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Enduring neuroimmunological consequences of developmental experiences: From vulnerability to resilience

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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.

1. Introduction

1.1. 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.

2. The immune system

2.1. Innate vs. adaptive

Immune function in vertebrates is broadly classified into innate and

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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 presenting 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.

2.2. 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

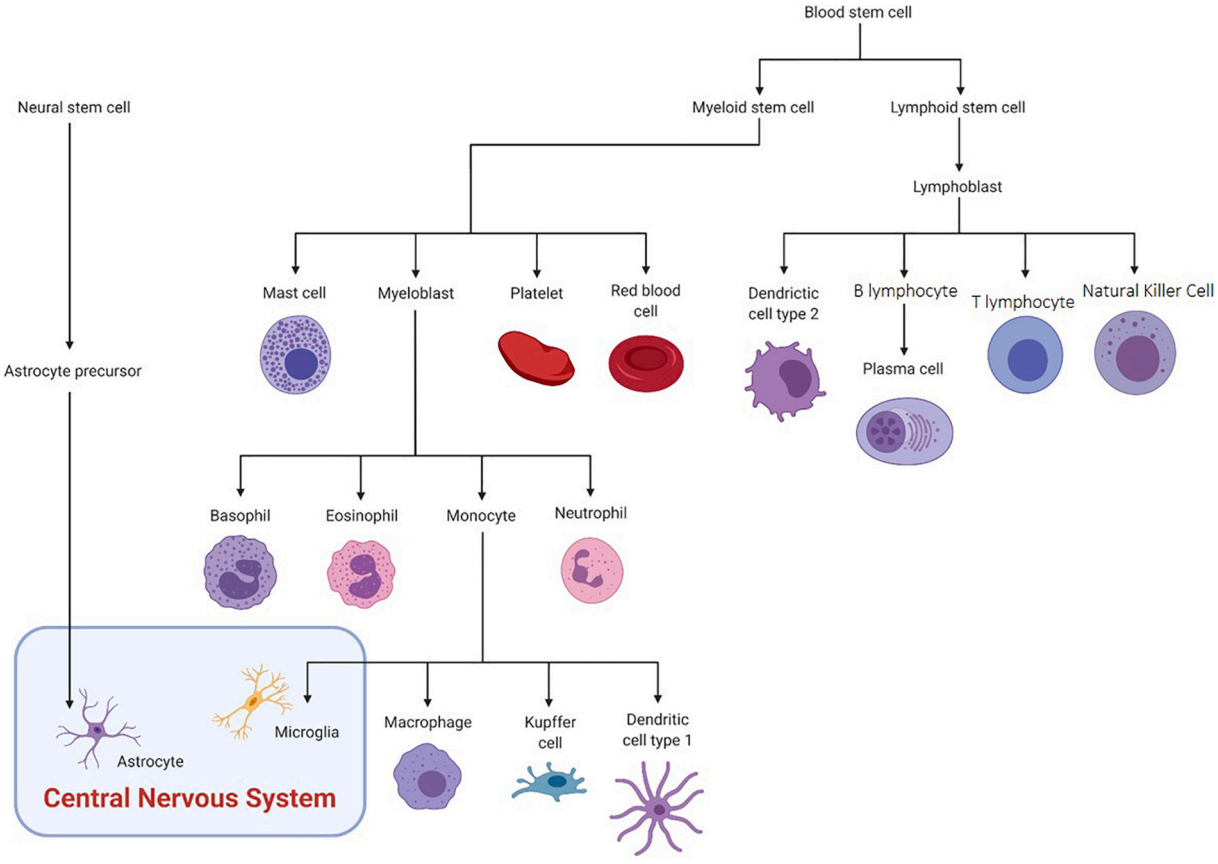

Fig. 1. Developmental origins of immune cells in the periphery and central nervous system. Blood stem cells are bipotent stem cells that are the origin of all blood cell types, differentiating into either myeloid or lymphoid stem cells. Lymphoid stem cells differentiate into natural killer cells, type 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, platlets, 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 I (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 astrocyte precursor stage before becoming fully mature astrocytes (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

differentiated form whereas others complete their differentiation in a wide array of target tissues (Medina, 2016) (Fig. 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 (Fig. 1).

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

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

3. The neuroimmune environment

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

We now know there are several mechanisms through which peripheral immune molecules can influence the healthy brain (Fig. 2). There is regulated transport of certain cytokines and chemokines across the BBB, and immune cells can interact with endothelial cells of the BBB, creating a cascade of effects in the brain (Banks, 2005; Daneman and Prat, 2015; Pan and Kastin, 2002). The lymphatic drainage systems of the brain (perivascular drainage, glymphatic system and meningeal lymphatic vessels) function to clear waste from the CNS, transport lipids, maintain interstitial fluid water and ion homeostasis, regulate cerebrospinal fluid and interstitial fluid pressure and provide links between the peripheral immune system and the CNS (Begley, 2012; Benveniste, 2018; Kipnis, 2016; Makinen, 2019; Sun et al., 2018; Thrane et al., 2013). Here, T lymphocytes can enter the brain via leptomeningeal vessels, choroid plexus and parenchymal postcapillary venule (efferent pathway) (Mastorakos and McGavern, 2019). Signalling works both ways - CNS derived antigens present in cerebrospinal fluid and interstitial fluid draining into cervical lymph 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 (Fig. 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, 2013; Rogers et al., 2016). This communication is modulated by shifts in diet, composition of the microbiome and gut inflammation (Foster and Neufeld, 2013; 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).

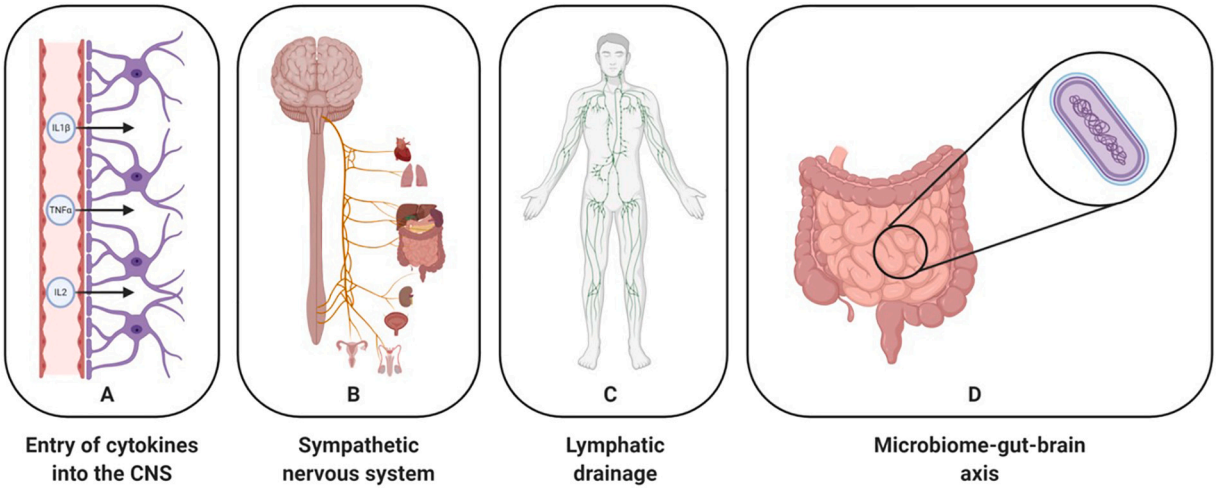

Fig. 2. Routes of peripheral immune system communication with the central nervous system (CNS). A. Cytokine diffusion (slow transmission): entry of cytokines into the brain through a disrupted or 'leaky' blood brain barrier and their active transport by endothelial cells of the blood brain barrier. B. Sympathetic nervous system (fast transmission): bidirectional signalling 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 immime 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.

3.2. 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.

3.2.1. 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 chemokine 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).

3.2.2. 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).

3.2.3. 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 fragment of the immunoglobulin A receptor and stem cell factor), which may alter their development and survival (Khalil et al., 2007; 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 presenting 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).

3.2.4. 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 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-activated 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 h 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).

3.2.5. 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 et al., 2007). 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.

4. 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 single nucleotide polymorphisms 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 18 kDa 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 disorder 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.

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

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

6. 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 Fig. 3 for a summary of the major types of positive and negative experiences and their neuroimmunological consequences throughout these periods in humans and animals.

7. Perinatal stress (prenatal & early postnatal)

7.1. 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 2019 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

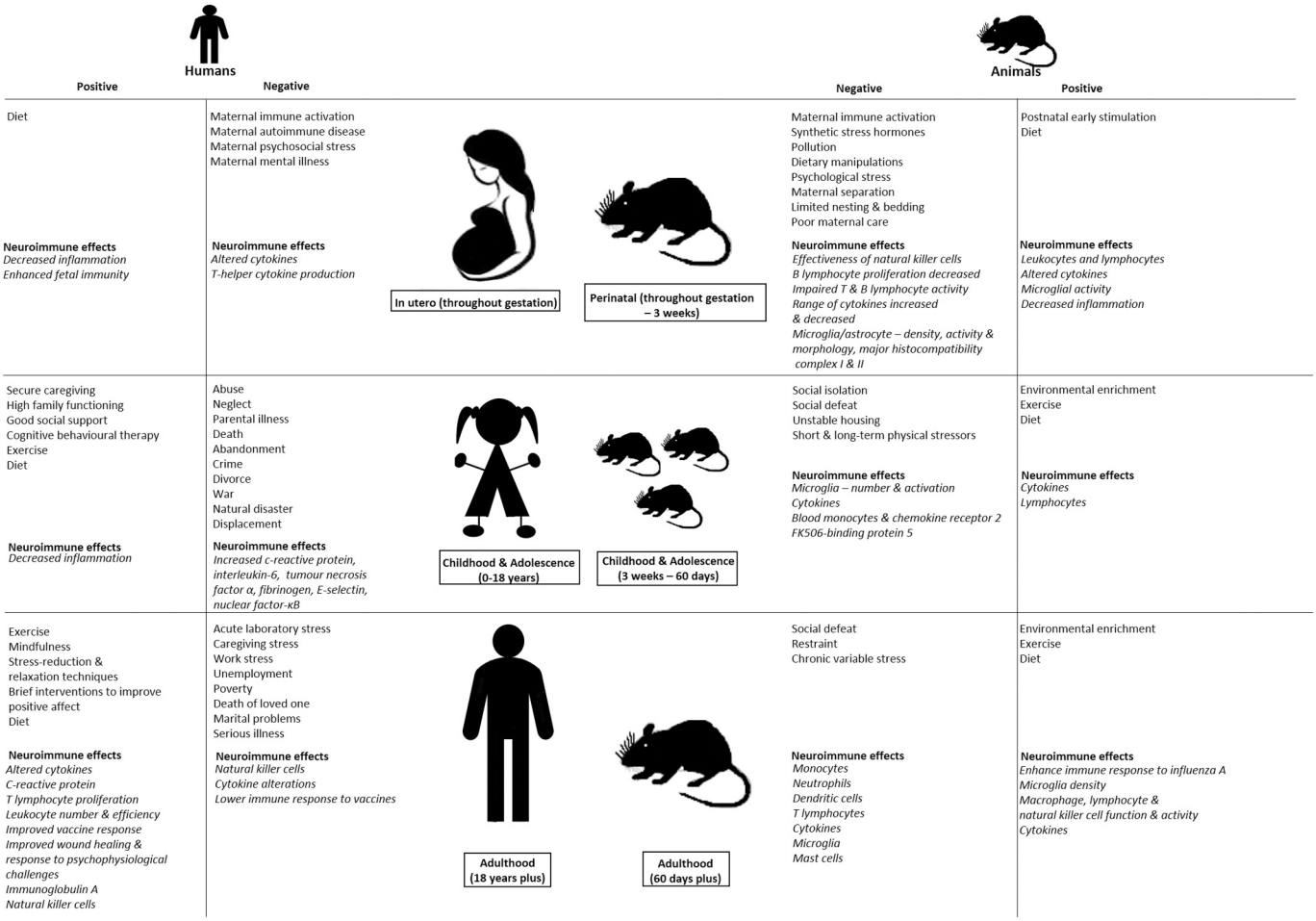

Fig. 3. Example types and timepoints of developmental experiences in humans and animals and their neuroimmunological consequences.

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

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

7.2. Animals – prenatal & early postnatal

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

8. Childhood/pre-pubertal/adolescent stress

8.1. 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., 2012; 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.

8.2. 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. However, similarly to perinatal stress, pre-pubertal and adolescent stress result 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.

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

Positive environmental experiences such as mindfulness are

beneficial for improving depression, anxiety, coping and mood in individuals with a history of childhood adversity, but the implications of such interventions for immune function in this population are largely unknown (Ortiz and Sibinga, 2017). There is research demonstrating that sensitive caregiving 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.

9.1. 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.

9.2. 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.

9.3. 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).

9.4. 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 PUFAs 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 and Darnaudery, 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.

10. 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.

11. 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 suggests 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.

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 chemokine 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

CRediT authorship contribution statement

Nichola Brydges: conceptualization, investigation, writing original draft, review and editing, visualization. **Jack Reddaway**: conceptualization, investigation, writing original draft, review and editing, visualization.

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References

Abbott, N.J., Ronnback, L., Hansson, E., 2006. Astrocyte-endothelial interactions at the blood-brain barrier. Nat. Rev. Neurosci. 7, 41–53.

Abel, K.M., Heuvelman, H.P., Jorgensen, L., Magnusson, C., Wicks, S., Susser, E., Hallkvist, J., Dalman, C., 2014. Severe bereavement stress during the prenatal and childhood periods and risk of psychosis in later life: population based cohort study. Br. Med. J. 348, 1–13.

Acharya, K.R., Ackerman, S.J., 2014. Eosinophil granule proteins: form and function. J. Biol. Chem. 289, 17406–17415.

Aghajani, M., Mahdavi, M., Najafabadi, M., Ghazanfari, T., Moghaddam, E., 2018. Effects of social stresses on immune response in female and male mice. Immunoregulation 1, 101–106.

Agorastos, A., Pervanidou, P., Chrousos, G.P., Baker, D.G., 2019. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Frontiers in Psychiatry 10, Article 118.

Amarante-Mendes, G.P., Adjemian, S., Branco, L.M., Zanetti, L.C., Weinlich, R., Bortoluci, K.R., 2018. Pattern recognition receptors and the host cell death molecular machinery. Frontiers in Immunology 9, Article 2379.
Ambree, O., Ruland, C., Scheu, S., Arolt, V., Alferink, J., 2018. Alterations of the innate immune system in susceptibility and resilience after social defeat stress. Frontiers in Behavioral Neuroscience 12, Article 141.
Akdis, M., Burgler, S., Crameri, R., Eiwegger, T., Fujita, H., Gomez, E., Klunker, S., Meyer, N., O'Mahony, L., Palomares, O., Rhyner, C., Ouaked, N., Schaffartzik, A., Van De Veen, W., Zeller, S., Zimmermann, M., Akdis, C., 2011. Interleukins, from 1 to 37, and interferon-gamma: receptors, functions, and roles in diseases. J. Allergy Clin. Immunol. 127, 701–721.
Anderson, M.L., Sisti, H.M., Il, D.M.C., Shors, T.J., 2011. Associative learning increases adult neurogenesis during a critical period. Eur. J. Neurosci. 33, 175–181.
Andoh, M., Shibata, K., Okamoto, K., Onodera, J., Morishita, K., Miura, Y., Ikegaya, Y., Koyama, R., 2019. Exercise reverses behavioral and synaptic abnormalities after maternal inflammation. Cell Rep. 27, 2817–2825.
Aoi, W., Naito, Y., 2019. Immune function, nutrition, and exercise. Academic Press, In Nutrition and Enhanced Sports Performance (Second Edition), Muscle Building, Endurance and Strength, pp. 83–95.
Aoki, T., Narumiya, S., 2012. Prostaglandins and chronic inflammation. Trends Pharmacol. Sci. 33, 304–311.
Arranz, L., De Castro, N.M., Baeza, I., Mate, I., Viveros, M.P., De la Fuente, M., 2010. Environmental enrichment improves age-related immune system impairment: long-term exposure since adulthood increases life span in mice. Rejuvenation Res. 13, 415–428.
Ashcraft, K.A., Hunzeker, J., Bonneau, R.H., 2008. Psychological stress impairs the local CD8(+) T cell response to mucosal HSV-1 infection and allows for increased pathogenicity via a glucocorticoid receptor-mediated mechanism. Psychoneuroendocrinology 33, 951–963.
Assary, E., Vincent, J.P., Keers, R., Pluess, M., 2018. Gene-environment interaction and psychiatric disorders: review and future directions. Semin. Cell Dev. Biol. 77, 133–143.
Ataka, K., Asakawa, A., Nagaishi, K., Kaimoto, K., Sawada, A., Hayakawa, Y., Tatezawa, R., Inui, A., Fujimiya, M., 2013. Bone marrow-derived microglia infiltrate into the paraventricular nucleus of chronic psychological stress-loaded mice. Plos One 8, Article e81744.
Avitsur, R., Hunzeker, J., Sheridan, J.F., 2006. Role of early stress in the individual differences in host response to viral infection. Brain Behav. Immun. 20, 339–348.
Avitsur, R., Maayan, R., Weizman, A., 2013. Neonatal stress modulates sickness behavior: role for proinflammatory cytokines. J. Neuroimmunol. 257, 59–66.
Ayling, K., Kanchan, S., Vedhara, K., 2020. Effects of brief mood-improving interventions on immunity: a systematic review and meta-analysis. Psychosom. Med. 82, 10–28.
Baartman, T.L., Swanepoel, T., Barrientos, R.M., Laburn, H.P., Mitchell, D., Harden, L.M., 2017. Divergent effects of brain interleukin-l beta in mediating fever, lethargy, anorexia and conditioned fear memory. Behav. Brain Res. 324, 155–163.
Babulas, V., Factor-Litvak, P., Goetz, R., Schaefer, C.A., Brown, A.S., 2006. Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. Am. J. Psychiatr. 163, 927–929.
Baldwin, D.R., Wilcox, Z.C., Zheng, G.P., 1997. The effects of voluntary exercise and immobilization on humoral immunity and endocrine responses in rats. Physiol. Behav. 61, 447–453.
Baldy, C., Fournier, S., Boisjoly-Villeneuve, S., Tremblay, M.E., Kinkead, R., 2018. The influence of sex and neonatal stress on medullary microglia in rat pups. Exp. Physiol. 103, 1192–1199.
Balschun, D., Wetzel, W., del Rey, A., Pitossi, F., Schneider, H., Zuschratter, W., Besedovsky, H.O., 2004. Interleukin-6: a cytokine to forget. FASEB J. 18, 1788–1790.
Banks, W.A., 2005. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. Curr. Pharm. Des. 11, 973–984.
Banqueri, M., Mendez, M., Gomez-Lazaro, E., Arias, J.L., 2019. Early life stress by repeated maternal separation induces long-term neuroinflammatory response in glial cells of male rats. Stress-the International Journal on the Biology of Stress 22, 563–570.
Barr, T., Helms, C., Grant, K., Messaoudi, I., 2016. Opposing effects of alcohol on the immune system. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 65, 242–251.
Baud, V., Karin, M., 2001. Signal transduction by tumor necrosis factor and its relatives. Trends Cell Biol. 11, 372–377.
Bauer, M.E., Teixeira, A.L., 2019. Inflammation in psychiatric disorders: what comes first? Ann. N. Y. Acad. Sci. 1437, 57–67.
Baumeister, D., Russell, A., Pariante, C.M., Mondelli, V., 2014. Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors. Soc. Psychiatry Psychiatr. Epidemiol. 49, 841–849.
Baumeister, D., Ciufolini, S., Mondelli, V., 2016. Effects of psychotropic drugs on inflammation: consequence or mediator of therapeutic effects in psychiatric treatment? Psychopharmacology 233, 1575–1589.
Baune, B.T., Dannlowski, U., Domschke, K., Janssen, D.G.A., Jordan, M.A., Ohrmann, P., Bauer, J., Biros, E., Arolt, V., Kugel, H., Baxter, A.G., Suslow, T., 2010. The interleukin 1 beta (IL 1B) gene is associated with failure to achieve remission and impaired emotion processing in major depression. Biol. Psychiatry 67, 543–549.
Begley, D.J., 2012. Brain superhighways. Sci. Transl. Med. 4, 1–3.
Bekhbat, M., Neigh, G.N., 2018. Sex differences in the neuro-immune consequences of stress: Focus on depression and anxiety. Brain Behav. Immun. 67, 1–12.
Bekhbat, M., Howell, P.A., Rowson, S.A., Kelly, S.D., Tansey, M.G., Neigh, G.N., 2019. Chronic adolescent stress sex-specifically alters central and peripheral neuro-immune reactivity in rats. Brain Behav. Immun. 76, 248–257.
Bellinger, F.P., Madamba, S., Siggins, G.R., 1993. Interleukin 1-beta inhibits synaptic strength and long-term potentiation in the rat CA1 hipocampus. Brain Res. 628, 227–234.
Benveniste, H., 2018. The brain's waste-removal system. Cerebrum. PMCID: PMC635118.
Bergdolt, L., Dunaevsky, A., 2019. Brain changes in a maternal immune activation model of neurodevelopmental brain disorders. Prog. Neurobiol. 175, 1–19.
Bilbo, S.D., Tsang, V., 2010. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB J. 24, 2104–2115.
Bilbo, S.D., Newsum, N.J., Sprunger, D.B., Watkins, L.R., Rudy, J.W., Maier, S.F., 2007. Differential effects of neonatal handling on early life infection-induced alterations in cognition in adulthood. Brain Behav. Immun. 21, 332–342.
Bjorkenstam, E., Burstrom, B., Vinnerljung, B., Kosidou, K., 2016. Childhood adversity and psychiatric disorder in young adulthood: An analysis of 107,704 swedes. J. Psychiatr. Res. 77, 67–75.
Black, C., Miller, B.J., 2015. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. Biol. Psychiatry 78, 28–37.
Black, D.S., Slavich, G.M., 2016. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. Ann. N. Y. Acad. Sci. 1373, 13–24.
Bland, S.T., Beckley, J.T., Young, S., Tsang, V., Watkins, L.R., Maier, S.F., Bilbo, S.D., 2010. Enduring consequences of early-life infection on glial and neural cell genesis within cognitive regions of the brain. Brain Behav. Immun. 24, 329–338.
Blandino, P., Barnum, C.J., Deak, T., 2006. The involvement of norepinephrine and microglia in hypothalamic and splenic IL-1 beta responses to stress. J. Neuroimmunol. 173, 87–95.
Blomstrom, A., Karlsson, H., Gardner, R., Jorgensen, L., Magnusson, C., Dalman, C., 2016. Associations between maternal infection during pregnancy, childhood infections, and the risk of subsequent psychotic disorder-a Swedish cohort study of nearly 2 million individuals. Schizophr. Bull. 42, 125–133.
Bock, J., Wainstock, T., Braun, K., Segal, M., 2015. Stress in utero: prenatal programming of brain plasticity and cognition. Biol. Psychiatry 78, 315–326.
Boehme, K.W., Compton, T., 2004. Innate sensing of viruses by toll-like receptors. J. Virol. 78, 7867–7873.
Bohlen, C.J., Friedman, B.A., Dejanovic, B., Sheng, M., 2019. Microglia in brain development, homeostasis, and neurodegeneration. Annu. Rev. Genet. 53, 263–288.
Bollinger, J.L., Burns, C.M.B., Wellman, C.L., 2016. Differential effects of stress on microglial cell activation in male and female medial prefrontal cortex. Brain Behav. Immun. 52, 88–97.
Bolton, J., Marinero, S., Hassanzadeh, T., Natesan, D., Le, D., Belliveau, C., Mason, S., Aute, R., Bilbo, S., 2017. Gestational exposure to air pollution alters cortical volume, microglial morphology, and microglia-neuron interactions in a sex-specific manner. Frontiers in synaptic neuroscience, 9, article 10.
Bordeleau, M., Carrier, M., Luheshi, G.N., Tremblay, M.E., 2019. Microglia along sex lines: from brain colonization, maturation and function, to implication in neurodevelopmental disorders. Semin. Cell Dev. Biol. 94, 152–163.
Borsini, A., Alboni, S., Horowitz, M.A., Tojo, L.M., Cannazza, G., Su, K.P., Pariante, C.M., Zunszain, P.A., 2017. Rescue of IL-1 beta-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain Behav. Immun. 65, 230–238.
Bowen, K.K., Dempsey, R.J., Vemuganti, R., 2011. Adult interleukin-6 knockout mice show compromised neurogenesis. Neuroreport 22, 126–130.
Branco, A., Yoshikawa, F.S.Y., Pietrobon, A.J., Sato, M.N., 2018. Role of histamine in modulating the immune response and inflammation. Mediators of Inflammation 2018, Article 9524075.
Brannigan, R., Cannon, M., Tanskanen, A., Huttunen, M.O., Leacy, F.P., Clarke, M.C., 2019. The association between subjective maternal stress during pregnancy and offspring clinically diagnosed psychiatric disorders. Acta Psychiatr. Scand. 139, 304–310.
Brannigan, R., Tanskanen, A., Huttunen, M.O., Cannon, M., Leacy, F.P., Clarke, M.C., 2020. The role of prenatal stress as a pathway to personality disorder: longitudinal birth cohort study. Br. J. Psychiatry 216, 85–89.
Breen, M.S., Beliakova-Bethell, N., Mujica-Parodi, L.R., Carlson, J.M., Ensign, W.Y., Woelk, C.H., Rana, B.K., 2016. Acute psychological stress induces short-term variable immune response. Brain Behav. Immun. 53, 172–182.
Breit, S., Kupferberg, A., Rogler, G., Hasler, G., 2018. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Frontiers in Psychiatry 9. Article 44.
Brenhouse, H.C., Schwarz, J.M., 2016. Immunoadolescence: Neuroimmune development and adolescent behavior. Neurosci. Biobehav. Rev. 70, 288–299.
Brevet, M., Kojima, H., Asakawa, A., Atsuchi, K., Ushika, M., Ataka, K., Inui, A., Kimura, H., Sevestre, H., Fujimiya, M., 2010. Chronic foot-shock stress potentiates the influx of bone marrow-derived microglia into hippocampus. J. Neurosci. Res. 88, 1890–1897.
Brietzke, E., Stertz, L., Fernandes, B.S., Kauer-Sant'Anna, M., Mascarenhas, M., Vargas, A.E., Chies, J.A., Kapczinski, F., 2009. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord. 116, 214–217.
Brodin, P., Davis, M.M., 2017. Human immune system variation. Nat. Rev. Immunol. 17, 21–29.
Brown, A.S., Cohen, P., Harkavy-Friedman, J., Babulas, V., Malaspina, D., Gorman, J.M., Susser, E.S., 2001. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol. Psychiatry 49, 473–486.
Brown, A.S., Begg, M.D., Gravenstein, S., Schaefer, C.A., Wyatt, R.J., Bresnahan, M., Babulas, V.P., Susser, E.S., 2004. Serologic-evidence of prenatal influenza in the etiology of schizophrenia. Arch. Gen. Psychiatry 61, 774–780.

Brown, R.C., Witt, A., Fegert, J.M., Keller, F., Rassenhofer, M., Plener, P.L., 2017. Psychosocial interventions for children and adolescents after man-made and natural disasters: a meta-analysis and systematic review. Psychol. Med. 47, 1893–1905.
Brunson, K.L., Chen, Y., Avishai-Eliner, S., Baram, T.Z., 2011. Stress and the developing hippocampus. Mol. Neurobiol. 27, 121–136.
Brydges, N.M. 2016. Pre-pubertal stress and brain development in rodents. Current Opinion in Behavioural Sciences 7, 8–14.
Brydges, N.M., Best, C., Thomas, K.L., 2020. Female HPA axis displays heightened sensitivity to pre-pubertal stress. Stress-the International Journal on the Biology of Stress 23, 190–200.
Bufalino, C., Hepgul, N., Aguglia, E., Pariante, C.M., 2013. The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. Brain Behav. Immun. 31, 31–47.
Buka, S.L., Tsuang, M.T., Torrey, E.F., Klebanoff, M.A., Bernstein, D., Yolken, R.H., 2001. Maternal infections and subsequent psychosis among offspring. Arch. Gen. Psychiatry 58, 1032–1037.
Buschert, J., Sakalem, M.E., Saffari, R., Hohoff, C., Rothermundt, M., Arolt, V., Zhang, W. Q., Ambree, O., 2016. Prenatal immune activation in mice blocks the effects of environmental enrichment on exploratory behavior and microglia density. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 67, 10–20.
Cabezas, R., Avila, M., Gonzalez, J., El-Bacha, R.S., Baez, E., Garcia-Segura, L.M., Coronel, J.C.J., Capani, F., Cardona-Gomez, G.P., Barreto, G.E., 2014. Astrocytic modulation of blood brain barrier: perspectives on parkinson's disease. Frontiers in Cellular Neuroscience 8, Article PMC4120694.
Caetano, L., Pinheiro, H., Patricio, P., Mateus-Pinheiro, A., Alves, N.D., Coimbra, B., Baptista, F.I., Henriques, S.N., Cunha, C., Santos, A.R., Ferreira, S.G., Sardinha, V.M., Oliveira, J.F., Ambrosio, A.F., Sousa, N., Cunha, R.A., Rodrigues, A.J., Pinto, L., Gomes, C.A., 2017. Adenosine A(2A) receptor regulation of microglia morphological remodeling-gender bias in physiology and in a model of chronic anxiety. Mol. Psychiatry 22, 1035–1043.
Cameron, H.A., Schoenfeld, T.J., 2018. Behavioral and structural adaptations to stress. Front. Neuroendocrinol. 49, 106–113.
Campbell, B.M., Charych, E., Lee, A.W., Moller, T., 2014. Kynurenines in CNS disease: regulation by inflammatory cytokines. Frontiers in Neuroscience 8, Article 12.
Campbell, J.P., Turner, J.E., 2018. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. Frontiers in Immunology 9, Article 648.
Canetta, S.E., Brown, A.S., 2012. Prenatal infection, maternal immune activation, and risk for schizophrenia. Transl. Neurosci. 3, 320–327.
Carpenter, L.L., Gawuga, C.E., Tyrka, A.R., Lee, J.K., Anderson, G.M., Price, L.H., 2010. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology 35, 2617–2623.
Carrasco, G.A., de Kar, L.D.V., 2003. Neuroendocrine pharmacology of stress. Eur. J. Pharmacol. 463, 235–272.
Carroll, J.E., Gruenewald, T.L., Taylor, S.E., Janicki-Deverts, D., Matthews, K.A., Seeman, T.E., 2013. Childhood abuse, parental warmth, and adult multisystem biological risk in the coronary artery risk development in Young adults study. Proc. Natl. Acad. Sci. U. S. A. 110, 17149–17153.
Carter, B.S., Meng, F., Thompson, R.C., 2012. Glucocorticoid treatment of astrocytes results in temporally dynamic transcriptome regulation and astrocyte-enriched mRNA changes in vitro. Physiol. Genomics 44, 1188–1200.
Caslin, H.L., Kiwanuka, K.N., Haque, T.T., Taruselli, M.T., MacKnight, H.P., Paranjape, A., Ryan, J.J., 2018. Controlling mast cell activation and homeostasis: work influenced by bill Paul that continues today. Frontiers in Immunology 9, Article 868.
Catale, C., Gironda, S., Lo Iacono, L., Carola, V., 2020. Microglial function in the effects of early-life stress on brain and behavioral development. Journal of Clinical Medicine 9, Article 468.
Chaplin, D.D., 2010. Overview of the immune response. J. Allergy Clin. Immunol. 125, S3–S23.
Chen, S.W., Zhong, X.S., Jiang, L.N., Zheng, X.Y., Xiong, Y.Q., Ma, S.J., Qiu, M., Huo, S. T., Ge, J., Chen, Q., 2016. Maternal autoimmune diseases and the risk of autism spectrum disorders in offspring: a systematic review and meta-analysis. Behav. Brain Res. 296, 61–69.
Cheng, C.Y., Pickler, R.H., 2014. Perinatal stress, fatigue, depressive symptoms, and immune modulation in late pregnancy and one month postpartum. Scientific World Journal 2014, Article 652630.
Childs, C.E., Calder, P.C., Miles, E.A., 2019. Diet and immune function. Nutrients 11, 1–9.
Chocyk, A., Dudys, D., Przyborowska, A., Majcher, I., Mackowiak, M., Wedzony, K., 2011. Maternal separation affects the number, proliferation and apotosis of glia cells in the substantia nigra and ventral tegmental area of juvenile rats. Neuroscience 173, 1–18.
Chou, A., Krukowski, K., Morganti, J.M., Riparip, L.K., Rosi, S., 2018. Persistent infiltration and impaired response of peripherally-derived monocytes after traumatic brain injury in the aged brain. International Journal of Molecular Sciences 19, Article 1616.
Choi, G., Yim, Y.S, Wong, H., Kim, S., Kim, H., Kim, S.V., Hoeffer, C.A., Littman, D.R., Huh, J.R., 2016. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 351, 933–939.
Chua, J.S., Cowley, C.J., Manavis, J., Rofe, A.M., Coyle, P., 2012. Prenatal exposure to lipopolysaccharide results in neurodevelopmetnal damage that is ameliorated by zinc in mice. Brain Behav. Immun. 26, 326–336.
Cirulli, F., Pistillo, L., de Acetis, L., Alleva, E., Aloe, L., 1998. Increased number of mast cells in the central nervous system of adult male mice following chronic subordination stress. Brain Behav. Immun. 12, 123–133.
Clark, R., Kupper, T., 2005. Old meets new: the interaction between innate and adaptive immunity. J. Investig. Dermatol. 125, 629–637.
Coelho, R., Viola, T.W., Walss-Bass, C., Brietzke, E., Grassi-Oliveira, R., 2014. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr. Scand. 129, 180–192.
Cohen, S., Ke, X.R., Liu, Q.L., Fu, Q., Majnik, A., Lane, R., 2016. Adverse early life environment increases hippocampal microglia abundance in conjunction with decreased neural stem cells in juvenile mice. Int. J. Dev. Neurosci. 55, 56–65.
Coiro, P., Padmashri, R., Suresh, A., Spartz, E., Pendyala, G., Chou, S., Jung, Y., Meays, B., Roy, S., Gautam, N., Alnouti, Y., Li, M., Dunaevsky, A., 2015. Impaired synaptic development in a maternal immune activation mouse model of neurodevelopmental disorders. Brain Behav. Immun. 50, 249–258.
Contarteze, R.V.L., Manchado, F.D.B., Gobatto, C.A., Mello, A.R.D., 2008. Stress biomarkers in rats submitted to swimming and treadmill running exercises. Comp. Biochem. Physiol. A Mol. Integr. Physiol. 151, 415–422.
Copeland, W.E., Wolke, D., Lereya, S.T., Shanahan, L., Worthman, C., Costello, E.J., 2014. Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. Proc. Natl. Acad. Sci. U. S. A. 111, 7570–7575.
Corwin, E.J., Guo, Y., Pajer, K., Lowe, N., McCarthy, D., Schmiege, S., Weber, M., Pace, T., Stafford, B., 2013. Immune dysregulation and glucocorticoid resistance in minority and low income pregnant women. Psychoneuroendocrinology 38, 1786–1796.
Coussons-Read, M.E., Okun, M.L., Nettles, C.D., 2007. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav. Immun. 21, 343–350.
Cowan, C.S.M., Stylianakis, A.A., Richardson, R., 2019. Early-life stress, microbiota, and brain development: probiotics reverse the effects of maternal separation on neural circuits uder;inning fear expression and extinction in infant rats. Developmental Cognitive Neuroscience 37, 1–10.
Crider, A., Feng, T., Pandya, C.D., Davis, T., Nair, A., Ahmed, A.O., Baban, B., Turecki, G., Pillai, A., 2018. Complement component 3a receptor deficiency attenuates chronic stress-induced monocyte infiltration and depressive-like behavior. Brain Behav. Immun. 70, 246–256.
Cuneo, A.A., Autieri, M.V., 2009. Expression and function of anti-inflammatory interleukins: the other side of the vascular response to injury. Curr. Vasc. Pharmacol. 7, 267–276.
Curran, B., O'Connor, J.J., 2001. The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. Neuroscience 108, 83–90.
Daneman, R., Prat, A., 2015. The blood-brain barrier. Cold Spring Harbor perspectives in biology 7, article a020412.
Danese, A., Lewis, S.J., 2017. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacology 42, 99–114.
Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc. Natl. Acad. Sci. U. S. A. 104, 1319–1324.
Dani, J.A., Harris, R.A., 2005. Nicotine addiction and comorbidity with alcohol abuse and mental illness. Nat. Neurosci. 8, 1465–1470.
Dantzer, R., 2001. Cytokine-induced sickness behavior: mechanisms and implications. Ann. N. Y. Acad. Sci. 933, 222–234.
Dantzer, R., 2009. Cytokine, sickness behavior, and depression. Immunol. Allergy Clin. N. Am. 29, 247–264.
Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–57.
Davis, I., Liu, A.M., 2015. What is the tryptophan kynurenine pathway and why is it important to neurotherapeutics? Expert. Rev. Neurother. 15, 719–721.
De Leon-Nava, M.A., Nava, K., Soldevila, G., Lopez-Griego, L., Chavez-Rios, J.R., Vargas-Villavicencio, J.A., Morales-Montor, J., 2009. Immune sexual dimorphism: effect of gonadal steroids on the expression of cytokines, sex steroid receptors, and lymphocyte proliferation. J. Steroid Biochem. Mol. Biol. 113, 57–64.
de Pablos, R.M., Villaran, R.F., Arguelles, S., Herrera, A.J., Venero, J.L., Ayala, A., Cano, J., Machado, A., 2006. Stress increases vulnerability to inflammation in the rat prefrontal cortex. J. Neurosci. 26, 5709–5719.
De Pitta, M., Brunel, N., Volterra, A., 2016. Astrocytes: orchestrating synaptic plasticity? Neuroscience 323, 43–61.
de Souza, D.F., Wartchow, K.M., Lunardi, P.S., Brolese, G., Tortorelli, L.S., Batassini, C., Biasibetti, R., Goncalves, C.A., 2015. Changes in astroglial markers in a maternal immune activation model of schizophrenia in wistar rats are dependent on sex. Frontiers in cellular neuroscience 9, article 489.
Delpech, J.C., Wei, L., Hao, J., Yu, X.Q., Madore, C., Butovsky, O., Kaffman, A., 2016. Early life stress perturbs the maturation of microglia in the developing hippocampus. Brain Behav. Immun. 57, 79–93.
Desai, M.K., Brinton, R.D., 2019. Autoimmune disease in women: endocrine transition and risk across the lifespan. Frontiers in Endocrinology 10, Article 265.
Dennison, U., Mc Kernan, D., Cryan, J., Dinan, T., 2012. Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype. Psychological Medicine 42, 1865–1871.
Dheen, S.T., Kaur, C., Ling, E.A., 2007. Microglial activation and its implications in the brain diseases. Curr. Med. Chem. 14, 1189–1197.
Dimatelis, J.J., Pillay, N.S., Mutyaba, A.K., Russell, V.A., Daniels, W.M.U., Stein, D.J., 2012. Early maternal separation leads to down-regulation of cytokine gene expression. Metab. Brain Dis. 27, 393–397.
Diz-Chaves, Y., Pernia, O., Carrero, P., Garcia-Segura, L.M., 2012. Prenatal stress causes alterations in the morphology of microglia and the inflammatory response of the hippocampus of adult female mice. J. Neuroinflammation 9, 71.

Diz-Chaves, Y., Astiz, M., Bellini, M.J., Garcia-Segura, L.M., 2013. Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice. Brain Behav. Immun. 28, 196–206.
do Prado, C.H., Narahari, T., Holland, F.H., Lee, H.N., Murthy, S.K., Brenhouse, H.C., 2016. Effects of early adolescent environmental enrichment on cognitive dysfunction, prefrontal cortex development, and inflammatory cytokines after early life stress. Dev. Psychobiol. 58, 482–491.
Domnich, A., Manini, I., Calabro, G.E., de Waure, C., Montomoli, E., 2019. Mapping host-related correlates of influenza vaccine-induced immune response: an umbrella review of the available systematic reviews and meta-analyses. Vaccines 7, 215.
Dong, H., Zhang, X., Qian, Y., 2014. Mast cells and neuroinflammation. Med. Sci. Monit. Basic Res. 20, 200–206.
Dong, Y.S., Benveniste, E.N., 2001. Immune function of astrocytes. Glia 36, 180–190.
Donoso, F., Egerton, S., Bastiaanssen, T.F.S., Fitzgerald, P., Gite, S., Fouhy, F., Ross, R.P., Stanton, C., Dinan, T.G., Cryan, J.F., 2020. Polyphenols selectively reverses early-life stres-induced behavioural, neurochemical and microbiota changes in the rat. Psychoneuroendcrinology 116, 1–12.
Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.
Druart, M., Le Magueresse, C., 2019. Emerging roles of complement in psychiatric disorders. Frontiers in Psychiatry 10, Article 573.
Dube, S.R., Felitti, V.J., Dong, M.X., Giles, W.H., Anda, R.F., 2003. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. Prev. Med. 37, 268–277.
Ducruet, A.F., Zacharia, B.E., Sosunov, S.A., Gigante, P.R., Yeh, M.L., Gorski, J.W., Otten, M.L., Hwang, R.Y., DeRosa, P.A., Hickman, Z.L., Sergot, P., Connolly, E.S., 2012. Complement inhibition promotes endogenous neurogenesis and sustained anti-inflammatory neuroprotection following reperfused stroke. PLoS One 7, e38664.
Dunkelberger, J.R., Song, W.C., 2010. Complement and its role in innate and adaptive immune responses. Cell Res. 20, 34–50.
Dunn, A.J., 2000. Cytokine activation of the HPA axis. Ann. N. Y. Acad. Sci. 917, 608–617.
Dunn, A.J., 2006. Effects of cytokines and infections on brain neurochemistry. Clin. Neurosci. Res. 6, 52–68.
Dunstan, J.A., Mori, T.A., Barden, A., Beilin, L.J., Taylor, A.L., Holt, P.G., Prescott, S.L., 2003. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J. Clin. Immunol. 112, 1178–1184.
Duque, E.D., Munhoz, C.D., 2016. The pro-inflammatory effects of glucocorticoids in the brain. Frontiers in Endocrinology 7, Article 78.
Edlow, A.G., Glass, R.M., Smith, C.J., Tran, P.K., James, K., Bilbo, S., 2019. Placental macrophages: a window into fetal microglial function in maternal obesity. Int. J. Dev. Neurosci. 77, 60–68.
Ehlert, U., 2013. Enduring psychobiological effects of childhood adversity. Psychoneuroendocrinology 38, 1850–1857.
Eiland, L., Ramroop, J., Hill, M.N., Manley, J., McEwen, B.S., 2012. Chronic juvenile stress produces corticolimbic dendritic architectural remodeling and modulates emotional behavior in male and female rats. Psychoneuroendocrinology 37, 39–47.
Elenkov, I.J., Iezzoni, D.G., Daly, A., Harris, A.G., Chrousos, G.P., 2005. Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation 12, 255–269.
Endrighi, R., Hamer, M., Steptoe, A., 2016. Post-menopausal women exhibit greater interleukin-6 responses to mental stress than older men. Ann. Behav. Med. 50, 564–571.
Entringer, S., Kumsta, R., Nelson, E.L., Hellhammer, D.H., Wadhwa, P.D., Wust, S., 2008. Influence of prenatal psychosocial stress on cytokine production in adult women. Dev. Psychobiol. 50, 579–587.
Erta, M., Quintana, A., Hidalgo, J., 2012. Interleukin-6, a major cytokine in the central nervous system. Int. J. Biol. Sci. 8, 1254–1266.
Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353, 772–777.
Eugen-Olsen, J., Afzelius, P., Andresen, L., Iversen, J., Kronborg, G., Aabech, P., Nielsen, J.O., Hofmann, B., 1997. Serotonin modulates immune function in T cells from HIV-seropositive subjects. Clin. Immunol. Immunopathol. 84, 115–121.
Fagundes, C.P., Glaser, R., Kiecolt-Glaser, J.K., 2013. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav. Immun. 27, 8–12.
Falcone, E.G., Liaudat, A.C., Alustiza, F.E., Mayer, N., Bosch, P., Vivas, A., Gauna, H., Rodriguez, N., 2017. IL-2 is involved in immune response of prenatally stressed rats exposed to postnatally stimulation. Austral Journal of Veterinary Sciences 49, 113–118.
Farooq, R.K., Asghar, K., Kanwal, S., Zulqernain, A., 2017. Role of inflammatory cytokines in depression: focus on interleukin-1beta. Biomedical Reports 6, 15–20.
Felger, J.C., Haroon, E., Woolwine, B.J., Raison, C.L., Miller, A.H., 2016. Interferon-alpha-induced inflammation is associated with reduced glucocorticoid negative feedback sensitivity and depression in patients with hepatitis C virus. Physiol. Behav. 166, 14–21.
Fensterl, V., Sen, G.C., 2009. Interferons and viral infections. Biofactors 35, 14–20.
Filiano, A.J., Xu, Y., Tustison, N.J., Marsh, R.L., Baker, W., Smirnov, I., Overall, C.C., Gadani, S.P., Turner, S.D., Weng, Z.P., Peerzade, S.N., Chen, H., Lee, K.S., Scott, M. M., Beenhakker, M.P., Litvak, V., Kipnis, J., 2016. Unexpected role of interferon-gamma in regulating neuronal connectivity and social behaviour. Nature 535, 425–429.
Finck, B.N., Johnson, R.W., 1997. Anorexia, weight loss and increased plasma interleukin-6 caused by chronic intracerebroventricular infusion of interleukin-1 beta in the rat. Brain Res. 761, 333–337.
Finnell, J.E., Lombard, C.M., Padi, A.R., Moffitt, C.M., Wilson, L.B., Wood, C.S., Wood, S. K., 2017. Physical versus psychological social stress in male rats reveals distinct cardiovascular, inflammatory and behavioral consequences. Plos One 12, e0172868.
Flynn, S.M., Schipper, L.J., Roach, A.R., Segerstrom, S.C., 2009. Gender differences in delayed-type hypersensitivity response: effects of stress and coping in first-year law students. Brain Behav. Immun. 23, 672–676.
Forthal, D., 2014. Functions of antibodies. Microbiology Spectrum 2, 1–17.
Foster, J., Neufeld, K.A., 2013. Gut-brain axis: how the microbiome influences anxiety and depression. Trends in Neuroscience 36, 305–312.
Fox, C., Merali, Z., Harrison, C., 2006. Therapeutic and protective effect of environmental enrichment against psychogenic and neurogenic stress. Behav. Brain Res. 175, 1–8.
Frank, M.G., Thompson, B.M., Watkins, L.R., Maier, S.F., 2012. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav. Immun. 26, 337–345.
Fritz, J., de Graaff, A.M., Caisley, H., van Harmelen, A.L., Wilkinson, P.O., 2018. A systematic review of amenable resilience factors that moderate and/or mediate the relationship between childhood adversity and mental health in young people. Frontiers in Psychiatry 9, Article 230.
Frost, J.L., Schafer, D.P., 2016. Microglia: architects of the developing nervous system. Trends Cell Biol. 26, 587–597.
Furukawa, K., Mattson, M.P., 1998. The transcription factor NF-KB mediates increases in calcium currents and decreases in NMDA- and AMPA/kainate-induced currents induced by tumor necrosis factor-alpha in hippocampal neurons. J. Neurochem. 70, 1876–1886.
Gasteiger, G., D'Osualdo, A., Schubert, D.A., Weber, A., Bruscia, E.M., Hartl, D., 2017. Cellular innate immunity: an old game with new players. Journal of Innate Immunity 9, 111–125.
Georgin-Lavialle, S., Gaillard, R., Moura, D., Hermine, O., 2016. Masocytosis in adulthood and neuropsychiatric disorders. Transational Research 174, 77–85.
Gill, J.M., Saligan, L., Woods, S., Page, G., 2009. PTSD is associated with an excess of inflammatory immune activities. Perspectives in Psychiatric Care 45, 262–277.
Ginhoux, F., Garel, S., 2018. The mysterious origins of microglia. Nat. Neurosci. 21, 897–899.
Giovanoli, S., Weber-Stadlbauer, U., Schedlowski, M., Meyer, U., Engler, H., 2016. Prenatal immune activation causes hippocampal synaptic deficits in the absence of overt microglia anomalies. Brain Behav. Immun. 55, 25–38.
Glaser, R., Kiecolt-Glaser, J.K., 2005. Science and society - stress-induced immune dysfunction: implications for health. Nat. Rev. Immunol. 5, 243–251.
Gleeson, M., Bishop, N.C., Stensel, D.J., Lindley, M.R., Mastana, S.S., Nimmo, M.A., 2011. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat. Rev. Immunol. 11, 607–615.
Glover, V., 2011. Prenatal stress and the origins of psychopathology: an evolutionary perspective. J. Child Psychol. Psychiatry 52, 356–367.
Goldberg, S.B., Tucker, R.P., Greene, P.A., Davidson, R.J., Wampold, B.E., Kearney, D.J., Simpson, T.L., 2018. Mindfulness-based interventions for psychiatric disorders: a systematic review and meta-analysis. Clin. Psychol. Rev. 59, 52–60.
Gollwitzer, E.S., Marsland, B.J., 2015. Impact of early-life exposures on immune maturation and susceptibility to disease. Trends Immunol. 36, 684–696.
Gomez-Gonzalez, B., Escobar, A., 2010. Prenatal stress alters microglial development and distribution in postnatal rat brain. Acta Neuropathol. 119, 303–315.
Goshen, I., Kreisel, T., Ounallah-Saad, H., Renbaum, P., Zatzstein, Y., Ben-Hur, T., Levy-Lahad, E., Yirmiya, R., 2007. A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology 32, 1106–1115.
Green, J.G., McLaughlin, K.A., Berglund, P.A., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Kessler, R.C., 2010. Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I associations with first onset of DSM-IV disorders. Arch. Gen. Psychiatry 67, 113–123.
Green, M.R., McCormick, C.M., 2013. Effects of stressors in adolescence on learning and memory in rodent models. Horm. Behav. 64, 364–379.
Guma, E., Plitrnan, E., Chakravarty, M.M., 2019. The role of maternal immune activation in altering the neurodevelopmental trajectories of offspring: a translational review of neuroimaging studies with implications for autism spectrum disorder and schizophrenia. Neurosci. Biobehav. Rev. 104, 141–157.
Habela, C.W., Song, H.J., Ming, G.L., 2016. Modeling synaptogenesis in schizophrenia and autism using human iPSC derived neurons. Mol. Cell. Neurosci. 73, 52–62.
Hackett, R.A., Steptoe, A., 2017. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. Nat. Rev. Endocrinol. 13, 547–560.
Hadar, R., Dong, L., del-Valle-Anton, L., Guneykaya, D., Voget, M., Edemann-Callesen, H., Schweibold, R., Djodari-Irani, A., Goetz, T., Ewing, S., Kettenmann, H., Wolf, S.A., Winter, C., 2017. Deep brain stimulation during early adolescence prevents microglial alterations in a model of maternal immune activation. Brain Behav. Immun. 63, 71–80.
Hammad, A., Westacott, L., Zaben, M., 2018. The role of the complement system in traumatic brain injury: a review. J. Neuroinflammation 15, 24.
Hanamsagar, R., Alter, M.D., Block, C.S., Sullivan, H., Bolton, J.L., Bilbo, S.D., 2018. Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity. Glia 65, 1504–1520.
Hansson, E., Ronnback, L., 1995. Atrocytes in glutamate neurotransmission. FASEB J. 9, 343–350.
Hantsoo, L., Jasarevic, E., Criniti, S., McGreen, B., Tanes, C., Sammel, M.D., Elovitz, M. A., Cmopher, C., Wu, G., Epperson, C.N., 2019. Childhood adversity impact on gut

microbiota and inflammatory response to stress during pregnancy. Brain Behav. Immun. 75, 240–250.
Hari, A., Cruz, S.A., Qin, Z.H., Couture, P., Vilmundarson, R.O., Huang, H., Stewart, A.F. R., Chen, H.H., 2017. IRF2BP2-deficient microglia block the anxiolytic effect of enhanced postnatal care. Sci. Rep. 7, 9836.
Hartmann, K., Sepulveda-Falla, D., Rose, I.V.L., Madore, C., Muth, C., Matschke, J., Butovsky, O., Liddelow, S., Glatzel, M., Krasemann, S., 2019. Complement 3(+)-astrocytes are highly abundant in prion diseases, but their abolishment led to an accelerated disease course and early dysregulation of microglia. Acta Neuropathologica communications 7. Article 83.
Havik, B., Le Hellard, S., Rietschel, M., Lybaek, H., Djurovic, S., Mattheisen, M., Muhleisen, T.W., Degenhardt, F., Priebe, L., Maier, W., Breuer, R., Schulze, T.G., Agartz, I., Melle, I., Hansen, T., Bramham, C.R., Nothen, M.M., Stevens, B., Werge, T., Andreassen, O.A., Cichon, S., Steen, V.M., 2011. The complement control-related genes CSMD1 and CSMD2 associate to schizophrenia. Biol. Psychiatry 70, 35–42.
Heesen, C., Nawrath, L., Reich, C., Bauer, N., Schulz, K.H., Gold, S.M., 2006. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J. Neurol. Neurosurg. Psychiatry 77, 34–39.
Heidt, T., Sager, H.B., Courties, G., Dutta, P., Iwamoto, Y., Zaltsman, A., von zur Muhlen, C., Bode, C., Fricchione, G.L., Denninger, J., Lin, C.P., Vinegoni, C., Libby, P., Swirski, F.K., Weissleder, R., Nahrendorf, M., 2014. Chronic variable stress activates hematopoietic stem cells. Nat. Med. 20, 754–758.
Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol. Psychiatry 49, 1023–1039.
Hellwig, S., Brioschi, S., Dieni, S., Frings, L., Masuch, A., Blank, T., Biber, K., 2016. Altered microglia morphology and higher resilience to stress-induced depression-like behavior in CX3CR1-deficient mice. Brain Behav. Immun. 55, 126–137.
Herr, N., Bode, C., Duerschmied, D., 2017. The effects of serotonin in immune cells. Frontiers in Cardiovascular Medicine 4, Article 48.
Hiles, S.A., Baker, A.L., de Malmanche, T., Attia, J., 2012. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol. Med. 42, 2015–2026.
Hughes, C.E., Nibbs, R.J.B., 2018. A guide to chemokines and their receptors. FEBS J. 285, 2944–2971.
Huh, G.S., Boulanger, L.M., Du, H.P., Riquelme, P.A., Brotz, T.M., Shatz, C.J., 2000. Functional requirement for class I MHC in CNS development and plasticity. Science 290, 2155–2159.
Hulsey, D.R., Shedd, C.M., Sarker, S.F., Kilgard, M.P., Hays, S.A., 2019. Norepinephrine and serotonin are required for vagus nerve stimulation directed cortical plasticity. Exp. Neurol. 320, 112975.
Jack, C.S., Arbour, N., Manusow, J., Montgrain, V., Blain, M., McCrea, E., Shapiro, A., Antel, J.P., 2005. TLR signaling tailors innate immune responses in human microglia and astrocytes. J. Immunol. 175, 4320–4330.
Janeway, C.J., Travers, P., Walport, M., Shlomchik, M.J., 2001. The Immune System in Health and Disease 5th Edition (Garland Science New York).
Jankord, R., Herman, J.P., 2008. Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann N Y Acad Sci 1148, 64–73.
Jeon, S.W., Kim, Y.K., 2016. Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness? World Journal of Psychiatry 6, 283–293.
Johnson, J.D., Barnard, D.F., Kulp, A.C., Mehta, D.M., 2019. Neuroendocrine regulation of brain cytokines after psychological stress. Journal of the Endocrine Society 3, 1302–1320.
Johnston, G.R., Webster, N.R., 2009. Cytokines and the immunomodulatory function of the vagus nerve. Br. J. Anaesth. 102, 453–462.
Joshi, A., Page, C.E., Damante, M., Dye, C.N., Haim, A., Leuner, B., Lenz, K.M., 2019. Sex differences in the effects of early life stress exposure on mast cells in the developing rat brain. Horm. Behav. 113, 76–84.
Jung, S., Aliberti, J., Graemmel, P., Sunshine, M.J., Kreutzberg, G.W., Sher, A., Littman, D.R., 2000. Analysis of fractalkine receptor CX(3)CR1 function by targeted deletion and green fluorescent protein reporter gene insertion. Mol. Cell. Biol. 20, 4106–4114.
Jung, S.H., Wang, Y.F., Kim, T., Tarr, A., Reader, B., Powell, N., Sheridan, J.F., 2015. Molecular mechanisms of repeated social defeat-induced glucocorticoid resistance: role of microRNA. Brain Behav. Immun. 44, 195–206.
Jurgens, H.A., Johnson, R.W., 2012. Environmental enrichment attenuates hippocampal neuroinflammation and improves cognitive function during influenza infection. Brain Behav. Immun. 26, 1006–1016.
Karrenbauer, B.D., Muller, C.P., Ho, Y.J., Spanagel, R., Huston, J.P., Schwarting, R.K.W., Pawlak, C.R., 2011. Time-dependent in-vivo effects of interleukin-2 on neurotransmitters in various cortices: relationships with depressive-related and anxiety-like behavior. J. Neuroimmunol. 237, 23–32.
Kay, G., Tarcic, N., Poltyrev, T., Weinstock, M., 1998. Prenatal stress depresses immune function in rats. Physiol. Behav. 63, 397–402.
Kelly, A., Lynch, A., Vereker, E., Nolan, Y., Queeman, P., Whittaker, E., O'Neill, L.A.J., Lynch, M.A., 2001. The anti-inflammatory cytokine, interleukin (IL)-10, blocks the inhibitory effect of IL-1 beta on long term potentiation - a role for JNK. J. Biol. Chem. 276, 45564–45572.
Kelly, R.R., McDonald, L.T., Jensen, N.R., Sidles, S.J., LaRue, A.C., 2019. Impacts of psychological stress on osteoporosis: clinical implications and treatment interactions. Frontiers in Psychiatry 10, Article PMC6465575.
Kessler, R.C., McGonagle, K.A., Swartz, M., Blazer, D.G., Nelson, C.B., 1993. Sex and depression in the national comorbidity survey 1. Lifetime prevelance, chronicity and recurrence. J. Affect. Disord. 29, 85–96.
Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry 62, 617–627.
Kessler, R.C., McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A. M., Aguilar-Gaxiola, S., Alhamzawi, A.O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O., Haro, J.M., Hu, C.Y., Karam, E.G., Kawakami, N., Lee, S., Lepine, J.P., Ormel, J., Posada-Villa, J., Sagar, R., Tsang, A., Ustun, T.B., Vassilev, S., Viana, M.C., Williams, D.R., 2010. Childhood adversities and adult psychopathology in the WHO world mental health surveys. Br. J. Psychiatry 197, 378–385.
Khalil, M., Ronda, J., Weintraub, M., Jain, K., Silver, R., Silverman, A.J., 2007. Brain mast cell relationship to neurovasculature during development. Brain Res. 1171, 18–29.
Khansari, D.N., Murgo, A.J., Faith, R.E., 1990. Effects of stress on the immune system. Immunol. Today 11, 170–175.
Kiecolt-Glaser, J.K., Glaser, R., Gravenstein, S., Malarkey, W.B., Sheridan, J., 1996. Chronic stress alters the immune response to influenza virus vaccine in older adults. Proc. Natl. Acad. Sci. U. S. A. 93, 3043–3047.
Kiecolt-Glaser, J.K., Gouin, J.P., Weng, N.P., Malarkey, W.B., Beversdorf, D.Q., Glaser, R., 2011. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. Psychosom. Med. 73, 16–22.
Kilic, M., Ulusoy, O., Cirrik, S., Hindistan, I.E., Ozkaya, Y.G., 2014. Effect of exercise intensity on cerebrospinal fluid interleukin-6 concentration during recovery from exhaustive exercise in rats. Acta Physiol. Hung. 101, 21–31.
Kim, W.G., Mohney, R.P., Wilson, B., Jeohn, G.H., Liu, B., Hong, J.S., 2000. Regional difference in susceptibility to lipopolysaccharide-induced neurotoxicity in the rat brain: role of microglia. J. Neurosci. 20, 6309–6316.
Kim, Y.K., Jung, H.G., Myint, A.M., Kim, H., Park, S.H., 2007. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J. Affect. Disord. 104, 91–95.
Kipnis, J., 2016. Multifaceted interactions between adaptive immunity and the central nervous system. Science 353, 766–771.
Ko, C.Y., Liu, Y.P., 2015. Isolation rearing impaired sensorimotor gating but increased pro-inflammatory cytokines and disrupted metabolic parameters in both sexes of rats. Psychoneuroendocrinology 55, 173–183.
Ko, C.Y., Liu, Y.P., 2016. Disruptions of sensorimotor gating, cytokines, glycemia, monoamines, and genes in both sexes of rats reared in social isolation can be ameliorated by oral chronic quetiapine administration. Brain Behav. Immun. 51, 119–130.
Kohler, O., Petersen, L., Mors, O., Gasse, C., 2015. Inflammation and depression: combined use of selective serotonin reuptake inhibitors and NSAIDs or paracetamol and psychiatric outcomes. Brain and Behavior 5, e00338.
Kohman, R.A., Bhattacharya, T.K., Wojcik, E., Rhodes, J.S., 2013. Exercise reduces activation of microglia isolated from hippocampus and brain of aged mice. J. Neuroinflammation 10, 114.
Kok, R., Thijssen, S., Bakernnans-Kranenburg, M.J., Jaddoe, V.W.V., Verhulst, F.C., White, T., van Ijzendoorn, M.H., Tiemeier, H., 2015. Normal variation in early parental sensitivity predicts child structural brain development. J. Am. Acad. Child Adolesc. Psychiatry 54, 824–831.
Konefal, S.C., Stellwagen, D., 2017. Tumour necrosis factor-mediated homeostatic synaptic plasticity in behavioural models: testing a role in maternal immune activation. Philosophical Transactions of the Royal Society B-Biological Sciences 372, Article 201660160.
Koo, J.W., Duman, R.S., 2008. IL-1 beta is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc. Natl. Acad. Sci. U. S. A. 105, 751–756.
Koo, J.W., Duman, R.S., 2009. Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression. Curr. Opin. Investig. Drugs 10, 664–671.
Koskinas, J., Merkouraki, P., Manesis, E., Hadziyannis, S., 2002. Assessment of depression in patients with chronic viral hepatitis: effect of interferon treatment. Dig. Dis. 20, 284–288.
Kriegsfeld, L.J., Hotchkiss, A.K., Demas, G.E., Silverman, A.J., Silver, R., Nelson, R.J., 2003. Brain mast cells are influenced by chemosensory cues associated with estrus induction in female prairie voles (Microtus ochrogaster). Horm. Behav. 44, 377–384.
Kuhlman, K., Horn, S., Chiang, J., Bower, J., 2019. Early life adversity exposure and circulating markers of inflammation in children and adolescents: a systematic review and meta-analysis. Brain Behav. Immun. 86, 30–42.
Kuijpers, M., van Gassen, K.L.I., de Graan, P.N.E., Gruol, D., 2010. Chronic exposure to the chemokine CCL3 enhances neuronal network activity in rat hippocampal cultures. J. Neuroimmunol. 229, 73–80.
Kulka, M., Sheen, C.H., Tancowny, B.P., Grammer, L.C., Schleimer, R.P., 2008. Neuropeptides activate human mast cell degranulation and chemokine production. Immunology 123, 398–410.
Kumar, B.V., Connors, T.J., Farber, D.L., 2018. Human T cell development, localization, and function throughout life. Immunity 48, 202–213.
Kunz, M., Cereser, K.M., Goi, P.D., Fries, G.R., Teixeira, A.L., Fernandes, B.S., Belmonte-de-Abreu, P.S., Kauer-Sant'Anna, M., Kapczinski, F., Gama, C.S., 2011. Serum levels of IL-6, IL-10 and TNF-alpha in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev. Bras. Psiquiatr. 33, 268–274.
Lacagnina, M.J., Kopec, A.M., Cox, S.S., Hanamsagar, R., Wells, C., Slade, S., Grace, P.M., Watkins, L.R., Levin, E.D., Bilbo, S.D., 2017. Opioid self-administration is attenuated by early-life experience and gene therapy for anti-inflammatory IL-10 in the nucleus accumbens of male rats. Neuropsychopharmacology 42, 2128–2140.

Lacey, R.E., Kumari, M., Bartley, M., 2014. Social isolation in childhood and adult inflammation: evidence from the National Child Development Study. Psychoneuroendocrinology 50, 85–94.
Lalo, U., Palygin, O., Rasooli-Nejad, S., Andrew, J., Haydon, P.G., Pankratov, Y., 2014. Exocytosis of ATP from astrocytes modulates phasic and tonic inhibition in the neocortex. PLoS Biol. 12, e1001747.
Lampron, A., Elali, A., Rivest, S., 2013. Innate immunity in the CNS: redefining the relationship between the CNS and its environment. Neuron 78, 214–232.
Lauro, C., Di Angelantonio, S., Cipriani, R., Sobrero, F., Antonilli, L., Brusadin, V., Ragozzino, D., Limatola, C., 2008. Activity of adenosine receptors type 1 is required for CX(3)CL1-mediated neuroprotection and neuromodulation in hippocampal neurons. J. Immunol. 180, 7590–7596.
Laviola, G., Rea, M., Morley-Fletcher, S., Di Carlo, S., Bacosi, A., De Simone, R., Bertini, M., Pacifici, R., 2004. Beneficial effects of enriched environment on adolescent rats from stressed pregnancies. Eur. J. Neurosci. 20, 1655–1664.
Lax, P., Limatola, C., Fucile, S., Trettel, F., Di Bartolomeo, S., Renzi, M., Ragozzino, D., Eusebi, F., 2002. Chemokine receptor CXCR2 regulates the functional properties of AMPA-type glutamate receptor GluR 1 in HEK cells. J. Neuroimmunol. 129, 66–73.
Le Page, C., Genin, P., Baines, M., Hiscott, J., 2000. Interferon activation and innate immunity. Reviews in Immunogenetics 2, 374–386.
LeGates, T.A., Kvarta, M.D., Thompson, S.M., 2019. Sex differences in antidepressant efficacy. Neuropsychopharmacology 44, 140–154.
Lenz, K.M., Nelson, L.H., 2018. Microglia and beyond: innate immune cells as regulators of brain development and behavioral function. Frontiers in Immunology 9, Article 698.
Lenz, K.M., Nugent, B.M., Haliyur, R., McCarthy, M.M., 2013. Microglia are essential to masculinization of brain and behavior. J. Neurosci. 33, 2761–2772.
Levandowski, M.L., Viola, T.W., Prado, C.H., Wieck, A., Bauer, M.E., Brietzke, E., Grassi-Oliveira, R., 2016. Distinct behavioral and immunoendocrine parameters during crack cocaine abstinence in women reporting childhood abuse and neglect. Drug Alcohol Depend. 167, 140–148.
Levin, S.G., Godukhin, O.V., 2017. Modulating effect of cytokines on mechanisms of synaptic plasticity in the brain. Biochemistry-Moscow 82, 264–274.
Levine, S., 2000. Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. Eur. J. Pharmacol. 405, 149–160.
Lewis, L.A., Ram, S., Prasad, A., Gulati, S., Getzlaff, S., Blom, A.M., Vogel, U., Rice, P.A., 2008. Defining targets for complement components C4b and C3b on the pathogenic neisseriae. Infect. Immun. 76, 339–350.
Li, L., Pereira, S.M.P., Power, C., 2019. Childhood maltreatment and biomarkers for cardiometabolic disease in mid-adulthood in a prospective British birth cohort: associations and potential explanations. Bmj Open 9, Article e024079.
Li, Q., Leung, Y.O., Zhou, I., Kong, W., Basil, P., Wei, R., Lam, S., ZZhang, X., Law, A.C., Chu, S.E., Sham, P.C., 2015. Dietary supplementaion with n-3 fatty acids from weaning limits brain biochemistry and behavioural changes elicited by prenatal exposure to maternal inflammation in the mouse model. Transl. Psychiatry 5, 1–10.
Li, Q.Y., Barres, B.A., 2018. Microglia and macrophages in brain homeostasis and disease. Nat. Rev. Immunol. 18, 225–242.
Lian, H., Litvinchuk, A., Chiang, A.C.A., Aithmitti, N., Jankowsky, J.L., Zheng, H., 2016. Astrocyte-microglia cross talk through complement activation modulates amyloid pathology in mouse models of Alzheimer's disease. J. Neurosci. 36, 577–589.
Liaudat, A.C., Rodriguez, N., Vivas, A., Gauna, F., Mayer, N., 2012. Effect of early stimulation on some immune parameters in a model of prenatally stressed rats. International Journal of Psychological Studies 4, 73–82.
Lin, A., Kenis, G., Bignotti, S., Tura, G.J.B., De Jong, R., Bosmans, E., Pioli, R., Altamura, C., Scharpe, S., Maes, M., 1998. The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr. Res. 32, 9–15.
Liu, C.Y., Yang, Y., Ju, W.N., Wang, X., Zhang, H.L., 2018. Emerging roles of astrocytes in neuro-vascular unit and the tripartite synapse with emphasis on reactive gliosis in the context of Alzheimer's disease. Frontiers in Cellular Neuroscience 12, Article 193.
Liu, W.N., Sheng, H., Xu, Y.J., Liu, Y., Lu, J.Q., Ni, X., 2013. Swimming exercise ameliorates depression-like behavior in chronically stressed rats: relevant to proinflammatory cytokines and IDO activation. Behav. Brain Res. 242, 110–116.
Liu, W.Q., Liu, F., Xu, X.F., Bai, Y., 2017. Replicated association between the European GWAS locus rs10503253 at CSMD1 and schizophrenia in Asian population. Neurosci. Lett. 647, 122–128.
Liu, Y.S., Cheng, Z.H., Wang, J., Jin, C.H., Yuan, J.M., Wang, G.Q., Zhang, F.Q., Zhao, X. D., 2016. No association between the rs10503253 polymorphism in the CSMD1 gene and schizophrenia in a Han Chinese population. BMC Psychiatry 16, 206.
Liukkonen, T., Rasanen, P., Jokelainen, J., Leinonen, M., Jarvelin, M.R., Meyer-Rochow, V.B., Timonen, M., 2011. The association between anxiety and C-reactive protein (CRP) levels: results from the northern Finland 1966 birth cohort study. European Psychiatry 26, 363–369.
Lopes, D., Cespedes, I., Viana, M., 2017. Effects of environmental enrichment on anxiety measurements: a review. Research and Reviews: Neuroscience 2, 1–6.
Lopez-Gallardo, M., Llorente, R., Llorente-Berzal, A., Marco, E., Prada, C., Di Marzo, V., Viveros, M., 2008. Neuronal and glial alterations in the cerebellar cortex of maternally deprived rats: gender differences and modulatory effects of two inhibitors of endocannabinoid inactivation. Developmental Neurobiology 68, 1429–1440.
Loram, L.C., Sholar, P.W., Taylor, F.R., Wiesler, J.L., Babb, J.A., Strand, K.A., Berkelhammer, D., Day, H.E.W., Maier, S.F., Watkins, L.R., 2012. Sex and estradiol influence glial pro-inflammatory responses to lipopolysaccharide in rats. Psychoneuroendocrinology 37, 1688–1699.
Lown, B., Dukta, M., 1987. Early handling enhances mitogen responses of splenic cells in adult C3H mice. Brain Behav. Immun. 1, 356–360.
Lown, E.A., Lui, C.K., Karriker-Jaffe, K., Mulia, N., Williams, E., Ye, Y., Li, L.B., Greenfield, T.K., Kerr, W.C., 2019. Adverse childhood events and risk of diabetes onset in the 1979 national longitudinal survey of youth cohort. BMC Public Health 19, 1–13.
Luan, W., Hammond, L.A., Vuillermot, S., Meyer, U., Walter, D., 2018. Maternal vitamin D prevents abnormal dopaminergic development and function in a mouse model of prenatal immune activation. Sci. Rep. 8, 1–12.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
MacDonald, A.J., Robb, J.L., Morrissey, N.A., Beall, C., Ellacott, K.L.J., 2019. Astrocytes in neuroendocrine systems: an overview. J. Neuroendocrinol. 31, e12726.
Madore, C., Yin, Z.R., Leibowitz, J., Butovsky, O., 2020. Microglia, lifestyle stress, and neurodegeneration. Immunity 52, 222–240.
Madry, C., Kyrargyri, V., Arancibia-Carcamo, I.L., Jolivet, R., Kohsaka, S., Bryan, R.M., Attwell, D., 2018. Microglial ramification, surveillance, and interleukin-1 beta release are regulated by the two-pore domain K+ channel THIK-1. Neuron 97, 299–312.
Maes, M., Van Bockstaele, D.R., Van Gastel, A., Song, C., Schotte, C., Neels, H., DeMeester, I., Scharpe, S., Janca, A., 1999. The effects of psychological stress on leukocyte subset distribution in humans: evidence of immune activation. Neuropsychobiology 39, 1–9.
Maity, S., Rah, S., Sonenberg, N., Gkogkas, C.G., Nguyen, P.V., 2015. Norepinephrine triggers metaplasticity of LTP by increasing translation of specific mRNAs. Learn. Mem. 22, 499–508.
Makinen, T., 2019. Lymphatic vessels at the base of the mouse brain provide direct drainage to the periphery. Nature 572, 34–35.
Makinson, R., Lloyd, K., Rayasam, A., McKee, S., Brown, A., Barila, G., Grissom, N., George, R., Marini, M., Fabry, Z., Elovitz, M., Reyes, T.M., 2017. Intrauterine inflammation induces sex-specific effects on neuroinflammation, white matter, and behavior. Brain Behav. Immun. 66, 277–288.
Malaspina, D., Corcoran, C., Kleinhaus, K.R., Perrin, M.C., Fennig, S., Nahon, D., Friedlander, Y., Harlap, S., 2008. Acute maternal stress in pregnancy and schizophrenia in offspring: a cohort prospective study. BMC Psychiatry 8, Artcile 71.
Mandyam, C.D., Crawford, E.F., Eisch, A.J., Rivier, C.L., Richardson, H.N., 2008. Stress experienced in utero reduces sexual dichotomies in neurogenesis, microenvironment, and cell death in the adult rat hippocampus. Developmental Neurobiology 68, 575–589.
Marashi, V., Barnekow, A., Ossendorf, E., Sachser, N., 2003. Effects of different forms of environmental enrichment on behavioral, endocrinological, and immunological parameters in male mice. Horm. Behav. 43, 281–292.
Marazziti, D., 2017. Understanding the role of serotonin in psychiatric disease. F1000. Research 6, 1–6.
Marketon, J.I.W., Glaser, R., 2008. Stress hormones and immune function. Cell. Immunol. 252, 16–26.
Marques, A.H., O'Connor, T.G., Roth, C., Susser, E., Bjorke-Monsen, A.-L., 2013. The influence of maternal prenatal and early childhood nutirtion and maternal prenatal stress on immune system development and neurdevelopmental disorders. Front. Neurosci. 7, 1–17.
Marsland, A.L., Walsh, C., Lockwood, K., John-Henderson, N.A., 2017. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. Brain Behav. Immun. 64, 208–219.
Masini, E., Fantozzi, R., Conti, A., Blandina, P., Brunelleschi, S., Mannaioni, P.F., 1985. Mast-cell heterogenity in response to cholinergic stimulation. International Archives of Allergy and Applied Immunology 77, 184–185.
Masten, A., Cutuli, J., Herbers, J., Reed, M.-G., 2009. Resilience in development. Oxford Library of Psychology. Oxford Handbook of Positive Psychology. Oxford University Press., pp. 117–131.
Mastorakos, P., McGavern, D., 2019. The anatomy and immunology of vasculature in the central nervous system. Science Immunology 4, Article eaav0492.
Matcovitch-Natan, O., Winter, D.R., Giladi, A., Aguilar, S.V., Spinrad, A., Sarrazin, S., Ben-Yehuda, H., David, E., Gonzalez, F.Z., Perrin, P., Keren-Shaul, H., Gury, M., Lara-Astaiso, D., Thaiss, C.A., Cohen, M., Halpern, K.B., Baruch, K., Deczkowska, A., Lorenzo-Vivas, E., Itzkovitz, S., Elinav, E., Sieweke, M.H., Schwartz, M., Amit, I., 2016. Microglia development follows a stepwise program to regulate brain homeostasis. Science 353, Article aad8670.
Mayer, E.A., Tillisch, K., Gupta, A., 2015. Gut/brain axis and the microbiota. J. Clin. Investig. 125, 926–938.
McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav. Rev. 33, 355–366.
McCormick, C.M., Mathews, I.Z., Thomas, C., Waters, P., 2010. Investigations of HPA function and the enduring consequences of stressors in adolescence in animal models. Brain Cogn. 72, 73–85.
McCutcheon, R.A., Marques, T.R., Howes, O.D., 2020. Schizophrenia-An overview. Jama Psychiatry 77, 201–210.
McEwen, B.S., 2016. Stress-induced remodeling of hippocampal CA3 pyramidal neurons. Brain Res. 1645, 50–54.
McEwen, B.S., Bowles, N.P., Gray, J.D., Hill, M.N., Hunter, R.G., Karatsoreos, I.N., Nasca, C., 2015. Mechanisms of stress in the brain. Nat. Neurosci. 18, 1353–1363.
McGoron, L., Gleason, M.M., Smyke, A.T., Drury, S.S., Nelson, C.A., Gregas, M.C., Fox, N. A., Zeanah, C.H., 2012. Recovering from early deprivation: attachment mediates effects of caregiving on psychopathology. J. Am. Acad. Child Adolesc. Psychiatry 51, 683–693.

McKlveen, J.M., Myers, B., Flak, J.N., Bundzikova, J., Solomon, M.B., Seroogy, K.B., Herman, J.P., 2013. Role of prefrontal cortex glucocorticoid receptors in stress and emotion. Biol. Psychiatry 74, 672–679.
McQuaid, R.J., Audet, M.C., Jacobson-Pick, S., Anisman, H., 2013. Environmental enrichment influences brain cytokine variations elicited by social defeat in mice. Psychoneuroendocrinology 38, 987–996.
McQuaid, R.J., Dunn, R., Jacobson-Pick, S., Anisman, H., Audet, M.C., 2018. Post-weaning environmental enrichment in male CD-1 mice: impact on social behaviors, corticosterone levels and prefrontal cytokine expression in adulthood. Frontiers in Behavioral Neuroscience 12, Article 145.
Medina, K., 2016. Chapter 4 - overview of the Immune system. Handbook of Clinical Neurology. Elsevier, pp. 61–76.
Mendoza-Fernandez, V., Andrew, R.D., Barajas-Lopez, C., 2000. Interferon-alpha inhibits long-term potentiation and unmasks a long-term depression in the rat hippocampus. Brain Res. 885, 14–24.
Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress. Anxiety 30, 297–306.
Miller, A.H., Haroon, E., Felger, J.C., 2017. The immunology of behavior-exploring the role of the immune system in brain health and illness. Neuropsychopharmacology 42, 1–4.
Miller, G., Chen, E., 2007. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom. Med. 69, 402–409.
Miller, G.E., Chen, E., 2010. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol. Sci. 21, 848–856.
Miller, G.E., Cole, S.W., 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol. Psychiatry 72, 34–40.
Minami, M., Kuraishi, Y., Yamaguchi, T., Nakai, S., Hirai, Y., Satoh, M., 1991. Immobilization stress induces interleukin-1-beta messenger-RNA in the rat hypothalmaus. Neurosci. Lett. 123, 254–256.
Miyamoto, A., Wake, H., Moorhouse, A.J., Nabekura, J., 2013. Microglia and synapse interactions: fine tuning neural circuits and candidate molecules. Frontiers in Cellular Neuroscience 7, Article 70.
Moller, M., Du Preez, J.L., Viljoen, F.P., Berk, M., Emsley, R., Harvey, B.H., 2013. Social isolation rearing induces mitochondrial, immunological, neurochemical and behavioural deficits in rats, and is reversed by clozapine or N-acetyl cysteine. Brain Behav. Immun. 30, 156–167.
Momtazmanesh, S., Zare-Shahabadi, A., Rezaei, N., 2019. Cytokine alterations in schizophrenia: an updated review. Frontiers in Psychiatry 10, Article 892.
Mondelli, V., Vernon, A.C., Turkheimer, F., Dazzan, P., Pariante, C.M., 2017. Brain microglia in psychiatric disorders. Lancet Psychiatry 4, 563–572.
Morimoto, K., Nakajima, K., 2019. Role of the immune system in the development of the central nervous system. Frontiers in Neuroscience 13, Article 916.
Moriyama, M., Fukuhara, T., Britschgi, M., He, Y.B., Narasimhan, R., Villeda, S., Molina, H., Huber, B.T., Holers, M., Wyss-Coray, T., 2011. Complement receptor 2 is expressed in neural progenitor cells and regulates adult hippocampal neurogenesis. J. Neurosci. 31, 3981–3989.
Moser, B., Willimann, K., 2004. Chemokines: role in inflammation and immune surveillance. Ann. Rheum. Dis. 63, 84–89.
Nair, A., Bonneau, R.H., 2006. Stress-induced elevation of glucocorticoids increases microglia proliferation through NMDA receptor activation. J. Neuroimmunol. 171, 72–85.
Nance, D.M., Sanders, V.M., 2007. Autonomic innervation and regulation of the immune system (1987-2007). Brain Behav. Immun. 21, 736–745.
Nautiyal, K.M., Ribeiro, A.C., Pfaff, D.W., Silver, R., 2008. Brain mast cells link the immune system to anxiety-like behavior. Proc. Natl. Acad. Sci. U. S. A. 105, 18053–18057.
Nelson, C., NA, F., Zeanah, C., 2014. Romania's Abandoned Children. Harvard University Press, Romania's Abandoned Children.
Nelson, L.H., Lenz, K.M., 2017. Microglia depletion in early life programs persistent changes in social, mood-related, and locomotor behavior in male and female rats. Behav. Brain Res. 316, 279–293.
Nelson, L.H., Warden, S., Lenz, K.M., 2017. Sex differences in microglial phagocytosis in the neonatal hippocampus. Brain Behav. Immun. 64, 11–22.
Nelson, T.E., Hao, C., Manos, J., Ransohoff, R.M., Gruol, D.L., 2011. Altered hippocampal synaptic transmission in transgenic mice with astrocyte-targeted enhanced CCL2 expression. Brain Behav. Immun. 25, S106–S119.
Neurauter, G., Schrocksnadel, K., Scholl-Burgi, S., Sperner-Unterweger, B., Schubert, C., Ledochowski, M., Fuchs, D., 2008. Chronic immune stimulation correlates with reduced phenylalanine turnover. Curr. Drug Metab. 9, 622–627.
Nimmerjahn, A., Kirchhoff, F., Helmchen, F., 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308, 1314–1318.
Nishi, M., Horii-Hayashi, N., Sasagawa, T., 2014. Effects of early life adverse experiences on the brain: implications from maternal separation models in rodents. Frontiers in Neuroscience 8, Article 166.
Nithianantharajah, J., Hannan, A.J., 2006. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat. Rev. Neurosci. 7, 697–709.
Nolan, Y., Maher, F.O., Martin, D.S., Clarke, R.M., Brady, M.T., Bolton, A.E., Mills, K.H. G., Lynch, M.A., 2005. Role of interleukin-4 in regulation of age-related inflammatory changes in the hippocampus. J. Biol. Chem. 280, 9354–9362.
Nusslock, R., Miller, G.E., 2016. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol. Psychiatry 80, 23–32.
Obanewa, O., Newell, M.-L., 2017. Maternal nutritional status during pregnancy and infant immune response to routine childhood vaccinations. Futur. Virol. 12, 525–536.
O'Connor, T.G., Tang, W., Gilchrist, M.A., Moynihan, J.A., Pressman, E.K., Blackmore, E. R., 2014. Diurnal cortisol patterns and psychiatric symptoms in pregnancy: short-term longitudinal study. Biol. Psychol. 96, 35–41.
Orr, S.K., Palumbo, S., Bosetti, F., Mount, H.T., Kang, J.X., Greenwood, C.E., Ma, D.W.L., Serhan, C.N., Bazinet, R.P., 2013. Unesterified docosahexaenoic acid is protectice in neuroinflammation. J. Neurochem. 127, 378–393.
Orsini, F., De Blasio, D., Zangari, R., Zanier, E.R., De Simoni, M.G., 2014. Versatility of the complement system in neuroinflammation, neurodegeneration and brain homeostasis. Front. Cell. Neurosci. 8, 380.
Ortiz, R., Sibinga, E.M., 2017. The role of mindfulness in reducing the adverse effects of childhood stress and trauma. Children 4, 2–19.
Osborne, B.F., Turano, A., Schwarz, J.M., 2018. Sex differences in the neuroimmune system. Curr. Opin. Behav. Sci. 23, 118–123.
Pace, T.W.W., Wingenfeld, K., Schmidt, I., Meinlschmidt, G., Hellhammer, D.H., Heim, C. M., 2012. Increased peripheral NF-kappa B pathway activity in women with childhood abuse-related posttraumatic stress disorder. Brain Behav. Immun. 26, 13–17.
Pan, W., Kastin, A.J., 2002. TNF alpha transport across the blood-brain barrier is abolished in receptor knockout mice. Exp. Neurol. 174, 193–200.
Pan, Z.H., Rosenblat, J.D., Swardfager, W., McIntyre, R.S., 2017. Role of proinflammatory cytokines in dopaminergic system disturbances, implications for anhedonic features of MDD. Curr. Pharm. Des. 23, 2065–2072.
Pandey, S., Kawai, T., Akira, S., 2015. Microbial sensing by toll-like receptors and intracellular nucleic acid sensors. Cold Spring Harbor Perspectives in Biology 7, Article 016246.
Pang, X., Letourneau, R., Rozniecki, J.J., Wang, L., Theoharides, T.C., 1996. Definitive characterization of rat hypothalamic mast cells. Neuroscience 73, 889–902.
Pang, Y., Fan, L.W., Tien, L.T., Dai, X.M., Zheng, B.Y., Cai, Z.W., Lin, R.C.S., Bhatt, A., 2013. Differential roles of astrocyte and microglia in supporting oligodendrocyte development and myelination in vitro. Brain and Behavior 3, 503–514.
Paolicelli, R.C., Bolasco, G., Pagani, F., Maggi, L., Scianni, M., Panzanelli, P., Giustetto, M., Ferreira, T.A., Guiducci, E., Dumas, L., Ragozzino, D., Gross, C.T., 2011. Synaptic pruning by microglia is necessary for normal brain development. Science 333, 1456–1458.
Pascoe, A.R., Singh, M.A.F., Edwards, K.M., 2014. The effects of exercise on vaccination responses: a review of chronic and acute exercise interventions in humans. Brain Behav. Immun. 39, 33–41.
Pascual, O., Ben Achour, S., Rostaing, P., Triller, A., Bessis, A., 2012. Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. Proc. Natl. Acad. Sci. U. S. A. 109, E197–E205.
Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhaes, P.V., Kapczinski, F., Kauer-Sant'Anna, M., 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry 2, 1002–1012.
Paternain, L., Martisova, E., Campion, J., Martinez, J.A., Ramirez, M.J., Milagro, F.I., 2016. Methyl donor supplementation in rats reverses the deleterious effect of maternal separation on depression-like behavior. Behav. Brain Res. 15, 51–58.
Pedersen, A.F., Zachariae, R., Bovbjerg, D.H., 2009. Psychological stress and antibody response to influenza vaccination: a meta-analysis. Brain Behav. Immun. 23, 427–433.
Pehlivanoglu, B., Bayrak, S., Gurel, E.I., Balkanci, Z.D., 2012. Effect of gender and menstrual cycle on immune system response to acute mental stress: apoptosis as a mediator. Neuroimmunomodulation 19, 25–32.
Pekny, M., Wilhelmsson, U., Bogestal, Y.R., Pekna, M., 2007. The role of astrocytes and complement system in neural plasticity. International Review of Neurobiology 82, 95–111.
Peng, Q., Li, K., Smyth, L.A., Xing, G.L., Wang, N.Y., Meader, L., Lu, B., Sacks, S.H., Zhou, W.D., 2012. C3a and C5a promote renal ischemia-reperfusion injury. J. Am. Soc. Nephrol. 23, 1474–1485.
Pervanidou, P., Kolaitis, G., Charitaki, S., Margeli, A., Ferentinos, S., Bakoula, C., Lazaropoulou, C., Papassotiriou, I., Tsiantis, J., Chrousos, G.P., 2007. Elevated morning serum interleukin (IL)-6 or evening salivary cortisol concentrations predict posttraumatic stress disorder in children and adolescents six months after a motor vehicle accident. Psychoneuroendocrinology 32, 991–999.
Peters, E.M.J., Kuhlmei, A., Tobin, D.J., Muller-Rover, S., Klapp, B.F., Arck, P.C., 2005. Stress exposure modulates peptidergic innervation and degranulates mast cells in murine skin. Brain Behav. Immun. 19, 252–262.
Petersen, A.M.W., Pedersen, B.K., 2006. The role of IL-6 in mediating the anti-inflammatory effects of exercise. J. Physiol. Pharmacol. 57, 43–51.
Pfau, M.L., Menard, C., Cathomas, F., Desland, F., Kana, V., Chan, K.L., Shimo, Y., LeClair, K., Flanigan, M.E., Aleyasin, H., Walker, D.M., Bouchard, S., Mack, M., Hodes, G.E., Merad, M.M., Russo, S.J., 2019. Role of monocyte-derived microRNA106b ~25 in resilience to social stress. Biol. Psychiatry 86, 474–482.
Piechota, M., Korostynski, M., Golda, S., Ficek, J., Jantas, D., Barbara, Z., Przewlocki, R., 2017. Transcriptional signatures of steroid hormones in the striatal neurons and astrocytes. BMC Neurosci. 18, 37.
Poeta, V.M., Massara, M., Capucetti, A., Bonecchi, R., 2019. Chemokines and chemokine receptors: new targets for cancer immunotherapy. Frontiers in Immunology 10, Article 379.
Porcelli, B., Pozza, A., Bizzaro, N., Fagiolini, A., Costantini, M.C., Terzuoli, L., Ferretti, F., 2016. Association between stressful life events and autoimmune diseases: a systematic review and meta-analysis of retrospective case-control studies. Autoimmun. Rev. 15, 325–334.
Powell, N.D., Bailey, M.T., Mays, J.W., Stiner-Jones, L.M., Hanke, M.L., Padgett, D.A., Sheridan, J.F., 2009. Repeated social defeat activates dendritic cells and enhances toll-like receptor dependent cytokine secretion. Brain Behav. Immun. 23, 225–231.

Pribiag, H., Stellwagen, D., 2014. Neuroimmune regulation of homeostatic synaptic plasticity. Neuropharmacology 78, 13–22.
Pyter, L.M., Kelly, S.D., Harrell, C.S., Neigh, G.N., 2013. Sex differences in the effects of adolescent stress on adult brain inflammatory markers in rats. Brain Behav. Immun. 30, 88–94.
Qiao, J., 2020. What are the risks of COVID-19 infection in pregnant women? Lancet 395, 760–762.
Quan, N., Avitsur, R., Stark, J.L., He, L.L., Lai, W.M., Dhabhar, F., Sheridan, J.F., 2003. Molecular mechanisms of glucocorticoid resistance in splenocytes of socially stressed male mice. J. Neuroimmunol. 137, 51–58.
Ragozzino, D., Renzi, M., Giovannelli, A., Eusebi, F., 2002. Stimulation of chemokine CXC receptor 4 induces synaptic depression of evoked parallel fibers inputs onto Purkinje neurons in mouse cerebellum. J. Neuroimmunol. 127, 30–36.
Ragozzino, D., Di Angelantonio, S., Trettel, F., Bertollini, C., Maggi, L., Gross, C., Charo, I.F., Limatola, C., Eusebi, F., 2006. Chemokine fractalkine/CX(3)CL1 negatively modulates active glutamatergic synapses in rat hippocampal neurons. J. Neurosci. 26, 10488–10498.
Raison, C.L., Demetrashvili, M., Capuron, L., Miller, A.H., 2005. Neuropsychiatric adverse effects of interferon-alpha - recognition and management. CNS Drugs 19, 105–123.
Ramsey, J.M., Cooper, J.D., Bot, M., Guest, P.C., Lamers, F., Weickert, C.S., Penninx, B., Bahn, S., 2016. Sex differences in serum markers of major depressive disorder in the Netherlands study of depression and anxiety (NESDA). PLoS One 11, e0156624.
Reinherz, E.L., Schlossman, S.F., 1980. The differentiation and function of human T lymphocytes. Cell 19, 821–827.
Remes, O., Brayne, C., van der Linde, R., Lafortune, L., 2016. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. Brain and Behavior 6, e00497.
Reus, G.Z., Silva, R.H., de Moura, A.B., Presa, J.F., Abelaira, H.M., Abatti, M., Vieira, A., Pescador, B., Michels, M., Ignacio, Z.M., Dal-Pizzol, F., Quevedo, J., 2019. Early maternal deprivation induces microglial activation, alters glial fibrillary acidic protein immunoreactivity and indoleamine 2,3-dioxygenase during the development of offspring rats. Mol. Neurobiol. 56, 1096–1108.
Riboni, F.V., Belzung, C., 2017. Stress and psychiatric disorders: from categorical to dimensional approaches. Curr. Opin. Behav. Sci. 14, 72–77.
Ricciotti, E., FitzGerald, G.A., 2011. Prostaglandins and inflammation. Arterioscler. Thromb. Vasc. Biol. 31, 986–1000.
Rimon, R., Laakso, R.L., 1985. Life stress and rheumatoid arthritis - a 15-year follow up study. Psychother. Psychosom. 43, 38–43.
Rincel, M., Darnaudery, M., 2020. Maternal separation in rodents: a journey from gut to brain and nutirtional perspectives. Proc. Nutr. Soc. 79, 113–132.
Ripke, S., & Psychiat Genomics Consortium. Psychosis endophenotypes, wellcome trust case-control, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–428.
Rivest, S., 2009. Regulation of innate immune responses in the brain. Nat. Rev. Immunol. 9, 429–439.
Rodriguez-Arias, M., Montagud-Romero, S., Carrion, A.M.G., Ferrer-Perez, C., Perez-Villalba, A., Marco, E., Gallardo, M.L., Viveros, M.P., Minarro, J., 2018. Social stress during adolescence activates long-term microglia inflammation insult in reward processing nuclei. PLoS One 13, 0206421.
Rogers, B., Keating, D.J., Young, R.L., Wong, M.-L., Licinio, J., Wesselingh, S., 2016. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol. Psychiatry 21, 738–748.
Rogers, J.T., Morganti, J.M., Bachstetter, A.D., Hudson, C.E., Peters, M.M., Grimmig, B. A., Weeber, E.J., Bickford, P.C., Gemma, C., 2011. CX3CR1 deficiency leads to impairment of hippocampal cognitive cunction and synaptic plasticity. J. Neurosci. 31, 16241–16250.
Rogers, M.P., Trentham, D.E., McCune, W.J., Ginsberg, B.I., Rennke, H.G., Reich, P., David, J.R., 1980. Effect of psychological stress on the induction of arthiritis in rats. Arthritis Rheum. 23, 1337–1342.
Rogers, M.P., Trentham, D.E., Dynesiustrentham, R., Daffner, K., Reich, P., 1983. Exacerbation of collagen collagen arhiritis by noise stress. J. Rheumatol. 10, 651–654.
Romeo, R.D., 2017. The impact of stress on the structure of the adolescent brain: implications for adolescent mental health. Brain Res. 1654, 185–191.
Roque, A., Ochoa-Zarzosa, A., Torner, L., 2016. Maternal separation activates microglial cells and induces an inflammatory response in the hippocampus of male rat pups, independently of hypothalamic and peripheral cytokine levels. Brain Behav. Immun. 55, 39–48.
Rostene, W., Dansereau, M.A., Godefroy, D., Van Steenwinckel, J., Goazigo, A.R.L., Melik-Parsadaniantz, S., Apartis, E., Hunot, S., Beaudet, N., Sarret, P., 2011. Neurochemokines: a menage a trois providing new insights on the functions of chemokines in the central nervous system. J. Neurochem. 118, 680–694.
Roumier, A., Bechade, C., Maroteaux, L., 2019. Chapter 10 - Serotonin and the Immune System. Academic Press, Serotonin, pp. 181–196.
Rouse, M.H., Goodman, S.H., 2014. Perinatal depression influences on infant negative affectivity: timing, severity, and co-morbid anxiety. Infant Behav. Dev. 37, 739–751.
Ryan, S.M., Nolan, Y.M., 2016. Neuroinflammation negatively affects adult hippocampal neurogenesis and cognition: can exercise compensate? Neurosci. Biobehav. Rev. 61, 121–131.
Saavedra, L.M., Navarro, B.F., Torner, L., 2017. Early life stress activates glial cells in the hippocampus but attenuates cytokine secretion in response to an immune challenge in rat pups. Neuroimmunomodulation 24, 242–255.
Sadeghi, M., Peeri, M., Hosseini, M.J., 2016. Adolescent voluntary exercise attenuated hippocampal innate immunity responses and depressive-like behaviors following maternal separation stress in male rats. Physiol. Behav. 163, 177–183.
Salter, M.W., Stevens, B., 2017. Microglia emerge as central players in brain disease. Nat. Med. 23, 1018–1027.
Sapolsky, R.M., Krey, L.C., McEwen, B.S., 1984. Glucocorticoid-sensitive hippocampal-neurons are involved in terminating the adrenocortical stress response. Proceedings of the National Academy of Sciences of the United States of America-Biological Sciences 81, 6174–6177.
Scarola, S.J., Trejo, J.R.P., Granger, M.E., Gerecke, K.M., Bardi, M., 2019. Immunomodulatory effects of stress and environmental enrichment in long-Evans rats (Rattus norvegicus). Comparative Medicine 69, 35–47.
Schafer, D.P., Lehrman, E.K., Kautzman, A.G., Koyama, R., Mardinly, A.R., Yamasaki, R., Ransohoff, R.M., Greenberg, M.E., Barres, B.A., Stevens, B., 2012. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 74, 691–705.
Schain, M., Kreisl, W.C., 2017. Neuroinflammation in neurodegenerative disorders - a review. Current Neurology and Neuroscience Reports 17, 1–11.
Schakel, L., Veldhuijzen, D.S., Crompvoets, P.I., Bosch, J.A., Cohen, S., van Middendorp, H., Joosten, S.A., Ottenhoff, T.H.M., Visser, L.G., Evers, A.W.M., 2019. Effectiveness of stress-reducing interventions on the response to challenges to the immune system: a meta-analytic review. Psychother. Psychosom. 88, 274–286.
Scher, J.U., Pillinger, M.H., 2009. The anti-inflammatory effects of prostaglandins. J. Investig. Med. 57, 703–708.
Schraufstatter, I.U., Trieu, K., Sikora, L., Sriramarao, P., DiScipio, R., 2002. Complement C3a and C5a induce different signal transduction cascades in endothelial cells. J. Immunol. 169, 2102–2110.
Schwarz, J.M., Hutchinson, M.R., Bilbo, S.D., 2011. Early-life experience decreases drug-induced reinstatement of morphine CPP in adulthood via microglial-specific epigenetic programming of anti-inflammatory IL-10 expression. J. Neurosci. 31, 17835–17847.
Schwarz, J.M., Sholar, P.W., Bilbo, S.D., 2012. Sex differences in microglial colonization of the developing rat brain. J. Neurochem. 120, 948–963.
Sciaraffa, M.A., Zeanah, P.D., Zeanah, C.H., 2018. Understanding and promoting resilience in the context of adverse childhood experiences. Early Childhood Educ. J. 46, 343–353.
Scott, K.M., Von Korff, M., Angermeyer, M.C., Benjet, C., Bruffaerts, R., de Girolamo, G., Haro, J.M., Lepine, J.P., Ormel, J., Posada-Villa, J., Tachimori, H., Kessler, R.C., 2011. The association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. Arch. Gen. Psychiatry 68, 838–844.
Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol. Bull. 130, 601–630.
Sekar, A., Bialas, A.R., de Rivera, H., Davis, A., Hammond, T.R., Kamitaki, N., Tooley, K., Presumey, J., Baum, M., Van Doren, V., Genovese, G., Rose, S.A., Handsaker, R.E., Daly, M.J., Carroll, M.C., Stevens, B., McCarroll, S.A., Schizophrenia Working, G., 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530, 177–183.
Selten, J.P., Frissen, A., Lensvelt-Mulders, G., Morgan, V., 2010. Schizophrenia and 1957 pandemic of influenza: meta-analysis. Schizophr. Bulletin 36, 219–228.
Seo, D.O., Carillo, M.A., Lim, S.C.H., Tanaka, K.F., Drew, M.R., 2015. Adult hippocampal neurogenesis modulates fear learning through associative and nonassociative mechanisms. J. Neurosci. 35, 11330–11345.
Serafini, G., Pompili, M., Seretti, M.E., Stefani, H., Palermo, M., Coryell, W., Girardi, P., 2013. The role of inflammatory cytokines in suicidal behavior: a systematic review. Eur. Neuropsychopharmacol. 23, 1672–1686.
Shanas, U., Bhasin, R., Sutherland, A.K., Silverman, A.J., Silver, R., 1998. Brain mast cells lack the c-kit receptor: immunocytochemical evidence. J. Neuroimmunol. 90, 207–211.
Shigemoto-Mogami, Y., Hoshikawa, K., Goldman, J.E., Sekino, Y., Sato, K., 2014. Microglia enhance neurogenesis and oligodendrogenesis in the early postnatal subventricular zone. J. Neurosci. 34, 2231–2243.
Shortall, S.E., Negm, O.H., Fowler, M., Fairclough, L.C., Tighe, P.J., Wigmore, P.M., King, M.V., 2018. Characterization of behavioral, signaling and cytokine alterations in a rat neurodevelopmental model for schizophrenia, and their reversal by the 5-HT6 receptor antagonist SB-399885. Molecular Neurobiology 55, 7413–7430.
Shtoots, L., Richter-Levin, G., Hugeri, O., Anunu, R., 2018. Juvenile stress leads to long-term immunological metaplasticity-like effects on inflammatory responses in adulthood. Neurobiol. Learn. Mem. 154, 12–21.
Sierra, A., Gottfried-Blackmore, A., Milner, T.A., McEwen, B.S., Bulloch, K., 2008. Steroid hormone receptor expression and function in microglia. Glia 56, 659–674.
Silver, R., Curley, J.P., 2013. Mast cells on the mind: new insights and opportunities. Trends Neurosci. 36, 513–521.
Silverman, A.J., Sutherland, A.K., Wilhelm, M., Silver, R., 2000. Mast cells migrate from blood to brain. J. Neurosci. 20, 401–408.
Simpson, R., Campbell, J., Gleeson, M., Kruger, K., Nieman, D., Pyne, D., Turner, J., Walsh, N., 2020. Can exercise affect immune function to increase susceptibility to infection? Exerc. Immunol. Rev. 26, 8–22.
Singhal, G., Jaehne, E.J., Corrigan, F., Baune, B.T., 2014. Cellular and molecular mechanisms of immunomodulation in the brain through environmental enrichment. Frontiers in Cellular Neuroscience 8, Article 97.
Slopen, N., McLaughlin, K.A., Dunn, E.C., Koenen, K.C., 2013. Childhood adversity and cell-mediated immunity in young adulthood: does type and timing matter? Brain Behav. Immun. 28, 63–71.
Smeets, P.A.M., Erkner, A., de Graaf, C., 2010. Cephalic phase responses and appetite. Nutr. Rev. 68, 643–655.
Smith, B.L., Reyes, T.M., 2017. Offspring neuroimmune consequences of maternal malnutirtion: potential mechanisms for behavioral impairments that underlie metabolic and neurodevelopmental disorders. Forntiers in Neuroendocrinology 47, 109–122.

Smith, S.E.P., Li, J., Garbett, K., Mirnics, K., Patterson, P.H., 2007. Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci. 27, 10695–10702.
Sonu, S., Post, S., Feinglass, J., 2019. Adverse childhood experiences and the onset of chronic disease in young adulthood. Prev. Med. 123, 163–170.
Stefanski, V., Gruner, S., 2006. Gender difference in basal and stress levels of peripheral blood leukocytes in laboratory rats. Brain Behav. Immun. 20, 369–377.
Stein, A., Pearson, R.M., Goodman, S.H., Rapa, E., Rahman, A., McCallum, M., Howard, L.M., Pariante, C.M., 2014. Effects of perinatal mental disorders on the fetus and child. Lancet 384, 1800–1819.
Steinman, L., 2004. Elaborate interactions between the immune and nervous systems. Nat. Immunol. 5, 575–581.
Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav. Immun. 21, 901–912.
Stevens, B., Allen, N.J., Vazquez, L.E., Howell, G.R., Christopherson, K.S., Nouri, K.D., Micheva, K.D., Mehalow, A.K., Huberman, A.D., Stafford, B, Sher, A, Litke, A.M., Lambris, J.D., Smith, S.J., John, S.W-M., Barres, B.A., 2007. The classical complement cascade mediates CNS synapse elimination. Cell 131, 1164–1178.
Strainic, M.G., Liu, J.B., Huang, D.P., An, F., Lalli, P.N., Muqim, N., Shapiro, V.S., Dubyak, G.R., Heeger, P.S., Medof, M.E., 2008. Locally produced complement fragments C5a and C3a provide both costimulatory and survival signals to naive CD4 (+) T cells. Immunity 28, 425–435.
Sun, B.L., Wang, L.H., Yang, T., Sun, J.Y., Mao, L.L., Yang, M.F., Yuan, H., Colvin, R.A., Yang, X.Y., 2018. Lymphatic drainage system of the brain: a novel target for intervention of neurological diseases. Prog. Neurobiol. 163, 118–143.
Suzuki, E., Shintani, F., Kanba, S., Asai, M., Nakaki, T., 1997. Immobilization stress increases mRNA levels of interleukin-1 receptor antagonist in various rat brain regions. Cell. Mol. Neurobiol. 17, 557–562.
Svensson, M., Lexell, J., Deierborg, T., 2015. Effects of physical exercise on neuroinflammation, neuroplasticity, neurodegeneration, and behavior: what we can learn from animal models in clinical settings. Neurorehabil. Neural Repair 29, 577–589.
Szpunar, M.J., Parry, B.L., 2018. A systematic review of cortisol, thyroid-stimulating hormone, and prolactin in peripartum women with major depression. Archives of Womens Mental Health 21, 149–161.
Tadic, A., Rujescu, D., Muller, M., Kohnen, R., Stassen, H., Szegedi, A., Dahmen, N., 2008. Association analysis between variants of the interleukin-1 β and the interleukin-1 receptor antagonist gene and antidepressant treatment response in major depression. Neuropsychiatr. Dis. Treat. 4, 269–276.
Takeuchi, O., Akira, S., 2010. Pattern recognition receptors and inflammation. Cell 140, 805–820.
Takizawa, R., Danese, A., Maughan, B., Arseneault, L., 2015. Bullying victimization in childhood predicts inflammation and obesity at mid-life: a five-decade birth cohort study. Psychol. Med. 45, 2705–2715.
Tan, Y.L., Yuan, Y., Tian, L., 2020. Microglial regional heterogeneity and its role in the brain. Mol. Psychiatry 25, 351–367.
Tancredi, V., Zona, C., Velotti, F., Eusebi, F., Santoni, A., 1990. Interleukin-2 supresses established long-term potentiation and inhibits its induction in the rat hippocampus. Brain Res. 525, 149–151.
Tancredi, V., D'Antuono, M., Cafe, C., Giovedi, S., Bue, M.C., D'Arcangelo, G., Onofri, F., Benfenati, F., 2000. The inhibitory effects of interleukin-6 on synaptic plasticity in the rat hippocampus are associated with an inhibition of mitogen-activated protein kinase ERK. J. Neurochem. 75, 634–643.
Tarlinton, D., 2019. B cells still front and Centre in immunology. Nat. Rev. Immunol. 19, 85–86.
Tausk, F., Gigli, I., 1990. The human C3B receptor - function and role in human disease. J. Investig. Dermatol. 94, S141–S145.
Teicher, M.H., Samson, J.A., 2013. Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am. J. Psychiatr. 170, 1114–1133.
Teicher, M.H., Samson, J.A., 2016. Annual research review: enduring neurobiological effects of childhood abuse and neglect. J. Child Psychol. Psychiatry 57, 241–266.
Theoharides, T.C., 1996. The mast cell: a neuroimmunoendocrine master player. International Journal of Tissue Reactions-Experimental and Clinical Aspects 18, 1–21.
Thrane, V.R., Thrane, A.S., Plog, B.A., Thiyagarajan, M., Iliff, J.J., Deane, R., Nagelhus, E. A., Nedergaard, M., 2013. Paravascular microcirculation facilitates rapid lipid transport and astrocyte signaling in the brain. Sci. Rep. 3, 2582.
Tiet, Q.Q., Bird, H.R., Davies, M., Hoven, C., Cohen, P., Jensen, P.S., Goodman, S., 1998. Adverse life events and resilience. J. Am. Acad. Child Adolesc. Psychiatry 37, 1191–1200.
Tiwari, A., Gonzalez, A., 2018. Biological alterations affecting risk of adult psychopathology following childhood trauma: a review of sex differences. Clin. Psychol. Rev. 66, 69–79.
Tomiyama, A.J., 2019. Stress and obesity. Annu. Rev. Psychol. 70, 703–718.
Tore, F., Tuncel, N., 2009. Mast cells: target and source of neuropeptides. Curr. Pharm. Des. 15, 3433–3445.
Tracey, K.J., Cerami, A., 1994. Tumor-necrosis factor - a pleitropic cytokine and therapeutic target. Annu. Rev. Med. 45, 491–503.
Tractenberg, S.G., Levandowski, M.L., de Azeredo, L.A., Orso, R., Roithmann, L.G., Hoffmann, E.S., Brenhouse, H., Grassi-Oliveira, R., 2016. An overview of maternal separation effects on behavioural outcomes in mice: evidence from a four-stage methodological systematic review. Neurosci. Biobehav. Rev. 68, 489–503.
Trepanier, M.O., Hopperton, K.E., Mizrahi, R., Mechawar, N., Bazinet, R.P., 2016. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. Mol. Psychiatry 21, 1009–1026.
Tsay, C., 2013. Julius Wagner-Jauregg and the legacy of malarial therapy for the treatment of general paresis of the insane. Yale J. Biol. Med. 86, 245–254.
Tsyglakova, M., McDaniel, D., Hodes, G.E., 2019. Immune mechanisms of stress susceptibility and resilience: Lessons from animal models. Frontiers in Neuroendocrinology 54, Article 100771.
Turner, M.D., Nedjai, B., Hurst, T., Pennington, D.J., 2014. Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease. Biochimica Et Biophysica Acta-Molecular Cell Research 1843, 2563–2582.
Turvey, S., Broide, D., 2010. Chapter 2: innate immunity. J. Allergy Clin. Immunol. 125, S24–S32.
Tyebji, S., Seizova, S., Hannan, A.J., Tonkin, C.J., 2019. Toxoplasmosis: a pathway to neuropsychiatric disorders. Neurosci. Biobehav. Rev. 96, 72–92.
Tynan, R.J., Naicker, S., Hinwood, M., Nalivaiko, E., Buller, K.M., Pow, D.V., Day, T.A., Walker, F.R., 2010. Chronic stress alters the density and morphology of microglia in a subset of stress-responsive brain regions. Brain Behav. Immun. 24, 1058–1068.
Udina, M., Castellvi, P., Moreno-Espana, J., Navines, R., Valdes, M., Forns, X., Langohr, K., Sola, R., Vieta, E., Martin-Santos, R., 2012. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J. Clin. Psychiatry 73, 1128–1138.
Ulrich-Lai, Y.M., Herman, J.P., 2009. Neural regulation of endocrine and autonomic stress responses. Nat. Rev. Neurosci. 10, 397–409.
Unemura, K., Kume, T., Kondo, M., Maeda, Y., Izumi, Y., Akaike, A., 2012. Glucocorticoids decrease astrocyte numbers by reducing glucocorticoid receptor expression in vitro and in vivo. J. Pharmacol. Sci. 119, 30–39.
Vainchtein, I.D., Chin, G., Cho, F.S., Kelley, K.W., Miller, J.G., Chien, E.C., Liddelow, S. A., Nguyen, P.T., Nakao-Inoue, H., Dorman, L.C., Akil, O., Joshita, S., Barres, B., Paz, J.T., Molofsky, A.B., Molofsky, A.V., 2018. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science 359, 1269–1273.
van Bodegom, M., Homberg, J.R., Henckens, M., 2017. Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. Frontiers in cellular neuroscience 11. Article 33.
van Kesteren, C., Gremmels, H., de Witte, L.D., Hol, E.M., Van Gool, A.R., Falkai, P.G., Kahn, R.S., Sommer, I.E.C., 2017. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl. Psychiatry 7, e1075.
van Mierlo, H.C., Broen, J.C.A., Kahn, R.S., de Witte, L.D., 2019. B-cells and schizophrenia: a promising link or a finding lost in translation? Brain Behav. Immun. 81, 52–62.
van Os, J., Kenis, G., Rutten, B.P.F., 2010. The environment and schizophrenia. Nature 468, 203–212.
van Praag, H., 2009. Exercise and the brain: something to chew on. Trends Neurosci. 32, 283–290.
VanRyzin, J.W., Yu, S.J., Perez-Pouchoulen, M., McCarthy, M.M., 2016. Temporary depletion of microglia during the early postnatal period induces lasting sex-dependent and sex-independent effects on behavior in rats. Eneuro 3, 1–19.
Vedhara, K., Cox, N.K.M., Wilcock, G.K., Perks, P., Hunt, M., Anderson, S., Lightman, S. L., Shanks, N.M., 1999. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet 353, 627–631.
Verwaerde, C., Delanoye, A., Macia, L., Tailleux, A., Wolowczuk, I., 2006. Influence of high-fat feeding on both naïve and antigen-experienced T-cell immune response in D010.11 mice. Scandanavian Journal of Immunology 64, 457–466.
Viviani, B., Boraso, M., Valero, M., Gardoni, F., Marco, E.M., Llorente, R., Corsini, E., Galli, C.L., Di Luca, M., Marinovich, M., Lopez-Gallardo, M., Viveros, M.P., 2014. Early maternal deprivation immunologically primes hippocampal synapses by redistributing interleukin-1 receptor type I in a sex dependent manner. Brain Behav. Immun. 35, 135–143.
Vyas, S., Rodrigues, A.J., Silva, J.M., Tronche, F., Almeida, O.F.X., Sousa, N., Sotiropoulos, I., 2016. Chronic stress and glucocorticoids: from neuronal plasticity to neurodegeneration. Neural Plasticity 2016, Article 6391686.
Wachholz, S., Knorr, A., Mengert, L., Plumper, J., Sommer, R., Juckel, G., Friebe, A., 2017. Interleukin-4 is a participant in the regulation of depressive-like behavior. Behav. Brain Res. 326, 165–172.
Wade, D., Varker, T., Kartal, D., Hetrick, S., O'Donnell, M., Forbes, D., 2016. Gender difference in outcomes following trauma-focused interventions for posttraumatic stress disorder: systematic review and meta-analysis. Psychological Trauma-Theory Research Practice and Policy 8, 356–364.
Walker, D.J., Zimmer, C., Larriva, M., Healy, S.D., Spencer, K.A., 2019. Early-life adversity programs long-term cytokine and microglia expression within the HPA axis in female Japanese quail. J. Exp. Biol. 222, 187039.
Walsh, E., Eisenlohr-Moul, T., Baer, R., 2016. Brief mindfulness training reduces salivary IL-6 and TNF-alpha in young women with depressive symptomatology. J. Consult. Clin. Psychol. 84, 887–897.
Wang, D.S., Chung, C.H., Chang, H.A., Kao, Y.C., Chu, D.M., Wang, C.C., Chen, S.J., Tzeng, N.S., Chien, W.C., 2020. Association between child abuse exposure and the risk of psychiatric disorders: a nationwide cohort study in Taiwan. Child Abuse Negl. 101, 104362.
Wang, Q.Z., Shelton, R.C., Dwivedi, Y., 2018a. Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: a systematic review and meta-analysis. J. Affect. Disord. 225, 422–428.
Wang, R., Wang, W., Xu, J.J., Liu, D.X., Jiang, H., Pan, F., 2018b. Dynamic effects of early adolescent stress on depressive-like behaviors and expression of cytokines and

JMJD3 in the prefrontal cortex and hippocampus of rats. Frontiers in Psychiatry 9, Article PMC6193509.
Weinhard, L., di Bartolomei, G., Bolasco, G., Machado, P., Schieber, N.L., Neniskyte, U., Exiga, M., Vadisiute, A., Raggioli, A., Schertel, A., Schwab, Y., Gross, C.T., 2018. Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. Nat. Commun. 9, 1228.
Weiser, M.J., Mucha, B., Denheyer, H., Atkinon, D., Schanz, N., Vassiliou, E., Benno, R. H., 2016. Dietary docosahexaenoic acid alleviated autistic-like behaviors resulting from maternal immune activation in mice. Prostaglandins Leukot. Essent. Fat. Acids 106, 27–37.
Wernersson, S., Pejler, G., 2014. Mast cell secretory granules: armed for battle. Nat. Rev. Immunol. 14, 478–494.
Westacott, L., Humby, T., Haan, N., Brian, S., Bush, E., Toneva, M., Moon, A., Reddaway, J., Owen, M., Hall, J., Hughes, T., Morgan, P., Gray, W., Wilkinson, L., 2020. Manipulating immune pathways differentially impact emotionality: dissociable effects of complement C3 and C3aR on learned fear and innate anxiety. Preprint:BioRxiv. https://doi.org/10.1101/685537.
Whitney, N.P., Eidem, T.M., Peng, H., Huang, Y.L., Zheng, J.C., 2009. Inflammation mediates varying effects in neurogenesis: relevance to the pathogenesis of brain injury and neurodegenerative disorders. J. Neurochem. 108, 1343–1359.
Wieck, A., Andersen, S.L., Brenhouse, H.C., 2013. Evidence for a neuroinflammatory mechanism in delayed effects of early life adversity in rats: relationship to cortical NMDA receptor expression. Brain Behav. Immun. 28, 218–226.
Wieczorek, M., Abualrous, E.T., Sticht, J., Alvaro-Benito, M., Stolzenberg, S., Noe, F., Freund, C., 2017. Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation. Frontiers in Immunology 8, Article 292.
Wilhelm, M., King, B., Silverman, A.J., Silver, R., 2000. Gonadal steroids regulate the number and activational state of mast cells in the medial habenula. Endocrinology 141, 1178–1186.
Williamson, L.L., Bilbo, S.D., 2013. Chemokines and the hippocampus: a new perspective on hippocampal plasticity and vulnerability. Brain Behav. Immun. 30, 186–194.
Wohleb, E.S., Fenn, A.M., Pacenta, A.M., Powell, N.D., Sheridan, J.F., Godbout, J.P., 2012. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social withdrawal in socially defeated mice. Psychoneuroendocrinology 37, 1491–1505.
Xie, P., Kranzler, H.R., Poling, J., Stein, M.B., Anton, R.F., Farrer, L.A., Gelernter, J., 2010. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. Neuropsychopharmacology 35, 1684–1692.
Xiong, H.G., Boyle, J., Winkelbauer, M., Gorantla, S., Zheng, J.L., Ghorpade, A., Persidsky, Y., Carlson, K.A., Gendelman, H.E., 2003. Inhibition of long-term potentiation by interleukin-8: implications for human immunodeficiency virus-1-associated dementia. J. Neurosci. Res. 71, 600–607.
Yirmiya, R., Winocur, G., Goshen, I., 2002. Brain interleukin-1 is involved in spatial memory and passive avoidance conditioning. Neurobiol. Learn. Mem. 78, 379–389.
Zafra, M.A., Molina, F., Puerto, A., 2006. The neural/cephalic phase reflexes in the physiology of nutrition. Neurosci. Biobehav. Rev. 30, 1032–1044.
Zalcman, S., Greenjohnson, J.M., Murray, L., Nance, D.M., Dyck, D., Anisman, H., Greenberg, A.H., 1994. Cytokine-specific central monoamine alterations induced by interleukin-1, interleukin-2 and interleukin-6. Brain Research 643, 40–49.
Zatti, C., Rosa, V., Barros, A., Valdivia, L., Calegaro, V.C., Freitas, L.H., Cereser, K.M.M., da Rocha, N.S., Bastos, A.G., Schuch, F.B., 2017. Childhood trauma and suicide attempt: a meta-analysis of longitudinal studies from the last decade. Psychiatry Res. 256, 353–358.
Zhang, J.-M., Jianxiong, A., 2007. Cytokines, inflammation and pain. Int. Anesthesiol. Clin. 45, 27–37.
Zhao, Z.M., Psychiat Genomics, C., 2015. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. Nat. Neurosci. 18, 199–209.
Zhou, C., Ye, H.H., Wang, S.Q., Chai, Z., 2006. Interleukin-1 beta regulation of N-type Ca2+ channels in cortical neurons. Neurosci. Lett. 403, 181–185.
Zhou, Y., Tang, H.M., Liu, J.U., Dong, J., Xiong, H.G., 2011. Chemokine CCL2 modulation of neuronal excitability and synaptic transmission in rat hippocampal slices. J. Neurochem. 116, 406–414.
Zhou, Z., Xu, M.J., Gao, B., 2016. Hepatocytes: a key cell type for innate immunity. Cell. Mol. Immunol. 13, 301–315.
Zhu, C.B., D Blakely, R., Hewlett, W.A., 2006. The proinflammatory cytokines interleukin-1 beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology 31, 2121–2131.
Zorn, J.V., Schur, R.R., Boks, M.P., Kahn, R.S., Joels, M., Vinkers, C.H., 2017. Cortisol stress reactivity across psychiatric disorders: a systematic review and meta-analysis. Psychoneuroendocrinology 77, 25–36.