Enduring neuroimmunological consequences of developmental experiences: from vulnerability to resilience

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Highlights

- The immune system is essential for development and function of the central nervous system (neuroimmune system)
- Environmental experiences can permanently alter neuroimmune function and associated brain development
- Dysregulation of the neuroimmune system following negative experiences during development may play a role in the aetiology of psychiatric illnesses
- Positive experiences can promote resilience and rescue the effects of negative experiences on the neuroimmune system
- The neuroimmune system is therefore a viable therapeutic target for preventing and treating psychiatric illnesses

Abstract

The immune system is crucial for normal neuronal development and function (neuroimmune system). Both immune and neuronal systems undergo significant postnatal development and are sensitive to developmental programming by environmental experiences. Negative experiences from infection to psychological stress at a range of different time points (in utero to adolescence) can permanently alter the function of the neuroimmune system: given its prominent role in normal brain development and function this dysregulation may increase vulnerability to psychiatric illness. In contrast, positive experiences such as exercise and environmental enrichment are protective and can promote resilience, even restoring the detrimental effects of negative experiences on the neuroimmune system. This suggests the neuroimmune system is a viable therapeutic target for treatment and prevention of psychiatric illnesses, especially those related to stress. In this review we will summarise the main cells, molecules and functions of the immune system in general and with specific reference to central nervous system development and function. We will then discuss the effects of negative and positive environmental experiences, especially during development, in programming the long-term functioning of the neuroimmune system. Finally, we will review the sparse but growing literature on sex differences in neuroimmune development and response to environmental experiences.

Keywords

Neuroimmune system; environment; developmental stress; enrichment; psychiatric illness; sex differences

Introduction

Developmental adversity & psychiatric illness

The environment can have a profound impact on brain development, conferring risk or resilience to psychiatric illness. Several meta analyses demonstrate that adverse experiences during development significantly increase the risk of developing neuropsychiatric disorders in adulthood (Lupien et al., 2009; Teicher and Samson, 2016). It is important to note that not all exposed individuals develop illness – some people demonstrate resilience due to genetics and positive environmental influences, such as high family functioning, close parental monitoring and good social support (Assary et al., 2018; Fritz et al., 2018; Tiet et al., 1998; Wang et al., 2018a; Xie et al., 2010). Research in human populations is confounded by difficulty in disentangling cause and effect, genetic factors and inaccessibility of brain tissue. Animal models circumnavigate these difficulties and support these findings, giving deeper insight into the molecular mechanisms governing susceptibility and resilience. Here we find that stress during development is typically detrimental for cognition, behaviour, neural plasticity and neurogenesis, whereas positive experiences such as exercise and environmental enrichment are beneficial (Lupien et al., 2009). The underlying mechanisms governing these relationships are not fully understood, but recent research reveals that the neuroimmune system plays a role and may be a viable therapeutic target (Nusslock and Miller, 2016). We will explore these topics, summarising recent advances in the impact of developmental experiences on vulnerability and resilience to psychiatric disorders via the neuroimmune system. We begin with an overview of the immune system, focussing on peripheral then central functions. Not all components of the immune system have been explored in the context of developmental experiences, but we provide this overview in the hope that it may inspire future areas of research.

The immune system

Innate vs. adaptive

Immune function in vertebrates is broadly classified into innate and adaptive. The innate immune system is a biologically ancient host defence strategy, which in modern vertebrates still provides a broad, rapid and essential line of defence against pathogens (Gasteiger et al., 2017; Turvey and Broide, 2010). Activation is dependent upon the recognition of pathogen-associated molecular patterns such as bacterial lipopolysaccharides (LPSs) and bacterial flagellin by toll-like receptors (TLRs) on various cells of the host immune system, and also by components of the complement system (part of the host immune system that enhances or complements other immune functions) (Boehme and Compton, 2004; Dunkelberger and Song, 2010; Pandey et al., 2015). Activation of these pattern recognition receptors triggers an array of downstream events including the production of cytokines (key signalling molecules of the immune system) and phagocytosis of the pathogen (Amarante-Mendes et al., 2018; Takeuchi and Akira, 2010). The adaptive immune system also recognises molecular signatures of foreign pathogens, but unlike the innate system generates highly specific antibodies to detect these antigens, taking longer to mount a defensive response (Chaplin, 2010). Antibodies are generated by B lymphocytes following the presentation of an immunogen by antigen presentation cells and are highly specific to the presented antigen (Tarlinton, 2019). These antibodies activate the complement system and opsonise (the coating of a body to facilitate phagocytosis), agglutinate and neutralise infecting pathogens (Dunkelberger and Song, 2010; Forthal, 2014). Presented antigens are also recognised by T cell receptors on T lymphocytes: this induces T lymphocyte maturation and subsequent production of cytokines and recruitment of additional lymphocytes and macrophages (effector cells of the innate immune system) (Kumar et al., 2018; Reinherz and Schlossman, 1980). There is overwhelming evidence that

both innate and adaptive immune systems play a key role in normal brain development and function, an intrinsic role not triggered by pathogens (Lenz and Nelson, 2018; Miller et al., 2017; Morimoto and Nakajima, 2019).

In practise the innate and adaptive immune systems complement each other and significantly overlap in their molecular pathways, the cells involved, cytokines generated and their effector functions (Clark and Kupper, 2005). We will now summarise the main cells and components of the peripheral immune system, before moving onto those found centrally, with a specific focus on the role of the immune system in normal brain development and function.

Cells of the immune system

A diverse array of cells and signalling molecules are involved in innate and adaptive immune responses. Cells of the innate immune system include macrophages, dendritic cells, mast cells, neutrophils, natural killer cells (NKCs), basophils and eosinophils (Medina, 2016). These cells originate from multipotent hematopoietic stem cells in the bone marrow, and some are released into circulation in a terminally differentiated form whereas others complete their differentiation in a wide array of target tissues (Medina, 2016) (Figure 1). The adaptive immune system comprises B and T lymphocytes which also derive from hematopoietic stem cells in the bone marrow and are further subdivided based on their function (Figure 1).

Immune system signalling

Cytokines are a broad category of small molecules which include interferons (IFN), interleukins (IL), chemokines and tumour necrosis factors, and they provide the primary source of signalling for the immune system (Turner et al., 2014; Zhang and Jianxiong, 2007). **Interferons** are released by eukaryotic cells in response to viral infection, and disrupt viral

139 replication, promote antigen presentation and activate macrophages and NKCs (Fensterl and
140 Sen, 2009; Le Page et al., 2000). **Interleukins** have a wide range of functions, are broadly
141 classified as either pro- or anti-inflammatory and are secreted by virtually all cells of the
142 immune system (Cuneo and Autieri, 2009). The more than 50 interleukins and associated
143 proteins bind to either type 1 or 2 interleukin receptors with downstream effector functions
144 including immune cell activation, maturation and proliferation (Akdis, 2011). **Chemokines** are
145 divided into 4 sub-families based on number and spacing of cytosine residues: CXC, CC,
146 CX3C and XC, all signal through G-protein coupled receptors and primarily coordinate the
147 immune response, attracting immune cells to sites of inflammation (Hughes and Nibbs, 2018;
148 Moser and Willimann, 2004; Poeta et al., 2019). **Tumour necrosis factors** (TNFs) are
149 transmembrane proteins, when cleaved they function as signalling molecules and bind to
150 members of the TNF receptor superfamily. Activation of TNF receptors promotes
151 inflammation, T lymphocyte regulation, apoptosis and immune cell activation (Baud and
152 Karin, 2001; Tracey and Cerami, 1994).

153 In addition to cytokines there are several other classes of signalling molecules involved
154 in the coordination of the immune response. **Complement proteins** are secreted by hepatocytes
155 in the liver and nearly all cell types in the central nervous system (CNS) (Orsini et al., 2014;
156 Zhou et al., 2016). The cleavage of complement cascade proteins generates fragments which
157 act as signalling molecules (Janeway et al., 2001). Fragments Complement component C3a
158 (C3a) and C5a bind to their receptors (C3aR and C5aR) on immune cells and tissue specific-
159 cells (e.g. neurons and renal cells), inducing the release of pro-inflammatory cytokines and the
160 accumulation of macrophages (Peng et al., 2012; Schraufstatter et al., 2002; Strainic et al.,
161 2008). Complement activation also generates the opsonin complement component C3b (C3b),
162 which tags cells for phagocytosis by macrophages (Lewis et al., 2008; Tausk and Gigli, 1990).
163 **Prostaglandins** are a family of fatty acid signalling molecules produced in almost all nucleated

cells and are generated from the metabolism of arachidonic acid by cyclooxygenases. Along with many non-immunological functions prostaglandins promote and regulate immune activation (Aoki and Narumiya, 2012; Ricciotti and FitzGerald, 2011; Scher and Pillinger, 2009). **Granule proteins** are cytotoxic proteins released by a subset of leukocytes (eosinophils) which disrupt lipid bilayers, degrade ribonucleic acid and generate reactive oxygen species (Acharya and Ackerman, 2014). Some granule proteins (major basic protein) induce the release of histamine from basophils and mast cells, and histamine is both a neurotransmitter and a potent activator and regulator of inflammation via histamine receptor 1 (Branco et al., 2018). Serotonin, another neurotransmitter, is produced by T lymphocytes and mast cells, and acts as a chemoattractant and a regulator of immune cell activation and proliferation (EugenOlsen et al., 1997; Herr et al., 2017; Roumier et al., 2019).

We will now explore the role that the immune system plays in normal brain development and function, exploring the interplay between peripheral and central mechanisms, before discussing how developmental experiences can perturb this normal functioning.

The neuroimmune environment

Immunological communication between peripheral and central nervous systems

Contrary to the traditional view of the brain being immune privileged, we now know there are considerable levels of immunological communication between the periphery and CNS (Lampron et al., 2013). Sickness behaviour is a classic example of this relationship, and is conserved across multiple species including humans and rodents. Here, activation of the immune system affects neuronal function in the brain, resulting in a specific collection of sickness behaviours. These include reduced activity, social interaction and sexual activity and increased responsiveness to pain, anorexia and depressed mood (Dantzer, 2009). This benefits

188 the infected individual by minimising energy expenditure, limiting exposure to predators and
189 allowing successful recovery from infection. The generation of proinflammatory cytokines
190 such as interleukin 1β (IL1-β), tumour necrosis factor α (TNFα) and interleukin 6 (IL-6) by
191 macrophages, B and T lymphocytes in the periphery drives these behaviours via two pathways
192 termed fast and slow transmission (Figure 2) (Dantzer, 2001; Heesen et al., 2006). Fast
193 transmission occurs via primary afferent nerves surrounding the point of inflammation, where
194 inflammation triggers action potentials which are relayed to the CNS (Breit et al., 2018;
195 Johnston and Webster, 2009). Slow transmission relies upon the volume diffusion of cytokines
196 including IL1-β and TNFα into the brain parenchyma through the circumventricular organs,
197 the endothelial cells of the blood-brain-barrier (BBB) and choroid plexus (Abbott et al., 2006;
198 Banks, 2005; Breit et al., 2018; Johnson et al., 2019).

199 We now know there are several mechanisms through which peripheral immune
200 molecules can influence the healthy brain (Figure 2). There is regulated transport of certain
201 cytokines and chemokines across the BBB, and immune cells can interact with endothelial cells
202 of the BBB, creating a cascade of effects in the brain (Banks, 2005; Daneman and Prat, 2015;
203 Pan and Kastin, 2002). The lymphatic drainage systems of the brain (perivascular drainage,
204 glymphatic system and meningeal lymphatic vessels) functions to clear waste from the CNS,
205 transport lipids, maintain interstitial fluid water and ion homeostasis, regulate cerebrospinal
206 ~~(CSF)~~ fluid and ~~ISF~~ interstitial fluid pressure and provides a link between the peripheral
207 immune system and the CNS (Begley, 2012; Benveniste, 2018; Kipnis, 2016; Makinen, 2019;
208 Sun et al., 2018; Thrane et al., 2013). Here, T lymphocytes can enter the brain via
209 leptomeningeal vessels, choroid plexus and parenchymal postcapillary venule (efferent
210 pathway) (Mastorakos and McGavern, 2019). Signalling works both ways - CNS derived
211 antigens present in cerebrospinal fluid and interstitial fluid ~~ISF~~ draining into cervical lymph
212 nodes activate the peripheral immune system, driving recruitment of immune cells to the CNS

(afferent pathway). The enteric nervous system (autonomic nerves of the gastrointestinal tract) and gut flora represent an additional link between the peripheral immune system and the CNS (Figure 2). Both enteric system neurons and intestinal bacteria produce neuroactive molecules including acetylcholine, histamine and serotonin, enabling communication between the intestines and the brain (gut-brain axis), and this can influence neural development, cognition and behaviour (Foster and Neufeld, 2014; Rogers et al., 2016). This communication is modulated by shifts in diet, composition of the microbiome and gut inflammation (Foster and Neufeld, 2014; Mayer et al., 2015). This crosstalk is required to sustain a variety of homeostatic functions such as the cephalic response (gastric secretion in response to the anticipation of food) in addition to the coordination of a body wide response to infection (Smeets et al., 2010; Zafra et al., 2006). In cases of severe infection, injury or degenerative diseases the BBB may be permeabilized allowing peripheral immune cells such as circulating macrophages, mast cells and T lymphocytes into the CNS (Chou et al., 2018; Dong et al., 2014; Nautiyal et al., 2008).

Immune cells of the CNS

The CNS has its own population of immune cells and signalling molecules which play crucial roles in shaping brain function and behaviour. These will now be summarised.

Microglia

Microglia are the resident macrophages of the CNS and comprise 10-15% of adult brain cells and 80% of brain immune cells (Li and Barres, 2018; Morimoto and Nakajima, 2019). Microglia colonise neural tissue early in brain development (5.5 weeks gestation in humans, E8 in rodents), originating from a pool of primitive macrophages in the yolk sac (Ginhoux and

Garel, 2018). Once the BBB is fully matured, microglia are confined to the brain under healthy conditions and self-renew throughout an individual's life (Daneman and Prat, 2015; Lenz and Nelson, 2018). This permanent population of cells experiences very little turnover, therefore the events that affect microglial development can potentially have long-term consequences for their function. Microglia are not evenly distributed throughout the CNS and concentrated pockets are found in the hippocampus, basal ganglia and substantia nigra (Rivest, 2009). In addition, microglial transcriptomes are phenotypically sculpted by the brain region they occupy (Tan et al., 2020). The heterogeneity of microglia in the CNS highlights their functional pluralism and contributes to the varying sensitivities of different regions to the same physical and psychological signals (Kim et al., 2000).

In the healthy adult brain microglia actively roam and survey their local environment for invading pathogens and necrotic cells by protruding and retracting their processes (Nimmerjahn et al., 2005). Often these surveying microglia are incorrectly described as 'resting', whereas in reality they are actively taking part in CNS homeostasis, supporting neurotransmission, facilitating synaptic pruning, long-term potentiation and depression (LTP and LDP), neuronal maintenance and regulating neurogenesis during development and adulthood (Frost and Schafer, 2016; Paolicelli et al., 2011; Salter and Stevens, 2017; Weinhard et al., 2018). Bi-directional signalling between neurons and microglia utilises the same array of signalling molecules as immune cells in the periphery, however there are some notable exceptions such as the fractalkine C-X3-C motif ligand 1 (CX3CL1) signalling axis which is exclusive to the CNS (Jung et al., 2000). Under inflammatory conditions microglia are activated by pathogen associated molecular patterns and damage associated molecular patterns, unleashing a cascade of inflammatory events including the release of pro-inflammatory cytokines, clearance of cellular debris and the presentation of antigens to activate additional microglia (Dheen et al., 2007). Once the threat (pathogen or injured cells) is resolved, anti-

inflammatory cytokines push microglia back into their surveying homeostatic state (Li and Barres, 2018; Madry et al., 2018). Throughout pre- and postnatal development microglia are highly active, shaping and fine-tuning neural circuits throughout the CNS via synaptic formation and pruning (through activation of the classical complement cascade), induction of apoptosis, myelination (by promoting differentiation, maturation and survival of oligodendrocytes) and regulating developmental neurogenesis (Bohlen et al., 2019; Pang et al., 2013; Shigemoto-Mogami et al., 2014). Depleting microglia during development results in working memory deficits and altered anxiety, whereas loss in adulthood has little effect on behaviour (Lenz and Nelson, 2018; Nelson and Lenz, 2017; VanRyzin et al., 2016).

Astrocytes

Astrocytes, another glial subtype, also play a critical role as an immune effector in the CNS (Dong and Benveniste, 2001). Unlike microglia, astrocytes arise from neuroectodermal origins but cooperate with microglia in brain homeostasis, excitatory neurotransmission, homosynaptic plasticity, adenosine triphosphate homeostasis and regulation of immune response (De Pitta et al., 2016; Hansson and Ronnback, 1995; Lalo et al., 2014; Pascual et al., 2012). In their neuroimmune role, astrocytes can act as antigen presenting cells using major histocompatibility complex (MHC) class II molecules which can be loaded with foreign or endogenous proteins to promote inflammation and recruitment of microglia (Dong and Benveniste, 2001; Wieczorek et al., 2017). Astrocytes also have a high expression of TLR3, and TLR3 signalling induces a highly robust pro-inflammatory response including the release of IL-2, TNFα and IL-6 (Jack et al., 2005). Through their production and release of complement system components, astrocytes contribute to the process of complement dependent pruning of synapses during development, synaptic plasticity and neurodegeneration (Hartmann et al.,

2019; Lian et al., 2016; Pekny et al., 2007). They also play a unique role in maintenance of the BBB and are therefore able to control the bidirectional flow of immune cells and mediators between the CNS and the periphery (Abbott et al., 2006). This interface of astrocytes means their response to inflammation directly influences the permeability of the BBB and therefore controls the influx of peripheral cytokines and immune cells into the CNS (Cabezas et al., 2014; Liu et al., 2018).

Mast cells

Mast cells located in the brain's perivasculature can also modulate the permeability of the BBB by secreting heparin, histamine, serotonin and nitric oxide to disrupt and degrade the basal lamina (Dong et al., 2014). Through their manipulation of the BBB mature mast cells can migrate between the periphery and the CNS and are found in healthy adult brain perivasculature (particularly concentrated in the thalamus) (Silverman et al., 2000). Mast cells in the brain differ from peripheral mast cells because they lack certain immunoglobulin receptors (high affinity immunoglobulin E receptor and the fragment crystallisable region ~~Fc~~ fragment of the immunoglobulin A receptor and stem cell factor), which may alter their development and survival (Khalil et al., 2008; Pang et al., 1996; Shanas et al., 1998; Silver and Curley, 2013). Following infection and injury mast cells become activated by antigens, complement, cytokines and neuropeptides: they can then increase vascular permeability and allow peripheral macrophages and T lymphocytes to enter the brain (Wernersson and Pejler, 2014). They then act as antigen presentation cells to these infiltrating immune cells, amplifying the immune response in the CNS (Caslin et al., 2018; Silver and Curley, 2013). Mast cells communicate with neurons and glia through secretion of cytokines and expression of neurotransmitter receptors (acetylcholine and substance P), and this relationship means they can influence

behaviour (Kulka et al., 2008; Masini et al., 1985; Tore and Tuncel, 2009). This is exemplified in mice lacking mast cells, which display abnormal neurogenesis, learning and memory and increased anxiety in adulthood (Nautiyal et al., 2008).

Cytokines

Cytokines and their cognate receptors are constitutively expressed by all cells in the healthy adult brain, can infiltrate from the periphery and are self-regulating, capable of inhibiting or increasing their own release (Banks, 2005; Pan and Kastin, 2002). In the brain, the hippocampus is vitally important for learning and memory, especially through synaptic plasticity (LTP and LTD) and neurogenesis, and low-level secretion of IL1-β, IL-6, IL-10, IL-4 and TNFα plays an essential role in these normal brain functions during development and adulthood (Druart and Le Magueresse, 2019; Erta et al., 2012; Levin and Godukhin, 2017; McAfoose and Baune, 2009; Pribiag and Stellwagen, 2014; Rostene et al., 2011; Whitney et al., 2009). IL1-β in particular plays a variety of roles, controlling neural transmission, promoting gamma aminobutyric acid (GABA)a receptor mediated inhibition of Purkinje cells in the cerebellum, inhibiting LTP and cell proliferation in the hippocampus and reducing calcium currents through N-type voltage gated calcium channels (Bellinger et al., 1993; Koo and Duman, 2008; Yirmiya et al., 2002; Zhou et al., 2006). Anti-inflammatory cytokines IL-4 and IL-10 are able to control the inhibitory effects of IL-1β on LTP through modulating expression of IL-1β and dampening of IL-1β driven activation of c-Jun N-terminal kinases (Kelly et al., 2001; Nolan et al., 2005). A range of other pro-inflammatory cytokines including IL-2, IL-6, IL-8, IL-18 and IFNα also inhibit hippocampal LTP *in vitro* (Curran and O'Connor, 2001; Mendoza-Fernandez et al., 2000; Tancredi et al., 2000; Tancredi et al., 1990; Xiong et al., 2003). Acute administration of IL-6 exhibits dose dependant inhibition of synaptic

plasticity in the hippocampus through the activation of intracellular tyrosine kinases and inactivation of mitogen-activate protein kinase/extracellular signal-regulated kinases (MAPK/ERK), and long-term memory is improved by administration of an anti-IL-6 antibody (Balschun et al., 2004; Tancredi et al., 2000). Interestingly, IL-6 expression is significantly upregulated 1-8 hours post LTP induction, suggesting a complex role for this interleukin in learning and memory (Balschun et al., 2004). IL-6 also plays a significant role in adult neurogenesis: animals lacking IL-6 have fewer newly proliferating cells in the dentate gyrus and subventricular zone (Bowen et al., 2011). TNFα acts via TNFR1 to increase the calcium conductivity of glutamatergic neurons, and circulating TNFα can also regulate homeostatic plasticity in the CNS through regulation of glutamate and GABA receptor trafficking (Furukawa and Mattson, 1998; Konefal and Stellwagen, 2017).

Chemokines are also crucial for development and neuronal plasticity (Williamson and Bilbo, 2013). Deletion of the chemokine C-X-C motif (CXC) chemokine 12 (CXCL12) or its receptor CXC chemokine receptor 4 (CXCR4) in mice is embryonically lethal in part due to a lack of neural migration during development (Levin and Godukhin, 2017; Rostene et al., 2011). Synaptic depression is also modulated by CXCR4, and fractalkine (CX3CL1) interacts with its receptor C-X3-C motif chemokine receptor 1 (CX3CR1) to reduce α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated currents and alter excitatory post-synaptic currents *in vitro* (Lauro et al., 2008; Ragozzino et al., 2006; Ragozzino et al., 2002). CXC ligand 2 (CXCL2) (CXC receptor 2 ligand) increases AMPA-type glutamatergic excitatory activity on cultured neurons, and application of C-C motif chemokine ligand 2 (CCL2) and C-C motif chemokine ligand 3 (CCL3) to hippocampal neurons increases excitatory post-synaptic currents, N-methly-D-aspartate (NMDA)-evoked $Ca2^{+}$ signalling and NMDA receptors *in vitro* (Kuijpers et al., 2010; Lax et al., 2002; Nelson et al., 2011; Zhou et

al., 2011). Alongside cytokines, MHC1 plays a role in synaptic plasticity and the development of appropriate neuronal connections in the mammalian brain (Huh et al., 2000).

We also see significant effects of cytokines on behaviour. For example, CXC3CL1 (fractalkine) knockout results in altered learning and memory in mice (Rogers et al., 2011). IL-2 modulates dopamine and dopamine-mediated depressive-type behaviours in developing and adult rodents and IL-6 promotes survival of catecholaminergic neurons which are responsible for increasing the release of dopamine in the hippocampus (Karrenbauer et al., 2011; Zalcman et al., 1994). Administration of IL-1β *in vivo* modulates hippocampal dependent memory in rodents, IFNγ regulates neuronal connectivity and social behaviour whereas IL-4 knockout results in a depressive phenotype (Baartman et al., 2017; Filiano et al., 2016; Goshen et al., 2007; Wachholz et al., 2017). IL-33 released from astrocytes can drive synaptic pruning by microglia, and IL-33 knockout alters sensorimotor behaviour (Vainchtein et al., 2018).

Complement system

Modulation of the complement system impacts developmental and adult neurogenesis. Neural progenitor cells express complement receptor 2 (CR2) and its ligand complement fragment C3d inhibits their proliferation, conversely antagonism of another complement receptor, complement component C3a receptor 1 (C3aR1), promotes neuroblast proliferation (Ducruet et al., 2012; Moriyama et al., 2011). Complement's regulation of neurogenesis continues past development and has been noted following traumatic brain injury and ischaemia (Hammad et al., 2018). Neurogenesis is also required for the neural plasticity that underlies homeostatic functions in the adult brain such as learning and memory, and thus represents another avenue for the complement system to drive the rearrangement of neural circuitry (Anderson et al., 2011; Seo et al., 2015). Mice lacking complement component 1q (C1q), C3 or complement

receptor 3 do not exhibit segregation of synaptic inputs from each eye, this along with staining showing the location of complement proteins with synapses suggests that complement drives synaptic elimination by microglia during development (Schafer et al., 2012; Stevens, 2008). Complement also affects behaviour: C3a receptor knockout mice are more resilient to stress-induced depressive behaviour, yet show increased levels of anxiety, whereas C3 knockout enhances fear responses (Crider et al., 2018; Westacott et al. 2020).

There is now overwhelming evidence that the immune system plays a critical role in normal brain development and function, as well as affecting behaviours with a direct relevance to psychiatric illness (e.g. anxiety and depressive-type behaviours, hippocampal dependent behaviours and sensorimotor gating). This suggests that dysregulation could result in abnormal brain development and function in adulthood, potentially increasing risk for psychiatric illnesses. We will explore links between the neuroimmune system and psychiatric illness in the following section.

Neuroimmune system and psychiatric illness

Given the vital importance of various immune components for normal brain development, neuronal function and behaviour, it is easy to imagine how altering the neuroimmune system could affect cognitive function. There is already a wealth of information supporting a role for neuroinflammation in neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's disease, and it is possible changes in neuroimmune function may play a causal role in the pathology of psychiatric illness (Schain and Kreisl, 2017).

Correlations between the immune system and psychiatric illness have been known for over a century. In 1927 Julius Wagner-Jauregg was awarded the Nobel Prize in Medicine for the development of malaria inoculation to treat syphilitic psychosis (Tsay, 2013). Here, malaria

was thought to induce a high fever that helped the patient's immune system combat syphilis, resolving psychiatric symptoms. Since that time, further associations have been found between components of the immune system and psychiatric symptoms. For example, IFNα and IL-2 are pro-inflammatory cytokines taken as treatments for diseases including hepatitis and to boost the immune system during tumour treatment. Such treatment increases the incidence of depression, anxiety and cognitive impairment, and can induce transient confusional states, including psychotic and manic symptoms (Dantzer et al., 2008; Felger et al., 2016; Raison et al., 2005). Both intracerebroventricular and peripheral administration of IL-1β produce depressive-like symptoms (anorexia, disturbed sleep, anhedonia and endocrine disruptions), which are attenuated by IL-1β receptor antagonism and antidepressants (Borsini et al., 2017; Finck and Johnson, 1997; Koo and Duman, 2009). Conversely, anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and certain antidepressants and antipsychotics have been associated with a decrease in inflammatory cytokines including IL-6, IFNγ, TNFα and c-reactive protein (CRP), and an increase in anti-inflammatory cytokines including IL-10, alongside improvement in psychiatric symptoms (Baumeister et al., 2016; Hiles et al., 2012; Kohler et al., 2015).

In the last few decades, alterations in immune function have been associated with a range of psychiatric illnesses. Mastocytosis (the excessive accumulation of mast cells in internal organs and skin) is often associated with anxiety, emotionality and memory alterations (Georgin-Lavialle et al., 2016). Several studies have found altered levels of peripheral cytokines and lymphocyte subtypes in schizophrenia, bipolar disorder (particularly in mania), post-traumatic stress disorder (PTSD) and major depression and levels of IL-1β, IL-2, IL-6, IL-8 and TNFα are associated with suicide (Black and Miller, 2015; Brietzke et al., 2009; Dowlati et al., 2010; Farooq et al., 2017; Gill et al., 2009; Jeon and Kim, 2016; Kim et al., 2007; Kunz et al., 2011; Lin et al., 1998; Momtazmanesh et al., 2019; Passos et al., 2015;

Serafini et al., 2013). Furthermore, IL-1β levels in the periphery of depressed patients have been found to correlate with age of onset, duration of illness and severity of symptoms (Farooq et al., 2017). Given the intimate functional relationship between immune and neuronal systems, coupled with the crucial role of the immune system in normal brain development and function, this has led to the neuroimmune hypothesis of psychiatric illness. This hypothesis states that aberrant neuroimmune function directly contributes to the aetiology of psychiatric disorders.

This neuroimmune hypothesis is especially appealing when we consider that immune molecules can influence levels of neurotransmitters with a known role in psychiatric illness. Serotonin modulates a diverse range of activities and behaviours in normal and psychiatric disorders, and a wealth of studies show serotonergic dysfunction in e.g. anxiety, depression, autism and schizophrenia (Marazziti, 2017). IL-1β and TNFα induce up-regulation of serotonin transporters, increasing uptake of serotonin and bringing on behavioural signs of depression (Baumeister et al., 2014; Zhu et al., 2006). INFγ and TNFα increase the expression of indoleamine 2,3 dioxygenase, which converts tryptophan to kynurenine, sequestering it away from serotonin synthesis and generating neuroactive metabolites that can regulate dopamine and glutamate (Campbell et al., 2014; Davis and Liu, 2015). Tetrahydrobiopterin (BH4) is a cofactor for tryptophan hydroxylase and tyrosine hydroxylase, rate limiting enzymes for serotonin and dopamine synthesis. Pro-inflammatory cytokines such as INFγ, IL-1 and TNFα can induce reactive oxygen species, which degrade BH4 (Miller et al., 2013; Neurauter et al., 2008; Pan et al., 2017).

Support for the neuroimmune hypothesis is also found in studies of genetic factors. Patients homozygous for the IL1-β 511T allele with major depression display a significantly faster and more pronounced response to the antidepressant paroxetine than IL1-β 511C carriers, and SNPs in this gene are associated with non-remission and decreased responsiveness to

emotional faces in depressed patients (Baune et al., 2010; Tadic et al., 2008). Variation in complement C4 alleles and the complement regulators CUB and sushi multiple domains 1 and 2 (CSMD1/CSMD2) are associated with schizophrenia and response to antipsychotic treatment (Havik et al., 2011; Liu et al., 2016; Liu et al., 2017; Sekar et al., 2016). Meta-analyses show that allelic variation in CRP, IL-1β, TNFα and T lymphocyte function are associated with major depressive disorder and response to antidepressant treatment (Bauer and Teixeira, 2019; Bufalino et al., 2013), and biological pathway analyses have revealed that multiple immune pathways are associated with schizophrenia, major depression and bipolar disorder (Zhao and Psychiat Genomics, 2015). The evidence for microglial activation is mixed: a meta-analysis of 22 studies using post-mortem tissue from schizophrenic and control brains found an increase in activated microglia in 11 studies, a decrease in 3 and no change in 8 studies (Mondelli et al., 2017; Trepanier et al., 2016). Similarly, in vivo positron emission tomography studies have found variable changes in microglial density and in radioligand binding (using radioligands for the 18kDa translocator protein, a protein located mainly in the mitochondrial membrane of endothelial and glial cells, increased levels are associated with microglial activation) in the brains of schizophrenic, psychotic and depressed patients when compared to controls (Mondelli et al., 2017; van Kesteren et al., 2017). Discrepancies are likely due to differences in the brain region investigated (e.g. cortex vs hippocampus), markers used (e.g. positron emission tomography markers vs. human leukocyte antigen vs. CD68 vs. Iba1) stage of the disorder (e.g. early vs. advanced) and issues with radiotracers as proxy measures of microglial activation (Trepanier et al., 2016). Likewise, a GWAS study in 2014 found that schizophrenia, depression and bipolar are associated with B lymphocytes (Ripke et al., 2014), yet studies investigating B lymphocyte number in the periphery of schizophrenic patients find little difference from controls (although levels of B lymphocyte related cytokines and autoantibodies are increased) (van Mierlo et al., 2019). Alongside genetic variation, the environment can also have a

profound influence on neuroimmune function, and ultimately gene x environment interactions will determine final functional outcomes. We will now explore how environmental factors influence the neuroimmune system, potentially conferring vulnerability or resilience to neuropsychiatric disorders.

Psychosocial stress and the immune system

The immune system is highly responsive to immunological stimuli, defending the host organism from disease (Chaplin, 2010). However, it also responds to non-disease related stimuli, especially stress (Khansari et al., 1990; Marketon and Glaser, 2008; Tsyglakova et al., 2019). In humans acute stressors, ranging from public speaking to laboratory stress tests and tandem skydiving, enhance immune function in the periphery, briefly increasing NKCs and pro-inflammatory mediators, especially IL-6, IL-1β, IL-10, TNFα and CRP (Breen et al., 2016; Marsland et al., 2017; Steptoe et al., 2007). This response is thought to give an evolutionary advantage by priming the immune system for action when stressful experiences, such as encounters with a predator, may have resulted in injury and infection (Segerstrom and Miller, 2004).

Stress is a normal part of everyday life, and results in a multitude of adaptive behavioural and molecular alterations as the organism attempts to maintain homeostasis. The sympathetic-adrenal-medullary axis (SAM axis) and hypothalamic-pituitary-adrenal axis (HPA axis) are major stress axes of the body. The sympathetic nervous system produces a rapid response, and involves the paraventricular nucleus, locus coeruleus and rostral ventrolateral medulla, as well as secretion of epinephrine and norepinephrine (NE) from the adrenal medulla, and norepinephrine from the sympathetic nerves (Carrasco and de Kar, 2003; Ulrich-Lai and Herman, 2009). The HPA axis produces a slower-acting response, secreting corticotropin

releasing hormone, arginine vasopressin and adrenocorticotropic hormone and glucocorticoids (GCs) from the hypothalamus, pituitary and adrenal glands (Ulrich-Lai and Herman, 2009). Limbic circuits including prefrontal cortex (PFC), amygdala, hippocampus, paraventricular nucleus, ventral tegmental area and nucleus accumbens play a role in regulating the stress response (Jankord and Herman, 2008; Maity et al., 2015; Ulrich-Lai and Herman, 2009). GCs bind to glucocorticoid receptors in selected brain regions (especially hippocampus and PFC), terminating the stress response (McKlveen et al., 2013; Sapolsky et al., 1984; Vyas et al., 2016). The HPA and SAM axes are intimately linked with one another and the immune system, with all immune cells expressing receptors for hormones of the HPA and SAM axes (Glaser and Kiecolt-Glaser, 2005).

There are several pathways through which the immune and stress systems communicate. GCs bind to receptors on immune cells in the periphery and brain, producing either a pro- or anti-inflammatory effect, depending on dose, duration and region (Duque and Munhoz, 2016). Cytokines in turn stimulate the HPA axis, perpetuating the stress response. In particular, IL-1, IL-6 and TNFα activate the HPA axis through direct and indirect mechanisms, increasing adrenocorticotropic hormone and corticosterone release (Dunn, 2006). Sympathetic pathways descend from the brain to bone marrow, thymus, spleen and lymphoid tissues, releasing hormones (especially NE) that bind to immune cells (Nance and Sanders, 2007; Steinman, 2004). NE activates the vagal nerve, increasing NE in the brain, and this regulates synaptic and structural plasticity (Hulsey et al., 2019). The vagal nerve is stimulated by peripheral cytokines as well as NE, providing another communication pathway between the brain and peripheral immune system (Johnston and Webster, 2009). There are therefore several direct and indirect routes through which the stress axes can affect both peripheral and central immune function, and many effects are considered to be normal, physiological mechanisms of activity (Dunn, 2000).

The intimate links between stress and immune systems mean that exposure to chronic or intense stress may negatively dysregulate both stress and immune functions. In support of this, severe acute or chronic stress has been linked to a range of physical (from diabetes to osteoporosis) and psychiatric disorders in humans (Hackett and Steptoe, 2017; Kelly et al., 2019; McEwen et al., 2015; Riboni and Belzung, 2017; Tomiyama, 2019; Zorn et al., 2017). Some of the earliest examples of this phenomenon demonstrate that psychosocial stress in the form of predator or noise exposure can dramatically alter the course of autoimmune diseases such as arthritis in animals (Rogers et al., 1980, 1983). In humans, a 15-year study from 1985 demonstrated that a period of psychosocial stress (death of a loved one, marital problems and serious illness) often preceded the development rheumatoid arthritis (Rimon and Laakso, 1985), and the link between stress and autoimmune diseases now has greater empirical support (Porcelli et al., 2016). Adults experiencing stressful events such as caring for someone with dementia, extended work stress, unemployment or poverty mount a lower immune response to influenza and hepatitis B vaccines (Domnich et al., 2019; KiecoltGlaser et al., 1996; Pedersen et al., 2009; Segerstrom and Miller, 2004; Vedhara et al., 1999). This suggests that psychological pressures can fundamentally alter the functioning of the immune system, increasing vulnerability to a range of diseases. We will now explore some of the molecular mechanisms underlying this phenomenon.

In animal models psychological stressors including social defeat, restraint and chronic variable stress alter peripheral immune responses, increasing monocytes, neutrophils, IL1-β, IL-6, IL-13, TNFα and IL-10 levels, decreasing dendritic cells and promoting T lymphocyte apoptosis (Ambree et al., 2018; Ashcraft et al., 2008; Finnell et al., 2017; Heidt et al., 2014; Pfau et al., 2019; Powell et al., 2009; Tsyglakova et al., 2019). Interestingly, some of these effects are specific only to stress susceptible animals, revealing individual differences in stress-immune system regulation (Ambree et al., 2018). Similar effects are seen in the CNS of

553 animals, where a range of psychosocial stressors (e.g. restraint, footshock and swim stress)
554 increase IL1-β expression in various brain regions, activate microglia and change number,
555 distribution and activation status of mast cells throughout the brain (Bollinger et al., 2016;
556 Cirulli et al., 1998; Hellwig et al., 2016; Kriegsfeld et al., 2003; Minami et al., 1991; Suzuki et
557 al., 1997; Theoharides, 1996; Tynan et al., 2010; Wilhelm et al., 2000; Wohleb et al., 2012).
558 Chronic stress can also disrupt the BBB, increasing the influx of peripherally-derived
559 monocytes into the brain, as well as altering the stress responsiveness of immune cells,
560 modulating their glucocorticoid receptor expression (Ataka et al., 2013; Blandino et al., 2006;
561 Brevet et al., 2010; Jung et al., 2015; Quan et al., 2003).

562 Microglia, astrocytes and mast cells are highly sensitive to GC's, and express both
563 glucocorticoid and mineralocorticoid receptors (the two main corticosteroid receptors) (Sierra
564 et al., 2008). GCs stimulate the proliferation of microglia, upregulating activation and
565 inflammatory markers such as MHCII, CD14, CD86 and TLR4 on these cells, acting through
566 NMDA, β-adrenergic and IL-1β receptors (de Pablos et al., 2006; Frank et al., 2012; Nair and
567 Bonneau, 2006; Wohleb et al., 2012). In animals, GCs alter the number of astrocytes in the
568 brain and their gene expression (Carter et al., 2012; MacDonald et al., 2019; Piechota et al.,
569 2017; Unemura et al., 2012), and psychological stress can induce mast cell degranulation in
570 the periphery, an effect mediated by corticotrophin releasing hormone (Peters et al., 2005;
571 Theoharides, 1996). Chronic or severe stressors are also associated with abnormal behaviour
572 (e.g. increased anxiety and depression-type symptoms) and structural changes in the brain (e.g.
573 atrophy in hippocampus, PFC and amygdala) in humans and animals (Cameron and
574 Schoenfeld, 2018; McEwen, 2016). Given the role the immune system plays in normal
575 behaviour and neuronal function, dysregulation of the immune system by severe acute or
576 chronic stress may play a direct role in such pathological states. Most studies investigate
577 immune changes shortly after stress exposure, but studies focussing on stress during

development demonstrate that these effects can be long-lasting and result in permanent re-programming of the developing neuroimmune system. Conversely, positive experiences may program resilience, and even mitigate the negative effects of stress. Resilience or pathology are likely dependent on the nature, duration and timing of the early life experience as well as individual genetics. We will explore this further in the next section.

Developmental stress and the neuroimmune system

There are well documented links between the experience of physical, immunological and psychological stressors during development such as trauma, abuse, neglect, infection and malnutrition and the development of physical (rheumatoid arthritis, cardiovascular disease, lung disease, metabolic syndrome and cancer) and psychiatric illnesses (depression, anxiety, PTSD, schizophrenia and borderline personality disorder) in humans (Carroll et al., 2013; Dube et al., 2003; Heim and Nemeroff, 2001; Sonu et al., 2019; Teicher and Samson, 2013, 2016; Tiwari and Gonzalez, 2018). Developmental stress can be experienced in utero, in the early or late postnatal periods and also later on in development, during adolescence. The CNS and immune systems follow distinct developmental trajectories throughout these periods as they mature towards their adult form (Brenhouse and Schwarz, 2016; Gollwitzer and Marsland, 2015). Intriguingly, it has even been suggested that BBB permeability to immune molecules may vary as a normal part of adolescent neuronal development (Brenhouse and Schwarz, 2016). Therefore, the long-term consequences of developmental stress may vary depending on the brain region or neuroimmunological process maturing at the time of insult. As with other domains (e.g. stress responses and hippocampal form and function (Brunson et al., 2011)) stressful challenges may produce greater or at least differential effects on neuroimmunological

function in development vs. adulthood, but there is not currently enough information to state this conclusively.

Developmental stressors can be broadly divided into four categories - i) prenatal and ii) early postnatal (generally pre-weaning), iii) post-weaning, pre-pubertal (childhood) and iv) adolescent, although there may be overlap between these categories. In the following discussion, we have grouped human prenatal with rodent prenatal and early postnatal stress, as the first two weeks of rodent life are often deemed equivalent to the third trimester in humans. Childhood and adolescent stress have been grouped as human studies generally fail to distinguish between these timepoints, although doing so would undoubtedly prove informative. See Figure 3 for a summary of the major types of positive and negative experiences and their neuroimmunological consequences throughout these periods in humans and animals.

Perinatal stress (prenatal & early postnatal)

Humans - prenatal

Studies of maternal infection provide a particularly striking example of the link between developmental stress in the form of immune activation and later vulnerability to psychiatric illness. 1964 saw a rubella epidemic which was significantly associated with an increase in incidences of autism and schizophrenia (from 1% to 13-20%) in offspring (Brown et al., 2001; Estes and McAllister, 2016). Historical outbreaks of measles, mumps, polio, influenza and maternal exposure to parasites and bacterial infections have been similarly associated with increased rates of psychiatric illness later in life (Babulas et al., 2006; Blomstrom et al., 2016; Brown et al., 2004; Buka et al., 2001; Canetta and Brown, 2012; Guma et al., 2019; Tyebji et

al., 2019) although some studies have found no association (Selten et al., 2010). It will be interesting to see whether similar effects are observed after the 2020 world-wide pandemic of COVID-19, and gives greater gravity to the public health advice that pregnant women should be considered a vulnerable population during such outbreaks (Qiao, 2020). Similar risks are observed following maternal autoimmune disorders, suggesting that activation of the maternal immune system is sufficient to increase risk of psychiatric illness in the offspring (Chen et al., 2016; Estes and McAllister, 2016). Maternal psychosocial stress and mental illness in the prenatal period is also associated with an increased risk of psychiatric illness and delayed cognitive development in the offspring, although some studies have found no association (Brannigan et al., 2019, 2020; Glover, 2011; Malaspina et al., 2008; Stein et al., 2014). Women experiencing psychosocial stress/mental illness during gestation have altered HPA axis function and increased circulating pro-inflammatory cytokines (Cheng and Pickler, 2014; Corwin et al., 2013; Coussons-Read et al., 2007; O'Connor et al., 2014; Szpunar and Parry, 2018), although note that some studies have found no association between perceived maternal stress/mental illness and cortisol (Rouse and Goodman, 2014). It is therefore hypothesised that offspring in utero are exposed to abnormal levels of maternally derived stress hormones and pro-inflammatory cytokines, which may interact to alter the development of biological systems, including the brain (Elenkov et al., 2005). Maternal malnutrition and over-nutrition are also associated with schizophrenia, autism and metabolic disorders in offspring, and here exposure to inflammatory factors is hypothesised to play a role (Smith and Reyes 2017). Despite this, there are very few human studies examining the lasting effects of prenatal stress on immune function in offspring. One study demonstrated that monocytes from women whose mothers had experienced psychosocial stress during pregnancy produced elevated levels of IL-6 and IL-10, and a bias for T helper cytokine production resulting from an overproduction of IL-4 relative to IFNγ (Entringer et al., 2008). Another found that maternal diets deficient in key nutrients

649 such as zinc, vitamins A, D and C, folate, iodine and iron are associated with poor immune
650 responses to vaccines in infancy (Obanewa and Newell., 2017).

651 Studies in humans are confounded by uncontrolled environmental factors (for example,
652 are offspring of prenatally stressed mothers at greater risk of depression due to parental prenatal
653 stress or subsequent postnatal depression/parenting styles or shared genetic factors?), genetic
654 variability and inaccessibility of neural tissue (with the exception of post-mortem studies). We
655 therefore know very little about the effects of developmental stress on immune system-related
656 function in the human brain. It can also be difficult to disentangle cause and effect - are
657 changes in the immune system a cause or a consequence of psychiatric illness? For example,
658 excessive alcohol consumption and tobacco smoking are often comorbid with psychiatric
659 illness, and known to alter immune function independently of psychiatric state (Barr et al.,
660 2016; Dani and Harris, 2005). Therefore, studying the direct effects of psychological stressors
661 on neuroimmune function of the brain is not straightforward. Animal models can give a greater
662 insight into the underlying mechanisms linking developmental stress with alterations in
663 neuroimmune function.

664

665 *Animals – prenatal & early postnatal*

666 Animal studies of perinatal stress range from maternal immune activation (MIA, using IL-1β,
667 lipopolysaccharide (LPS), polyinosinic-polycytidilic acid (poly (I:C)), injection of stress
668 hormones (e.g. dexamethasone), dietary manipulations and psychological stress (e.g. restraint,
669 bright lighting) in utero to maternal separation, limited nesting and bedding and poor maternal
670 care in the first few weeks of life, and similarly find negative outcomes for brain, behaviour
671 and immunity. Behavioural changes often reflect those found in autism spectrum disorder,
672 schizophrenia, depression and anxiety, and include abnormal social behaviour and

communication, repetitive behaviours, altered sensorimotor gating, increased anxiety, impaired working memory and cognitive flexibility (Bock et al., 2015; Nishi et al., 2014; Smith and Reyes, 2017; Tractenberg et al., 2016). These are accompanied by structural changes in hippocampus and PFC and altered dopamine and serotonin signalling (Estes and McAllister, 2016; Smith and Reyes, 2017). Enhanced immune signalling from the mother appears to be one key mechanism underlying these changes - injection of IL-6 alone is capable of producing many prenatal-stress induced behavioural, structural and molecular changes in the offspring (Smith et al., 2007). Furthermore, co-injecting poly (I:C) with an antibody that blocks the function of IL-6 or IL-17 partially rescues the phenotype (Choi, 2016; Smith et al., 2007). This demonstrates that immune challenge in early life is causal in producing altered brain development in offspring.

Alongside behavioural and neuronal changes, perinatal stress permanently alters immune function peripherally and centrally in the offspring. Psychological stressors including noise, light and restraint stress during gestation decrease the effectiveness of NKCs and B lymphocyte proliferation in the periphery, and maternal malnutrition/high fat diet impair T and B lymphocyte activity (Falcone et al., 2017; Kay et al., 1998; Liaudat et al., 2012; Verwaerde et al., 2006) Maternal psychological stressors, MIA, maternal separation/deprivation and dietary manipulations alter expression of numerous cytokines in plasma or brain, either at baseline or following a subsequent immune challenge, and there are many excellent reviews on these topics (Avitsur et al., 2006, 2013; Bekhbat and Neigh, 2018; Bergdolt and Dunaevsky, 2019; Dimatelis et al., 2012; Diz-Chaves et al., 2013; Falcone et al., 2017; Saavedra et al., 2017; Smith and Reyes, 2017; Wieck et al., 2013). These changes often occur in an age and region-specific pattern, and suggest that similar to MIA, psychosocial stress may alter brain development via regulation of the immune system.

A wide range of perinatal stressors (e.g. MIA, maternal psychosocial stress, brief daily separation, prenatal high fat diet and neonatal exposure to diesel particles) alter the developmental trajectory, density and morphology of microglia and astrocytes throughout the developing brain (Baldy et al., 2018; Banqueri et al., 2019; Bekhbat and Neigh, 2018; Bergdolt and Dunaevsky, 2019; Bilbo and Tsang, 2010; Bland et al., 2010; Bolton et al., 2017; Catale et al., 2020; Cohen et al., 2016; Delpech et al., 2016; Diz-Chaves et al., 2012, 2013; Edlow et al., 2019; Gomez-Gonzalez and Escobar, 2010; Lopez-Gallardo et al., 2008; Makinson et al., 2017; Matcovitch-Natan et al., 2016; Reus et al., 2019; Roque et al., 2016; Saavedra et al., 2017; Smith and Reyes, 2017), although note that some studies find no change (Bergdolt and Dunaevsky, 2019; Giovanoli et al., 2016). Some of these changes are transitory in nature, others persist into adulthood, and effects are often exacerbated following a further immune challenge in adulthood. Temporarily depleting microglia in the early neonatal period causes anxiety, despair and working-memory deficits in adulthood, highlighting their importance for the development of normal behaviour (Nelson and Lenz, 2017; VanRyzin et al., 2016). MIA alters MHCII levels on microglia and MHC1 on neurons in the brains of offspring (Coiro et al., 2015; Hadar et al., 2017). MHCI is involved in the regulation of synaptic pruning and circuits, is regulated by cytokines and co-localises with C1q, which also plays a role in synaptic elimination during early postnatal refinement of the functional visual system (Miyamoto et al., 2013). Altered synaptogenesis and pruning have been suggested as potential mechanisms contributing to neurodevelopmental disorders such as schizophrenia and autism spectrum disorder (Habela et al., 2016; McCutcheon et al., 2020). Together, this suggests that psychosocial stress during early life has profound effects on the immune system which correlates with altered postnatal brain developmental processes.

Childhood/pre-pubertal/adolescent stress

Humans

Abuse, neglect, parental illness, death, abandonment, crime, divorce, war, displacement and natural disaster in childhood are associated with psychiatric illnesses and suicide attempts (Abel et al., 2014; Bjorkenstam et al., 2016; Green et al., 2010; Kessler et al., 2010; van Os et al., 2010; Wang et al., 2020; Zatti et al., 2017). They are also associated with significant changes in the immune system in childhood and adulthood, especially altered CRP, IL-6, TNFα, fibrinogen, E-selectin (expressed on cells activated by cytokines) and nuclear factor kappa-light-chain enhancer of activated B cells (NFκβ, controls cytokine production) (Baumeister et al., 2014; Carpenter et al., 2010; Coelho et al., 2014; Copeland et al., 2014; Danese and Lewis, 2017; Danese et al., 2007; Fagundes et al., 2013; Kiecolt-Glaser et al., 2011; Kuhlman et al., 2019; Lacey et al., 2014; Levandowski et al., 2016; Miller and Chen, 2007, 2010; Pace et al., 2012; Slopen et al., 2013; Takizawa et al., 2015). Sometimes these effects are only seen after exposure to a subsequent stressor. In humans, IL-6 increases in response to a variety of acute stressors, and this response is exaggerated in adults that were exposed to early life adversity (Carpenter et al., 2010; Pace et al., 2012). Effects of developmental stress on immune expression are also often exacerbated in individuals with a psychiatric disorder. For example, childhood adversity (CA) predicted increased levels of TNFα and IL-6 in patients with schizophrenia, and higher levels of IL-6 following CA are predictive of PTSD (Dennison et al., 2013; Pervanidou et al., 2007). In women at risk for depression, a transition to depression was accompanied by increases in pro-inflammatory markers CRP and IL-6 only in those exposed to CA (Miller and Cole, 2012). This suggests that in the future, inflammatory phenotype may be a useful diagnostic for stratifying psychiatric populations and considering treatment options.

Longitudinal studies demonstrate an association between CA and physical illnesses, diabetes and metabolic disorders and obesity (Li et al., 2019; Lown et al., 2019; Scott et al., 2011). There is a high rate of medical problems in those with mental illness, suggesting there may be common inflammatory mechanisms at work (Agorastos et al., 2019; Ehlert, 2013). An alternative explanation is that this association arises due to lifestyle factors. A study providing support for the former notion followed 1037 people since birth and found that cumulative developmental stress was associated with elevated inflammatory markers CRP, fibrinogen and white cell counts 20 years later, and this was not explained by potential confounders (Danese et al., 2007). Stronger evidence is again provided through animal studies.

Animals

A range of paradigms are used in animals to simulate stress in the childhood (or pre-pubertal) and adolescent phases of life, and include social isolation, social defeat, an unstable housing environment (e.g. constant light, wet bedding, unstable social groups) and short and long term physical stressors (e.g. forced swim, restraint, elevated platform and foot shocks). This is less well studied than perinatal stress, particularly in the context of neuroimmune alterations. Similarly to perinatal stress, pre-pubertal and adolescent stress results in characteristics reminiscent of human psychiatric illness, including HPA axis alterations and depressive/anxious phenotypes (although precise effects are often affected by exact time of exposure and sex) (Eiland et al., 2012; Green and McCormick, 2013; McCormick et al., 2010; Romeo, 2017; van Bodegom et al., 2017). Long-term changes in neuroimmune function are also observed. Social defeat and chronic unpredictable stress during adolescence alter the number and activation of microglia throughout the brain (Rodriguez-Arias et al., 2018; Wang et al., 2018b). Cytokines are also affected: isolation rearing and chronic unpredictable stress

throughout adolescence alter IL-4, IL-1β, TNFα, INFγ (plasma) and TNFα, IL1-β and IL-6 in the brain (Ko and Liu, 2015, 2016; Moller et al., 2013; Shortall et al., 2018; Wang et al., 2018b). The majority of studies use rodents, but a study using Japanese quail found that unpredictable food availability during adolescence altered IL1-β, IL-10 and the microglia-dependent gene colony simulating factor 1 receptor (CSF1R) in pituitary, amygdala and hypothalamus (Walker et al., 2019). This suggests the nature of the stress-immune axis relationship is conserved across species.

Chronic adolescent stress (social defeat and restraint) sensitises the rat hippocampus immune profile to react more strongly to LPS challenge weeks later, exaggerating the expression of NFκβ, IL-1β, TNFα and CD11b in the hippocampus (Bekhbat et al., 2019; Pyter et al., 2013). Interestingly, these central changes are not reflected in the periphery, suggesting that peripheral changes are not always a suitable proxy measure for the CNS. As we have discussed, this does not mean that peripheral changes have no consequence for brain and behaviour, however, it does suggest that peripheral changes cannot reveal everything about how stress alters central neuroimmune function, information which is vital for developing novel therapeutics for psychiatric illnesses. Animal models provide a unique opportunity to address the largely unanswered question of whether stress affects central and peripheral immune function comparably: unfortunately most studies do not take advantage of this.

Virtually nothing is known of the long-term neuroimmune consequences of stress in the post-weaning, pre-pubertal phase, a time point akin to human childhood (Brydges, 2016). In humans, childhood is a particularly vulnerable timepoint where stress exposure can significantly increase the risk of psychiatric illness. Exposing animals to short-term physical stressors in the juvenile or pre-pubertal phase enhances blood monocytes and blood chemokine ligand type 2 (CCL2) following peritoneal inflammation. There was a decreased level of

chemokine receptor type 2 (CCR2) on these monocytes, which indicated a reduced ability for these monocytes to be recruited to the inflammatory site. Reduced levels of macrophages were found in the peritoneal cavity, alongside a reduced activation ratio for the release of peritoneal IL-10 by LPS activation (Shtoots et al., 2018). Pre-pubertal stress also alters FK506-binding protein 5 (FKBP5) in the hippocampus (Brydges et al. 2020). FKBP5 is an immunophilin which also plays a crucial role in regulating the HPA axis, making this an ideal candidate molecule linking developmental stress with neuroimmune dysfunction and psychiatric illness. Polymorphisms in FKBP5 have been associated with depression, PTSD and response to antidepressant treatment, and interact with childhood adversity to confer risk or resilience to these disorders (Wang et al., 2018a; Xie et al., 2010). Other gene x childhood adversity interactions have been explored, including monoamine oxidase A, solute carrier family 6 member 4, catechol-O-methyl transferase and brain-derived neurotrophic factor, and are reviewed elsewhere (Assary et al., 2018).

These studies suggest that stress-related alteration of the neuroimmune system during development may contribute to abnormal brain development and behaviour, increasing vulnerability to psychiatric illness. This provides a potential therapeutic avenue for psychiatric illness.

P**ositive environmental experience and the neuroimmune system**

Just as chronic or intense stress is capable of negatively modulating neuroimmune function, there is emerging evidence that positive experiences can enhance it, potentially providing resilience to psychiatric illness. For example in adult humans, regular bouts of moderate intensity exercise prevents cardiovascular disease, cancer, diabetes, obesity and osteoporosis, improves mood and enhances immune performance (although there is debate over whether

817 strenuous or unaccustomed exercise is actually detrimental to immune function) (Aoi and
818 Naito, 2019; Campbell and Turner, 2018; Gleeson et al., 2011; Pascoe et al., 2014; Simpson et
819 al., 2020). Meta-analyses demonstrate that not only is mindfulness beneficial for subjective
820 wellbeing (particularly in the context of depression and pain) but also reduces inflammation as
821 measured by IL-6, TNFα, NF-kβ transcription activity and CRP levels and increases cell
822 mediated immunity by increasing CD4+ cell count and activity, and also increases telomerase
823 activity (Black and Slavich, 2016; Goldberg et al., 2018; Walsh et al., 2016). Another meta-
824 analysis of 75 studies showed that a variety of stress-reduction and relaxation techniques,
825 including cognitive behavioural therapy, meditation, hypnosis, emotional disclosure and
826 counselling had small but positive effects on immune performance as measured by physical
827 immune challenges (e.g. skin tests and wound healing) and psychophysiological challenges
828 (speech task, cold pressor test, exams and treadmill exercise) (Schakel et al., 2019). Brief
829 interventions aimed at improving positive affect (e.g. comedy, massage, music, relaxation and
830 physical exertion) are also effective in enhancing immune responses (as measured by secretory
831 immunoglobulin A, NKCs and IL-6 (Ayling et al., 2020)). However, interventions are largely
832 given in adulthood and it is possible that earlier interventions following developmental stress
833 may provide greater benefits, before alterations in immune function have become more
834 established later in life. Further studies are also needed to establish whether these effects are
835 long-lasting or represent an immediate, transient response, and whether repeated/continuous
836 intervention is needed to maintain positive benefits.

837 Positive environmental experiences such as mindfulness are beneficial for improving
838 depression, anxiety, coping and mood in individuals with a history of childhood adversity, but
839 the implications of such interventions for immune function in this population are largely
840 unknown (Ortiz and Sibinga, 2017). There is research demonstrating that sensitive caregiving
841 promotes optimal brain development in children, and that factors such as secure environments

and caregiver attachments, high family functioning, close parental monitoring, good social support and cognitive behavioural therapy can mitigate and protect against the negative effects of developmental stress, but again, effects on neuroimmune function are unknown (Brown et al., 2017; Fritz et al., 2018; Kok et al., 2015; Masten et al., 2009; McGoron et al., 2012; Nelson et al., 2014; Sciaraffa et al., 2018; Tiet et al., 1998). One area which has received investigation across the life course is diet. We have seen that malnutrition and over-nutrition during development can negatively impact immune function, cognition and emotion, conversely, optimal diet can exert the opposite effects. Here, interactions between the gut-brain axis are thought to be particularly influential (Rogers et al. 2016). For example, breastfed infants display decreased inflammation, and the Mediterranean diet, which is high in vegetables, fish and 'healthy' dietary fats is also associated with reduced inflammation (Childs et al., 2019). Addition of anti-inflammatory dietary omega-3 polyunsaturated fatty acids (PUFA) via fish oil to the maternal diet reduced neonatal responses to allergens (decreased IL-5, 13 and 10 and INFγ) (Dunstan et al., 2003). PUFA in the form of docosahexaenoic acid (DHA) has also been found to normalise immune reactions to stress in pregnant women with two or more adverse childhood experiences (Hantsoo et al., 2019). Finally, supplementation of maternal diet with nutrients including folate, iodine and vitamin D are associated with enhanced fetal immunity and paralleled by a decreased incidence of psychiatric illness in adulthood (Marques et al., 2013). This suggests that diet may be a promising, viable, modifiable target for prevention and treatment of psychiatric illnesses, although more research is needed. All measures in humans are necessarily peripheral, so we can again turn to animal models to investigate central changes.

Animal models of positive environmental experiences face some translational challenges. It is not possible to administer mindfulness or similar relaxation techniques to rodents, but we can still provide meaningful positive experiences with translational validity.

There are four main methods of inducing positive affect in rodents: postnatal stimulation (akin to sensitive caregiving in humans), environmental enrichment, exercise and diet, we will examine the effects of each in turn.

Postnatal early stimulation

Postnatal early stimulation (also called early neonatal handling, early postnatal handling, early handling, enhanced postnatal care or brief handling stress) involves removing rodent pups from their dam for a few minutes daily during the first few weeks of life. Unlike prolonged separation during this period (a method of invoking developmental stress through deprivation of maternal nutrition, warmth and littermates), postnatal early stimulation (PES) is thought to stimulate the mother to pay increased attention to the pups upon their return (e.g. increased licking and grooming), and provide an enriching experience which can mitigate many adverse effects of prenatal stress, particularly with regards to HPA axis function (Levine, 2000). A handful of studies demonstrate that PES can also improve immune function. In rodents, PES enhances peripheral T and B lymphocyte proliferation, and within the brain increases baseline expression of IL-10 in the nucleus accumbens, an effect which is maintained into adulthood via decreased methylation of IL-10, specifically in microglia (Lown and Dukta, 1987; Schwarz et al., 2011). Expression of pro-inflammatory cytokines and chemokines, including CXC3CR1, TLR2, IL1-β and CLL2 are also decreased following PES in the nucleus accumbens (Lacagnina et al., 2017). PES reduced anxiety in WT mice but not in those lacking expression of the inflammation suppressing factor interferon regulatory factor 2 binding protein 2 (IRF2BP2) on microglia, suggesting the anxiolytic effects of PES may work through suppressing microglial inflammation (Hari et al., 2017). PES increases mast cell number in and around the hippocampus: whether it can reverse the effects of perinatal stress on mast cells is unknown

(Joshi et al., 2019). Prenatal restraint stress increases leukocytes and lymphocytes and decreases neutrophils, T lymphocyte proliferation and IL-2 release in the periphery following adult restraint stress, and these effects were rescued by PES (Falcone et al., 2017; Liaudat et al., 2012). E-coli infection on postnatal day 4 increases microglia reactivity in the hippocampus, exaggerates IL-1β expression in response to LPS and impairs memory: again, these effects are reversed by PES (Bilbo et al., 2007). There is therefore good evidence that interventions at critical times in early life could be used to rescue otherwise damaging effects of developmental stress on neuroimmune function and associated behaviours.

Environmental enrichment

In rodent models, environmental enrichment (EE) involves exposing animals to enhanced social and physical stimuli in the home cage. This includes provision of toys, tunnels and larger social groups which promotes physical activity, exploration and social interaction. Sometimes running wheels are included as part of the treatment, but effects of exercise are often dissociable from other aspects of EE, so will be considered further in the section *exercise* below. EE is often administered in adulthood, and provides a robust method for improving a range of behavioural and molecular alterations, including those associated with psychiatric illness (e.g. anxiety and depression), and those resulting from stress (Fox et al., 2006; Lopes et al., 2017; Nithianantharajah and Hannan, 2006). A few studies have investigated the effects of EE on immune function. EE improves response to influenza A infection in mice, enhances macrophage, lymphocyte and NKC function and activity and microglial density, and decreases inflammatory cytokines in periphery and brain (Arranz et al., 2010; Buschert et al., 2016; Jurgens and Johnson, 2012; Marashi et al., 2003; McQuaid et al., 2013; Singhal et al., 2014). EE also reverses increases in pro-inflammatory cytokines (IL1-β, IL-6) resulting from stress

(including social stress and predator exposure) in adulthood (McQuaid et al., 2018; Scarola et al., 2019). When given during adolescence, EE can reverse the effects of developmental stress on the immune system. Animals subjected to prenatal restraint stress displayed decreased CD4 T lymphocytes, increased IL-1β and IL-10 in spleen and brain, effects which were reversed by EE (Laviola et al., 2004). Maternally separated rats display increased TNFα and TNFα:IL-10: this was reversed by EE (do Prado et al., 2016). Those given short-term variable stress in the post-weaning, pre-pubertal phase had higher levels of blood monocytes with an increase in CCL2 and decrease in CCR2 following immunological challenge (peritoneal inflammation), and peritoneal cells expressed less IL-10 after LPS challenge in vitro. In this case, EE did not reverse monocyte number or CCL2/CCR2, but did normalise IL-10 expression (Shtoots et al., 2018). Enrichment protocols last 3-5 weeks, but the minimal or optimal duration or time of intervention for effects to be observed is unknown. Similarly, it is unknown whether a single bout of enrichment is sufficient to rescue immunological changes, or whether continual enrichment is required, and whether effects last beyond early adulthood.

Exercise

Exercise and diet are conceptually the most translatable positive environmental experiences between species. Running wheels, treadmills and swimming are typically used to exercise animals, and protocols may be voluntary or forced. The advantage of forced exercise is administration of precise doses, but such regimes may cause stress. Indeed, all exercise types initially cause stress, but this effect is minimised through provision of adaptation periods (Contarteze et al., 2008; Liu et al., 2013). Animal models show that exercise has beneficial effects on cognition, neuroinflammation and behaviour (Ryan and Nolan, 2016; Svensson et al., 2015). There is a large literature on the beneficial effects of exercise for neuroinflammation

(cytokines and microglial activation) in models of Alzheimer's and Parkinson's disease, and this is reviewed elsewhere (Svensson et al., 2015; van Praag, 2009). In general, exercise reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines and decreases the inflammatory phenotype of microglia (Delpech et al., 2016; Kohman et al., 2013; Madore et al., 2020; Svensson et al., 2015). In particular, exercise induces IL-6 in muscle, blood and cerebrospinal fluid, and IL-6 can suppress TNFα and IL1-β, promoting an anti-inflammatory phenotype (Kilic et al., 2014; Petersen and Pedersen, 2006). Exercise is also effective in alleviating depressive-type behaviour and decreasing INFγ in the prefrontal cortex (Liu et al., 2013). The evidence for exhaustive exercise is less clear. Some studies show this is detrimental for immune function, leaving animals more susceptible to severe symptoms of infection, others demonstrate a protective effect (Simpson et al., 2020).

There is some evidence that exercise can rescue the neuroimmune effects of developmental stress. Maternal separation decreases TLR-4 and its main signalling protein Myd88 in the hippocampus, an effect that is rescued by voluntary but not forced exercise (Sadeghi et al., 2016). Exercise has also been shown to rescue deficient microglial activity resulting from MIA (Andoh et al., 2019).

Diet

Positive dietary manipulations in animals involve addition of beneficial compounds to the diet, and a few studies demonstrate this can reverse the effects of developmental stress. Addition of polyphenols (naturally occurring compounds with several health benefits) and probiotics to the diet postnatally reverses the effects of maternal separation on depressive, anxiety and fear behaviours and gut microbiota, suggesting alterations to the gut-brain axis can influence behaviour (e,g. Cowan et al., 2019; Donoso et al., 2020). Furthermore, addition of PUFA's to

the post-weaning diet and high maternal vitamin D reverse the effects of MIA on pre-pulse inhibition, anxiety, dopaminergic development and brain chemistry, and dietary supplementation with methyl donors (choline, betaine, folate and vitamin B12) in adulthood rescues the effects of maternal separation on depression-like behaviour (Li et al., 2015; Luan et al., 2018; Paternain et al., 2016; Rincel et al., 2020). The role of the immune system in this rescuing effect is currently unknown. However, this is a plausible mechanism, as dietary manipulations can improve immune function. For example, addition of DHA (a polyunsaturated fatty acid crucial for brain development) to the diet attenuates neuroinflammation, and high maternal zinc prevents astrogliosis and TNFα increases resulting from prenatal MIA (Chua et al., 2012; Orr et al., 2013). One study linking diet to immune function *and* behaviour found that offspring from mothers given poly I:C (MIA) develop autism-like behaviours (such as impaired social function) and greater immune system reactivity (IL-6 response to adult immune challenge): this was normalised by supplementing the maternal and postnatal diet with DHA (Weiser et al., 2016). Dietary manipulations, especially those aimed at reducing inflammation, appear to be a promising avenue for protecting against or rescuing the effects of developmental stress on neuroimmune function and psychiatric behaviours, but research in this area is in its infancy and more studies are needed.

Sex differences

There are striking sex differences in the prevalence of neuroimmune and psychiatric disorders and in treatment response (Tiwari and Gonzalez, 2018). Despite this, the majority of clinical and preclinical studies focus on males, an imbalance that urgently needs addressing in order to provide effective therapeutic avenues for both sexes (Coiro et al., 2015). Women are more susceptible to neuroinflammatory diseases such as multiple sclerosis, chronic pain, rheumatoid

arthritis, psoriasis and Alzheimer's disease, accounting for 78% of patients, and display 2-3 times higher rates of anxiety, affective disorders, post-traumatic stress disorder and major depressive disorder (Desai and Brinton, 2019; Kessler et al., 1993, 2005; Remes et al., 2016). There is evidence that men show a better therapeutic response to tricyclic antidepressants, women to selective serotonin reuptake inhibitors (although interestingly this effect is abolished post-menopause), and there is also evidence of sex differences in response to psychological interventions (LeGates et al., 2019; Wade et al., 2016). As we have discussed, stress results in increased inflammation associated with disease, and it has been hypothesised that this effect is greater in women, leaving them more vulnerable to stress related psychopathologies such as anxiety and depression (Bekhbat and Neigh, 2018). This is supported by studies showing that INFα and antiviral treatment results in greater depressive symptoms in women (Koskinas et al., 2002; Udina et al., 2012). However, the links between low grade inflammation and psychiatric illness have been questioned: when sex is accounted for this relationship appears to be specific to men (Liukkonen et al., 2011; Ramsey et al., 2016). Although not well studied, sex differences in basal neuroimmune function and subsequent response to drugs and environmental experiences may help to explain these differences (Brodin and Davis, 2017). In humans, sex differences in the relationship between stress and neuroimmune function are hard to disentangle, as women and men may perceive and cope with stress in divergent manners, so again animal models can provide more closely controlled insights into underlying mechanisms. We will now briefly summarise sex differences in the neuroimmune system, and their subsequent responses to environmental experiences.

A handful of studies have compared sex differences in stress-related immune changes in humans, relying on peripheral measures. One study found that laboratory induced stress (using the Stroop colour-word interference and cold pressor test) affects T lymphocytes in a similar manner in males and females, yet increases NKCs in women whilst decreasing them in

men (Pehlivanoglu et al., 2012). Sex hormones are likely to play a role in these divergent responses. Estrogen and progesterone in particular suppress immune function at physiological levels, and women taking oral contraceptives demonstrate higher immune responses to laboratory stress tests than unmedicated females and males (leukocytes, neutrophils and CD19+ B lymphocytes (Maes et al., 1999)). Laboratory stress also induces greater expression of IL-6 in post-menopausal women and chronic stress appears to result in greater immune suppression in women (Endrighi et al., 2016; Flynn et al., 2009). In animals, male and female lymphocytes display different levels of progesterone receptors (De Leon-Nava et al., 2009). Ex-vivo, microglia and astrocytes from neonatal rodent males release more IL-1β when given LPS: co-stimulation with estradiol suppresses this release in male yet enhances release in female cells (Loram et al., 2012). Sex based immune differences at baseline and in response to social, sound and restraint stress are observed in leukocytes, NKCs, neutrophils and microglia in adult animals (Aghajani et al., 2018; Baldwin et al., 1997; Bollinger et al., 2016; Stefanski and Gruner, 2006).

In the brain, microglia and mast cells show sex differences in number, morphology and activity during development, and are influential in masculinizing neural circuits in the rodent preoptic area (Hanamsagar et al., 2018; Lenz and Nelson, 2018; Lenz et al., 2013; Osborne et al., 2018; Schwarz et al., 2012). Rodent males have more microglia in early postnatal development, whereas females have more microglia with an activated morphology from puberty through adulthood (Schwarz et al., 2012), and female microglia reach an adult phenotype earlier and have higher levels of phagocytosis and phagocytic gene expression (Bordeleau et al., 2019; Nelson et al., 2017). Such differences could result in divergent consequences of developmental stress, which could be altered in a sex-specific manner depending on the time of insult. A few animal studies provide support for this hypothesis. Prenatal administration of dexamethasone alters morphology of microglia, reducing and

shortening their processes in females, lengthening and increasing them in males (Caetano et al., 2017). In the hippocampus, prenatal restraint stress increases the proportion of active microglial in the CA1 in males, the dentate gyrus in females, and maternal separation decreases glial cells in the substantia nigra and ventral tegmental area in males but not females (Chocyk et al., 2011; Diz-Chaves et al., 2012, 2013). Time of assessment is also likely to prove crucial in determining long-term consequences of developmental stress: MIA increases glia cell markers in PFC and hippocampus in both sexes at 30 days, whereas at 60 days this increase is only evident in male PFC (de Souza et al., 2015).

In animals, developmental stress also alters expression of inflammation-related genes in a sex-dependent manner, and generally, effects appear more pronounced in males. Two studies in mice found that prenatal light/restraint stress increases TNFα and IL1-β in the hippocampus of males, but only IL1-β is increased in females (Diz-Chaves et al., 2012, 2013). Another study using rats found that a similar prenatal protocol reduced expression of IL-1β in the male rat hippocampus with no change in females (Mandyam et al., 2008). Discrepancies likely arise due to exact protocols and species used, and age of adult assessment. Maternal separation/deprivation increases circulating TNFα and TNFα:IL-10 and increases IL-1 receptor type 1 expression in hippocampal synapses in males only (do Prado et al., 2016; Viviani et al., 2014), and MIA potentiates the expression of IL1-β, CXC ligand 10, TNFα and suppressor of cytokine signalling 3 in the adult male hypothalamus, amygdala and PFC in response to LPS stimulation (Makinson et al., 2017). A similar effect is seen in adolescence. Here, mixed modality stress (restraint and social defeat) enhances hippocampal expression of IL1-β, TNFα and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα, inhibits NFκβ transcription) in males following an LPS challenge, this is not observed in females (Pyter et al., 2013).

Although our knowledge on even basal sex differences in immune function are incomplete, there is mounting evidence that the neuroimmunological consequences of stress can diverge significantly between males and females. This is an area ripe for further exploration, and increased knowledge will assist in tailoring sex-specific treatments for a range of stress related disorders.

Conclusions & future directions

It is now well established that the immune system plays a key role in the normal development and function of the CNS. This neuroimmune system responds to a wide range of environmental stimuli in adulthood and during development. Positive and negative environmental experiences throughout development can permanently alter the developing neuroimmune system, with accompanying behavioural alterations. Chronic or intense acute stress results in an abnormal neuroimmunological phenotype, which may result in abnormal brain structure and function, predisposing individuals to psychiatric illness. Although less well studied, positive experiences may promote resilience and can reverse the effects of developmental stress on the neuroimmune system. This proposes the neuroimmune system as a therapeutic target for psychiatric illnesses, especially those related to stress, and suggest that restoration of the neuroimmune system may be necessary for restoring proper brain function. Going forward, greater emphasis should be placed on the protective and restorative role that exposure to positive environmental experiences may provide for neuroimmune function. In particular, unlike negative experiences, the persistence of neuroimmune effects resulting from positive environmental experiences are virtually unknown, as are the potential existence of critical periods for maximum benefits, particularly in reversing the effects of developmental stress. The majority of studies focus on male subjects, yet those including females often find striking

sex differences not only in basal neuroimmune function but also in response to developmental experiences. Future studies should strive to include females in order to tailor treatments based on sex where necessary.

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Abbreviations

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid); BBB (blood brain barrier); C3aR1 (complement component C3a receptor 1); CA (childhood adversity); CCL2 (C-C motif chemokine ligand 2); CCL3 (C-C motif chemokine ligand 3); CCR2 (C-C motif chemokine receptor 2); CNS (central nervous system); CRP (c reactive protein); CXC (C-X-C motif); CX3CL1 (C-X3-C motif ligand 1, also known as fractalkine); CXCL2 (CXC ligand 2); CXCL12 (CXC chemokine 12); CXCR4 (CXC chemokine receptor 4); DHA (docosahexaenoic acid); EE (environmental enrichment); FKBP5 (FK506-binding protein 5); GC (glucocorticoid); HPA (hypothalamic-pituitary-adrenal); IFN (interferon); IL (interleukin); LPS (lipopolysaccharide); LTD (long term depression); LTP (long term potentiation); MHC (major histocompatibility complex); MIA (maternal immune activation); NE (norepinephrine); NFκβ (nuclear factor kappa-light-chain enhancer of activated B cells); NKC (natural killer cells); NMDA (N-methly-D-aspartate); PES (postnatal early stimulation); PFC (prefrontal cortex); PTSD (post-traumatic stress disorder); PUFA (polyunsaturated fatty acids); SAM (sympathetic-adrenal-medullary); TLR (toll-like receptors); TNF (tumour necrosis factor).

Figures

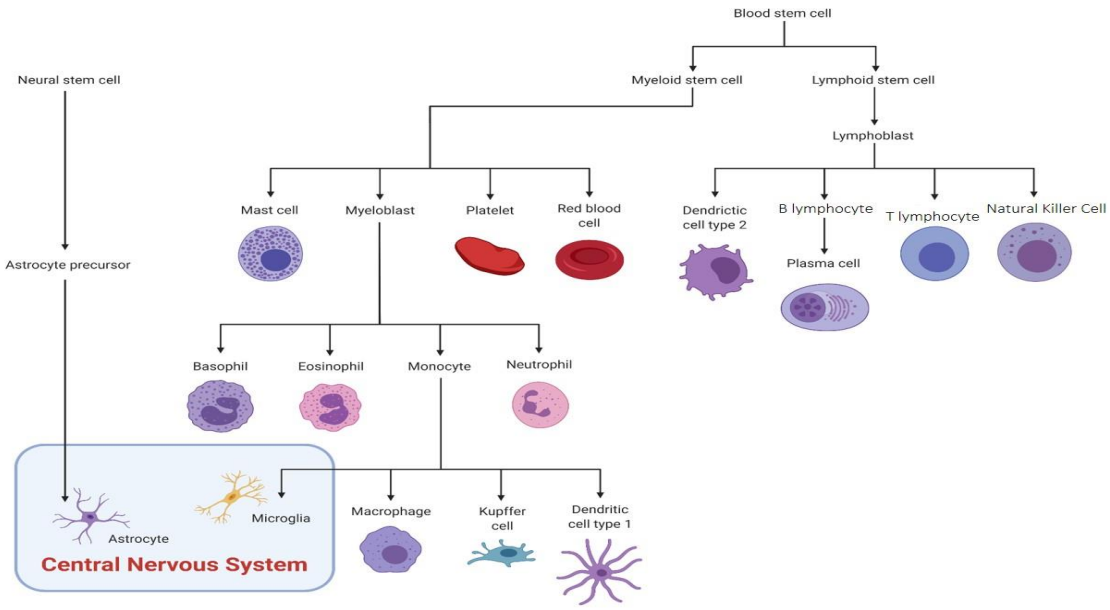

Figure 1: Developmental origins of immune cells in the periphery and central nervous system. Blood stem cells are bipotent stem cells that are the origin of all blood cell types, differentiating into either myeloid or lymphoid stems cells. Lymphoid stem cells differentiate into natural killer cells, type 2 (plasmacytoid) dendritic cells, T lymphocytes and B lymphocytes. B lymphocytes, when fully differentiated and capable of secreting antibodies, are termed plasma cells. Myeloid stem cells undergo further differentiation into mast cells, platelets, red blood cells and myeloblasts, which in turn differentiate into basophils, eosinophils, monocytes, and neutrophils. Monocytes in the blood and some tissues become macrophages and type 1 (conventional) dendritic cells, however monocytes that take residence in some organs differentiate into tissue specific macrophages such as: microglia (central nervous system), Kupffer cells (liver) and osteoclasts (bone). Astrocytes are a brain and spinal cord specific cell type essential for mounting an immune response in these tissues, and are derived from neural stem cells which go through an astrocytes precursor stage before becoming fully mature astrocytes.

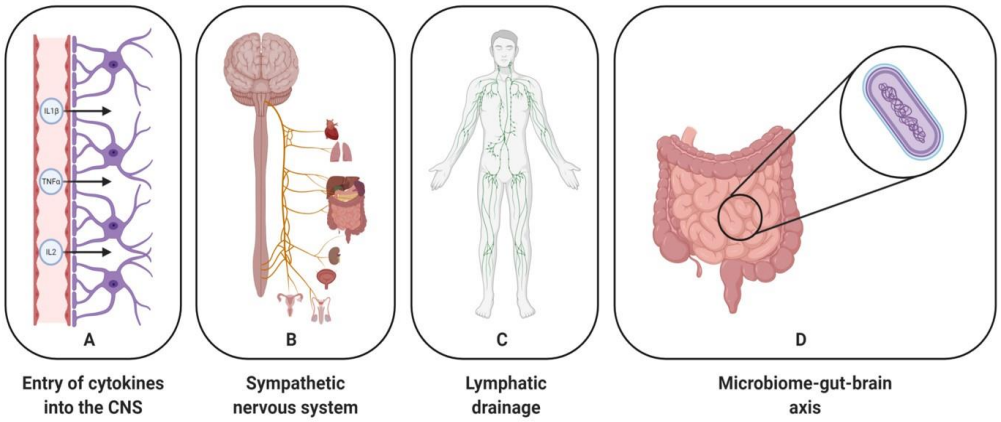

Figure 2. Routes of peripheral immune system communication with the central nervous system (CNS). **A.** Cytokine diffusion (slow transmission): entry of cytokines into the brain through a disrupted or 'leaky' blood brain barrier and their active transport by endothelial cells of the blood brain barrier. **B.** Sympathetic nervous system (fast transmission): bidirectional signaling via the vagal nerves from peripheral organs including the spleen, lung and heart allows action potentials generated by primary afferent neurons innervating organs to be transmitted to the CNS, and signals originating in the brain to induce the release of hormones in periphery. **C.** Lymphatic system: lymphatic drainage for the brain is essential for waste clearance and ion balance however emerging evidence suggest it may be a mechanism by which the CNS can present antigens to the peripheral immune system. **D.** Microbiome-gut-brain axis: neurons innervating the gut and its resident bacteria produce acetylcholine, histamine and serotonin which provide a direct route of communication between the gut and the brain.

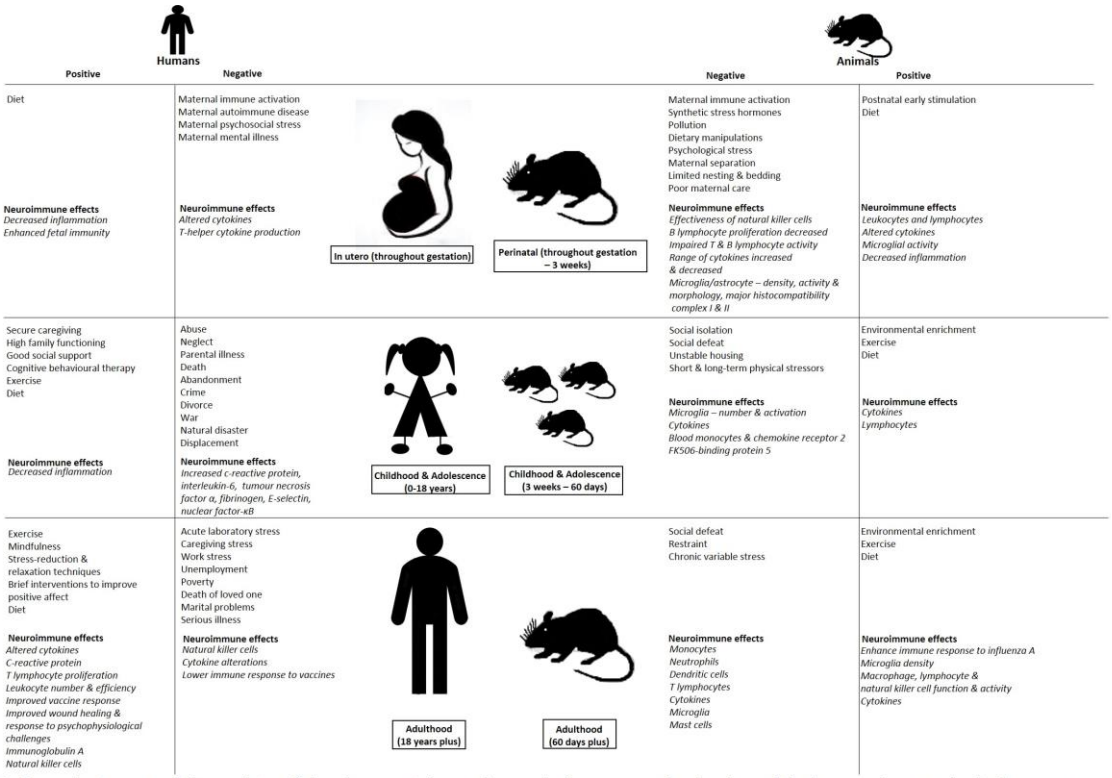

Figure 3. Example types and timepoints of developmental experiences in humans and animals and their neuroimmunological consequences.