et al., 2017b). Importantly, these effects coincided with an increase in the population of PNN-coated PV$^+$ interneurons in the CA1, which receive decreased excitatory input, presumably due to the non-permissive environment supported by PNNs presence.

Interestingly, re-analysis of our previous data with the inclusion of inhibitory input onto PV$^+$-interneurons, allowed us to express the ratio of excitatory and inhibitory inputs by type of PV$^+$-interneuron (PNN-coated, PNN$^+$ *vs.* PNN-free, PNN$^-$). This showed an increase of E/I balance in PNN$^-$-PV$^+$ cells (Fig. 2) in SDPS, possibly reflecting a compensatory mechanism that aims at counteracting the overall reduced output of PV$^+$ interneurons onto pyramidal cells.

Despite the lack of electrophysiological data supporting this observation, we could speculate on the activity state of PV$^+$ cells based on their PNN coverage. As shown before in the hippocampus, enzymatic removal of PNNs is associated with increased PV$^+$ neuron excitability *in vitro* (Dityatev et al., 2007), as well as increased output onto both pyramidal neurons and inhibitory neurons *in vivo* when applied in the CA2 region (Hayani et al., 2018). Likewise, in a quadruple ECM KO (Gottschling et al., 2019) the number of inhibitory neurons was decreased, favoring excitatory neurons in culture, where both PNN-

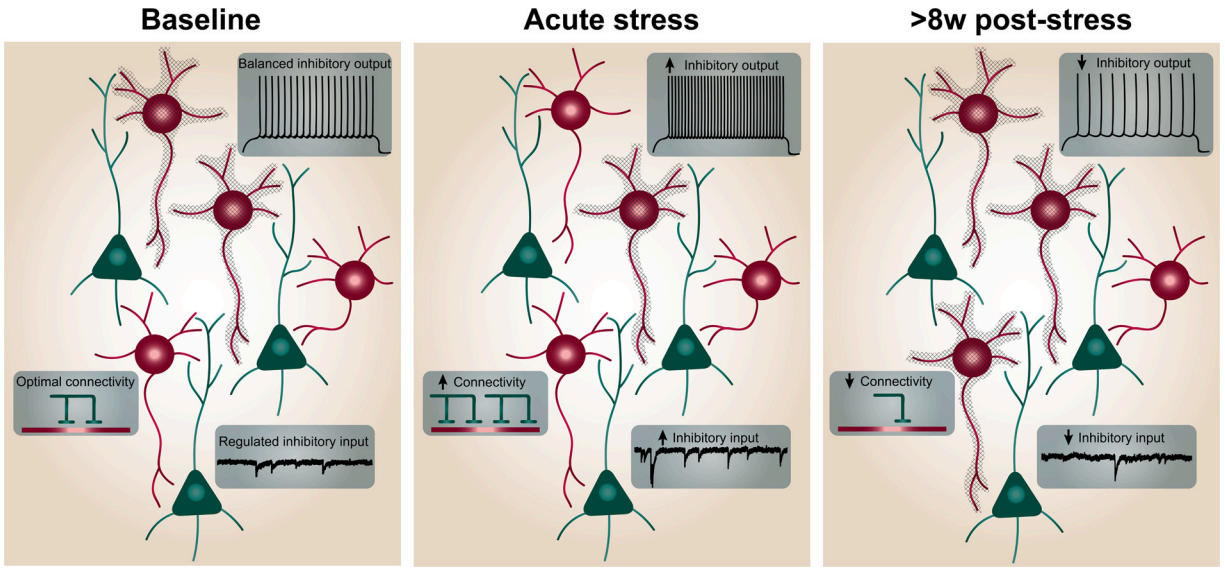

Fig. 3. Hypothetical model of stress-induced hippocampal ECM regulation, and its implication in plasticity during and long-after stress exposure. Under normal conditions, ECM and PNNs ensure optimal connectivity between neuronal cells, by stabilization of existing synaptic contacts and inhibition of the formation of unnecessary ones. In turn, balanced excitatory/inhibitory input onto parvalbumin-expressing interneurons warrants optimal excitability and inhibitory output. As a result, excitation/inhibition (E/I) balance is maintained. During, and in the first days after stress exposure, reduction in ECM levels and PNN density, possibly *via* an arrest in the production and/or release of ECM components, takes place, promoting a period of increased structural and synaptic plasticity. Novel synaptic contacts form, and a reshuffling of the E/I network occurs, which leads to increased PV^+ excitability and, by extension, enhanced inhibitory drive onto pyramidal neurons (Knowland et al., 2017). Presumably, this plastic phase facilitates learning and memory of the adverse event (Donato et al., 2013), *e.g.*, consolidation of associations between a context and its emotional value. In the weeks and months following stress exposure, especially in absence of environmental and/or social enrichment, an increase in ECM levels and PNN density occurs. This could be partly mediated *via* reduced MMP-mediated proteolysis (Koskinen et al., 2019), as observed in depressed patients (Shibasaki et al., 2016). As a result, excessive ECM deposition creates a non-permissive environment of limited plasticity. In this rigid milieu, reduced excitatory input onto PV^+ interneurons and an overall reduction in inhibitory tone onto pyramidal neurons (Riga et al., 2017b) could be accompanied by decreased excitability of PV^+ cells. Such E/I imbalance could then impede neuronal communication, hindering the incorporation of updated information, and in turn, promoting the maintenance of maladaptive memories (Gogolla et al., 2009). Note that the putative change in E/I input ratio onto PV^+-interneurons (*c.f.* Fig. 2) is not depicted in this scheme.

bearing and PNN-free neurons received more excitatory input. Taken together, there is evidence supporting the basic hypothesis (Fig. 3) that early effects of stress on ECM induce PV^+-interneuron hyperexcitability in the HPC, whereas lasting effects of stress co-occur with hypofunction of PV^+-interneurons, which in turn contributes to the observed reduction in inhibitory transmission in the HPC. On the other hand, viral knock-down of Bcan as well as *Bcan* deletion increased the action potential halfwidth and decreased the action potential threshold of PV^+ neurons (Favuzzi et al., 2017), hence increasing intrinsic excitability. At the same time these neurons showed decreased glutamatergic input, and a decrease in overall or maximum firing frequency. This indicates that the system's output could be more complex, not directly reflecting the sum of its parts. In support, in genetic models of AD (Hijazi et al., 2019; Végh et al., 2014; Hijazi et al., 2020), which, similarly to depression, are characterized by changes in hippocampal ECM that are causally linked to memory deficits, both hyper- and hypo-activity of PV network have been reported at different developmental stages. Thus, a simplistic model as presented in Fig. 3 should be interpreted with caution. It is important to realize that different brain regions could react differently to stressors, as exemplified by an increase in ECM in PFC *versus* a decrease in the hippocampus after restraint stress (Pesarico et al., 2019) as discussed above. A similar pattern can be observed for the effects of ECM removal, as demonstrated by *in vivo* studies outside the hippocampus. For example, chABC-mediated breakdown of ECM reduced inhibitory activity in the cortex and brainstem (Lensjø et al., 2016; Balmer, 2016), supporting the notion that PNN presence could in some cases promote PV^+ interneuron firing. In this respect, it should be noted that ECM in cortical areas and hippocampus CA2 also surrounds pyramidal neurons (Carstens et al., 2016; Dityatev et al., 2010), whereas in the hippocampus CA1 this is almost exclusively around interneurons (Härtig et al., 1992).

Apart from region-specific mechanisms, which possibly depend on molecular heterogeneity of PNNs (Riga et al., 2017b) and connectivity within neural circuits, an important consideration is the time elapsed between ECM enzymatic breakdown and the physiological recordings, as time-dependent effects are likely to occur. Early effects (within hours) (Balmer, 2016) can significantly differ from later effects (days to weeks) (Hayani et al., 2018) during which slower homeostatic mechanisms (*e.g.*, remodeling of synaptic inputs onto PV^+ neurons in response to altered excitability) have taken place (Dityatev et al., 2010). In case of the hippocampus, given that approximately half of CA1 PV^+-interneurons are surrounded by PNNs, homeostatic plasticity in the weeks after social stress could lead to a cell-specific offset, with PNN-coated cells being hypoexcitable and PNN-free cells being hyperexcitable. This view is supported by the fact that ECM removal, and hence full participation of all PV^+ neurons in the network, rescues late electrophysiological and behavioral deficits induced by social stress (Riga et al., 2017b).

Another possible mechanism linking ECM changes to regulation of PV^+ cell activity involves the role of PNNs in ion homeostasis, and their neuroprotective effects, particularly their antioxidant capacity (Suttkus et al., 2014; Morawski et al., 2015). It has been proposed that the high negative charge of the condensed CSPGs in PNNs could create cationic microenvironments that are crucial for maintenance of high-frequency firing of PV^+ cells. Stress-induced changes in the composition or density of the ECM can, therefore, alter ion sorting properties of PNNs, thereby affecting the activity of the surrounding PV^+ cells (Morawski et al., 2015). Importantly, the capacity of PNNs to bind ions has been associated with their ability to buffer against oxidative stress (Cabungcal et al., 2013b), to which PV^+ interneurons are highly susceptible. Indeed, effective antioxidant mechanisms which protect from high oxidative stress load are crucial to maintain PV^+ vitality (Steullet

et al., 2017). In the hippocampus, stress-induced ECM loss, and the subsequent increase in PV excitability, could result in high metabolic demands and high production of reactive oxygen species (ROS) (Kann, 2015; Fontella et al., 2005; Rossetti et al., 2018), in turn increasing the burden of oxidative stress on PV^+ neurons. Although in our studies we did not observe loss of PV^+ interneurons, others have reported a concurrent decrease in cortical PNNs and PV^+ cells (Ueno et al., 2017, 2018), supporting a model in which stress-driven reduction in PNN integrity affects not only PV^+ activity but also its survival.

6. Discussion

In the paragraphs above, we reviewed multiple experimental evidence showcasing the detrimental effects of stress on ECM organization and PV^+ networks, linking these changes back to pathological states, such as anxiety and depression. It is of note that the effects of stress vary considerably, as they depend on methodological differences, to name a few, an animal's age, the brain region under investigation and the type, duration and timing of stress. Importantly, it is crucial to account not only for the chronicity of stress exposure, but also, its recency. This could be viewed as the time elapsed between the last stress exposure and experimental assessment of its effects. For example, although most CMS variations utilize long-lasting stressors (up to 12 weeks), behavioral readouts and brain collection often take place during or at 24 h after stress cessation. It is then a matter of interpretation whether the observed effects should be attributed to the short-lived effects of stress on animal physiology and behavior, or are due to changes that developed over time during the weeks and months of stress exposure. This led us to consider the concept of "incubation of depression", a phenomenon in which neurophysiological adaptations continue to occur in absence of stress. When left unaddressed, these inconspicuous changes could set the tone for stress-induced psychopathology in the long-run. To draw parallels with the addiction field, large gene expression changes have been observed in the nucleus accumbens upon cessation of systemic morphine injections, *e.g.*, in terms of signaling related to ionotropic and metabotropic receptors (Spijker et al., 2004). This supports the notion that absence of the stimulus to a system that has been adapting to that same stimulus, constitutes a new physiological challenge.

The ECM is a suitable molecular substrate for the mediation of such backdrop adaptations, as consistently reported in the field of drug addiction (see Smith et al., 2015 for an excellent review). Indeed, drug-related synaptic plasticity that underlies craving and eventually relapse requires ECM modifications occurring both acutely and in the long run, independently of the class of drug of abuse, including stimulants (Lubbers et al., 2016; Xue et al., 2014; Smith et al., 2014; Slaker et al., 2015) and opiates (den Oever et al., 2010; Xue et al., 2014; Smith et al., 2014). Our comprehensive survey of the stress field depicts a similar pattern, namely it highlights ECM changes occurring not only during but also long-after stress exposure / cessation. These latter adaptations might be instrumental in defining the end phenotype when attempting to model depression, a disorder of perpetual and recurring nature similar to that of drug addiction.

After systematically reviewing the current literature, it became apparent that stress recency is the most important factor in determining the direction of stress-induced alterations in ECM organization and PV^+ interneurons, followed by the brain region under investigation and stress timing (Table 1). For example, the majority of studies that performed analyses during stress exposure, *i.e.*, while animals were still exposed to mild stressors or were socially isolated at the time of sample collection, revealed a global reduction in the number of PNNs, PV^+ interneurons and/or PNN-coated PV^+ cells, independent of brain region and stress timing. The importance of stress recency was further illustrated when analyzing effects long after the main stressor stopped. For example, although initially the results of different studies might appear conflicting, *e.g.*, the absence of ECM regulation 1.5 month after CMS stress (Gomes et al., 2019) *vs.* the upregulation 3 months after social defeat stress (Riga et al., 2017b; Koskinen et al., 2019) during adulthood, plotting them in a timeline with all available studies illustrates a clear progression of ECM effects over time in the hippocampus (Fig. 4). In particular, it becomes apparent that following an initial downregulation, in the weeks after stress cessation, the number of PNNs, and/or PNN-coated PV^+ cells normalized, and later increased. This phenomenon was recently shown by us (Koskinen et al., 2019), but different studies (ELS effects in mPFC (Gildawie et al., 2020); CMS effects in mPFC (de A. C. Folha, 2017) strengthen the concept that these homeostatic plasticity changes take weeks to months. In this respect, stress recency could be defined as the time elapsed after *e.g.*, a first week of stress exposure, considering the perpetual effects (*e.g.*, homeostatic plasticity) of stress, stress chronicity and the presence of subthreshold stressors (*e.g.*, isolation) as biological meaningful (Fig. 4b,d), as it generated a more smooth pattern of stress-evoked effects in the hippocampus.

Similarly, the application of stress during a specific developmental period has different effects in the long-term. As is apparent from the distinction between stress applied during adulthood *vs.* that applied during early adolescence (P28), the long-term effects in terms of ECM and PV changes are substantially different. Whereas early adolescent stress perpetuates into a steady pattern of decreased ECM and PV density or intensity, stress exposure during adulthood evoked the homeostatic response with a long-lasting increase in ECM (Fig. 4).

7. Future directions

With the realization that stress recency, and hence the 'incubation' of its effects in the weeks following stress exposure, plays an important role, it would be of great interest to assess the functional implication of the initial ECM downregulation early after stress and how this relates to the long-term effects of stress (Fig 3Figure 3 and 4). Hypothetically, since ECM downregulation allows for increased structural and synaptic plasticity, this re-organization during and shortly after stress might represent a well-adapted response to stressful stimuli, for example, promoting memory of the adverse event and its associated cues and context, with manifold evolutionary advantages. Yet, once initiated, or due to continuation of stressful events, these initially adaptive changes may become maladaptive, facilitating the emergence and maintenance of behavioral deficits later on. It is then possible that late increases in ECM and PNNs create a non-permissive environment, characterized by low plasticity that sustains maladaptive responses to stress, such as the formation of persistent traumatic memories (Gogolla et al., 2009). It remains to be seen whether early effects of stress on ECM and PNN composition are due to an acute arrest in ECM production and/or release from nearby neurons and astrocytes, or due to an elevation in the activity of ECM-targeting proteases (Koskinen et al., 2019). Given the heterogeneity of ECM proteins in regard to their cellular origin and proteolytic cleavage, more research is needed to dissect their individual contribution.

Several of the CSPGs are expressed and released from astrocytes (Roll and Faissner, 2014; Faissner et al., 2010). On the other hand, aggrecan, versican and tenascinR are enriched in oligodendrocyte progenitor cells (OPCs), and individual ECM components have also been reported in neurons (Favuzzi et al., 2017; Hamel et al., 2005; Zeisel et al., 2015). As a result, there is a large interest to identify individual ECM components that mediate stress effects, and the corresponding cell type(s) that are critically involved in their production or proteolysis. Astrocytes, for example, are optimally located to orchestrate the maintenance of ECM homeostasis in response to environmental challenges as they surround a multitude of synapses and are actively involved in synaptic transmission. Extensive evidence supports the involvement of astrocytes both in depression and in antidepressant response, yet, the underlying molecular mechanism remain poorly understood (Peng et al., 2015). Notably, temporal profiling of astrocyte-

Table 1
Overview of literature showing ECM/PNN effects and/or effects on PV^+ cells after different type of stressors (restraint, social isolation, CMS, social defeat, maternal deprivation) in the HPC and frontal cortical areas. Studies are further sorted by age when the stressor was applied (age; postnatal day/week, PN; adolescent, adult). The stress duration has been indicated, as well as the timing of analysis (during stress, or as days/weeks after stress cessation), as a measure of recency. An alternative measure of recency, as time passed (day/weeks post-stress) after a brief 7-day period of stress exposure, independent of the total duration of the stress period, is given between brackets (underlined, see Fig. 4b,d). Both terms have been used to test the direction of ECM/PV effects in terms of recency after stress (see Fig. 4).

Author	Species	Timing of stress (age)	Stress duration	Age at analysis	Sex	Stress type	Timing of ECM/PV testing	Behavioral Readout	Brain Region	ECM (genes/proteins)	PNNs	PNN^+-PV^+	PVs
Pesarico et al. (2019)	Rat	13 weeks (adult)	6 h/day x 10 days	13 − 15 weeks	♂	Restraint	24 h post-stress (4 days post-stress)		mPFC (PrL, IL, Ac)		↑Density	Not affected	↑Density
									BLA		Not affected	Not affected	↑Density
									HPC (CA1)[a]		↓Density	Not affected	Not affected
Harte et al. (2007)	Rat	PN23 (early adolescent)	11 weeks	3–3.5 months	♀	Social isolation	During stress (10 weeks post-stress)	↓PPI	HPC (DG, CA2/3; no effect in CA1)				↓Density
Ueno et al. (2017)	Mouse	P21 (early adolescent)	5 weeks	P56	♂	Social isolation	During stress (4 weeks post-stress)		dHPC (DG, CA1, CA3)		Not affected	DG&CA1: ↓ Density	Only DG: ↓ Density All: ↓Intensity DG&CA3: ↓ Soma area
									PrL (L2/3)		↓Density & Intensity	Not affected	↓Soma area
									Visual cortex (L2/3)		↓Density	↓Density	
									dACC (L2/3)		Not affected	↓Density	↓Intensity
Deng et al. (2019)	Mouse	P28 (early adolescent)	8.5 weeks	P102	N/D	Social isolation	During stress (7.5 weeks post-stress)	↓Memory (SR)	vHPC (CA1, CA2/3)				↓Density
								Not affected Memory (NOR)	dHPC (CA1, CA2/3)				Not affected
Perić et al. (2019)	Rat	2.5 months (adult)	6 weeks	4 months	♂	Social isolation	24 h post-stress (5 weeks post-stress)	↑Anhedonia (SP)	dHPC				↓Density
Filipović et al. (2018)	Rat	2.5 months (adult)	3 weeks	3–3.5 months	♂	Social isolation	24 h post-stress (2 weeks post-stress)		HPC				↓Density
Ueno et al. (2018)	Mouse	P21-P30 (early adolescent)	once/day x 10 days	P34-P43	♂	CMS	3 days post-stress (6 days post-stress)	Not affected: Anxiety (EPM)	HPC (CA1, CA3, DG)		CA1, CA3 only: ↓ Intensity	CA3 only: ↓Soma area	Not affected
								↑ Despair (FST)	dACC (L2/3, L5/6)		↓Intensity		L2/3: ↓Soma area
								↓ Sociability (SI)	IL (L5/6)		↓Intensity		↓Soma area
								Not affected: Memory (Y maze)					
de A. C. Folha (2017)	Rat	P28 (early adolescent)	once/day x 7 days	P35, P63	♂	CMS	During stress (0 days post-stress)	↑ Working memory (SAAT)	mPFC		↑Density		
			once/day x 35 days				During stress (28 days post-stress)	↑ Anxiety (Thigmotaxis)	OFC		↓Density		
								↓Working memory (SAAT)	mPFC		↓Density		
Page and Coutellier (2018)	Mouse	P28 (early adolescent)	2 weeks	P48, P80–83	♂,♀	CMS	8 days / 5–6 weeks post-stress (15 days / 5.5 week post-stress)	All: ↑ Anxiety (EPM, OF) All: Unaffected Despair (FST)	mPFC (PrL, IL)		Not affected	IL stressed females 8 days post-stress only: ↑ Density	mPFC: stress by age of testing effect
Page et al. (2018)	Mouse	P28 (early adolescent)	2 weeks	P66	♂	CMS	3.5 weeks post-stress (4.5 weeks post-stress)	↑ Anxiety (EPM, OF) ↓Cognitive Flexibility (ASST)	mPFC (v, d)			(v)mPFC: ↑ Density	

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Table 1 (*continued*)

Author	Species	Timing of stress (age)	Stress duration	Age at analysis	Sex	Stress type	Timing of ECM/PV testing	Behavioral Readout	Brain Region	ECM (genes/proteins)	PNNs	PNN^+-PV^+	PVs
Barzilay et al. (2016)	Mouse[&]	P35 (mid-adolescent)		4 weeks	♂	CMS	24 h post-stress	↑Anhedonia (SP) ↑ Despair (FST) –Memory (NOR) ↓ Sociability (SI) ↑ Anxiety (EPM)	HPC	GE: ↓*Hmmr*; *MMP-9* not affected			
Gomes et al. (2019)	Rat	P31 (early adolescent)	10 days (daily foot shock & 3 restraint sessions)	P41, P48–53, P76-83	♂	CMS	24 h post-stress (4 days)		vHPC (sub)		Not affected	Not affected	Not affected
							1 − 2 weeks post-stress				↓Density	↓Density	↓Density
							5 − 6 weeks post-stress				Not affected	↓Density	↓Density
		P64 (young adult)		P81, P109			1 or 5 weeks post-stress				Not affected	Not affected	Not affected
Yu et al. (2020)	Rat	8 weeks (young adult)	2/day x 10, 20 or 30 days	Adult	♂	CMS	48 h to 1 week post-stress	30 days only: ↑Anhedonia (SP) ↑ Despair (FST) ↑Response to novelty (NSFT)	mPFC (PrL)	PE: ↓ Expression			
			2/day x 20 days CMS-vulnerable subgroup					↑Anhedonia (SP) ↑ Despair (FST)		PE: ↓ Expression	↓Density		
Simard et al. (2018)	Mouse	Adult	36 days	Adult	♂	CMS	During stress (28 days post-stress)	↑Anxiety (OF) –Anxiety (EPM) ↑Despair (FST)	Motor cortex, posterior cingulate cortex		↑Density (astroglial cells)		
Riga et al. (2017b)	Rat	week 9 (young adult)	once/day x 5 days	8–23 weeks	♂	Social defeat	≥ 8 weeks post-stress	↓Sociability (SAA) ↓Memory (SR, OPR)	dHPC	PE: ↑ Expression	↑Density	↑Density	Density: Not affected; ↑ Intensity
Koskinen et al. (2019)	Rat	week 9 (young adult)	once/day x 5 days	10, 13, 15, 19 weeks	♂	Social defeat	3 days post-stress (24 h post-stress)	Not affected Sociability (SAA) ↓Memory (OPR)	dHPC	PE: ↓ Expression		↓Density	Not affected
							> 2 weeks post-stress	↓Sociability (SAA) Not affected memory (OPR)		PE: Not affected		Not affected	
							> 4 weeks post-stress	↓Sociability (SAA) Not affected memory (OPR)		PE: Not affected		Not affected	
							> 8 weeks post-stress	↓Sociability (SAA) ↓Memory (OPR)				↑Density	
Dimatelis et al. (2013)	Rat	P2-P14 (early life)	3 h/day x 2 weeks	P74	♂	Maternal deprivation	> 8 weeks post-stress		HPC	PE: ↑TenR & Bcan			

(*continued on next page*)

Table 1 (*continued*)

Author	Species	Timing of stress (age)	Stress duration	Age at analysis	Sex	Stress type	Timing of ECM/PV testing	Behavioral Readout	Brain Region	ECM (genes/proteins)	PNNs	PNN^+-PV^+	PVs
Gildawie et al. (2020)	Rat	P2-P20 (early life)	4 h/day x 3 weeks	P20, P40 & P70	♂,♀	Maternal deprivation & social isolation	24 h, 3 & 7 weeks post-stress (1.5, 4.5 & 9 weeks post-stress)		PFC (PrL, IL)		↓Density (only P20 PrL); Intensity: Not affected	Density: Not affected; ↑ Intensity (only ♂ P70 PrL)	Density & Intensity: Not affected
				P20, P40 & P70	♂,♀		24 h, 3 & 7 weeks post-stress (1.5, 4.5 & 9 weeks post-stress)		BLA		Density & Intensity: Not affected	Density & Intensity: Not affected	↑ Density (only ♂ P40); Intensity: Not affected
Murthy et al. (2019)	Mouse	P2-P16 (early life)	4 – 8 h/day x 2 weeks & weaned at P17	P2-P70	♂	Maternal separation with early weaning	> 7 weeks post-stress (8 weeks post-stress)	↑Anxiety (EPM) ↑Response to novelty	vHPC		DG: Density: Not affected; ↑ Intensity CA1: Not affected		DG: ↓Density, ↓ Intensity CA1–3: Not affected

GE: gene expression; PE: protein expression.
[a] Layer-specific regulation was observed.

mediated ECM changes in response to stress would unravel whether ECM changes precede astrocytic dysfunction or, vice versa, if astrocytic dysfunction precipitates stress-induced ECM reorganization.

The implication of proteolytic ECM processing in stress and antidepressant response constitutes another challenge. As mentioned before, proteolytic remodeling of ECM is tightly regulated by several proteinases, including MMP-2/9 and ADAMTS-4/5, that are expressed by both astrocytes and neurons (Conant et al., 2005; Ethell and Ethell, 2007). In turn, ECM degrading proteinases are intrinsically inhibited by the tissue inhibitors of metalloproteinases (TIMPs) (Reinhard et al., 2015), whose role in stress effects is still largely unexplored. We recently found decreased MMP-2 activity to coincide with increased ECM levels present months after initial stress exposure suggesting that aberrant MMP-mediated proteolysis of ECM components is involved in hippocampal dysfunction associated with sustained depressive-like state (Koskinen et al., 2019). Yet more importantly, although scarce, clinical findings linking the two processes exist. Reduced serum MMP-2 levels were observed in MDD patients and shown to be restored after electroconvulsive treatment (ECT), which also regulates serum MMP-9 levels (Shibasaki et al., 2016). Furthermore, increased serum levels of MMP-9 were found in patients suffering from bipolar disorder (Rybakowski et al., 2013). Although the correlation between serum and brain MMP levels remains unknown, these studies hint to the involvement of protease-mediated ECM remodeling in major depression pathology and in antidepressant response.

As highlighted above, PNN changes commonly coincide with alterations in PV^+ interneurons, yet the cross-talk between the two remains poorly understood, especially in relation to stress response. As changes in PNNs can affect PV^+ activity (Favuzzi et al., 2017; Lensjø et al., 2016) and, conversely, PV^+ activity can modulate PNNs (Devienne et al., 2019) the directionality of stress-induced changes is challenging to dissect. Speculatively, loss of PNN integrity in response to stress could alter PV^+ cell activity, possibly *via* modulating synaptic inputs onto these cells or by altering the transmission of external molecular cues (Hensch, 2004, 2014). Likewise, stress-induced changes in PV^+ activity could result in loss or accumulation of PNNs around them, consequently modulating network function. Shifts in PV^+ network plasticity states were recently demonstrated to be integral to optimal learning and memory processes (Donato et al., 2013). Of note, the authors showed that chABC administration induced a change from high- to low- PV^+ plasticity state, indicating that ECM remodeling is key in modulating PV^+-mediated experience-dependent plasticity.

Collectively, stress-induced changes in ECM and PV^+ networks appear prevalent, but more studies are required to fill in the gaps in the temporal profile to elucidate the development of the depressive-like state. In this respect, stress duration (acute *vs.* chronic), timing of stress (early life, adolescent, adulthood) and time elapsed after stress exposure are important aspects to include in study designs. Taking lessons from the addiction field, it seems crucial to account for developing neuroadaptations in the weeks and months after stress that might precipitate the “incubation” of stress-induced psychopathology.

A bidirectionality in ECM/PNNs regulation in response to stress is typically observed, however it is yet to be seen whether early reductions are functionally related to late ECM build-up, *e.g.*, *via* a compensatory mechanism gone rogue. In this respect, understanding of the complex mechanisms underlying ECM production and break-down, and relating these processes to physiological changes at the molecular, cellular and network level is crucial to further decipher the implications of stress-associated ECM remodeling. Notably, similar stress-induced profiles in ECM and PV^+ circuitry are observed in several brain regions that are involved in anxiety and mood disorders, including the mPFC, amygdala and HPC, indicating common neurobiological substrates. By advancing our understanding of ECM remodeling in stress responses, new therapeutic avenues against stress-related pathologies can emerge.

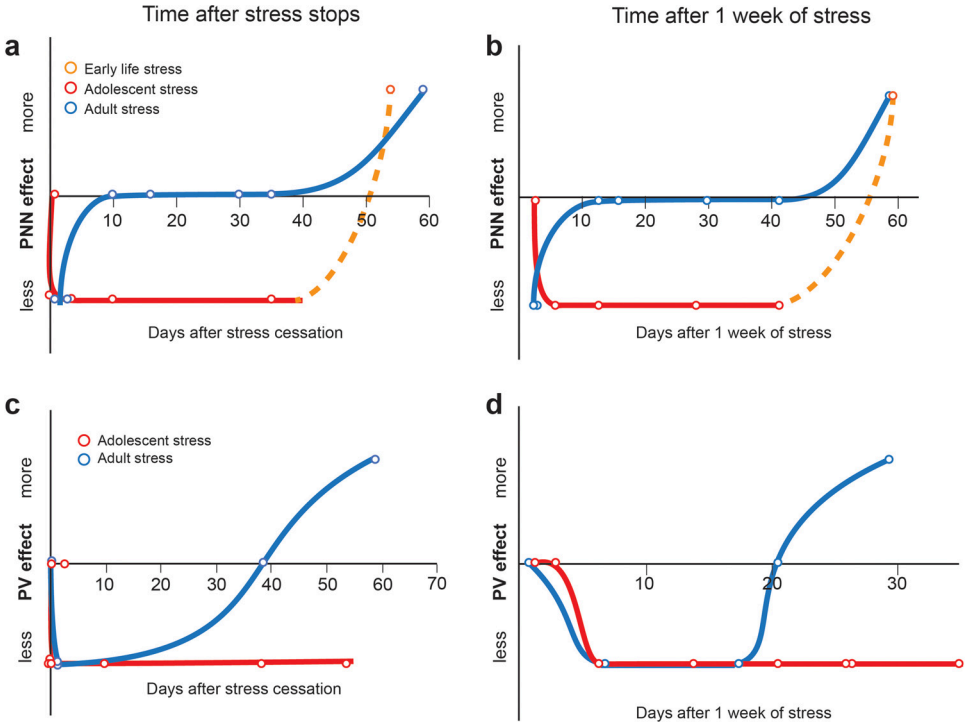

Fig. 4. Incubation of stress: effects of stress recency on PNNs and PV$^+$ interneurons. **a,b,c,d**) Taking stress recency into account for the molecular and cellular effects of stress on the brain generates a more complete profile of the homeostatic adaptations that occur, and can explain seemingly opposing regulation observed in different studies. Note that another factor of importance is stress timing (prenatal/early life, orange; adolescent, red; adult, blue), as the trajectory in the long-term is different. Using two ways to analyze stress recency, namely as days after stress cessation (a,c) or as days after a short period of stress (i.c. 1 week; b,d) different curves appeared, with the latter (b,d) giving a better smoothing of the curve, where a better distinction could be made between time points in the short-term after stress. Hence is of interest to consider this when analyzing data across different studies and paradigms (Table 1). **a,b)** Effects of stress recency on the number (density) of PNNs and/or PNN-coated PV$^+$ cells in the HPC. Overall, during adulthood, a transient reduction in PNNs and/or PNN PV$^+$ coverage is seen early after stress, which normalizes and is followed by an increase at later stages (Riga et al., 2017b; Koskinen et al., 2019). Stress during adolescence shows an enduring down-regulation. However, an increase in PNN intensity is also observed in a study of early life stress (Murthy et al., 2019), highlighting the importance of studying long-term effects of adolescent stress. **c,d**) Effects of stress recency on the number (density) or intensity of PV$^+$ cells in the hippocampus. A similar difference in trajectory appeared when taking timing of stress into account. Note that lines drawn between the data points (denoting less, none or more) are an artistic impression and do not correspond to absolute values. Due to the sparsity of data on female rodents, and because sex-specific effects have been shown to occur, only the data points from male rodents are shown.

Declaration of Competing Interests

None.

Acknowledgements

MKK, DR, and SS were supported by an NWO VICI grant (ALW-Vici 016.150.673/865.14.002); DR was supported by the EU Research and Innovation Framework Programme Horizon 2020: Marie Skłodowska Curie Actions, Individual Fellowship (MSCA-IF-EF-ST; 793106).

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