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Neuroimmunological effects of early life experiences

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Abstract

Exposure to adverse experiences during development increases the risk of psychiatric illness later in life. Growing evidence suggests a role for the neuroimmune system in this relationship. There is now substantial evidence that the immune system is critical for normal brain development and behaviour, and responds to environmental perturbations experienced early in life. Severe or chronic stress results in dysregulated neuroimmune function, concomitant with abnormal brain morphology and function. Positive experiences including environmental enrichment and exercise exert the opposite effect, promoting normal brain and immune function even in the face of early life stress. The neuroimmune system may therefore provide a viable target for prevention and treatment of psychiatric illness. This review will briefly summarise the neuroimmune system in brain development and function, and review the effects of stress and positive environmental experiences during development on neuroimmune function. There are also significant sex differences in how the neuroimmune system responds to environmental experiences early in life, which we will briefly review.

Keywords

Neuroimmune system, stress, exercise, enrichment, psychiatric illness, sex differences

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Introduction

Adverse experiences early in life are robustly associated with an elevated risk of developing psychiatric illnesses (Lupien et al., 2009; Teicher et al., 2016). Positive experiences including high social and parental support and good family functioning and genetics can mitigate this risk, promoting resilience (Assary et al., 2018; Fritz et al., 2018). We are beginning to understand the biological mechanisms linking early life experiences with risk and resilience to later mental illness. Mounting evidence suggests the neuroimmune system plays a key role and may provide a feasible target for prevention and treatment of some psychiatric disorders (Nusslock and Miller, 2016).

A role for immune function in psychiatric illness was discovered over a century ago, in patients with syphilitic psychosis. In these patients, malaria inoculation induced a high fever, assisting the immune system in fighting syphilis and resolving psychiatric symptoms (Tsay, 2013). There are now many examples of correlations between immune function (or dysfunction) and psychiatric symptoms. Extreme accumulation of mast cells (effector cells of the immune system) in the body (mastocytosis) is correlated with anxiety and emotionality (Georgin-Lavialle et al., 2016). Interleukin-2 (IL-2) and interferon alpha (IFNα) are pro-inflammatory cytokines (signalling molecules of the immune system) which can treat hepatitis and boost immune function during cancer therapy. This treatment is associated with psychotic and manic symptoms, anxiety, depression and cognitive impairment (Dantzer et al., 2008; Felger et al., 2016). Administration of the pro-inflammatory cytokine IL-1β centrally or peripherally induces anhedonia, endocrine disruptions, anorexia and disturbed sleep. These effects are ameliorated by antidepressants and IL-1β receptor antagonists (Finck and Johnson, 1997; Koo and Duman, 2009). Drugs which decrease pro-inflammatory cytokines such as non-steroidal anti-inflammatory drugs, antipsychotics and antidepressants can resolve psychiatric symptoms (Baumeister et al., 2016; Kohler et al., 2015).

We also find changes in the immune system in psychiatric patients. Alterations in peripheral expression of pro-inflammatory cytokines are found in bipolar disorder (BPD), post-traumatic stress disorder (PTSD), major depression (MD) and schizophrenia, and are associated with suicide (Black and Miller, 2015; Brietzke et al., 2009; Dowlati et al., 2010; Momtazmanesh et al., 2019; Passos et al., 2015). Microglia are resident macrophage immune cells in the central nervous system (CNS) and are traditionally described as either inactive/resting (we now know they actively survey the local environment in this state) or activated (pro-inflammatory state). Microglia activation has been found in all psychiatric illnesses, although results vary (Mondelli et al., 2017). For example, a meta-analysis of 22 studies of

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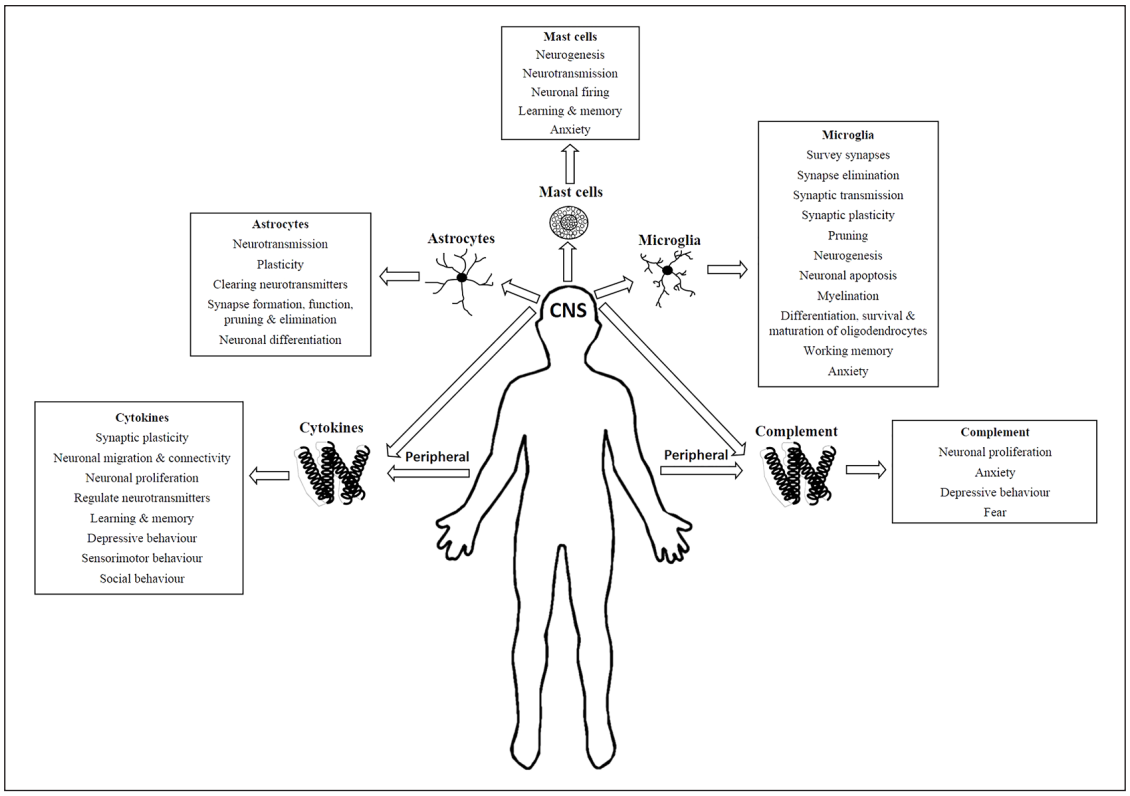

Figure 1. The role of the neuroimmune system in brain mechanisms associated with psychiatric disease.

schizophrenic brains found increased microglial activation in 11 studies, decrease in 3 and no change in 8 (Trepanier et al., 2016). Whether this activation is neurotoxic or neuroprotective in the context of psychiatric illness is currently unknown.

Genetic heterogeneity in the immune system also associates with psychiatric illness. Genetic analyses show that BPD, schizophrenia and MD associate with several immune pathways (Zhao and Psychiatric Genomics Consortium, 2015). Allelic variation in numerous cytokines predicts depression and response to antidepressant treatment (Bauer and Teixeira, 2019; Baune et al., 2010; Bufalino et al., 2013; Tadic et al., 2008). Complement is a system of plasma proteins that drives immune responses, and allelic variation in complement 4 (C4) alleles and complement regulators CUB and Sushi multiple domains (CSMD) 1 and 2 associate with schizophrenia and response to treatment (Havik et al., 2011; Sekar et al., 2016). BPD, schizophrenia and MD associate with B-cells (adaptive arm of the immune response, produce antibodies) in genome-wide association studies, although investigations into peripheral B-cells in schizophrenia find no difference to controls (O'Dushlaine et al., 2015; Van Mierlo et al., 2019).

This extensive association between immune system and psychiatric disorders/symptoms has led to the neuroimmune hypothesis of psychiatric illness. This postulates that immune system dysfunction plays a role in the aetiology of psychiatric illnesses and could therefore provide opportunities for therapeutic intervention. This hypothesis is supported by the crucial role the immune system plays in normal brain development and function. We will now review the role of the neuroimmune system in brain mechanisms associated with psychiatric disease (summarised in Figure 1) and discuss how environmental experiences during development can perturb or promote functioning, potentially generating vulnerability or resilience to psychiatric illness.

The neuroimmune system

The CNS contains a unique population of resident immune cells–microglia. Microglia arise from primitive macrophages in the yolk sac, colonise neural tissue early in development and are confined to the brain once the blood–brain barrier (BBB) is fully formed (Ginhoux and Garel, 2018). Microglia constitute 10% to 15% of adult brain cells and 80% of brain immune cells (Li and Barres, 2018; Morimoto and Nakajima, 2019). Alongside their traditional role in actively detecting invading pathogens and necrotic cells, generating and maintaining inflammatory responses, microglia play a key role in CNS development and function (Nimmerjahn et al., 2005). Microglia use their processes to interact with presynaptic boutons and dendritic spines, surveying several synapses simultaneously (Nimmerjahn et al., 2005). This allows them to regulate processes including synapse elimination, pruning of dendritic spines, neuronal apoptosis, neurogenesis and myelination, shaping neural circuitry in the developing and adult brain (Bohlen et al., 2019; Jung and Chung, 2018; Pang et al., 2013; Paolicelli et al., 2011; Sato, 2015; Schafer et al., 2012; Shigemoto-Mogami et al., 2014; Tremblay and Majewska, 2011; Wakselman et al., 2008; Zhan et al., 2014). Microglia release a variety of signalling molecules that influence the CNS. Synaptic neurotransmission is regulated by adenosine

triphosphate (ATP) which binds to P2Y1R located on astrocytes, enhancing excitatory postsynaptic currents, and tumour necrosis factor alpha (TNFα) and brain-derived neurotrophic factor (BDNF), which alter α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-d-aspartic acid (NMDA receptor expression in neurons (Konefal and Stellwagen, 2017; Parkhurst et al., 2013; Stellwagen et al., 2005). Neuronal development and synaptic function are modulated by microglial interleukin-10 (IL-10), which binds to IL-10 receptors on neurons (Lim et al., 2013). The activity of microglia has functional relevance for behaviours related to psychiatric illness: depleting microglia during development results in working memory deficits and altered anxiety (Lenz and Nelson, 2018; Nelson and Lenz, 2017; VanRyzin et al., 2016).

Astrocytes have a neuroectodermal origin and are crucial regulators of the immune response, brain development and function (Dong and Benveniste, 2001). They associate intimately with synapses, enwrapping up to 600 dendrites, contacting ~100,000 synapses. This places them in an ideal location to regulate synapse formation, function and elimination, neurotransmission and neuronal plasticity, and clearance of neurotransmitters (Chung et al., 2015; De Pitta et al., 2016; Halassa et al., 2007; Um, 2017). Neurotransmitter receptors, transporters and cell-adhesion molecules on astrocytic processes mediate astrocyte–synapse communication (Chung et al., 2015). Astrocytes also promote microglia-dependent synaptic pruning through stimulating release of complement system components and direct release of IL-33, as well as engulfing synapses themselves (Bosworth and Allen, 2017; Chung et al., 2015; Pekny et al., 2007; Vainchtein et al., 2018). Astrocytes are vital for appropriate in vivo differentiation of neurons, and elimination of astrocyte precursors results in neurodegeneration and early postnatal death (Klapper et al., 2019; Reddy et al., 2003). Interestingly, in the rodent brain, the majority of excitatory synapse formations occur in postnatal weeks 2 and 3: coinciding with maturation and differentiation of astrocytes (Chung et al., 2015).

Mast cells perform a wide variety of immune functions, from recognising pathogens, initiating and enhancing immune responses, to eliminating bacteria through release of antibacterial compounds (Krystel-Whittemore et al., 2016). Brain-resident mast cells exhibit bidirectional communication with neurons and glia, via release of prestored mediators including histamine, serotonin, cytokines and growth factors (Silver and Curley, 2013). This regulates processes including glutamatergic neurotransmission, hippocampal neurogenesis, neuronal firing, learning and memory, anxiety, astrocyte–mast cell communication and microglial activity (Kim et al., 2011; Nautiyal et al., 2008, 2012; Skaper et al., 2012). Mice lacking mast cells have impaired learning and memory, increased anxiety and abnormal neurogenesis, demonstrating a role for mast cells in normal brain function and behaviour (Nautiyal et al., 2008).

A range of signalling molecules traditionally identified for their roles in immune function are now known to regulate normal brain development and function. Cytokines (small protein signalling molecules) are the primary source of signalling for the immune system and include interferons, interleukins, chemokines and tumour necrosis factor (TNF; Turner et al., 2014). All cells in the healthy adult brain secrete cytokines and express their receptors, and cytokines play a role in neuronal development, synaptic function and normal behaviour (Cuneo and Autieri, 2009). During development, mice lacking the chemokine C-X-C motif chemokine ligand 12 (CXCL12) or its receptor C-X-C chemokine receptor type 4 (CXCR4) die during gestation, partly due to lack of neuronal migration (Levin and Godukhin, 2017; Ragozzino et al., 2002). Several studies have shown that chemokines regulate hippocampal plasticity (Williamson and Bilbo, 2013). CXCR4 modulates synaptic depression, C-X3-C motif ligand 1 (CX3CL1, or fractalkine) alters postsynaptic currents via C-X3-C motif chemokine receptor 1 (CX3CR1) and synaptic activity is increased by C-X-C motif ligand 2 (CXCL2), C-C-motif chemokine ligand 2 (CCL2) and C-C-motif chemokine ligand 3 (CCL3) in vitro through a variety of mechanisms, including glutamatergic activity and NMDA signalling (Kuijpers et al., 2010; Lax et al., 2002; Levin and Godukhin, 2017; Ragozzino et al., 2002, 2006; Zhou et al., 2011). Chemokines also play an important role in behaviour. Knockout of CX3CR1 in mice impairs learning and memory and LTP via increased IL-1β, and IL-1β has independently been shown to regulate hippocampal-dependent behaviours, with physiological levels promoting and excessive levels impairing performance (Goshen et al., 2007; Rogers et al., 2011; Yirmiya et al., 2002). Several other studies show that interleukins are important mediators of hippocampal plasticity. Hippocampal infusion of IL-1β in vivo inhibits cell proliferation and controls neural transmission, altering hippocampal-dependent memory (Baartman et al., 2017; Goshen et al., 2007; Koo and Duman, 2008; Yirmiya et al., 2002). In vitro, IL-1β inhibits hippocampal long-term potentiation (LTP) and synaptic strength and reduces calcium currents, as well as promoting gamma aminobutyric acid (GABA)a receptor–mediated inhibition of cerebella Purkinje cells (Bellinger et al., 1993; Yirmiya et al., 2002; Zhou et al., 2006). Anti-inflammatory cytokines IL-4 and IL-10 can regulate the expression of IL-1β, controlling its inhibitory effects on LTP (Nolan et al., 2005). Other pro-inflammatory cytokines including IL-2, IL-6, IL-8, IL-18 and IFNα exert similar effects to IL-1β, inhibiting hippocampal LTP (Curran and O'Connor, 2001; Mendoza-Fernandez et al., 2000; Tancredi et al., 1990, 2000; Xiong et al., 2003). In particular, synaptic plasticity in the hippocampus is inhibited in a dose-dependent manner by IL-6, and administration of anti-IL-6 antibody improves long-term memory (Balschun et al., 2004; Gruol, 2015; Tancredi et al., 2000). IL-6 also affects neuronal development, promoting the production of adult-born neurons in the hippocampus and survival of catecholaminergic neurons, which increase dopamine release in the hippocampus (Bowen et al., 2011; Erta et al., 2012). Knockout models and direct administration demonstrate the importance of interleukins for psychiatrically relevant behaviour. IL-4 knockout increases depressive behaviour, IL-33 knockout affects sensorimotor behaviour and neural circuitry and IL-1 receptor knockout in glutamatergic neurons rescues stress-induced impairments in social behaviour and working memory (DiSabato et al., 2020; Vainchtein et al., 2018; Wachholz et al., 2017). In addition, IL-2 infusion affects depressive-type behaviours (Karrenbauer et al., 2011). There is limited evidence that TNFα and interferons may also regulate neuronal processes and behaviour. Homeostatic plasticity in the CNS is regulated by TNFα (via TNFR1) through regulation of glutamate and GABA receptor trafficking and neuronal connectivity, and social behaviour is affected by interferon γ (Filiano et al., 2016; Furukawa and Mattson, 1998; Konefal and Stellwagen, 2017). This suggests a complex, interdependent role for cytokines in neuronal development, synaptic plasticity and behaviour.

Cytokines also affect levels of neurotransmitters with convincing links to psychiatric disorders. Dysregulation of and polymorphisms in monoamines including serotonin and dopamine are linked to depression, anxiety, schizophrenia and BPD, especially when combined with early life stress (ELS; Andrews et al., 2015; Conio et al., 2020; Songtachalert et al., 2018; Uher and McGuffin, 2008). TNFα and IL-1β up-regulate neuronal serotonin transporter activity, increasing serotonin uptake and decreasing the amount of available serotonin (Malynn et al., 2013; Tsao et al., 2006; Zhu et al., 2006). Tryptophan is a serotonin precursor, but indoleamine 2,3-dioxygenase diverts tryptophan away from this pathway, converting it instead to kynurenine. This creates metabolites which regulate dopamine and glutamate (Campbell et al., 2014). Several enzymes in the kynurenine pathway are under the control of cytokines (Campbell et al., 2014).

Complement proteins are another source of signalling in the immune system and are secreted by all CNS cells (Orsini et al., 2014). Limited evidence links complement proteins to neuronal development and behaviour. Complement receptor 2 (CR2) agonism inhibits neuronal proliferation, whereas antagonism of complement component 3a receptor (C3aR) promotes proliferation (Ducruet et al., 2012; Moriyama et al., 2011). Mice lacking C3aR are more anxious yet resilient to depressive behaviour, and those lacking complement 3 (C3) display enhanced fear (Crider et al., 2018; Westacott et al., 2020). The immune system clearly plays a crucial role in normal brain development, function and behaviour. Dysregulation by environmental experiences early in life may therefore alter brain development and function, promoting risk or resilience to psychiatric illness later in life. In the next section, we will review the evidence for the effects of early life experiences on neuroimmune function (summarised in Figure 2).

Early life experiences and neuroimmune function

Stress

Many psychological and physical experiences are perceived as stressful and provoke stress responses. Most are a regular part of life, and the stress response causes a range of normal behavioural and molecular alterations as the individual regains homeostasis. The hypothalamic–pituitary–adrenal (HPA) axis and sympathetic–adrenal–medullary (SAM) axis are major mediators of the stress response. A fast response is produced by the SAM axis, involving epinephrine and norepinephrine; the HPA axis produces a slower acting response, using corticotrophin releasing hormone, arginine vasopressin, adrenocorticotropin hormone and glucocorticoids (Carrasco and de Kar, 2003; Ulrich-Lai and Herman, 2009). Prolonged or excessive stress can result in dysregulated stress responses: a core feature of several stress-related psychiatric illnesses (Cherian et al., 2019). Stress axes are intricately linked with the immune system; therefore, excessive stress could permanently alter immune function. All cells of the immune system express receptors for stress hormones. Glucocorticoid stress hormones bind to receptors on immune cells in the brain, producing both anti- and pro-inflammatory effects (Duque and Munhoz, 2016; Frank et al., 2010; Glaser and Kiecolt-Glaser, 2005). The HPA axis is, in turn, stimulated by cytokines, especially IL-1α/β, IL-6 and TNFα, bolstering stress responses (Dunn, 2006). Stress–immune interactions rely on synergy between CNS and peripheral mechanisms, and there are several routes of communication between the two. Peripheral immune molecules affect CNS function by passive diffusion, active transport across the BBB or interaction with endothelial cells of the BBB (Banks, 2005; Daneman and Prat, 2015). Recent research demonstrates that the lymphatic drainage system of the brain (crucial for clearing waste from the CNS, regulating fluid balance and transporting lipids) allows peripheral immune molecules to enter the brain, and CNS-derived antigens to enter the periphery (Mastorakos and McGavern, 2019). The autonomic nerves of the gastrointestinal tract and gut flora are an often-overlooked source of neurotransmitters, including acetylcholine, histamine, GABA, BDNF and serotonin, a relationship which is mediated by gut inflammation and is essential in coordinating appropriate immunological and psychological responses (Bonaz et al., 2018; El Aidy et al., 2014; Foster and Neufeld, 2014).

Early life stress (ELS)

The immune system, CNS and brain are formed in utero, but development and maturation continue throughout the postnatal period and into adolescence (Brenhouse and Schwarz, 2016; Foulkes and Blakemore, 2018; Gilmore et al., 2018). A growing body of literature demonstrates that prolonged or intense stress during development can permanently alter brain development, and increase the incidence of psychiatric-related behaviours (e.g. anxiety and depression) and increase the risk for psychiatric illness. Several meta-analyses now demonstrate robust associations between stress at all developmental time points (in utero, perinatal, childhood and adolescence) and increased risk of psychiatric illness later in life (e.g. Green et al., 2010; Kessler et al., 2010; Knuesel et al., 2014; McLaughlin et al., 2012; Scola and Duong, 2017). The underlying neurobiological mechanisms responsible for this phenomenon may vary depending on the exact timing of exposure, and which brain regions are most sensitive at that time point, and support for this notion is found in animal models. One potential mechanism is the neuroimmune system, and we will now review the neuroimmune effects of ELS.

Neuroimmune effects of ELS in humans

ELS in utero takes a variety of different forms, from maternal immune activation (MIA) to psychological stress. Maternal exposure to viral, parasitic and bacterial infection in pregnancy increases psychiatric illness, especially autism and schizophrenia, in offspring (Babulas et al., 2006; Blomstrom et al., 2016; Estes and McAllister, 2016; Guma et al., 2019; Tyebji et al., 2019). This suggests pregnant women should take extra care during outbreak situations, such as the current worldwide COVID-19 pandemic (Cowan, 2020). Maternal autoimmune disorders produce similar increases in psychiatric illnesses, suggesting MIA is a key feature of this relationship (Chen et al., 2016; Estes and McAllister, 2016). It has been hypothesised that increased pro-inflammatory cytokines resulting from MIA cross the placenta, activating foetal immune responses and affecting brain development (Scola and Duong, 2017). Psychological stress and mental illness during pregnancy also increase risk of psychiatric disorder in offspring, although some studies do not support this (Brannigan et al., 2020; Malaspina et al., 2008; Stein et al., 2014).

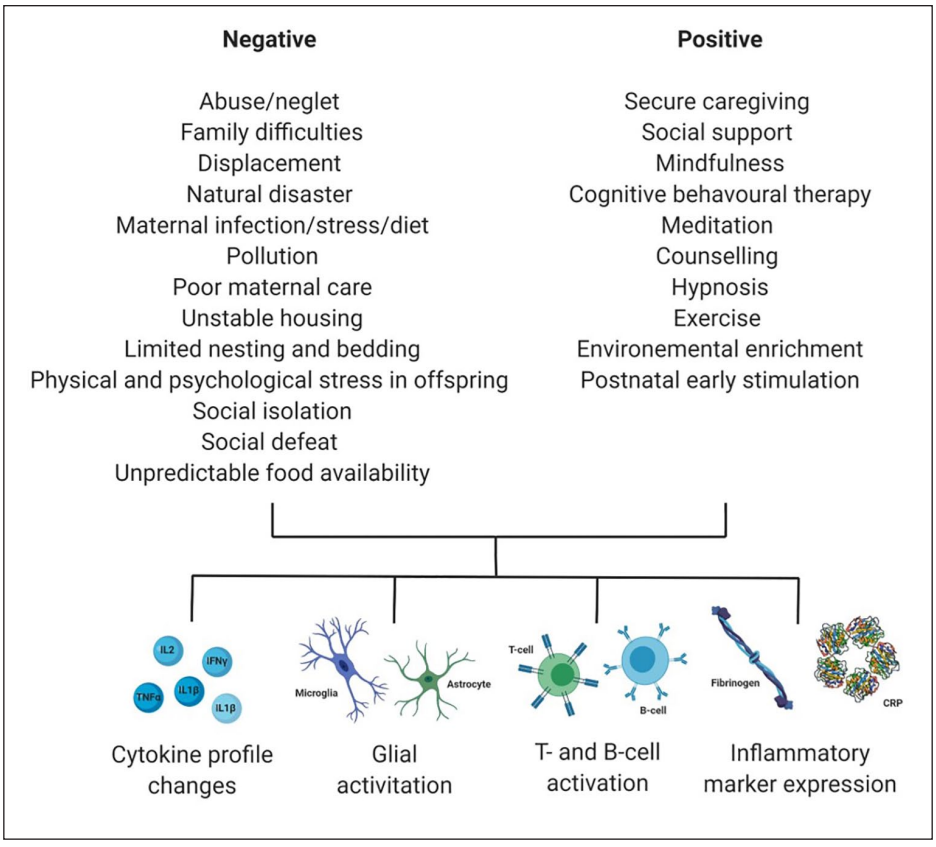

Figure 2. Summary of main negative and positive early life experiences and their effects on the immune system.

Abnormal circulating stress hormones and pro-inflammatory cytokines in stressed mothers may be a mechanism directly affecting the developing offspring, permanently programming the neuroimmune system and brain development (Cheng and Pickler, 2014; Corwin et al., 2013; Coussons-Read et al., 2007; Elenkov et al., 2005; O'Connor et al., 2014; Szpunar and Parry, 2018). Support for this is found in the offspring of mothers who experienced psychosocial stress during pregnancy. Peripheral monocytes from their daughters produce increased IL-6 and IL-10, and an increase in T-helper cell cytokine production (Entringer et al., 2008). As there are several pathways of communication between peripheral and central immune systems, this could have an impact on CNS development and function. To our knowledge, this is the only study in humans investigating the effects of maternal stress in utero on later immune function.

Stressful experiences in childhood and adolescence such as abuse, neglect, family difficulties, displacement and natural disaster increase rates of mental disorders (Abel et al., 2014; Green et al., 2010; Kessler et al., 2010; McLaughlin et al., 2012; Van Os et al., 2010). Several studies show a correlation between childhood adversity (CA) and altered immune function in childhood and adulthood, where a pro-inflammatory phenotype is commonly observed. Peripheral markers such as IL-6 and TNFα, nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκβ, regulates cytokine production), C-reactive protein (CRP, complement system activator), fibrinogen (involved in blood clot formation), E-selectin (controls inflammatory responses) and leukocytes are affected by CA (Carpenter et al., 2010; Danese et al., 2017; Danese and Lewis, 2007; Fagundes et al., 2013; Kuhlman et al., 2019; Pace et al., 2012). CA also affects immune function within the context of psychiatric illness. Patients with schizophrenia and a history of CA have higher levels of IL-6 and TNFα, and TNFα levels correlate with severity of trauma (Dennison et al., 2013). Increased IL-6 and CRP accompanied a transition to depression only in adolescents exposed to CA, and high IL-6 was predictive of depression 6 months later (Miller and Cole, 2012). It is now widely accepted that many psychiatric populations are heterogeneous, with different causal mechanisms underlying the same disorder and producing subtypes, and going forward, inflammatory phenotype may be a useful stratification when considering treatment options (Feczko et al., 2019).

Neuroimmune effects of ELS in animal models

Animal models provide greater support for the link between ELS and long-term neuroimmunological programming and allow deeper investigation of the underlying neurobiological mechanisms without many of the confounds that plague human study (e.g. uncontrolled genetic and environmental factors, and inaccessibility of neural tissue). Prenatal stressors include MIA, stimulation of maternal stress responses via physiological (injection of stress hormones) and psychological (e.g. bright lighting, restraint) methods and dietary manipulations. In the early postnatal period, stress is commonly induced through poor maternal

care, maternal separation, unstable housing and limited nesting and bedding. Following weaning, in the prepubertal and adolescent stages, stressors include unstable housing (e.g. variable social groups, wet bedding and constant light), short- and long-term physical/psychological stress (including foot shocks, elevated platform, forced swim and restraint), social defeat and isolation. ELS throughout development causes anxiety and depressive-type behaviours, abnormal social functioning, altered HPA axis function, impaired memory and cognitive flexibility, abnormal sensorimotor gating and repetitive behaviour, phenotypes reminiscent of anxiety, depression, schizophrenia and autism disorders (Bock et al., 2015; Green and McCormick, 2013; Nishi et al., 2014; Romeo, 2017; Tractenberg et al., 2016; Van Bodegom et al., 2017). Structural changes are also observed in the brain, especially in the prefrontal cortex, amygdala and hippocampus (Eiland and Romeo, 2013; Estes and McAllister, 2016). Importantly, exact effects may vary depending on precise time of exposure and nature of the stress (Gee and Casey, 2015).

A growing body of literature demonstrates that ELS has lasting implications for neuroimmune function in a range of animal models. Here, considerable study has been directed at the effects of prenatal and early postnatal stressors on cytokine expression. MIA and maternal separation alter the expression of cytokines peripherally and throughout the brain, during development and into adulthood (Bergdolt and Dunaevsky, 2019; Brenhouse et al., 2018; Dimatelis et al., 2012; Ganguly and Brenhouse, 2015). The exact profile of cytokine alterations depends on timing of stress, region assessed and timing of assessment. Less research has been directed at post-weaning and adolescent phases, but peripheral and central cytokine expression is also affected by chronic unpredictable stress and isolation rearing throughout adolescence, especially TNFα, IL-1β and IL-6 (Ko and Liu, 2015, 2016; Moller et al., 2013; Shortall et al., 2018; Wang et al., 2018b). Restraint and social defeat during adolescence enhance the expression of IL-1β and TNFα in the hippocampus after immune challenge, effects that are not mirrored in the periphery (Bekhbat et al., 2019; Pyter et al., 2013). This suggests peripheral measures are not always a suitable proxy for central changes, and both must be considered. Animal models provide a unique opportunity for such comparisons; unfortunately most studies do not take advantage of this. IL-1β and IL-10 are affected centrally in Japanese quail experiencing stress during adolescence (unpredictable food availability), suggesting these effects are conserved across species (Walker et al., 2019).

Several studies have shown that microglia and astrocytes demonstrate long-term responses to ELS. Morphology, density and developmental trajectory are altered by perinatal stressors (high fat diet, diesel particles, maternal separation and MIA), producing a pro-inflammatory phenotype with long-term consequences for microglial developmental programming and behaviours such as anxiety and spatial memory (Banqueri et al., 2019; Bilbo and Tsang, 2010; Bolton et al., 2017; Catale et al., 2020; Delpech et al., 2016; Edlow et al., 2019; Makinson et al., 2017; Matcovitch-Natan et al., 2016; Reus et al., 2019; Saavedra et al., 2017). Number and activation of microglia are changed throughout the brain as a result of unpredictable and social stress in adolescence, concomitant with increased depressive-type behaviours (Rodriguez-Arias et al., 2018; Wang et al., 2018b).

T- and B-cells, natural killer cells (cytotoxic lymphocyte) and chemokine expression also respond to ELS. During gestation, malnutrition impairs T- and B-cell activity, and restraint, light and noise stress decrease peripheral immune function, with B-cells demonstrating lower proliferation and natural killer cells demonstrating lower effectiveness (Kay et al., 1998; Liaudat et al., 2012). Short-term stress in the post-weaning, pre-adolescent phase reduces peritoneal macrophages and increases blood CCL2 and blood monocytes after peritoneal inflammation (Shtoots et al., 2018). The same stress increases hippocampal expression of FK506-binding protein 5 (FKBP5), an immunophilin which helps regulate the HPA axis, providing a potential link between neuroimmune alterations and dysregulated HPA axis function (Brydges et al., 2020). In humans, FKBP5 polymorphisms interact with CA, promoting resilience or susceptibility to depression and PTSD (Wang et al., 2018a; Xie et al., 2010). These studies show that ELS can alter the neuroimmune system throughout development and into adulthood, contributing to abnormal brain function and behaviour, potentially increasing vulnerability to psychiatric illness. However, it is presently unclear to what extent the neuroinflammatory consequences of ELS are directly causal in the precipitation of psychiatric disorders, and more research is urgently needed to address this. Studies utilising neuroimmune modulators as therapeutic agents following ELS would shed light onto causality, as well as providing novel treatment avenues for stress-related psychiatric illnesses. A whole host of suitable compounds already exist, including those which modulate glia (e.g. minocycline, fluorocitrate, ibudilast, methionine sulfoximine and propentofylline; Romero-Sandoval and Horvath, 2008), complement system inhibitors (e.g. eculizumab, soluble CR1, anti-factor B, OmCI and others; Carpanini et al., 2019) and cytokine inhibitors (e.g. etanercept, infliximab, adalimumab and ustekinumab; Schmidt et al., 2016).

Positive environmental experiences early in life and the neuroimmune system

Although less well studied than ELS, there is growing evidence that positive, enriching experiences early in life can enhance neuroimmune function and protect against the negative effects of ELS. In humans, interventions including mindfulness improve psychiatric symptomatology in those exposed to CA, and a secure caregiving environment protects against the negative effects of ELS (Brown et al., 2017; Fritz et al., 2018; McGoron et al., 2012; Ortiz and Sibinga, 2017; Sciaraffa et al., 2018). Whether these effects are mediated through neuroimmune function is presently unknown. However, evidence from adults indicates enriching, positive experiences improve immune function. Mindfulness, cognitive–behavioural therapy, meditation, hypnosis and counselling reduce inflammation and promote immune performance in adults (Black and Slavich, 2016; Goldberg et al., 2018; Schakel et al., 2019; Walsh et al., 2016). Therefore, research on the potential neuroimmunological benefits of enriching experiences early in life is warranted.

Animal models employ three main categories of positive environmental experiences: exercise, environmental enrichment (EE) and postnatal early stimulation (PES). Exercise ranges from swimming to treadmill regimes; EE provides animals with stimulating environments, including larger cages with toys, tunnels and large social groups, and promoting exploration and physical activity; and PES stimulates the mother to take greater care of her pups (e.g. increased licking and grooming)

by removing the pups briefly (few minutes) each day. These interventions improve abnormal behaviour and brain development resulting from ELS, and there is growing evidence this may be partially mediated through the neuroimmune system (Harrison and Baune, 2014; Liu et al., 2013; Lopes et al., 2017). When given in adolescence, exercise reverses detrimental effects of maternal separation on immune function in the hippocampus and normalises depressive behaviour (Sadeghi et al., 2016). Adolescent exercise also rescues abnormal microglial activity and anxiety, sociability and repetitiveness resulting from MIA (Andoh et al., 2019; Sadeghi et al., 2016). EE throughout adolescence prevents the effects of prenatal restraint stress on T-cells and cytokine expression in the brain and spleen, as well as rescuing play and emotional behaviour (Laviola et al., 2004). TNFα and TNFα:IL-10 ratio are increased by maternal separation, and cognitive function is decreased: EE improves cognitive function and normalises cytokine expression (Do Prado et al., 2016). In contrast, EE could not rescue the effects of post-weaning, prepubertal stress on monocyte number, but did normalise IL-10 expression (Shtoots et al., 2018). PES rescues the detrimental effects of early life infection on memory, IL-1β and microglial activity in the hippocampus (Bilbo et al., 2007). Prenatal restraint decreases T-cell proliferation, neutrophils and IL-2; increases lymphocytes and leukocytes; and impacts HPA axis function: these effects are prevented by PES (Falcone et al., 2017; Liaudat et al., 2012). One study found PES reduces anxiety only in rodents expressing interferon regulatory factor-2–binding protein-2 (IRF2BP2, a microglial anti-inflammatory transcriptional suppressor), suggesting microglial inflammation may play a role in anxiety (Hari et al., 2017). PES also enhances immune function per se, increasing T- and B-cell proliferation and central expression of the anti-inflammatory cytokine IL-10, while decreasing pro-inflammatory cytokines and reducing self-administration of drugs (Lacagnina et al., 2017; Lown and Dukta, 1987; Schwarz et al., 2011).

These studies demonstrate that a range of positive experiences early in life can have beneficial effects on the neuroimmune system and rescue detrimental effects of ELS. However, more research is needed.

Sex differences in neuroimmune function following ELS

Studies investigating the effects of negative and positive experiences early in life generally focus on males. However, there are prominent sex differences in the prevalence of psychiatric illnesses, with increased rates of PTSD, MD, affective disorders and anxiety in women (Kessler et al., 2005; Remes et al., 2016). Studies including males and females often do find striking sex differences. Prenatal stress increases IL-1β in the female mouse hippocampus, and IL-1β and TNFα in males (Diz-Chaves et al., 2012, 2013). In contrast, a study with rats found that prenatal stress had no effect on female IL-1β, yet reduced expression in males (Mandyam et al., 2008). This highlights potential species differences, as well as effects of time of assessment. Early postnatal and adolescent stress appears to have greater effects in males, with MIA increasing pro-inflammatory responses in the male but not female brain, maternal separation increasing peripheral and central cytokine expression only in males and adolescent stress increasing expression of IL-1β and TNFα in the male hippocampus only (Do Prado et al., 2016; Makinson et al., 2017; Pyter et al., 2013; Viviani et al., 2014).

Male and female microglia also respond in a divergent manner to prenatal stress, as dexamethasone (synthetic stress hormone) lengthens and increases microglial process in males, shortening and reducing them in females (Caetano et al., 2017). The proportion of active microglia are affected in the dentate gyrus of females and CA1 of males following prenatal restraint stress (Diz-Chaves et al., 2012, 2013). In addition, maternal separation decreases microglia number in males but not females (Chocyk et al., 2011). Sex differences in neuroimmune responses to positive experience are also predicted: to our knowledge, there are no studies on this topic.

Conclusion

The immune system plays a key role in normal brain development and function, and a wide range of environmental stimuli during development can permanently alter the functioning of the neuroimmune system. Stress early in life results in altered neuroimmune function, and this may underlie perturbed brain development and abnormal behaviour, potentially predisposing individuals to psychiatric illness. However, more research is urgently needed to establish causality. Conversely, positive experiences promote enhanced immune function and can rescue effects of ELS on neuroimmune function, brain development and behaviour, suggesting the neuroimmune system may be a viable target in the treatment of stress-related disorders. Research in this area is sparse (and virtually non-existent in humans), and future effort should be directed at determining the most beneficial positive environmental experiences for preventing and treating the detrimental effects of ELS. In particular, little is known of optimal time points or necessary duration of intervention. As sex differences are often found in studies of ELS, greater effort should be directed at including both sexes in studies of long-term consequences of negative and positive early life experiences.

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