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From early adversities to immune activation in psychiatric disorders: the role of the sympathetic nervous system

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Summary

Increased peripheral levels of cytokines and central microglial activation have been reported in patients with psychiatric disorders. The degree of both innate and adaptive immune activation is also associated with worse clinical outcomes and poor treatment response in these patients. Understanding the possible causes and mechanisms leading to this immune activation is therefore an important and necessary step for the development of novel and more effective treatment strategies for these patients. In this work, we review the evidence of literature pointing to childhood trauma as one of the main causes behind the increased immune activation in patients with psychiatric disorders. We then discuss the potential mechanisms linking the experience of early life adversity (ELA) to innate immune activation. Specifically, we focus on the innervation of the bone marrow from sympathetic nervous system (SNS) as a new and emerging mechanism that has the potential to bridge the observed increases in both central and peripheral inflammatory markers in patients exposed to ELA. Experimental studies in laboratory rodents suggest that SNS activation following early life stress exposure causes a shift in the profile of innate immune cells, with an increase in proinflammatory monocytes. In turn, these cells traffic to the brain and influence neural circuitry, which manifests as increased anxiety and other relevant behavioural phenotypes. To date, however, very few studies have been conducted to explore this candidate mechanism in humans. Future research is also needed to clarify whether these pathways could be partially reversible to improve prevention and treatment strategies in the future.

Keywords: depression, early adversity, inflammation, psychosis, sympathetic nervous system

Introduction

In the past two decades, converging lines of evidence from several studies suggest a role for activation and/or dysfunction of the immune system in the pathogenesis of major psychiatric disorders such as depression and psychotic disorders. Specifically, there is evidence for increased peripheral immune activation, typically characterized by elevations in the levels of circulating pro-inflammatory cytokines such as interleukin (IL)-6 or IL-1β. In addition, other inflammatory markers, such as C reactive protein (CRP) are also commonly increased in these patients. Finally, in both depression and psychotic disorder there is evidence from post-mortem brain tissue and *in-vivo* neuroimaging studies to suggest central microglia activation, the brain's resident innate immune cell, although these data are not unequivocal [1,2]. The increased innate immune activation in these patients may be of particular clinical relevance, based on the findings of our group and others that the degree of

immune activation, at least in terms of peripheral cytokines and CRP, is associated with more severe clinical symptoms, suicidal ideation and poor response to treatment [2–4].

In order to develop novel treatment and/or preventative measures for these patients, we need to understand more clearly what are the causes and potential mechanisms underlying the immune activation in patients with psychiatric disorders. In this review we seek to address this question by first reviewing the evidence that links the experience of traumatic and stressful events during childhood to innate immune activation and development of psychopathology in later life [1]. Childhood trauma is, unfortunately, highly prevalent in our society and one of the most widely recognized risk factors for development of psychiatric disorders later in life, including major depression, psychosis and post-traumatic stress disorder (PTSD) [5–7]. Research carried out in the past two decades has clearly identified a role for the activation of the immune system as a potential biological mechanism connecting childhood trauma and the subsequent development of psychopathology [8]. In the second part of this review, we focus on the emerging evidence for a role of the sympathetic nervous system (SNS) as one of the main mechanisms behind the link between early life adversities (ELA) and peripheral and central inflammation. With this critical overview, the paper shows and identifies necessary next steps for research in this field, to enable the future development of clinical preventative and treatment strategies in victims of childhood trauma.

Evidence for the association between ELA and activation of the innate immune system

Increased circulating cytokines and acute-phase proteins

The presence of increased immune activation in patients with psychiatric disorders across different diagnostic categories has generated increasing interest in unravelling causes behind this immune activation. In the context of peripheral immune activation, several clinical studies so far have shown that inflammatory markers, such as IL-6 and CRP, are particularly high in patients who had experienced childhood traumatic events, including physical or sexual abuse, emotional abuse or neglect that occur in childhood; this has been demonstrated in patients suffering with psychosis, major depression or bipolar disorder [9–13]. These primary research findings are supported by evidence from systematic reviews that provide evidence for prolonged peripheral inflammation following exposure to traumatic events in childhood [8,11,14]. Increased levels of other peripheral circulating inflammatory markers, such as the acute-phase protein CRP, are also widely reported in young children exposed to adverse psychosocial events [15,16]. Moreover, this initial early immune activation appears to persist and thus become chronic throughout adult life [14]. In a previous meta-analysis, we reported evidence to suggest that adult subjects with experience of childhood trauma have higher levels not only of CRP, but also of the major proinflammatory cytokines IL-6 and tumour necrosis factor (TNF)-α, when compared with adults without such experience [8].

One important point in this regard is that the magnitude of the increases in these inflammatory markers is not comparable to that found following acute infections. Rather, it more closely resembles a low-threshold, chronic inflammation, which is broadly comparable to detectable levels of these markers in patients with cardiovascular disease or rheumatoid arthritis. Although modest in terms of intensity, this persistent immune activation appears to be relevant for development of psychiatric disorders later in life. Specifically, data derived from longitudinal cohorts of children provide evidence for statistically significant associations between experiencing childhood traumatic events and increases in peripheral CRP levels, which are particularly pronounced in those individuals who later developed depression in adult life [17,18].

Circulating immune cell populations – evidence for changes in both innate and adaptive immunity following ELA exposure

In contrast to the wealth of data on circulating cytokines following early life trauma exposure, proportionally far fewer studies have directly investigated the effects of exposure to childhood adversities on circulating immune cell populations using, for example, fluorescence activated cell sorting (FACS). In adolescents who experienced early life stress compared to those without such experience, do Prado and colleagues reported increases in circulating T cells expressing the activation markers $CD2^+/CD4^+/CD25^+$ and $CD3^+/CD69^+$, but also an increase in senescent T cells ($CD8^+/CD28^-$ and $CD4^+/CD28^-$ cells) [19]. These changes were further accompanied by decreased percentages of natural killer (NK; $CD3^-/CD56^+$) and NK T cells ($CD3^+/CD56^+$) [19]. Comparing individuals separated from their mothers in early life to those reared by their parents, Elwenspoek and colleagues also reported increased T cell senescence ($CD57^+$ cells) [20]. In another FACS study from this group, comparing individuals with a history of ELA to those without, a reduction in the numbers of $CD69^+/CD8^+$ T cells and increased numbers of human leucocyte antigen D-related $HLA\text{-}DR^+/CD4^+$, $HLA\text{-}DR^+/CD8^+$ and $CD25^+/CD8^+$ T cells was reported [21].

Collectively, these results suggest that ELA exposure is associated with a sustained activation of adaptive immunity and accelerated immune ageing, as indexed by the increase in T cell senescence. These effects appeared to be independent of either stress or health-risk behaviours, suggestive of a primary effect of early life programming on specific immune cell populations [20–22]. Exploring how social adversity may affect peripheral immune cells, Counotte *et al*. observed that individuals with high clinical risk for psychosis who were exposed to ELA were characterized by an increased number of $CD4^+$ T helper type 17 (Th17) cells when compared with those at lower risk [23]. There were also significant predictive relationships between increased numbers of T regulatory (T_{reg}) cells and decreased NK cell numbers, with the increased degree of stress experienced during exposure to virtual social stressors [23]. If and how these different associations fit together still needs to be elucidated. Other studies characterizing the effects of social adversities on peripheral leucocyte populations have mainly identified increases in circulating monocytes and dendritic cells (DCs) following exposure to traumatic experiences in early life [24,25]. Furthermore, Schwaiger and colleagues identified an altered stress-induced gene expression in $CD14^+$ monocytes of adults with history of childhood trauma; the differences were particularly linked to the expression of genes involved in steroid hormone activity and signal transduction which were, in turn, associated with increased activity of pro-inflammatory signalling upstream [26].

These clinical data are supported by a large body of evidence from preclinical studies in adult mice exposed to repeated social defeat (RSD), which results in a significant accumulation of neutrophils and $CD11b^+LyC6^{high}$ monocytes in both the circulation and spleen [27,28]. Splenic DCs from mice exposed to RSD also have increased surface expression of major histocompatibility complex (MHC) class I, CD80 and CD44, indicative of an activated state [29]. It should also be noted, however, that CD44 is commonly used as a T cell activation marker [29]. Furthermore, following *in-vitro* stimulation, these cells display an up-regulated proinflammatory gene expression signature and produce comparatively higher levels of pro- and anti-inflammatory cytokines, including IL-6, TNF-α and IL-10 [29]. Extending these findings, exposure to RSD in mice and low socio-economic status (SES) in humans results in a relative expansion of a transcriptional profile associated with immature proinflammatory monocytes in peripheral blood mononuclear cells (PMBCs) [30]. This is characterized (at least in the mouse) by increased activity of transcription factors that regulate both differentiation to the myeloid lineage and also the proinflammatory effector functions of these cells, such as PU.1 [30]. In addition, exposure to RSD in mice results in increased formation of $Ly6C^{high}$ monocytes, which could be prevented using β-adrenoreceptor antagonists [30]. Collectively, these data suggest a role for the sympathetic nervous system driving, at least in part, up-regulation of myelopoiesis, characterized by a proinflammatory state which we will return to later in this review [30]. Data on the effects of social stress on adaptive immunity in preclinical models are less developed, although there are data suggesting a reduction in the numbers of T cells in the circulation and spleen [27,28], which is at odds with some of the aforementioned clinical findings. Conversely, RSD is reported to result in enhanced $CD4^+$ and $CD8^+$ memory T cell responses when this stress is experienced before a viral infection [31–33]. These data suggest a view that exposure to RSD in adult mice may significantly enhance virus-specific immune memory through the augmentation of specific memory T cell populations [31–33]. Interestingly, using a mediation analysis, Elwenspoek and colleagues found that cytomegalovirus (CMV) infection largely explained the increase in T cell senescence markers ($CD57^+$) following ELA exposure, suggesting that viral infections may affect T cell populations in humans following ELA exposure [20]. When comparing these data it should be remembered that the great majority of preclinical studies that have characterized the peripheral immune response to stress exposure have primarily focused on the effects of repeated RSD exposure in adult animals. Detailed peripheral immunophenotyping data regarding the specific effects of early life stress in preclinical models is, however, currently lacking. Another important point is that the effects of any experimental stress paradigm in animals may have both common and distinct effects on the immune system, depending on the nature and duration of the stressor [34–36]. In this context, preclinical studies could be immensely valuable, as they allow the experimenter to probe the effects of different types of early life stress with a precise control of genetic and other environmental variables, something that is very challenging in humans. Preclinical studies therefore have the clear potential to help dissect the specific peripheral immune cell responses associated with exposure to different stressors at different vulnerable periods from the prenatal period, throughout early postnatal life and into adolescence.

Overall, the evidence from the few studies available suggests that ELA exposure is associated with: (1) direct programming of innate and adaptive immune cell function; (2) increased numbers of circulating innate and adaptive immune cells with a proinflammatory phenotype, a finding consistent with the elevation in circulating pro-inflammatory cytokines and acute-phase proteins in those exposed to ELA; and (3) accelerated immune ageing, as indicated by T cell senescence. What remains unclear from these data is whether these peripheral changes are

related to central immune activation. Here again, studies of preclinical models of stress exposure are vital, as they permit invasive assessments in both the brain and periphery to aid dissection of the mechanisms governing immune-to-brain communication and vice versa [37,38]. However, in addressing this question, we must first consider the clinical evidence base for central immune activation as a function of ELA exposure.

Central immune activation following ELA exposure

Assessment of central immune activation in clinical samples is typically achieved through post-mortem neuropathological assessment at either the cellular or molecular level or *in vivo*, using positron emission tomography (PET) combined with selective radioligands for the translocator protein (TSPO) comparing patient groups with healthy age- and sex-matched controls [37]. Searching the extant literature, we found only one TSPO PET study which had tested for an association between psychosocial risk factors for psychosis, including childhood trauma and central TSPO radioligand binding. Dahoun and colleagues [39] measured TSPO binding in a small sample of healthy individuals who were classified into two groups on the basis of exposure to psychosocial risk (high-risk group; $n = 12$) or no significant exposure to psychosocial risk (low-risk group; $n = 12$). However, there were no significant group differences in TSPO volume of distribution (V_T) in either total grey matter or the frontal, parietal, temporal and occipital lobes [39]. At first glance, these data are not consistent with the hypothesis that exposure to stress and/or ELA is associated with increased central microglial activation. It should be noted however, that these were healthy individuals without a psychiatric diagnosis, raising the possibility that the 'high-risk' group in this case are a resilient group in whom putative central microglial activation may not be seen [39]. Moreover, although some of the stressors assessed in these individuals occurred recently, there was a temporal separation between stress exposure and TSPO PET imaging. Hence, it remains possible that acute stress exposure could be associated with increased TSPO, which may normalize over time [39]. Further studies are clearly required to address these issues and explore in more detail the effect of ELA on central TSPO binding in both preclinical models and clinical populations. In contrast, several TSPO PET studies have been conducted to search for any evidence of central immune activation in the psychiatric disorders for which ELA is a known risk factor, such as schizophrenia and depression. The data published so far suggest that there is evidence for putative central innate immune activation associated with psychiatric disorders for which ELA exposure is a known risk factor [37], but evidence for specific effects of ELA on central immune cells in humans is currently lacking. Hence, to address this question, we must consider the evidence from preclinical rodent models of ELA exposure.

Exposing rodents or non-human primates to early life stress increases anxiety-like behaviours and impairs cognitive function in adulthood, suggesting that animal models may provide important insights into the effects of ELA in humans [40–42]. As already mentioned, it should be remembered when comparing data from preclinical models to clinical studies that the effects of any experimental stress paradigm in animals may have both common and distinct effects on the immune system, depending on the nature and duration of the stressor. This is no less true for central immune activation following stress exposure in rodents [36,37]. Interestingly, genetically controlled depletion of brain microglia in healthy rodents in early life is associated with abnormal social and motivated behaviour in a sex-specific manner, strongly implying that microglia play a role in the early life programming of behaviour [43,44]. With regard to the evidence that early life stress exposure influences central microglia, several preclinical studies in different early life stress models provide converging lines of evidence for increased innate immune activation in the central nervous system (CNS). Prenatal stress exposure, induced by exposing pregnant rat dams to restraint or other physical stressors, is reported to increase the number of $Iba1^+/CD68^+$ microglia, coupled with a shift in their morphology to an activated, amoeboid state and decreased process motility, as well as increasing proinflammatory cytokine expression in the brains of the affected offspring early in postnatal life primarily (but not exclusively) in the hippocampus, amygdala and prefrontal cortex [45–54]. None of these studies, however, have investigated the effects of ELA exposure on TSPO binding, limiting cross-species comparisons to humans. At the molecular level, Delpech and colleagues have examined the effect of brief daily separation (BDS) stress on the microglial transcriptome in the affected offspring, providing evidence that this early life stress actually perturbs the normal functional development of microglia in the developing hippocampus, with these cells displaying increased phagocytic activity and reduced expression of genes that normally increase across development [55]. It is increasingly appreciated that microglia cells play critical roles in shaping the processes of synaptic maturation and axonal guidance in the developing and maturing rodent brain [56–64]. Hence, any stress-induced perturbation of microglial physiology during these critical developmental windows would be predicted to result in the defective maturation of neural circuits [56,57,65]. This could have long-lasting consequences on synaptic

function and may be another mechanism whereby activation of central innate immunity after ELA exposure may directly increase the vulnerability to develop psychopathology in later life. These cells may also play a role in central to peripheral immune communication, as we discuss in the next section.

How does ELA lead to immune activation?

Although both clinical and preclinical studies provide converging lines of evidence for both central and peripheral immune activation following ELA exposure (notably for both innate and adaptive immunity), a critical question remains as to how ELA exposure specifically triggers both central and peripheral inflammation. Although the precise mechanisms by which peripheral immunity may influence central immunity and neuronal function (and vice versa) remain largely unknown, a number of interesting candidate mechanisms have been advanced. These include: (1) the development of glucocorticoid resistance and therefore an impairment in the anti-inflammatory action of glucocorticoids; (2) activation of the SNS; (3) a change in the composition of gut microbiota; (4) exposure to physical injuries or infection as part of the early life trauma; and (5) behavioural mechanisms, including obesity, alcohol consumption and poor sleep, which may themselves promote immune activation [66]. For the purposes of this concise review, we will focus on the link between SNS activation in response to stress exposure and immune activation, for which there is a recent increasing body of evidence [67].

The role of the SNS in the link between early adversities and immune activation

The SNS is one of the main biological systems involved in the stress response. Its activation also results in a cascade of signals that affect the regulation of the innate immune system, which occurs in a cell-state and organ-specific manner. Of particular interest is the bone marrow (BM), which is densely innervated by the SNS [68]. Activation of the SNS in response to stress, for example, leads to the production and release of noradrenaline (NA), which binds to β-adrenergic (βAR) and α-adrenergic (αAR) receptors expressed on peripheral immune cell populations in both rodents and humans [68,69]. Preclinical studies in animals show that SNS activation and NA production triggers the release of monocytes into the circulation, which can be modulated pharmacologically by systemic administration of either a β_2AR agonist (increase) or βAR antagonist (decrease) [27,30,32]. Increased numbers of circulating monocytes is also correlated with oscillations in SNS tone as a function of circadian rhythm [70] and can occur following other forms of SNS stimuli, such as exercise [71]. These observations are also true for lymphocytes, with exposure to acute stress in humans resulting in mobilization of total monocytes and lymphocytes and $CD8^+$ T lymphocytes [71]. NA released during SNS activation may, however, lead to different immunomodulatory effects, depending on the cell type, state and organ involved. For example, Case and Zimmerman [72] propose a model in which NA release can have a suppressive effect on naive T lymphocytes in lymphoid organs such as the spleen, but in other regions, such as the vasculature and renal system, NA may drive the activation of proinflammatory Th17 T lymphocytes.

Taken together, the aforementioned lines of evidence clearly show that SNS activation is well placed to mediate both innate and adaptive immunity and brain–immune communication across species. There are no studies in healthy humans, either alone or in comparison to clinical populations, that provide direct evidence for a link between ELA exposure, SNS activation and elevated peripheral and central immunity, beyond the observations that stress-exposed individuals who have developed psychopathology have elevated numbers of circulating proinflammatory monocytes and lymphocytes – as already evidenced in this review. Here, again, we must therefore turn to preclinical studies in rodent models to dissect this mechanism.

As already stated, the SNS innervates peripheral lymphoid tissues including the spleen and bone marrow. Preclinical data suggest that chronic stress exposure is associated with a decrease in expression of the chemokine CXCL12 in the haematopoietic stem cell niche which, in turn, accelerates proliferation of haematopoietic stem cells resulting in enhanced production of neutrophils and monocytes [73]. Increases in SNS outflow and NA release following RDS exposure also drives mobilization of lymphocytes from the murine spleen and bone marrow, which then enter the circulation [27,28,30,32,71,74,75]. These data are consistent with the aforementioned findings in humans of increased number of leucocytes in the circulation of individuals with stress-related psychiatric disorders [76], and the aforementioned studies reported increases in these cells in the circulation of individuals exposed to ELA. The specific contribution of the rodent models, however, has been to elegantly demonstrate a potential connection between central and peripheral immunity, which highlights the involvement of the SNS. Specifically, RDS in adult mice increases neural activation (indexed by increased immunostaining for the immediate early gene c-Fos) in mouse brain regions that regulate fear and threat sensing, such as the amygdala which, in turn, is associated with both social avoidance and anxiety-like behaviour that is sensitive to βAR

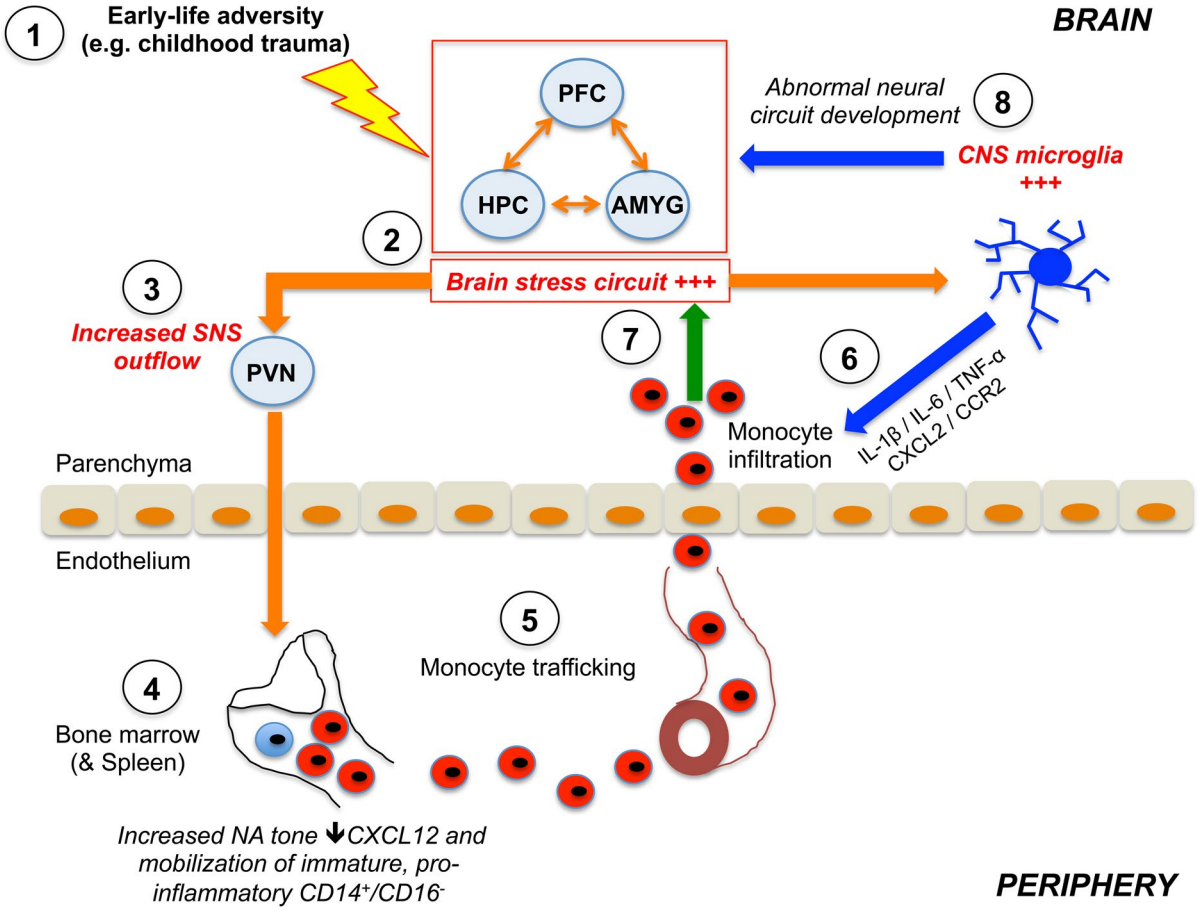

Fig. 1. A schematic representation of how early life adversities may contribute to peripheral and central immune activation through activation of the sympathetic nervous system (SNS). Orange arrows indicate neural pathways, blue indicate central microglial effects and green the influence of peripheral monocytes. (1) Exposure to early life adversity (ELA) such as childhood trauma results in (2) activation of the brain stress circuitry and (3) increased outflow of the sympathetic nervous system to the bone marrow with increased noradrenaline (NA) release. (4) This decreases the expression of the chemokine CXCL12 in the bone marrow haematopoietic stem cell niche, which accelerates proliferation of haematopoietic stem cells resulting in enhanced production of proinflammatory $CD14^+/CD16^-$ monocytes, which are released into circulation and (5) traffic to the blood–brain barrier through the vasculature. (6) At the same time, central microglial cells are also activated in response to neural cues as a result of stress circuit activation. These cells facilitate the infiltration of the peripheral monocytes through secretion of specific cytokines and chemokines, which modulate endothelial cell permeability and allow ingress of the monocytes from the vasculature to the perivascular space and the brain parenchyma. (7) The infiltrating proinflammatory monocytes lead to further sustained activation of neural stress circuits, resulting in the emergence of abnormal behaviour. (8) In parallel, ELA exposure may also influence the development and function of central microglia. Converging lines of evidence suggest that microglia play key roles in shaping the development of the brain including the formation and pruning of dendritic spines and synapses. Hence, any disruption of this process following stress exposure in early life may result in the abnormal neural circuit development which, by itself, may predispose an individual to psychopathology in later life. PFC = prefrontal cortex; AMYG = amygdala; HPC = hippocampus; SNS = sympathetic nervous system.

antagonism, suggesting SNS involvement downstream of the activation of neural stress circuitry [75]. In parallel to this increased neural activity, RDS results in central microglial activation, with increased density of amoeboid microglia in the amygdala, PFC and hippocampus, with higher surface expression of CD68, CD14 and Toll-like receptor (TLR)-4 and increased expression of both IL-1β and glucocorticoid-responsive genes (e.g. FKBP5) in these microglia, indicative of activation [67,74,75,77,78]. Moreover, $CD11b^+CD45^{high}Ly6C^{high}$ macrophages are increased in the circulation, but also trafficked into the mouse brain, where they express higher amounts of IL-1β and adopt a proinflammatory phenotype (see Fig. 1) [67,74,75,77,78]. These effects are dependent on βAR, as they may be blocked by propranolol (a βAR antagonist), suggestive of a role for SNS activation in the initial

mobilization of the monocytes [75]. Consistent with this view, the trafficking of monocytes from the spleen to the brain is necessary for the re-establishment of anxiety in stress-sensitized mice, and this also occurs downstream of SNS activation [74,79]. Depletion of central microglia also prevents monocyte trafficking to the brain and blocks the development of anxiety behaviour following repeated RDS exposure [77]. These data suggest a model in which stress exposure results in elevated neural activity in stress circuits, leading to increased SNS outflow. The former triggers a microglial response, the latter triggers the mobilization of proinflammatory monocyte-derived macrophages, which subsequently traffic to the brain in a CCR2- and IL-1β-dependent manner, involving communication between central microglia and the endothelial cells of the blood–brain barrier [38,67,80,81]. These elegant studies demonstrate a potential pathway by which SNS activation is a key part of a larger multi-faceted interaction between central neural activity in specific circuits, central microglial activation and mobilization of peripheral immunity, which then traffics to the brain to close the loop by influencing neural dynamics in the same circuits, promoting the emergence of anxiety-like phenotypes.

It is worth emphasizing again that this model has been developed based on experiments conducted in adult animals and in the context of the RDS paradigm. Hence, two important preclinical extensions of this work are necessary: first, to confirm whether this mechanism is necessary and sufficient for the development of abnormal behaviour (such as anxiety) following exposure to other types of stressor, including social isolation (SI), repeated social defeat stress (RSDS) or chronic unpredictable mild stress (CUMS). In this context, exposure to chronic variable stress is reported to increase $Lin^{-}Sca\text{-}1^{+}c\text{-}Kit^{+}$ haematopoietic stem cells in the BM [73]. Moreover, in mice susceptible to RSDS, elevated peripheral IL-6 and increased circulating proinflammatory $Ly6C^{high}$ monocytes are reported, which also traffic to the perivascular space to increase central IL-6 leading to depressive-like behaviour [80]. Lastly, as already described herein, there is also evidence for central microglial activation in several animal models of early life stress, although forward translation of this evidence to humans using TSPO binding for example is currently lacking [39]. These data may suggest that there are indeed common mechanisms across different stress exposures, but further work is needed in this respect to clarify this mechanistically. Secondly, studies in the pre-, perinatal and adolescent period are necessary to directly test if the model proposed from adult animals contributes to the association between ELA exposure and psychopathology in later life. It is worth recalling here that microglia depletion by itself in this period (without stress exposure) was sufficient to induce long-term emotional behavioural changes in mice [43]. Moreover, molecular studies suggest that microglia development may be abnormal following ELA exposure, perhaps indicative of later loss-of-function or reduced flexibility of these cells [55,82]. Hence, the relationships between neural circuit activity central and peripheral immunity may differ in the developing compared to the adult brain, which requires investigation [82,83].

From the clinical perspective, direct evidence for involvement of the SNS *per se* following ELA exposure still needs to be provided. Indeed, the evidence supporting the link between childhood trauma, for example, and hyperactivation of the SNS in humans, is conflicting, with some studies reporting an increased reactivity of SNS following high levels of family adversities, while others find no such association [84]. For example, no study has so far investigated immune markers together with markers of SNS activation in individuals with experience of childhood trauma compared with relevant controls. This would be an extremely important step to understand if the immune activation is found mainly in those who present an enhanced reactivity of the SNS.

Conclusions

In conclusion, increasing evidence points towards a fundamental role of ELA exposure in the activation of both innate and adaptive arms of the immune system in patients with psychiatric disorders. The SNS appears to play a central role in this link by increasing the activation of T cells and shifting the differentiation of haematopoietic stem cells in the bone marrow to proinflammatory monocytes, with elevated expression of proinflammatory molecules. Preclinical studies in adult animals suggest that trafficking of peripheral immune cells to the brain is an important mechanism for the development of anxiety following stress exposure. We highlight an important lack of studies addressing these issues, insofar as it is possible to do so in human samples, but also the lack of detailed work on these potential mechanisms which link central and peripheral immunity following early life stress exposure in preclinical models. Future studies to address these questions have the potential to identify molecular targets and time windows of opportunity for both prevention and treatment strategies to ameliorate the devastating long-term effects of ELA on mental health.

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