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None declared.

Perineuronal net structure as a non-cellular mechanism of affective state, a scoping review

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Review question / Objective: Is the perineuronal net structure within emotional processing brain regions associated with changes in affective state? The objective of this scoping review is to bring together the literature on human and animal studies which have measured perineuronal net structure in brain regions associated with emotional processing (such as but not limited to amygdala, hippocampus and prefrontal cortex). Perineuronal nets are a specialised form of condensed extracellular matrix that enwrap and protect neurons (Suttkus et al., 2016), regulate synaptic plasticity (Celio and Blumcke, 1994) and ion homeostasis (Morawski et al., 2015). Perineuronal nets are dynamic structures that are influenced by external and internal environmental shifts – for example, increasing in intensity and number in response to stressors (Blanco and Conant, 2021) and pharmacological agents (Riga et al., 2017). This review's objective is to generate a compilation of existing knowledge regarding the structural changes of perineuronal nets in experimental studies that manipulate affective state, including those that alter environmental stressors. The outcomes will inform future research directions by elucidating non-cellular central nervous system mechanisms that underpin positive and negative emotional states. These methods may also be targets for manipulation to manage conditions of depression or promote wellbeing. Population: human and animal Condition: affective state as determined through validated behavioural assessment methods or established biomarkers. This includes both positive and negative affective states. Context: PNN structure, measuringPNNs.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 August 2021 and was last updated on 20 August 2021 (registration number INPLASY202180075).

INTRODUCTION

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Rationale: Depression affected 3.4% of the global population in 2018 (Ritchie and Roser, 2018). With the mental toll of lockdowns and uncertainty from the COVID-19 pandemic this number is expected to rise (Bueno-Notivol et al., 2021). Depression reduces quality of life and productivity in the workforce (Simon, 2003), and in extreme circumstances leads to suicide (Bertolote and Fleischmann, 2002). Treatments are anti-depressants and Cognitive Behaviour Therapy which are not effective for over 30% of sufferers (Gartlehner et al.,2011). Revealing underlying neurobiological mechanisms of affective states will enhance the discovery of biomarkers and therapeutic targets to aid identification and treatment of depression. In addition, animal welfare science is concerned with improving recognition of affective states in animals to provide optimal husbandry practices for promotion of wellbeing. This aids maintenance of a social license for a range of animal industries. Experiencing a positive affective state improves well-being (Fredrickson, 2001), immune responses (Lutgendorf and Costanzo, 2003), and increases resilience to stress (Rutten et al., 2013). An understanding of molecular changes occurring or responsible for negative and positive affective states may inform discovery of a biomarker to assess the emotional experience of the animal and allow inference of its welfare status. Perineuronal nets (PNNs) are a specialized form of extracellular matrix that surround subgroups of neurons. PNNs provide a controlled microenvironment around neurons, providing neuroprotection (Suttkus et al., 2016), synaptic plasticity (Celio and Blumcke, 1994) and ionic homeostasis (Morawski et al., 2015) to the neurons they enwrap (See Reichelt et al., 2019 for review). In the cortex, they mostly co-localise with inhibitory GABAergic interneurons that express parvalbumin (Balmer, 2016), which play key roles in the maturing prefrontal cortex and in cognitive control. Perineuronal nets reach peak density at the end of the adolescent critical period (Balmer et al., 2009) where they help to strengthen information processing pathways and lock in learned memories. This scoping review will investigate perineuronal net structure in brain regions associated with emotional processing under conditions of experiencing a negative or positive affective state. It is hypothesized that structural change informs functional change, such that PNN structural differences may reveal non-cellular neurobiological mechanisms underlying affective states.

Condition being studied: This review will include studies concerning affective state and interventions manipulating affective states. Affective state is the subjective experience of feeling the underlying emotion. Affective states are described in

terms of their valence or direction (negative or positive) and arousal (high or low). Affective state comprises the components of physiology, behaviour, and cognition among which there is an inter-related association. For example, smiling reduces negative thoughts. Affective state biases how environmental stimuli are sensed, perceived, interpreted, and which responses are given. Depression is an affective disorder that causes suffering for 3.4% of the global population (Ritchie and Roser, 2018). Depression is associated with altered decision making and maladaptive reward circuitry through inducing negative bias. Depression lowers quality of life and is often co-morbid with other pathological states and in severe cases can lead to suicide. The opposingly valenced affective state, being a positive affective state, is known to improve well-being (Fredrickson, 2001), immune response (Lutgendorf and Costanzo, 2003), and resilience to stress (Rutten et al., 2013). Animal welfare scientists are searching for biomarkers of positive affective state to inform best agricultural practice to maintain and improve standards of animal welfare.

METHODS

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 Wellbeing or well-being or welfare or judgement bias*).mp. or exp Emotions/ph or fear.mp. or depression.mp. or antidepressants.mp. or anti-depressants.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.).

Participant or population: Population includes both human and animal studies at all life stages including juvenile, adolescent and adult.

Intervention: The conditions considered for the review will be associated with affective state. These include studies of depression and depressive-like behaviour in animals, studies altering affective states through applying chemical, mechanical and psychosocial stress, and studies using environmental enrichment and novelty; plus other models/conditions considered relevant.

Comparator: Not applicable.

Study designs to be included: Inclusion criteria: Primary research articles. Any study design considered. Studies are likely to be controlled trials (animals) and observational designs for human studies. Exclusion criteria: Review articles, methods articles, news reports, conference abstracts.

Eligibility criteria: Population Inclusion criteria: Human and animal studies at juvenile, adolescence and adult lifestages. Exclusion criteria: Studies on populations with neuropsychotic disorders such as schizophrenia and bipolar disorder and developmental disorders such as autism, Fragile X and epilepsy or studies inducing models of these disorders. Conditions Inclusion criteria: Studies of affective state including depression and depressive-like behaviour, reward-seeking and fear; studies involving the use of anti-depressants, enriched environments or novelty. These are not exhaustive. Exclusion criteria: Studies involving neuropsychotic disorders such as schizophrenia and bipolar disorder and developmental disorders such as autism, Fragile X and epilepsy or studies inducing models of these disorders. Context Inclusion criteria: PNN structure (numbers, intensity, co-localisations - measured in affective state associated brain regions such as but not limited to amygdala, hippocampus and prefrontal cortex). Exclusion criteria: Any other parameters not directly related to PNNs.

Information sources: Information sources will include the electronic databases

Medline via OVID, Embase and PsychINFO via OVID.

Main outcome(s): The outcome of the review will be measures of perineuronal net numbers, intensity and co-localisation with parvalbumin interneurons and other neuron types within brain regions associated with affective state. These brain regions will include, but not limited to, limbic structures such as amygdala, hippocampus, and prefrontal cortex.

Data management: Following the search, all identified citations will be collated and uploaded into EndNoteX8.0.1 and duplicates removed. Potentially relevant studies will be retrieved in full and their citation details imported into Covidence (Veritas Health Innovation, Melbourne, Australia).Titles will be screened by one reviewer for assessment against the inclusion criteria for the review. Abstract and full text screening will be performed by two independent reviewers, with study inclusion needing to be certified by both reviewers. Disagreements between reviewers at each stage of the study selection process will be resolved through discussion with a third reviewer. Extraction will be performed using a modified version of the Covidence 2.0 data extraction template.

Quality assessment / Risk of bias analysis: Risk of bias determination is not usually required as part of a scoping review and will not be performed in this review.

Strategy of data synthesis: Data will be mapped for evidence of subgroups where there is logical linkage between studies- this may be based on valence of affective state, outcomes measures of affective state or brain region investigated. Data will be assimilated narratively and presented tabulated or graphically as appropriate.

Subgroup analysis: As a scoping review a meta-analysis in inappropriate.

Sensitivity analysis: N/A since no meta-analysis will be done.

Language: Only articles written in English will be considered.

Country(ies) involved: Australia.

Keywords: perineuronal nets; medial prefrontal cortex; amygdala; hippocampus; parvalbumin interneurons; depression.

Dissemination plans: This scoping review is intended for publication.

Contributions of each author:

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