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Perineuronal net structure as a non-cellular mechanism contributing to affective state: A scoping review

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ABSTRACT

Affective state encompasses emotional responses to our physiology and influences how we perceive and respond within our environment. In affective disorders such as depression, cognitive adaptability is challenged, and structural and functional brain changes have been identified. However, an incomplete understanding persists of the molecular and cellular mechanisms at play in affective state. An exciting area of newly appreciated importance is perineuronal nets (PNNs); a specialised component of extracellular matrix playing a critical role in neuroprotection and synaptic plasticity. A scoping review found 24 studies demonstrating that PNNs are still a developing field of research with a promising general trend for stress in adulthood to increase the intensity of PNNs, whereas stress in adolescence reduced (potentially developmentally delayed) PNN numbers and intensity, while antidepressants correlated with reduced PNN numbers. Despite promising trends, limited research underscores the need for further exploration, emphasizing behavioral outcomes for validating affective states. Understanding PNNs' role may offer therapeutic insights for depression and inform biomarker development, advancing precision medicine and enhancing well-being.

1. Introduction

Affective state is an enduring emotional response to our physiology and influences how we perceive and react to our environment. The experience of a negative affective state changes behaviour and cognition where one perceives the environment through a negative bias. This can induce a negativity spiral of catastrophising thoughts, where maladaptive/altered behaviour and thought patterns, such as social withdrawal and anhedonia, further enhance the negative affective state (Ao et al., 2020). Over time this can lead to depressive disorders and suicidal thoughts. On the other hand, experiencing a positive affective state encourages engagement with novelty and the environment, broadening outlook and increasing cognitive adaptability that can provide resilience to stressors (Fredrickson, 2001). Stress, especially perceived stress, can be a major disruptor of affective state, blocking the experience of positive emotions and inducing negativity (Boelen, 2021).

Exposure to stressors alters physiology inducing an inflammatory signalling response whether it be mechanical, chemical, or psychosocial stress. Acute stress can be beneficial, releasing hormones and neurotransmitters that induce a physiological response that aids the flight or fight response. However, if the stress becomes chronic the physiology may be irreversibly altered with associated maladaptive cognitive and behavioural patterns resilient to change. The molecular mechanisms underlying cognitive and behavioural changes associated with affective state are thought to be caused by neuronal alterations in the form of synaptic connectivity, neurotransmitter release and receptor density, and synaptic plasticity (Vose and Stanton, 2017). Non-neuronal contributions in the form of microglia and the extracellular matrix (ECM) also have the potential to be involved (Dityatev and Schachner, 2003; Crapser et al., 2020; Wegrzyn et al., 2021).

The limbic regions and those regions regulating the limbic regions such as the amygdala, hippocampus and prefrontal cortex are the most commonly assessed brain regions for studies of affective state. These are the regions of most interest due to their known associations with emotive behavioural changes. However, some argue there is no specific region associated with affective state and have identified valence-encoding neurons in many regions with some neurons able to encode both the negative and positive valence through alteration in firing rates

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(Namburi et al., 2016; Beyeler et al., 2018; Pignatelli and Beyeler, 2019). Interestingly, perineuronal nets (PNNs) are capable of influencing neuronal firing rates of cortical inhibitory interneurons (Balmer, 2016).

Perineuronal nets (PNNs) are a specialised form of condensed extracellular matrix that are well placed to be part of the mechanism underlying affective disorders such as depression and changes between a negative and a positive affective state. Structurally, PNNs are composed of chondroitin sulphate proteoglycans with glycosaminoglycan (GAG) chains attached that are linked together via proteins. Tenascins such as R and C cross-link lecticans (aggrecan, neurocan, versican and brevican), and HAPLN proteins (1−4) attach these lecticans to the hyaluronan backbone which is synthesised from HA synthases (1−3) located in neuronal membranes (Carulli et al., 2006). (see Fig. 1.) The GAG chains include non-sulphated and sulphated positions (4 S,6 S, 2S6S and 4S6S) on the glycans, (repeating d-glucuronic acid (GlcA) and N-acetyl-d-galactosamine (GalNAc) disaccharide units) with studies showing sulphation sites relate to developmental periods, vary functions such as affecting social memory and determining the excitatory/inhibitory balance within the brain (Huang et al., 2023). PNNs are formed through secretions of both the neuron they surround and nearby glia (Testa et al., 2019). PNNs form part of the 'tetrapartite synapse' (Dityatev and Rusakov, 2011) which describes the interaction of the pre- and post-synaptic elements, glial processes, and ECM. PNNs enwrap neuronal soma and dendrites providing neuroprotection to the neurons they surround while functioning as an anionic buffer and regulating synaptic plasticity (Reichelt et al., 2019).

PNNs can be detected through immunohistochemical or immunofluorescent staining with the lectin Wisteria floribunda agglutinin (WFA) and Vicia villosa agglutinin (VVA) that recognise the N-acetylgalactosamine (GalNAc) residues within chondroitin sulfate chains (Härtig et al., 1992). Quantification of PNNs is typically determined through 1) number counts of PNNs, 2) intensity of PNNs, and 3) colocalization of PNNs and parvalbumin (PV) neurons. PV neurons are fast-spiking GABAergic interneurons which are vulnerable to the environment and are implicated in various neurodevelopmental disorders (Ruden et al., 2021). PNNs mostly surround these fast-spiking inhibitory PV neurons (Härtig et al., 1999) and begin to appear early in life reaching peak in late adolescence, corresponding to the end of the critical period (Reichelt et al., 2019). This coincides with the maturing brain when inhibitory neurons are stabilising reactivity (Pizzorusso et al., 2002). The excitatory/inhibitory balance is important for efficient brain functioning. Imbalances have been associated with behavioural and cognitive dysfunction in psychiatric disorders (Ferguson and Gao, 2018). Microglia regulate the ECM during normal brain homeostasis maintaining PNNs structure through their secretion of matrix metallopeptidase 9 (MMP9), an enzyme that belongs to the zinc-metalloproteinases family (Crapser et al., 2021). Given that chronic stress alters microglia numbers, activity, and morphology (Sugama and Kakinuma, 2020) this provides a mechanism for stress-induced alterations in PNN architecture.

Despite this rapidly evolving literature it is unclear whether PNNs contribute to the underlying mechanisms of affective state, and or whether therapies that harness structural components of PNNs may alleviate symptoms of negative affective state. Therefore, the objective of this scoping review is to generate a compilation of existing knowledge regarding measures of PNNs in experimental studies associated with affective state, including those studies that alter environmental stressors. The outcomes will inform future research directions by elucidating non-cellular PNN structural changes within central nervous system mechanisms that may underpin and/or contribute to positive and negative affective states. These mechanisms may also be targets for manipulation to manage conditions of depression or promote wellbeing.

2. Methods

JBI's methodology for conducting scoping reviews was followed in the conduct of this review (Peters et al., 2020), and the PRISMA guidelines were used to guide review reporting (Page et al., 2021). An a priori protocol for this scoping review was registered through INPLASY (ref: INPLASY REGISTRATION NUMBER: INPLASY202180075, DOI 10.37766/inplasy2021.8.0075).

2.1. Search strategy

A comprehensive search using Medline via OVID, PsychINFO via OVID, and Embase was conducted to source eligible peer reviewed publications in English. Keywords for the search included perineuronal nets, medial prefrontal cortex, amygdala, hippocampus, parvalbumin interneurons, and depression. The search strategy was constructed with the help of an information specialist to envelop all studies which include measures of perineuronal nets. The search string was developed for Medline via OVID and then adapted to PsychINFO via OVID and Embase (see appendix for details). Publications were excluded if they were conference abstracts lacking full results or review articles.

2.2. Inclusion and exclusion criteria

This scoping review included articles adhering to the following criteria: 1) Human and animal studies at juvenile, adolescent and adult life stages; 2) Studies of affective state including depression and depressive-like behaviour, reward-seeking and fear and/or studies

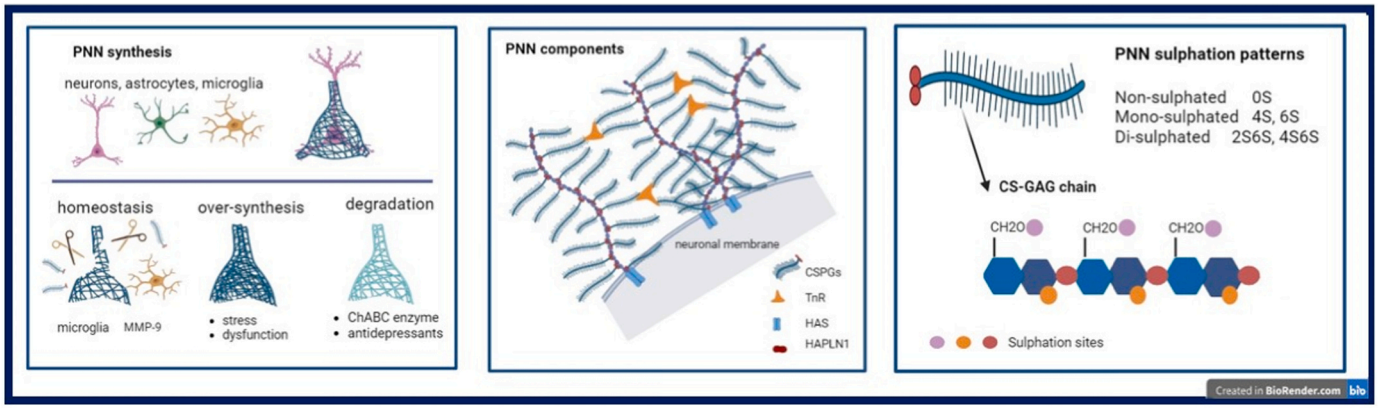

Fig. 1. Perineuronal nets are formed from neuronal and glial expressions of glycans and proteins which a) bind the PNN structure to the neuronal membrane, b) cross-link the chondroitin sulphate proteoglycans (CSPGs) and c) bind the Glycosaminoglycan (GAG) chains to the hyaluronan backbone. Sulphation patterns on the GAG chains within PNNs vary developmentally and are associated with levels of plasticity. (Diagram constructed in BioRender).

involving the use of anti-depressants, enriched environments or novelty i.e. modifiers of affective state; 4) measures of PNN structure (numbers, intensity, co-localisations - measured in affective state associated brain regions such as but not limited to amygdala, hippocampus and prefrontal cortex). All study designs were eligible for inclusion.

Exclusion criteria for this review were as follows: 1) Studies on populations with neuropsychiatric disorders such as schizophrenia and bipolar disorder and developmental disorders such as autism, Fragile X and epilepsy or studies inducing models of these disorders.

2.3. Study selection

Citation details were imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) where duplicates were identified and removed. Titles and abstracts were screened by one reviewer (JCM) against the pre-determined inclusion and exclusion criteria. Full text screening was performed by two independent reviewers (ALW and JCM) with any disagreements on inclusion being resolved through discussion.

2.4. Data extraction

Data were extracted from the included studies by one reviewer (JM) using an adapted version of the Covidence Extraction 2.0 template. Only data directly relevant to the review question were extracted. This included counts of PNN, intensity of PNNs and co-localisations of PNN with parvalbumin neurons as well as general citation details and animal/human information. Study quality appraisal was not performed in accordance with guidance on scoping reviews (Pollock et al., 2023). As such a full evidence critique process has not been applied here.

2.5. Data synthesis

Publications were grouped by year of publication, country of study, animal model type and species used: sex and age. Study model and brain regions assessed were tabled. Extracted data were tabled into groupings of adolescent and adult stress paradigms, antidepressant paradigms, non-stress paradigms, and enzymatic degradation of PNN studies. Correlations between behavioural tests and PNN outcomes were also tabled.

3. Results

A search of the three databases with the forementioned search strategy resulted in identifying 398 records. Duplicate records were removed resulting in 257 records eligible for title and abstract screening. A total of 216 records were excluded according to the inclusion and

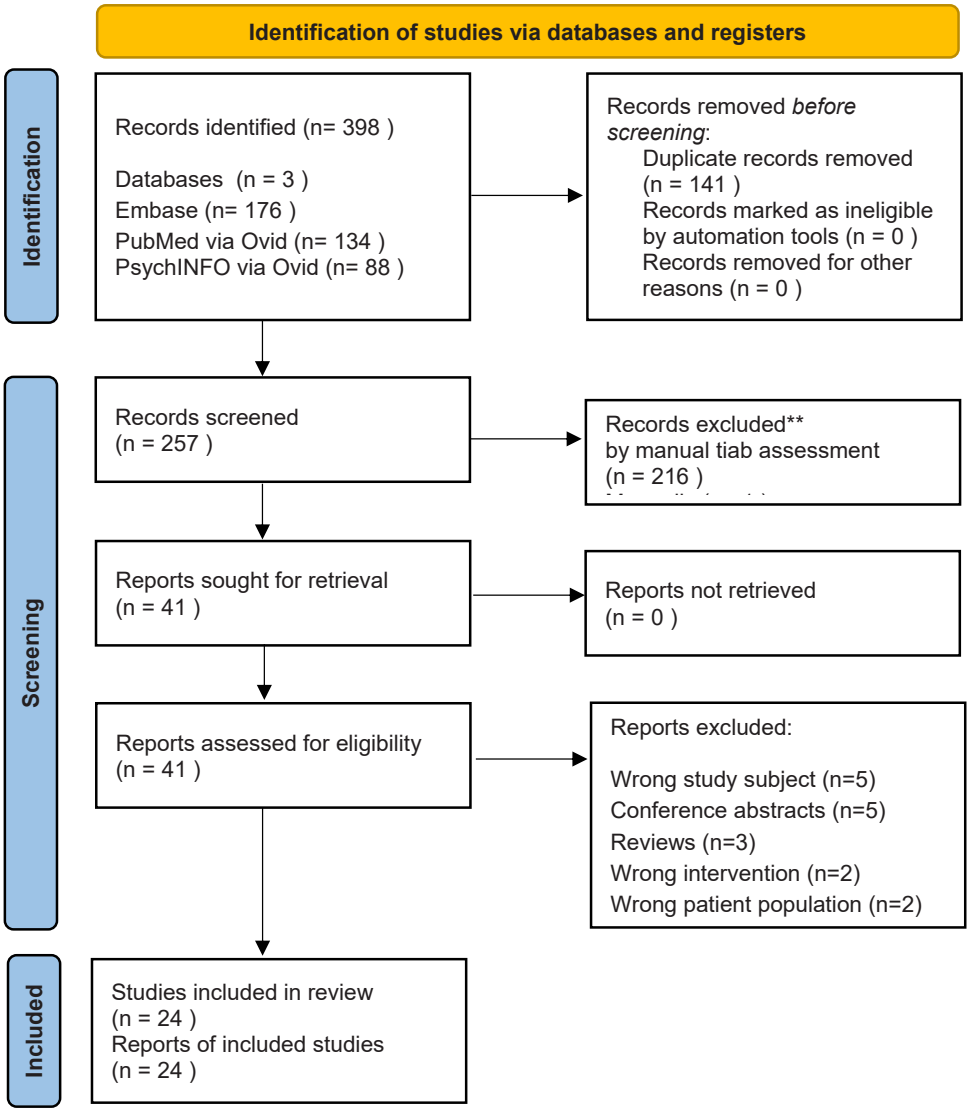

Fig. 2. PRISMA flow diagram (Page et al., 2021).

exclusion criteria with the remaining full text articles assessed for eligibility. A final count of 24 studies were identified as meeting eligibility criteria and were included in the scoping review (Fig. 2). Publication dates ranged from 2013 to 2022 with 88% of studies occurring since 2017 (Fig. 3). Selected studies were conducted in 12 countries (Brazil, Canada, China, Germany, India, Japan, Korea, Netherlands, Poland, Spain, Serbia, and USA) with a third of studies conducted in the USA (Fig. 4).

Only one human study was identified where PNNs were measured in the context of affective state. Rodent studies were conducted with rats (46%) and mice (54%) but only 29% of studies assessed PNNs in female animals (Fig. 5). Of all rodent studies 69% measured PNN in adulthood although some of these studies were measuring adult PNNs after adolescent or juvenile stress. Adolescence is considered here as being between 4–8 weeks while juveniles are classed as under 4 weeks. No studies examined PNNs in aged animals.

Within the included studies, PNNs were measured in several conditions: 1) when conditions were imposed that were expected to induce a positive or negative affective state, 2) administration of a treatment to alleviate affective disorders, 3) in correlation with basal levels of anxiety or 4) postmortem brains of depressed patients who suicided (Fig. 6.) Multiple stress paradigms associated with inducing a negative affective state were imposed with subsequent measure of PNNs. Those affecting juveniles were maternal separation stress and limited bedding models. Adult models of stress included chronic unpredictable mild stress (CUMS), chronic variable stress (CVS), restraint stress and social defeat induced persistent stress (SDPS). Out of the 15 rodent studies using stress paradigms 4 studied the effects of adult stress only, 3 studied both adult and adolescent stress, 4 studied adolescent stress only, and 4 applied a stress model to pups. From the 9 antidepressant studies, 7 were conducted on adult animals while one study administered antidepressants from postnatal day 2 and one study administered to adolescents only. Only one study, an environmental enrichment study by Foggetti et al., 2019 assessed PNN in the context of an assumed positive experience (Foggetti et al., 2019), although no behavioural testing was undertaken to validate the affective state of the animals. One study assessed PNN measures directly correlating with a behavioural measure of anxiety (Lee and Lee, 2021). The only human study measured PNNs in postmortem brain tissue of depressed people who had died by suicide (Tanti et al., 2022).

CUMS: Chronic unpredictable mild stress, CVS: Chronic variable stress, DS: depressed suicides,
EE: environmental enrichment
FLX: Fluoxetine, LB: Limited bedding, MD: Maternal deprivation, MS: Maternal separation,
RMS/EW: Repeated maternal separation/ early weaning, SDPS: Social defeat induced persistent stress, VFX: Venlafaxine

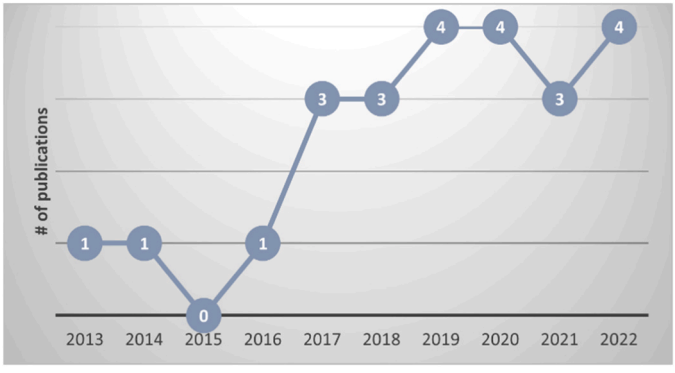

Fig. 3. The number of studies measuring PNNs in association with affective state are on the increase.

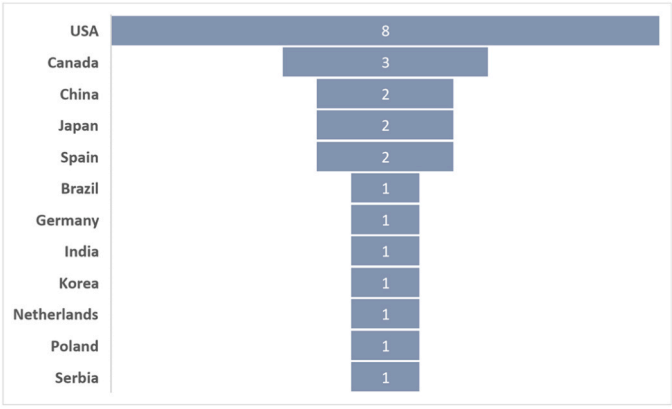

Fig. 4. Northern America had the greater number of publications measuring PNN outcomes in relation to affective state. Colours represent number of studies published per country.

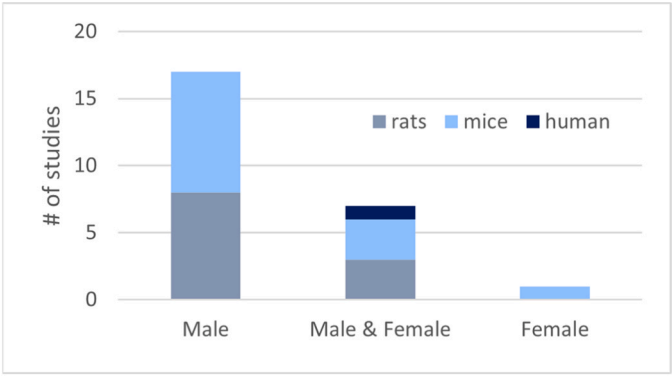

Fig. 5. Only 25% of studies assessing PNNs in rodents included both male and female animals while 54% of studies were conducted in mice.

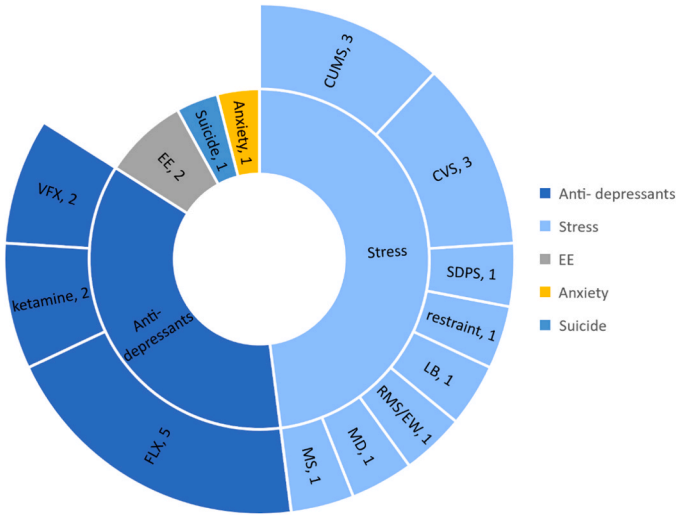

Fig. 6. Most studies measured PNNs in association with negative affective state. Only one study measured PNNs within a positive affective state context of environmental enrichment. NB. One study included two antidepressants.

A full summary of the characteristics of the twenty-four studies, including brain regions and behavioural tests assessing affective state, has been compiled in Table 1. Various brain regions were assessed for changes in PNN numbers, intensity, and co-localisation with

Table 1
Summary characteristics of the included papers with behavioural tests of affective state.

Author, Year, Country	Model	Brain regions	Species, strain and sex	Age at treatment	Age at PNN analysis	Behavioural tests
(Alaiyed et al., 2019), USA	Antidepressant: VFX (30 mg/kg) for 2 weeks, daily by i.p	HIP	Mice-C57BL/ 6 J Male & Female Mice- MMP9 KO	P28	P40	No
(Alaiyed et al., 2020), USA	Antidepressant: VFX (30 mg/kg) in last 2 weeks, daily by i.p of CORT exposure (5 mg/kg/day) for 6 weeks	HIP PFC	Mice- C57BL/6 mice Male Mice- MMP9 KO Human	P28 adult	P70 adult	EPM
(De Araújo Costa Folha et al., 2017), Brazil	Chronic Variable Stress daily for 7, 15 or 35 days	PFC, OFC	Rats- Wistar, Male	P28	adult	EPM, OFT
(Donegan and Lodge, 2017), USA	Removal of PNN with ChABC (0.75 μL) Antidepressant Ketamine (single dose 10 mg/kg, i.p) @ 30 mins or 1 week	HIP	Rats- Sprague Dawley, Male	adult	adult	FST
(Foggetti et al., 2019), Germany	Environmental Enrichment for 8 days	HIP	Mice, Male	P38-P70	adult	No
(Gildawie et al., 2020), USA	Maternal Separation 4 hrs/day	PFC	Rats- Sprague Dawley, Male & Female	P2-P20	P20, P40, P60	No
(Guadagno et al., 2020), Canada	Limited Bedding	BLA	Rats- Sprague Dawley, Male & Female	pups	Juvenile P22-P29	No
(Guirado et al., 2014), Spain	Antidepressant: FLX for 2 weeks, (20 mg/kg) daily i.p	HIP	Mice, Male	adult	adult	No
(Jakovljevic et al., 2022), Serbia	Maternal depravation 24hrs	HIP, mPFC	Rats, Wistar albino, Male	PND 9/10	PND 60	No
(Lee and Lee, 2021), Korea	Basal anxiety measures	PFC, OFC	Mice, Male	adult	adult	OFT
(Mukhopadhyay et al., 2021), India	Antidepressant: FLX (10 mg/kg) daily for 18 days, orally	HIP	Rats- Sprague Dawley	P2-P21	P21 and P80	No
(Murthy et al., 2019), USA	Repeated Maternal Separation with Early Weaning, 4 h daily from P2-P5 and 8 h daily from P6-P16.	HIP	Mice- C57BL/ 6 J, Male and Female	P2-P16	Adult (P60 to P70) male	EPM, OFT
(Ohira et al., 2013) Japan	Antidepressant: FLX (15 mg/kg) daily by i.p for 3 weeks	HIP, RTN	Mice- C57BL/ 6 J, Male	adult	adult	No
(Page and Coutellier, 2018), USA	unpredictable chronic mild stress for 2 weeks	PFC	Mice- C57BL/ 6 J, Male and Female	P28	adolescent P48 adult P80-83	EPM, OFT, FST
(Pesarico et al., 2019), Spain	repeated restraint stress, 6 h per day for 10 consecutive days	BLA, Hb, HIP and PFC	Rats- Sprague Dawley, Male	adult	adult	No
(Puścian et al., 2021), Poland	Antidepressant: FLX Chronic; (10 mg/kg) daily for 8 weeks, orally Acute; (20 mg/kg) by i.p & killed after 30 mins	BLA, HIP and PFC	Mice- C57BL6/ cmdb, Female Mice- MMP9 KO Female	adult	adult	Discrimination task and Reward seeking
(Riga et al., 2017), Netherlands	1. Social Defeat-induced Persistent Stress Acute: after 5 social defeat sessions Long-term: 5 social defeat session followed by 2-3 mths social isolation 2. social defeat- social isolation ChABC: single infusion of 0.03 U / side	HIP, perirhinal cortex HIP	Rats- Wistar, Male	6-8 weeks	adult	2. Social Approach Avoidance task
(Sanders and Mayford, 2016), USA	Antidepressant: FLX 24-30 days in drinking water	HIP	Mice- C57BL/ 6 J, Male	adult	adult	Contextual Fear memory and Auditory fear memory
(Simard et al., 2018), Canada	Chronic Variable Stress 2-3 stressors daily for 35 days ChABC injected on day 33 into PFC	PFC	Mice- C57/BL6, Male	adult	adult	FST, OFT, EPM
(Smail et al., 2022), USA	Housing environment 6 weeks	BLA	Rats, Sprague Dawley, Male	adult	adult	Passive avoidance, Social threat, Acoustic startle, and Cued fear conditioning
(Tanti et al., 2022), Canada	adult depressed suicides, who died during an episode of major depression	vmPFC	Post mortem adult human M&F	35-50 yrs old	35-50 yrs old	No
(Ueno et al., 2018), Japan	Variable Stressors, 1/day for 8 days	PFC, dACC	Mice- C57BL/ 6 N, Male	P21 (juvenile) and P71 (adult)	Adolescent (P30) & adult	EPM, FST, Locomotor activity test, Social interaction test, Tail suspension test
(Yu et al., 2020), China	Chronic Unpredictable Mild Stress, 2 stressors/day for 10, 20 and 30 days	PFC	Rats-Sprague Dawley, Male	adult	adult	FST, OFT, Novelty-Suppressed Feeding Test, Sucrose preference test
(Yu et al., 2022), China	subthreshold chronic unpredictable mild stress paradigm (SCUMS) 10 days ChABC + SCUMS 10 days SCUMS 10 days then ketamine (IP 20 mg/kg) Fluoxetine before and during SCUMS 10 days	PFC	Rats, Sprague-Dawley, Male	P28 adolescent and P70 adult Adult Adolescent Adolescent	P28 adolescent and P70 adult	Sucrose preference test, Novelty-suppressed feeding test and food consumption test, FST

BLA: basolateral amygdala, dACC: dorsal anterior cingulate cortex, Hb: habenula, HIP: hippocampus, OFC: orbitofrontal cortex. PFC: prefrontal cortex, RTN: reticular thalamic nucleus
FLX: fluoxetine, VFX: venlafaxine, i.p: intraperitoneal injection, KO: knockout
EPM: elevated plus maze, FST: forced swim test, OFT: open field test

parvalbumin (PV) neurons. These regions included the basolateral amygdala, dorsal anterior cingulate cortex, habenula, hippocampus, orbitofrontal cortex, prefrontal cortex, perirhinal cortex, and reticular thalamic nucleus. Studies showed significant heterogeneity between regions. The hippocampus, prefrontal cortex, and basolateral amygdala were the brain regions most commonly assessed for PNNs; these brain regions being widely researched in the context of emotional processing and regulation.

3.1. Stress related PNN changes in adult rats and mice

Stress-related PNN changes seen in adults (Table 2.) varied across the ten studies. Only six studies assessed behaviour to validate the assumed valence of affective state with these generally showing the expected results, for example anxiety-like and depressive-like behaviours were increased by the stress paradigms. PNN outcomes across these studies were mixed but do suggest a trend of increased intensity in PNNs across brain regions.

Pesarico et al. (2019) used restraint stress in adult male Sprague Dawley rats and showed mostly increases in PNN density (measured by mean gray area using image analysis) and PNN intensity (measured by intensity of fluorescent PNN-associated signal) in the habenula, reticular thalamic nucleus and prefrontal cortex. The hippocampus (CA1) region of these male rats differed with PNN density decreasing with no change of PNN co-localisations of PV neurons. In contrast, Riga et al. (2017) saw an increase in PNN density in the hippocampus CA1 region after social defeat persistent stress in male Wistar rats.

Simard et al. (2018) found an increase in PNN density in the prefrontal cortex of adult male mice exposed to chronic variable stress which corresponded with increases in anxiety-like and depressive-like behaviour in the Open Field Test, Elevated Plus Maze and Forced Swim Tests respectively. However, Yu et al. (2020) found adult male rats exposed to the chronic variable stress model expressed similar behavioural phenotypes as Simard et al. (2018) (i.e. increased anxiety-like behaviour and depression like behaviour in Sucrose Preference Test, Novel- Suppressed Feeding Test and Forced Swim Test) but showed a reduction in both the PNN numbers and the co-localisations with PV neurons in the prelimbic region. When the chronic variable stress was experienced in adolescence (Page and Coutellier, 2018), and later measured in adult mice, there were no changes to PNN number and co-localisation with PV neurons.

Smail et al. (2022) analysed PNN in the basolateral amygdala after enrichment removal and found PNN density, PNN intensity and PNN co-localisations with PV neurons all increased. These changes in the specialised extracellular matrix were associated with an increase in startle response, impaired fear recall and reduced adaptability. The one human study by Tanti et al. (2022) also found increases in PNN density, PNN intensity and PNN co-localisations with PV neurons in the prefrontal cortex of depressed people who died by suicide and had experienced child abuse.

PNN intensity was not measured in all studies however 5 out of the 10 studies identified in this scoping review showed PNN intensity increased in adulthood after enduring a stress paradigm, whilst two studies yielded no change or found a decrease in PNN intensity. Various brain regions were explored (basolateral amygdala, hippocampus, prefrontal cortex, and the reticular thalamic nucleus). Gildawie et al. (2020) used a maternal separation model, and recorded an increase in the intensity of PNNs in the basolateral amygdala in female rats. However, in the male rats an increase was seen in the prefrontal cortex and only in the prelimbic area. Murthy et al. (2019) measured PNN intensity in the hippocampal region of adult mice that had undergone the Repeated Maternal Separation with an Early Weaning model. They found that increased anxiety and locomotion corresponded with an increase in PNN intensity in the adult (P60 to P70) dentate gyrus. However, young adult rats who had endured 24 h neonatal stress from maternal deprivation showed a reduction in PNN intensity in the prefrontal cortex in the study by Jakovljevic et al. (2022). In this study, neonatal stress also reduced PNN density and PNN co-localisations with PV neurons in the prefrontal cortex but no PNN changes were seen in the hippocampus.

Table 2
Stress related PNN changes seen in adults.

Brain Region	Stress paradigm	Behaviour	PNN density	PNN intensity	PV/PNN co-localisation	Studies
HIP	RMS/EW	Anxiety ↑ Locomotion ↑		↑ vDG (granule cell layer)	no change	Murthy et al. (2019)
HIP	restraint	None	↓CA1		no change	Pesarico et al. (2019)
HIP	SDPS	No sig diff in social approach-avoidance	↑CA1	no change CA1	↑CA1	Riga et al. (2017)
HIP	MD	None	no change	no change	No change	Jakovljevic et al. (2022)
PFC	MS	None	↓IL	↑ in males (PrL), no change (IL)	no change (PrL), ↓(IL)	Gildawie et al. (2020)
PFC	MD	None	↓mPFC, IL	↓PrL, IL	↓IL	Jakovljevic et al. (2022)
PFC	CVS in adolescence	Anxiety-like ↑	no change		no change	Page and Coutellier (2018)
PFC	restraint	None	↑		no change	Pesarico et al. (2019)
PFC	CVS	Anxiety- and depressive-like ↑	↑			Simard et al. (2018)
PFC	Child abuse	None	↑ layers 3-6	↑	↑	Tanti et el., 2022
PFC	CVS	Anxiety- and depressive-like ↑	↓ in PrL		↓ in PrL	(Yu et al., 2020
BLA	MS	None		↑ in females	no change	Gildawie et al. (2020)
BLA	Restraint	None	no change		no change	Pesarico et al. (2019)
BLA	Enrichment removal	Startle response↑ Impaired fear recall & adaptability	↑	↑	↑	Smail et al. (2022)
TRN	restraint	None		↑		Pesarico et al. (2019)
Habenula	restraint	None	↑			Pesarico et al. (2019)
RoCg1	MD	None			↓	Jakovljevic et al. (2022)

CVS chronic variable stress; MS maternal separation; RMS/EW repeated maternal separation/early weaning; SDPS social defeat persistent stress; IL infralimbic; PrL prelimbic

3.2. Stress related PNN changes seen in adolescent rats and mice

The outcome of measurements of PNNs in adolescent animals exposed to stress contrast with those observed in adult animals (Table 3). Whereas PNN intensity increases were seen in adult animals exposed to stressors, the PNN intensity results of Ueno et al. (2018) showed the opposite in adolescents, with decreases across brain regions (hippocampus, prefrontal cortex, dorsal anterior cingulate cortex). Although an important point of note is this was also associated with a decrease in anxiety-like behaviour and no depressive-like behaviour in the adolescent animals implying that the model may not have created stress. Page and Coutellier (2018) found sex differences in adolescent mice in the number of PNN colocalising with PV neurons in the prefrontal cortex with females showing increased numbers and males reduced numbers. However, Guadagno et al. (2020) found male rats that had experienced limited bedding stress as neonates had a greater number of PNN-PV colocalisations than female rats. Although Gildawie et al. (2020) saw a decrease in PNN density in the prefrontal cortex of rats, males showed a trend-level increase in the basolateral amygdala compared to control male rats. De Araújo Costa Folha et al. (2017) interestingly saw an increase in anxiety-like behaviour in rats corresponding with an increase in PNN number in the medial prefrontal cortex at day 7 of chronic variable stress and both the anxiety-like behaviour and the PNN number diminished at day 15 and 35.

3.3. PNN changes with antidepressant administration

Exposure to stressful events has been linked to the development of depression-like phenotypes in animal models. Antidepressant medications in the form of serotonin or serotonin-norepinephrine reuptake inhibitor classes (SSRIs/SSNRIs) are the most widely used treatment for mood disorders. Given that depression is hypothesised to be an affective disorder linked to aberrant synaptic plasticity (Wainwright and Galea, 2013) and PNNs are regulators of synaptic plasticity (Reichelt et al., 2019), PNN expression changes created by antidepressant drug treatment has been a research focus. The studies measuring PNN outcomes with antidepressant use (Table 4) showed a similar pattern in both adult and adolescent animals. Reductions in PNN density and intensity were found in various brain regions with antidepressant administration in stress naïve animals. PNN co-localisations with PV neurons followed a similar pattern; mostly decreasing with antidepressant administration in stress naïve animals.

Opposing these findings, the Yu et al. (2022) study subjected adolescent rats to a subthreshold chronic unpredictable mild stress paradigm and measured increases. PNN density and PNN co-localisations with PV neurons were increased in the prefrontal cortex of the adolescent rats while behaviourally ketamine and fluoxetine administration reversed depressive-like behaviours which occurred from the stress paradigm.

Other models of PNN changes in adults (Table 5) includes two studies of PNN outcomes that are not related to stress-inducing paradigms. One study explored positive affective state using environmental enrichment for adult mice and found decreased numbers of PNNs; although no behaviour was measured to validate the affective state (Foggetti et al., 2019). The other study by Lee and Lee (2021) found that PNN co-localisations with PV neurons in the orbitofrontal cortex showed an inverse correlation with basal anxiety measures.

3.4. Studies administering ChondroitinaseABC

Five studies enzymatically degraded PNN (Table 6) using ChondroitinaseABC (ChABC) microinfusions to specific brain regions. These studies varied in the rodent model used, and brain region sampled (dorsal hippocampus, ventral hippocampus, prefrontal cortex, and basolateral amygdala).

Three studies injected ChABC to degrade PNNs before treatment. Donegan and Lodge (2017) found PNNs were necessary for the sustained antidepressant effect of ketamine but not for the acute effect. Smail et al. (2022) found reducing PNNs blocked the effects of enrichment removal. Yu et al. (2022) administered ChABC to the prefrontal cortex of adult rats to mimic the adolescent rat brain; reducing PNN numbers. These adult rats then expressed depressive and anxiety-like behaviour as seen in the adolescent rats.

ChABC was administered to rodents after enduring stress paradigms in two studies. Riga et al. (2017) found ChABC infusion into the hippocampus did not alter rat behaviour following chronic social stress, whereas Simard et al. (2018) found ChABC infusion into the prefrontal cortex of chronic variable stress-exposed mice reversed the stress-induced behavioural phenotypes.

4. Discussion

This scoping review aimed to bring together the evidence on associations between perineuronal net characteristics and affective state valence, providing guidance on the direction of any effect. Out of the twenty four studies sourced fourteen studies measured PNN outcomes from stress paradigms which would be expected to induce a negative affective state. Negative affect is increased when experiencing stress and perceiving situations as stressful (Zautra et al., 2000). Only one study investigated assumed positive affective state through addition of

Table 3
Stress related PNN changes seen in adolescence.

Brain Region	Stress Paradigm	Affective Behaviour	PNN density	PNN intensity	PV/PNN colocalisation	Studies
HIP	CVS	Anxiety-like↓ No depressive- like	no change	↓CA1	no change	Ueno et al. (2018)
PFC	MS	Not tested	↓PrL	no change	no change	Gildawie et al. (2020)
PFC	CVS	Anxiety-like↓ No depressive- like		↓IL		Ueno et al. (2018)
PFC	CVS	Anxiety-like ↑	no change		↑female & ↓male	Page and Coutellier (2018)
PFC	CVS	Anxiety-like ↑ day 7 Anxiety-like ↓ day 15&35	↑ @ day 7, ↓@ day 15 & 35 in mPFC ↓ @ day 7,15 & 35 in OFC			De Araujo Costa Folha et al., 2017
BLA	MS	Not tested	↑ in males		no change	Gildawie et al. (2020)
BLA	LB	Not tested			LB males>LB females in right BLA	Guadagno et al. (2020)
dACC	CVS	Anxiety-like↓ No depressive- like		↓IL		Ueno et al. (2018)

BLA basolateral amygdala; dACC dorsal anterior cingulate cortex; HIP hippocampus; PFC prefrontal cortex
CVS chronic variable stress; LB limited bedding; MS maternal separation, IL infralimbic; PrL prelimbic
NB.(arrows relating to sex infer increase/decrease as a result of stress paradigm not in contrast with other sex)

Table 4
PNN changes with antidepressant administration.

Brain Region	Antidepressant	Age	Affective Behaviour	Stress naïve	PNN density	PNN intensity	PV/PNN colocalisation	Studies
HIP	VLX	adolescence	Not tested	Y		↓	↓	(Alaiyed et al., 2019
HIP	VLX	adolescence	Anxiety-like ↓	N		↓ in CORT exposed		(Alaiyed et al., 2020
HIP	FLX	adolescence	Not tested	Y	↓CA1, CA3		↓CA1,CA3	(Mukhopadhyay et al., 2021
PFC	Ketamine	adolescence	Reversed behavioral deficits in FST,	N	↑		↑	(Yu et al., 2022
PFC	FLX	adolescence	NSFT, sucrose preference Reversed depressive-like behaviour	N	↑			
HIP	FLX	adult	Not tested	Y	↓CA1		no change	(Mukhopadhyay et al., 2021
HIP	FLX	adult	Not tested	Y			↓CA1	(Guirado et al., 2014
HIP	FLX	adult	Not tested	Y	↓CA3			(Ohira et al., 2013
HIP	FLX	adult	impaired contextual fear memory, but spared auditory fear memory	N	no change			(Sanders and Mayford, 2016
PFC	FLX	adult	Not tested	Y	no change			(Mukhopadhyay et al., 2021
PFC	FLX	adult	Not tested	Y			↓	(Guirado et al., 2014
PFC	FLX	adult	Not tested	Y			↓	(Ohira et al., 2013
BLA	FLX	adult	Anhedonia ↑ reward learning ↓	Y			↓	(Puścian et al., 2021
RTN	FLX	adult	Not tested	Y	no change			(Ohira et al., 2013

VLX Venlafaxine; FLX fluoxetine, HIP hippocampus; PFC prefrontal cortex; BLA basolateral amygdala; RTN reticular thalamic nucleus

Table 5
Other models of PNN changes in adult.

Brain Region	Model	PNN density	PNN intensity	PV/PNN colocalization	Studies
HIP	EE		↓	↓	(Foggetti et al., 2019
PFC	Basal anxiety			OFC but not PrL showed inverse correlation with basal anxiety	(Lee and Lee, 2021

EE environmental enrichment; ER: enrichment removal, HIP hippocampus; PFC prefrontal cortex; OFC orbitofrontal cortex; PrL prelimbic

Table 6
Studies administering ChondroitinaseABC to locally degrade PNNs in adult male animals.

Region	Treatment	Outcome	Behavioural tests	Authors
vHIP	ChABC, then FST at 30 mins/ 1 week after ketamine administration	PNN required for sustained antidepressant effect of ketamine but not for acute effect	FST	(Donegan and Lodge, 2017
dHIP	SDPS + social isolation, then ChABC	ChABC no sig diff in social approach avoidance - reduced PNN numbers	SAA	(Riga et al., 2017
PFC	5 weeks Chronic Variable Stress, then ChABC	ChABC reversed stress induced phenotype	FST, OFT	(Simard et al., 2018
BLA	ChABC at start of ER period	Blocked effects of ER (see stress and Adults)	Passive avoidance, startle response, social threat	(Smail et al., 2022
PrL	ChABC before SCUMS	Reduced PNN, showed depressive and anxiety like behaviour	FST,NSFT, Sucrose preference	(Yu et al., 2022

ChABC: chondroitinaseABC, dHIP: dorsal hippocampus, vHIP: ventral hippocampus, PFC: prefrontal cortex
ER: enrichment removal, FST: forced swim test, NSFT: novelty-suppressed feeding test, OFT: open field test, SAA: Social approach, SCUMS: subthreshold chronic unpredictable mild stress paradigm, SDPS: Social defeat persistent stress

environmental enrichment. One study used basal measures of anxiety. Antidepressants, which are used clinically to ameliorate depressive or negative affective symptoms in the human population, were administered in eight rodent studies where PNN outcomes were measured. Overall, stress appears to increase PNN measures while degrading PNNs alters stress behaviours suggesting a causative relationship.

In the literature examined, stress paradigms were conducted on rodents at various developmental stages: early life (juvenile period), adolescence, and adulthood. The adolescent brain experiences stress differently from the adult brain and adolescents show different long term behavioural outcomes to that of adults (Romeo, 2013). If the structural and molecular composition of PNNs contributes to the altered behavioural responses to stress a specific signature of PNNs may be associated with behavioural phenotypes.

4.1. PNNs in the juvenile and adolescent brain

The behavioural paradigms examining affective state changes in these few studies were inconclusive at the adolescent stage with some studies finding a decrease in anxiety after exposure to stressors. This decrease in anxiety observed after experiencing a stress-inducing situation (Mccormick et al., 2008) suggests an adaptable profile which could be associated with fewer PNNs, which has been associated with enhanced synaptic plasticity in the CNS (Reichelt et al., 2019). This assumption is supported by the observations by Ueno et al. (2018) which observed decreased PNN intensities following stress across HIP, PFC and dACC. However, Gildawie et al. (2020) found a decrease in PNN numbers in the PFC but an increase in the BLA in adolescent males. Detectable PNNs peak at the end of adolescence, hence the experience of stress may potentially alter the developmental formation of PNNs. The neuroprotective capacity of PNNs has also been demonstrated with the co-localisation of PNNs surrounding parvalbumin inhibitory interneurons, which have high metabolic demands and hence are susceptible to functional disruption by oxidative stress (Morawski et al., 2004; Cabungcal et al., 2013). PV neurons are important for the increased inhibitory tone which develops throughout brain maturation (Caballero et al., 2020). Disruption of the natural developmental pattern

of PNNs through experiencing stress as a juvenile or adolescent may therefore cause an alteration in the developmental trajectory of this inhibitory tone in late maturing brain regions such as the prefrontal cortex (Caballero et al., 2020). Thus, interrupted PNN formation could have long term consequences for synaptic connectivity and contribute to the different long term behavioural outcomes of experiencing stress at a young age compared to in adulthood. The few studies identified in this review mainly found a downturn in PNN numbers and intensity from experiencing stressful situations while young which may suggest a delaying mechanism. Any delay in PNN formation may impact the optimal developmental trajectory of PV neurons and affect the maturing brain (Mauney et al., 2013).

4.2. PNNs in the adult brain

From the studies identified here, the adult experience of stress tended to result in an increase in anxiety and depression-like symptoms and more indications of stress being associated with an increase in PNN numbers, intensity, and co-localisations with PV neurons. By adulthood, following the end of the critical period, PNNs have reached the peak of their appearance (Reichelt et al., 2019, Drzewiecki et al., 2020) and thereby experiences of stress as an adult would no longer affect the developmental trajectory of the PNNs. However, stress induced alterations in PNNs may affect the optimal functioning of PV neurons and result in dysfunction of the excitatory/inhibitory balance altering synaptic connectivity. Behavioural changes following the experience of stress may arise from synaptic connectivity changes brought about through alterations in PNNs. Some studies did not validate the affective state with a phenotypic measure, e.g. behaviour, thereby making any association less clear. More studies measuring PNN outcomes in parallel with validated affective behavioural changes are warranted.

4.3. PNN variation between brain regions and sex

In the studies examined, the direction of effect of the PNN measurement varied, showing both increases and decreases across brain regions within the same study. In the study by Pesarico et al. (2019), restraint stress led to increased PNN numbers in the habenula and PFC, two regions critical for emotional processes, with no observed change in the BLA and a decrease in the HIP. This variation in measured PNN outcomes in different brain regions may collectively explain the type of behavioural changes seen from encountering stress. For example, a stress-induced increase in PNNs surrounding neurons in the BLA may strengthen fear behaviour while a reduction in the PNNs of the PFC may increase plasticity and thereby reduce regulatory control over the fear behaviour. In addition, sex differences in measured PNN outcomes of the BLA and PFC were found between male and female animals from the same stressful experience. Therefore, variance in the response to stress at the molecular level of the extracellular matrix may explain behavioural difference in response to stress between the sexes.

Three studies, where a stress-inducing paradigm was experienced during the adolescent life stage, identified differences in PNN measures between the sexes. The study by Page and Coutellier (2018) found opposing results of PV/PNN colocalisation in the PFC between male and female animals from the same early life adversity (ELA) paradigm. PNN numbers and PV/PNN colocalisations were variant between sexes in the BLA of the studies of Gildawie et al. (2020) and Guadagno et al. (2020) respectively. This may indicate different mechanisms of coping between the male and female animals, and an influence of sex hormones on PNN number and structure. Developmental pathways and temporal maturity development between the male and female animals is dissimilar due to hormone differences (Verma 2011); varying behavioural outcomes between male and female animals under stress from ELA are often due to personality differences and social needs (Dettmer and Chusyd, 2023). A study by Laham et al., 2022 found that PNNs are altered throughout the estrous cycle, however female mice exposed to maternal separation and early weaning showed disruption in these PNN changes which suggest reduced plasticity (Laham et al., 2022). However, behavioural differences seen between sexes may also be associated with differential changes in PNNs in various brain regions related to emotional regulation, cognition, and social interaction (Goodwill et al., 2018).

4.4. PNNs under different stress paradigms

Systematic reviews by Thomaes and McLaughlin (Thomaes et al., 2014; Mclaughlin et al., 2019) consolidate evidence regarding changes in the adolescent brain when exposed to trauma and long-term stress. Brain regions such as PFC, hippocampus and amygdala show variation in neural activity and volume changes occurring from the different experiences of stress between studies. PNNs influence neural activity; when PNNs are reduced dendritic spine densities are seen to increase allowing new neuronal connections to be formed (De Vivo et al., 2013). Conversely intensified PNN may hamper new synaptic connections while strengthening and protecting those already formed; lack of neurogenesis has been linked to depression (Snyder et al., 2011; Schoenfeld and Cameron, 2015). The differences in the type of stress paradigms used and the temporal effects of experiencing stress, whether it be acute or chronic stress, may provide reason for differences in PNN outcomes seen between studies in this scoping review.

Only four of the studies subjected animals to stress-inducing paradigms which lasted thirty or more days. Shorter durations of stress-induction may not be capturing the chronic stress physiology. Restraint stress is a predominantly physical stress which may be mechanistically experienced differently in the brain to psychological stressors (Li et al., 2019). However, even psychological stress results in a cascade of neuroinflammatory signalling (Gu et al., 2012) and it may be this inflammatory signalling which is sufficient to induce changes in glial reactivity and subsequent alterations of the extracellular PNNs. The studies identified here conducted the stress paradigms over various timeframes between 7 and 35 days with the study by Riga et al. (2017) adding two to three months of social isolation after social defeat. This temporal dimension is important as the initial response to stress may differ to that of chronic stress and the PNNs may change accordingly. The study by de Araujo Costa Folha et al., 2017 showed PNN numbers increased after 7 days of stress in the adolescent in line with increased anxiety, however by day 15 PNN numbers had decreased with an associated decrease in anxiety.

Acute and chronic stress affect biology in different ways. The acute stressor can be beneficial; the body has its natural defence mechanisms to confront the stressor and return the body to homeostasis. However, with repeated experiences of stressors these mechanisms can falter, and the body's mechanistic response of hormones and other molecules needed to counteract the stressors can become depleted (Mcewen, 2004). "Studies conducted with humans indicate that chronic stress often precedes mood disorders" (Beauchaine et al., 2011). The temporal nature of PNN alterations is important as the structural integrity of PNNs is dynamic and PNN structural changes paralleling circadian rhythms have been reported (Harkness et al., 2021). Mood is also dynamic and has a temporal dimension; moods can fluctuate with time of day and energy levels suggesting a mechanism which can be altered rapidly (Stolarski et al., 2016).

The molecular mechanisms underlying cognitive and behavioural changes associated with affective state are thought to be caused by neuronal alterations in the form of synaptic connectivity, and synaptic plasticity (Vose and Stanton, 2017). PNNs influence synaptic formation and plasticity which can alter signalling between brain regions (Reichelt et al., 2019). However, whether the appearance of PNNs affects the behavioural outcome or the resultant stressor induced behaviour influences the PNN structure is unknown. Either way more studies measuring PNNs in association with validation of affective behaviour over multiple timepoints are needed to elucidate any relationship.

4.5. PNNs and antidepressants increasing structural plasticity

In this review, eight studies were identified where PNNs were measured in association with the use of selective serotonergic reuptake inhibitor (SSRI) antidepressants or ketamine, including studies in both adolescent and adult rodents (Alaiyed et al., 2019; Alaiyed et al., 2020; Guirado et al., 2014; Mukhopadhyay et al., 2021; Ohira et al., 2013; Puścian et al., 2021; Sanders and Mayford, 2016; Yu et al., 2022). These studies were included as SSRIs and ketamine are common pharmacotherapy for depression (Dale et al., 2015), which can be conceptualised as a negatively biased affective disorder. The period of antidepressant administration ranged from 30 mins to 8 weeks and were administered either orally or through intraperitoneal injection. In the studies reviewed here a reduction in PNN measures was predominant from antidepressant administration in both the adolescent cohorts and the adult cohorts across all brain regions analysed. This suggests an association between the mechanism of antidepressants and a reduction in PNN number, intensity and colocalization with PV neurons. A study by Ampuero et al. (2010) found an increase in dendritic spines in the prefrontal cortex after 28 days administration of fluoxetine, indicating an increase in synaptic plasticity which may include reduced PNNs as a part of the mechanism. Some antidepressants such as Venlafaxine increase the expression of matrix metalloproteinases (MMPs) which attenuate PNNs and reduce parvalbumin neuron-mediated inhibition on pyramidal cells (Alaiyed and Conant, 2019). However, five of these studies administered anti-depressants on stress naïve animals and mostly on adult animals. Future research should consider antidepressant administration on animals exposed to stressors to mirror the human experience of antidepressant use. Additionally, with the increase in adolescent mood disorders in current times (WHO, 2021), research designs should include antidepressant administration to animals at the adolescent stage.

Although not complying with the selection criteria of this scoping review (see DOI10.37766/inplasy2021.8.0075) and not included in detail here, studies using ketamine as a model of schizophrenia in rats also found that ketamine reduces the density of PNNs and the intensity of PNNs around dendrites of parvalbumin cells (Matuszko et al., 2017; Kaushik et al., 2021). However, ketamine administered to adolescent rats after experiencing stress in the study by Yu et al. (2022) increased PNN numbers and the density of PNNs surrounding PV neurons in the prelimbic region while promoting resilience to stress in behavioural tests. The increase in PNN outcomes in this study after ketamine administration is in opposition to that found in the other studies with antidepressants administered to stress naïve animals. As the PNN may not yet have reached peak numbers in the adolescent rat brain ketamine may be increasing PNN in compensation in order to facilitate the optimal functioning of the PV neurons in retaliation to the stressful experience. The other study by Alaiyed et al. (2020) that used mice that had endured a stress paradigm also showed VLX reduced anxiety-like behaviour while PNN intensity was reduced, albeit in the hippocampus. With regard to PNNs, the adolescent experience of stress may be mechanistically different to that of adults due to the developmental stages of PNN formation and the maturing of the PV neurons they encompass.

A reduction in PNN density or intensity in the adult would potentially lead to increased plasticity and adaptability allowing new pathways of resilience to form to cope with the experience of stress. Increases in PNN structures associate with inflexibility of connections and a locking in of established pathways which may be dysfunctional and maladaptive.

However, the majority of these studies were conducted in non-stressed animals and behavioural testing was not conducted. Without the validation of affective state from behavioural testing there can be no direct association between affective state and PNN outcomes. A more comprehensive examination of PNN measures paralleled with behavioural outcomes is needed to determine whether in fact PNNs play a role in the mechanism of antidepressants as these few studies may suggest.

4.6. Environmental Enrichment may mirror antidepressant effect – the impact on PNNs

Similar to the reductions seen in PNN measures from antidepressant administration, the one environmental enrichment study reviewed also saw a reduction in PNN measures (Foggetti et al., 2019). Environmental enrichment is associated with increases in positive affect (Brydges et al., 2011; Douglas et al., 2012) and can augment synaptic plasticity in key brain regions involved in cognition and emotional regulation (Kempermann, 2019). Positive affective state is challenging to define and validate especially in animals but is associated with beneficial effects in physiology, cognition, and immune response (Salovey et al., 2000). Determining a corroborative validation of positive affective state through molecular biomarkers and behavioural measures in animal models is an ongoing challenge within the research community (Boissy et al., 2007).

Although there was only one study where PNNs were measured in the context of environmental enrichment, there is the possibility that the mechanistic effect of antidepressants on PNNs has some similarity to that of inducing a positive affective state, ie. the induction of plasticity (Umemori et al., 2018). Antidepressants and environmental enrichment may both alter synaptic plasticity in the human brain, promoting positive behavioural change. Studies of PNN structural modifications across periods of EE or antidepressant administration may provide insight of shared neurobiological mechanisms between experiencing a positive affective state and the mechanism of SSRI antidepressants in alleviating depressive symptoms.

4.7. Degrading PNNs alters affective behaviour

The bacterial-derived enzyme chondroitinaseABC (ChABC) can be infused into specific brain regions to locally degrade PNNs. Simard et al. (2018) degraded PNNs in the PFC with ChABC after exposing mice to CVS and reported a reversal of the stress induced behaviours. However, Riga et al. (2017), found after an initial increase in PNNs in the dorsal hippocampus from the SDSP stress model, no significant change occurred in social approach-avoidance behaviour after ChABC infusion to the dHIP. These differential behavioural outcomes could be explained by the brain region where the PNNs were locally degraded. The mPFC is important in the regulation of emotional behaviour and emotions, whereas the hippocampal region is involved in memory and learning (Godsil et al., 2013). Removal of PNNs from areas of the PFC would be expected to increase plasticity and allow new synapses to form, possibly allowing emotional flexibility and adaptable cognitive pathways providing resilience to stress induction. However, PNN removal in the hippocampal region while allowing new connections for memory and learning (Fawcett et al., 2022) may not result in acute behavioural changes.

Degrading PNNs has been used in many studies to re-instate a juvenile-like developmental stage of PNN coverage and allow a return to enhanced plasticity as seen in the juvenile state (Pizzorusso et al., 2002; Lensjø et al., 2017). Administering ChABC before a stress paradigm would return the plasticity to that brain region enabling similar patterns of behaviour relating to depression and anxiety to those seen in the juveniles when exposed to the same stress paradigm. This was indeed the case in the studies of Smail et al. (2022) and Yu et al. (2022). Administering ChABC to the PFC and degrading PNNs in the regulatory region of emotional processing after a chronic stress paradigm may allow for a breakage in dysfunctional patterns of behaviour, enabling more flexibility of thought and adaptability in behaviour.

Other methods known to degrade PNNs are ketamine; used to degrade PNNs to achieve a rodent model of schizophrenia in studies by Matuszko et al. (2017) and Kaushik et al., (2020) and light entrainment using 60 Hz frequency which degraded PNNs in the V1 region

(Venturino et al., 2021).

4.8. Limitations and Future directions

As discussed in Scarlett et al., (2022), WFA staining alone for quantifying PNNs may not be revealing the whole and true story of PNNs as the WFA lectin preferentially stains PNNs with non-sulphated CS-GAG chains but not 4 and 6 chondroitin sulphate residues (Scarlett et al., 2022). Hartig et al., (2022) using the WFA lectin stain and CSPG aggrecan antibody showed limited overlap of stained PNNs between the two approaches (Härtig et al., 2022). Findings from studies that solely used WFA should be revaluated with this information. Furthermore, future studies should use WFA as well as antibody to PNN components such as aggrecan and antibodies selective to 4 or 6 CS for a more comprehensive understanding of PNN contribution.

Qualitative assessment of PNNs is a more recent look into how the morphology of the PNNs changes between treatments allowing insightful delving into the functionality of PNNs. The study by Kaushik et al., 2022 assessed number and area of PNN units (the holes in the PNN lattice with surrounding ECM) and found modifications between groups. This qualitative assessment of PNNs opens the field to new and exciting future measures to elucidate the functional roles of PNNs.

5. Conclusion

In conclusion, this scoping review has examined the intricate relationship between perineuronal net (PNN) characteristics and affective state valence. Through the analysis of diverse studies encompassing stress paradigms, antidepressant interventions, and environmental enrichment, insights into the potential role of PNNs in modulating affective behaviours have emerged. The findings presented herein suggest that PNNs exhibit a complex interplay with affective states, with varying outcomes dependent on factors such as developmental stage, brain region, and sex.

The reviewed studies indicate that stress-induced alterations in PNN characteristics may influence the behavioural response to stressors. The distinct patterns observed between developmental stages—adolescence and adulthood—underscore the significance of PNNs in shaping behavioural outcomes following stress exposure. Notably, stress during the juvenile and adolescent stages was associated with changes in PNN numbers and intensities, suggesting a potential impact on the developmental trajectory of inhibitory tone regulation and synaptic connectivity in later maturing brain regions. Conversely, stress experienced by adults correlated with increased PNN measures and depression-like symptoms, highlighting the potential role of PNNs in regulating synaptic plasticity and connectivity.

Studies examining antidepressant interventions and environmental enrichment both showed reductions in PNN measures. This convergence in outcomes suggests a potential shared mechanism underlying the improvements to affective states induced by these interventions. Furthermore, the study examining the enzymatic degradation of PNNs supported the notion that PNN alterations can influence affective behaviours, potentially by restoring plasticity and enabling adaptive responses to stress.

The present review underscores the need for further investigations that address key limitations and gaps in the current understanding of the relationship between PNNs and affective states. Future studies should explore the influence of factors such as sex, brain region specificity, and developmental stages in a unified framework. Conducting experiments that involve male and female animals across various life stages within the same study could provide more comprehensive insights into the impact of PNNs on affective behaviours. Additionally, examining the role of other neuronal subtypes and potential peripheral biomarkers of PNN integrity could enhance the mechanistic understanding.

To fully elucidate the role of PNNs in affective state regulation, future research should focus on conducting longitudinal studies that measure PNN outcomes alongside validated affective behavioural changes. Incorporating various stress paradigms, investigating the temporal nature of stress exposure, and assessing other biomarkers of affective state could provide a more nuanced understanding of the interactions between PNNs and affective behaviours.

In summary, this scoping review has shed light on the intricate associations between PNN characteristics and affective state valence. While the current evidence presents promising insights, further interdisciplinary investigations combining neurobiology, behaviour, and physiology are imperative to unravel the intricate mechanisms through which PNNs modulate affective behaviours. Such research endeavours hold the potential to pave the way for novel therapeutic interventions targeting PNNs to ameliorate affective disorders and enhance overall well-being.

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Data Availability

Data will be made available on request.

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None.

Declaration of Interest Statement

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.

Appendix

Searches were conducted in November 2021 and May 2023 using the following developed search strategy: (perineuronal nets or Perineuronal nets or PNN or PN or PNNs).mp. and ((affective state or cognitive bias* or Emotion* or Mood* or Negative affect* or Positive affect* or Well-being or well-being or welfare or judgement bias*).mp. or exp Emotions/ph or fear.mp. or depression.mp. or antidepressants.mp. or antidepressants.mp. or stress.mp. or enriched environment.mp. or novelty.mp.) and (Limbic.mp. or exp limbic system/ or PFC.mp. or mPFC.mp. or Prefrontal cortex.mp. or Amygdala.mp. or basolateral amygdala.mp. or infralimbic.mp. or prelimbic.mp. or pre-limbic.mp. or orbitofrontal.mp.).

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