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Citation for final published version:

Reddaway, Jack and Brydges, Nichola M. 2020. Enduring neuroimmunological consequences of developmental experiences: from vulnerability to resilience. *Molecular and Cellular Neuroscience* 109 , 103567. 10.1016/j.mcn.2020.103567 file

Publishers page: <http://dx.doi.org/10.1016/j.mcn.2020.103567>
<<http://dx.doi.org/10.1016/j.mcn.2020.103567>>

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1 **Enduring neuroimmunological consequences of developmental experiences: from**
2 **vulnerability to resilience**

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23 **Highlights**

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

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43 **Abstract**

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

61

62 **Keywords**

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

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66

67 **Introduction**

68 *Developmental adversity & psychiatric illness*

69 The environment can have a profound impact on brain development, conferring risk or
70 resilience to psychiatric illness. Several meta analyses demonstrate that adverse experiences
71 during development significantly increase the risk of developing neuropsychiatric disorders in
72 adulthood (Lupien et al., 2009; Teicher and Samson, 2016). It is important to note that not all
73 exposed individuals develop illness – some people demonstrate resilience due to genetics and
74 positive environmental influences, such as high family functioning, close parental monitoring
75 and good social support (Assary et al., 2018; Fritz et al., 2018; Tiet et al., 1998; Wang et al.,
76 2018a; Xie et al., 2010). Research in human populations is confounded by difficulty in
77 disentangling cause and effect, genetic factors and inaccessibility of brain tissue. Animal
78 models circumnavigate these difficulties and support these findings, giving deeper insight into
79 the molecular mechanisms governing susceptibility and resilience. Here we find that stress
80 during development is typically detrimental for cognition, behaviour, neural plasticity and
81 neurogenesis, whereas positive experiences such as exercise and environmental enrichment are
82 beneficial (Lupien et al., 2009). The underlying mechanisms governing these relationships are
83 not fully understood, but recent research reveals that the neuroimmune system plays a role and
84 may be a viable therapeutic target (Nusslock and Miller, 2016). We will explore these topics,
85 summarising recent advances in the impact of developmental experiences on vulnerability and
86 resilience to psychiatric disorders via the neuroimmune system. We begin with an overview of
87 the immune system, focussing on peripheral then central functions. Not all components of the
88 immune system have been explored in the context of developmental experiences, but we
89 provide this overview in the hope that it may inspire future areas of research.

90

91 **The immune system**

92 *Innate vs. adaptive*

93 Immune function in vertebrates is broadly classified into innate and adaptive. The innate
94 immune system is a biologically ancient host defence strategy, which in modern vertebrates
95 still provides a broad, rapid and essential line of defence against pathogens (Gasteiger et al.,
96 2017; Turvey and Broide, 2010). Activation is dependent upon the recognition of pathogen-
97 associated molecular patterns such as bacterial lipopolysaccharides (LPSs) and bacterial
98 flagellin by toll-like receptors (TLRs) on various cells of the host immune system, and also by
99 components of the complement system (part of the host immune system that enhances or
100 complements other immune functions) (Boehme and Compton, 2004; Dunkelberger and Song,
101 2010; Pandey et al., 2015). Activation of these pattern recognition receptors triggers an array
102 of downstream events including the production of cytokines (key signalling molecules of the
103 immune system) and phagocytosis of the pathogen (Amarante-Mendes et al., 2018; Takeuchi
104 and Akira, 2010). The adaptive immune system also recognises molecular signatures of foreign
105 pathogens, but unlike the innate system generates highly specific antibodies to detect these
106 antigens, taking longer to mount a defensive response (Chaplin, 2010). Antibodies are
107 generated by B lymphocytes following the presentation of an immunogen by antigen
108 presentation cells and are highly specific to the presented antigen (Tarlinton, 2019). These
109 antibodies activate the complement system and opsonise (the coating of a body to facilitate
110 phagocytosis), agglutinate and neutralise infecting pathogens (Dunkelberger and Song, 2010;
111 Forthal, 2014). Presented antigens are also recognised by T cell receptors on T lymphocytes:
112 this induces T lymphocyte maturation and subsequent production of cytokines and recruitment
113 of additional lymphocytes and macrophages (effector cells of the innate immune system)
114 (Kumar et al., 2018; Reinherz and Schlossman, 1980). There is overwhelming evidence that

115 both innate and adaptive immune systems play a key role in normal brain development and
116 function, an intrinsic role not triggered by pathogens (Lenz and Nelson, 2018; Miller et al.,
117 2017; Morimoto and Nakajima, 2019).

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

123

124 *Cells of the immune system*

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

133

134 *Immune system signalling*

135 **Cytokines** are a broad category of small molecules which include interferons (IFN),
136 interleukins (IL), chemokines and tumour necrosis factors, and they provide the primary source
137 of signalling for the immune system (Turner et al., 2014; Zhang and Jianxiong, 2007).

138 **Interferons** are released by eukaryotic cells in response to viral infection, and disrupt viral

139 replication, promote antigen presentation and activate macrophages and NKC's (Fensterl and
140 Sen, 2009; Le Page et al., 2000). **Interleukins** have a wide range of functions, are broadly
141 classified as either pro- or anti-inflammatory and are secreted by virtually all cells of the
142 immune system (Cuneo and Autieri, 2009). The more than 50 interleukins and associated
143 proteins bind to either type 1 or 2 interleukin receptors with downstream effector functions
144 including immune cell activation, maturation and proliferation (Akdis, 2011). **Chemokines** are
145 divided into 4 sub-families based on number and spacing of cytosine residues: CXC, CC,
146 CX3C and XC, all signal through G-protein coupled receptors and primarily coordinate the
147 immune response, attracting immune cells to sites of inflammation (Hughes and Nibbs, 2018;
148 Moser and Willmann, 2004; Poeta et al., 2019). **Tumour necrosis factors** (TNFs) are
149 transmembrane proteins, when cleaved they function as signalling molecules and bind to
150 members of the TNF receptor superfamily. Activation of TNF receptors promotes
151 inflammation, T lymphocyte regulation, apoptosis and immune cell activation (Baud and
152 Karin, 2001; Tracey and Cerami, 1994).

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

164 cells and are generated from the metabolism of arachidonic acid by cyclooxygenases. Along
165 with many non-immunological functions prostaglandins promote and regulate immune
166 activation (Aoki and Narumiya, 2012; Ricciotti and FitzGerald, 2011; Scher and Pillinger,
167 2009). **Granule proteins** are cytotoxic proteins released by a subset of leukocytes (eosinophils)
168 which disrupt lipid bilayers, degrade ribonucleic acid and generate reactive oxygen species
169 (Acharya and Ackerman, 2014). Some granule proteins (major basic protein) induce the release
170 of histamine from basophils and mast cells, and histamine is both a neurotransmitter and a
171 potent activator and regulator of inflammation via histamine receptor 1 (Branco et al., 2018).
172 Serotonin, another neurotransmitter, is produced by T lymphocytes and mast cells, and acts as
173 a chemoattractant and a regulator of immune cell activation and proliferation (EugenOlsen et
174 al., 1997; Herr et al., 2017; Roumier et al., 2019).

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

178

179 **The neuroimmune environment**

180 *Immunological communication between peripheral and central nervous systems*

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

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

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

213 (afferent pathway). The enteric nervous system (autonomic nerves of the gastrointestinal tract)
214 and gut flora represent an additional link between the peripheral immune system and the CNS
215 (Figure 2). Both enteric system neurons and intestinal bacteria produce neuroactive molecules
216 including acetylcholine, histamine and serotonin, enabling communication between the
217 intestines and the brain (gut-brain axis), and this can influence neural development, cognition
218 and behaviour (Foster and Neufeld, 2014; Rogers et al., 2016). This communication is
219 modulated by shifts in diet, composition of the microbiome and gut inflammation (Foster and
220 Neufeld, 2014; Mayer et al., 2015). This crosstalk is required to sustain a variety of homeostatic
221 functions such as the cephalic response (gastric secretion in response to the anticipation of
222 food) in addition to the coordination of a body wide response to infection (Smeets et al., 2010;
223 Zafra et al., 2006). In cases of severe infection, injury or degenerative diseases the BBB may
224 be permeabilized allowing peripheral immune cells such as circulating macrophages, mast
225 cells and T lymphocytes into the CNS (Chou et al., 2018; Dong et al., 2014; Nautiyal et al.,
226 2008).

227

228 *Immune cells of the CNS*

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

231 *Microglia*

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

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

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

261 inflammatory cytokines push microglia back into their surveying homeostatic state (Li and
262 Barres, 2018; Madry et al., 2018). Throughout pre- and postnatal development microglia are
263 highly active, shaping and fine-tuning neural circuits throughout the CNS via synaptic
264 formation and pruning (through activation of the classical complement cascade), induction of
265 apoptosis, myelination (by promoting differentiation, maturation and survival of
266 oligodendrocytes) and regulating developmental neurogenesis (Bohlen et al., 2019; Pang et al.,
267 2013; Shigemoto-Mogami et al., 2014). Depleting microglia during development results in
268 working memory deficits and altered anxiety, whereas loss in adulthood has little effect on
269 behaviour (Lenz and Nelson, 2018; Nelson and Lenz, 2017; VanRyzin et al., 2016).

270

271 *Astrocytes*

272 Astrocytes, another glial subtype, also play a critical role as an immune effector in the CNS
273 (Dong and Benveniste, 2001). Unlike microglia, astrocytes arise from neuroectodermal origins
274 but cooperate with microglia in brain homeostasis, excitatory neurotransmission,
275 homosynaptic plasticity, adenosine triphosphate homeostasis and regulation of immune
276 response (De Pitta et al., 2016; Hansson and Ronnback, 1995; Lalo et al., 2014; Pascual et al.,
277 2012). In their neuroimmune role, astrocytes can act as antigen presenting cells using major
278 histocompatibility complex (MHC) class II molecules which can be loaded with foreign or
279 endogenous proteins to promote inflammation and recruitment of microglia (Dong and
280 Benveniste, 2001; Wieczorek et al., 2017). Astrocytes also have a high expression of TLR3,
281 and TLR3 signalling induces a highly robust pro-inflammatory response including the release
282 of IL-2, TNF α and IL-6 (Jack et al., 2005). Through their production and release of complement
283 system components, astrocytes contribute to the process of complement dependent pruning of
284 synapses during development, synaptic plasticity and neurodegeneration (Hartmann et al.,

285 2019; Lian et al., 2016; Pekny et al., 2007). They also play a unique role in maintenance of the
286 BBB and are therefore able to control the bidirectional flow of immune cells and mediators
287 between the CNS and the periphery (Abbott et al., 2006). This interface of astrocytes means
288 their response to inflammation directly influences the permeability of the BBB and therefore
289 controls the influx of peripheral cytokines and immune cells into the CNS (Cabezas et al., 2014;
290 Liu et al., 2018).

291

292 *Mast cells*

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

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

312

313 *Cytokines*

314 Cytokines and their cognate receptors are constitutively expressed by all cells in the healthy
315 adult brain, can infiltrate from the periphery and are self-regulating, capable of inhibiting or
316 increasing their own release (Banks, 2005; Pan and Kastin, 2002). In the brain, the
317 hippocampus is vitally important for learning and memory, especially through synaptic
318 plasticity (LTP and LTD) and neurogenesis, and low-level secretion of IL1- β , IL-6, IL-10, IL-
319 4 and TNF α plays an essential role in these normal brain functions during development and
320 adulthood (Druart and Le Magueresse, 2019; Erta et al., 2012; Levin and Godukhin, 2017;
321 McAfoose and Baune, 2009; Pribiag and Stellwagen, 2014; Rostene et al., 2011; Whitney et
322 al., 2009). IL1- β in particular plays a variety of roles, controlling neural transmission,
323 promoting gamma aminobutyric acid (GABA)_a receptor mediated inhibition of Purkinje cells
324 in the cerebellum, inhibiting LTP and cell proliferation in the hippocampus and reducing
325 calcium currents through N-type voltage gated calcium channels (Bellinger et al., 1993; Koo
326 and Duman, 2008; Yirmiya et al., 2002; Zhou et al., 2006). Anti-inflammatory cytokines IL-4
327 and IL-10 are able to control the inhibitory effects of IL-1 β on LTP through modulating
328 expression of IL-1 β and dampening of IL-1 β driven activation of c-Jun N-terminal kinases
329 (Kelly et al., 2001; Nolan et al., 2005). A range of other pro-inflammatory cytokines including
330 IL-2, IL-6, IL-8, IL-18 and IFN α also inhibit hippocampal LTP *in vitro* (Curran and O'Connor,
331 2001; Mendoza-Fernandez et al., 2000; Tancredi et al., 2000; Tancredi et al., 1990; Xiong et
332 al., 2003). Acute administration of IL-6 exhibits dose dependant inhibition of synaptic

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

344 Chemokines are also crucial for development and neuronal plasticity (Williamson and
345 Bilbo, 2013). Deletion of the chemokine C-X-C motif (CXC) chemokine 12 (CXCL12) or its
346 receptor CXC chemokine receptor 4 (CXCR4) in mice is embryonically lethal in part due to a
347 lack of neural migration during development (Levin and Godukhin, 2017; Rostene et al.,
348 2011). Synaptic depression is also modulated by CXCR4, and fractalkine (CX3CL1) interacts
349 with its receptor C-X3-C motif chemokine receptor 1 (CX3CR1) to reduce α -amino-3-
350 hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated currents and alter excitatory
351 post-synaptic currents *in vitro* (Lauro et al., 2008; Ragozzino et al., 2006; Ragozzino et al.,
352 2002). CXC ligand 2 (CXCL2) (CXC receptor 2 ligand) increases AMPA-type glutamatergic
353 excitatory activity on cultured neurons, and application of C-C motif chemokine ligand 2
354 (CCL2) and C-C motif chemokine ligand 3 (CCL3) to hippocampal neurons increases
355 excitatory post-synaptic currents, N-methyl-D-aspartate (NMDA)-evoked Ca²⁺ signalling and
356 NMDA receptors *in vitro* (Kuijpers et al., 2010; Lax et al., 2002; Nelson et al., 2011; Zhou et

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

359 We also see significant effects of cytokines on behaviour. For example, CXC3CL1
360 (fractalkine) knockout results in altered learning and memory in mice (Rogers et al., 2011). IL-
361 2 modulates dopamine and dopamine-mediated depressive-type behaviours in developing and
362 adult rodents and IL-6 promotes survival of catecholaminergic neurons which are responsible
363 for increasing the release of dopamine in the hippocampus (Karrenbauer et al., 2011; Zalcman
364 et al., 1994). Administration of IL-1 β *in vivo* modulates hippocampal dependent memory in
365 rodents, IFN γ regulates neuronal connectivity and social behaviour whereas IL-4 knockout
366 results in a depressive phenotype (Baartman et al., 2017; Filiano et al., 2016; Goshen et al.,
367 2007; Wachholz et al., 2017). IL-33 released from astrocytes can drive synaptic pruning by
368 microglia, and IL-33 knockout alters sensorimotor behaviour (Vainchtein et al., 2018).

369

370 *Complement system*

371 Modulation of the complement system impacts developmental and adult neurogenesis. Neural
372 progenitor cells express complement receptor 2 (CR2) and its ligand complement fragment
373 C3d inhibits their proliferation, conversely antagonism of another complement receptor,
374 complement component C3a receptor 1 (C3aR1), promotes neuroblast proliferation (Ducruet
375 et al., 2012; Moriyama et al., 2011). Complement's regulation of neurogenesis continues past
376 development and has been noted following traumatic brain injury and ischaemia (Hammad et
377 al., 2018). Neurogenesis is also required for the neural plasticity that underlies homeostatic
378 functions in the adult brain such as learning and memory, and thus represents another avenue
379 for the complement system to drive the rearrangement of neural circuitry (Anderson et al.,
380 2011; Seo et al., 2015). Mice lacking complement component 1q (C1q), C3 or complement

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

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

394

395 **Neuroimmune system and psychiatric illness**

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

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

405 was thought to induce a high fever that helped the patient's immune system combat syphilis,
406 resolving psychiatric symptoms. Since that time, further associations have been found between
407 components of the immune system and psychiatric symptoms. For example, IFN α and IL-2 are
408 pro-inflammatory cytokines taken as treatments for diseases including hepatitis and to boost
409 the immune system during tumour treatment. Such treatment increases the incidence of
410 depression, anxiety and cognitive impairment, and can induce transient confusional states,
411 including psychotic and manic symptoms (Dantzer et al., 2008; Felger et al., 2016; Raison et
412 al., 2005). Both intracerebroventricular and peripheral administration of IL-1 β produce
413 depressive-like symptoms (anorexia, disturbed sleep, anhedonia and endocrine disruptions),
414 which are attenuated by IL-1 β receptor antagonism and antidepressants (Borsini et al., 2017;
415 Finck and Johnson, 1997; Koo and Duman, 2009). Conversely, anti-inflammatory agents such
416 as non-steroidal anti-inflammatory drugs (NSAIDs) and certain antidepressants and
417 antipsychotics have been associated with a decrease in inflammatory cytokines including IL-
418 6, IFN γ , TNF α and c-reactive protein (CRP), and an increase in anti-inflammatory cytokines
419 including IL-10, alongside improvement in psychiatric symptoms (Baumeister et al., 2016;
420 Hiles et al., 2012; Kohler et al., 2015).

421 In the last few decades, alterations in immune function have been associated with a
422 range of psychiatric illnesses. Mastocytosis (the excessive accumulation of mast cells in
423 internal organs and skin) is often associated with anxiety, emotionality and memory alterations
424 (Georgin-Lavialle et al., 2016). Several studies have found altered levels of peripheral
425 cytokines and lymphocyte subtypes in schizophrenia, bipolar disorder (particularly in mania),
426 post-traumatic stress disorder (PTSD) and major depression and levels of IL-1 β , IL-2, IL-6,
427 IL-8 and TNF α are associated with suicide (Black and Miller, 2015; Brietzke et al., 2009;
428 Dowlati et al., 2010; Farooq et al., 2017; Gill et al., 2009; Jeon and Kim, 2016; Kim et al.,
429 2007; Kunz et al., 2011; Lin et al., 1998; Momtazmanesh et al., 2019; Passos et al., 2015;

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

436 This neuroimmune hypothesis is especially appealing when we consider that immune
437 molecules can influence levels of neurotransmitters with a known role in psychiatric illness.
438 Serotonin modulates a diverse range of activities and behaviours in normal and psychiatric
439 disorders, and a wealth of studies show serotonergic dysfunction in e.g. anxiety, depression,
440 autism and schizophrenia (Marazziti, 2017). IL-1 β and TNF α induce up-regulation of serotonin
441 transporters, increasing uptake of serotonin and bringing on behavioural signs of depression
442 (Baumeister et al., 2014; Zhu et al., 2006). INF γ and TNF α increase the expression of
443 indoleamine 2,3 dioxygenase, which converts tryptophan to kynurenine, sequestering it away
444 from serotonin synthesis and generating neuroactive metabolites that can regulate dopamine
445 and glutamate (Campbell et al., 2014; Davis and Liu, 2015). Tetrahydrobiopterin (BH4) is a
446 cofactor for tryptophan hydroxylase and tyrosine hydroxylase, rate limiting enzymes for
447 serotonin and dopamine synthesis. Pro-inflammatory cytokines such as INF γ , IL-1 and TNF α
448 can induce reactive oxygen species, which degrade BH4 (Miller et al., 2013; Neurauter et al.,
449 2008; Pan et al., 2017).

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

454 emotional faces in depressed patients (Baune et al., 2010; Tadic et al., 2008). Variation in
455 complement C4 alleles and the complement regulators CUB and sushi multiple domains 1 and
456 2 (CSMD1/CSMD2) are associated with schizophrenia and response to antipsychotic treatment
457 (Havik et al., 2011; Liu et al., 2016; Liu et al., 2017; Sekar et al., 2016). Meta-analyses show
458 that allelic variation in CRP, IL-1 β , TNF α and T lymphocyte function are associated with major
459 depressive disorder and response to antidepressant treatment (Bauer and Teixeira, 2019;
460 Bufalino et al., 2013), and biological pathway analyses have revealed that multiple immune
461 pathways are associated with schizophrenia, major depression and bipolar disorder (Zhao and
462 Psychiat Genomics, 2015). The evidence for microglial activation is mixed: a meta-analysis of
463 22 studies using post-mortem tissue from schizophrenic and control brains found an increase
464 in activated microglia in 11 studies, a decrease in 3 and no change in 8 studies (Mondelli et al.,
465 2017; Trepanier et al., 2016). Similarly, in vivo positron emission tomography studies have
466 found variable changes in microglial density and in radioligand binding (using radioligands for
467 the 18kDa translocator protein, a protein located mainly in the mitochondrial membrane of
468 endothelial and glial cells, increased levels are associated with microglial activation) in the
469 brains of schizophrenic, psychotic and depressed patients when compared to controls (Mondelli
470 et al., 2017; van Kesteren et al., 2017). Discrepancies are likely due to differences in the brain
471 region investigated (e.g. cortex vs hippocampus), markers used (e.g. positron emission
472 tomography markers vs. human leukocyte antigen vs. CD68 vs. Iba1) stage of the disorder (e.g.
473 early vs. advanced) and issues with radiotracers as proxy measures of microglial activation
474 (Trepanier et al., 2016). Likewise, a GWAS study in 2014 found that schizophrenia, depression
475 and bipolar are associated with B lymphocytes (Ripke et al., 2014), yet studies investigating B
476 lymphocyte number in the periphery of schizophrenic patients find little difference from
477 controls (although levels of B lymphocyte related cytokines and autoantibodies are increased)
478 (van Mierlo et al., 2019). Alongside genetic variation, the environment can also have a

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

483

484 **Psychosocial stress and the immune system**

485 The immune system is highly responsive to immunological stimuli, defending the host
486 organism from disease (Chaplin, 2010). However, it also responds to non-disease related
487 stimuli, especially stress (Khansari et al., 1990; Marketon and Glaser, 2008; Tsyglakova et al.,
488 2019). In humans acute stressors, ranging from public speaking to laboratory stress tests and
489 tandem skydiving, enhance immune function in the periphery, briefly increasing NKCs and
490 pro-inflammatory mediators, especially IL-6, IL-1 β , IL-10, TNF α and CRP (Breen et al., 2016;
491 Marsland et al., 2017; Steptoe et al., 2007). This response is thought to give an evolutionary
492 advantage by priming the immune system for action when stressful experiences, such as
493 encounters with a predator, may have resulted in injury and infection (Segerstrom and Miller,
494 2004).

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

503 releasing hormone, arginine vasopressin and adrenocorticotrophic hormone and glucocorticoids
504 (GCs) from the hypothalamus, pituitary and adrenal glands (Ulrich-Lai and Herman, 2009).
505 Limbic circuits including prefrontal cortex (PFC), amygdala, hippocampus, paraventricular
506 nucleus, ventral tegmental area and nucleus accumbens play a role in regulating the stress
507 response (Jankord and Herman, 2008; Maity et al., 2015; Ulrich-Lai and Herman, 2009). GCs
508 bind to glucocorticoid receptors in selected brain regions (especially hippocampus and PFC),
509 terminating the stress response (McKlveen et al., 2013; Sapolsky et al., 1984; Vyas et al.,
510 2016). The HPA and SAM axes are intimately linked with one another and the immune system,
511 with all immune cells expressing receptors for hormones of the HPA and SAM axes (Glaser
512 and Kiecolt-Glaser, 2005).

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

528 The intimate links between stress and immune systems mean that exposure to chronic
529 or intense stress may negatively dysregulate both stress and immune functions. In support of
530 this, severe acute or chronic stress has been linked to a range of physical (from diabetes to
531 osteoporosis) and psychiatric disorders in humans (Hackett and Steptoe, 2017; Kelly et al.,
532 2019; McEwen et al., 2015; Riboni and Belzung, 2017; Tomiyama, 2019; Zorn et al., 2017).
533 Some of the earliest examples of this phenomenon demonstrate that psychosocial stress in the
534 form of predator or noise exposure can dramatically alter the course of autoimmune diseases
535 such as arthritis in animals (Rogers et al., 1980, 1983). In humans, a 15-year study from 1985
536 demonstrated that a period of psychosocial stress (death of a loved one, marital problems and
537 serious illness) often preceded the development rheumatoid arthritis (Rimon and Laakso,
538 1985), and the link between stress and autoimmune diseases now has greater empirical support
539 (Porcelli et al., 2016). Adults experiencing stressful events such as caring for someone with
540 dementia, extended work stress, unemployment or poverty mount a lower immune response to
541 influenza and hepatitis B vaccines (Domnich et al., 2019; KiecoltGlaser et al., 1996; Pedersen
542 et al., 2009; Segerstrom and Miller, 2004; Vedhara et al., 1999). This suggests that
543 psychological pressures can fundamentally alter the functioning of the immune system,
544 increasing vulnerability to a range of diseases. We will now explore some of the molecular
545 mechanisms underlying this phenomenon.

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

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

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

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

583

584 **Developmental stress and the neuroimmune system**

585 There are well documented links between the experience of physical, immunological and
586 psychological stressors during development such as trauma, abuse, neglect, infection and
587 malnutrition and the development of physical (rheumatoid arthritis, cardiovascular disease,
588 lung disease, metabolic syndrome and cancer) and psychiatric illnesses (depression, anxiety,
589 PTSD, schizophrenia and borderline personality disorder) in humans (Carroll et al., 2013; Dube
590 et al., 2003; Heim and Nemeroff, 2001; Sonu et al., 2019; Teicher and Samson, 2013, 2016;
591 Tiwari and Gonzalez, 2018). Developmental stress can be experienced in utero, in the early or
592 late postnatal periods and also later on in development, during adolescence. The CNS and
593 immune systems follow distinct developmental trajectories throughout these periods as they
594 mature towards their adult form (Brenhouse and Schwarz, 2016; Gollwitzer and Marsland,
595 2015). Intriguingly, it has even been suggested that BBB permeability to immune molecules
596 may vary as a normal part of adolescent neuronal development (Brenhouse and Schwarz,
597 2016). Therefore, the long-term consequences of developmental stress may vary depending on
598 the brain region or neuroimmunological process maturing at the time of insult. As with other
599 domains (e.g. stress responses and hippocampal form and function (Brunson et al., 2011))
600 stressful challenges may produce greater or at least differential effects on neuroimmunological

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

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

613

614 **Perinatal stress (prenatal & early postnatal)**

615 *Humans - prenatal*

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

624 al., 2019) although some studies have found no association (Selten et al., 2010). It will be
625 interesting to see whether similar effects are observed after the 2020 world-wide pandemic of
626 COVID-19, and gives greater gravity to the public health advice that pregnant women should
627 be considered a vulnerable population during such outbreaks (Qiao, 2020). Similar risks are
628 observed following maternal autoimmune disorders, suggesting that activation of the maternal
629 immune system is sufficient to increase risk of psychiatric illness in the offspring (Chen et al.,
630 2016; Estes and McAllister, 2016). Maternal psychosocial stress and mental illness in the
631 prenatal period is also associated with an increased risk of psychiatric illness and delayed
632 cognitive development in the offspring, although some studies have found no association
633 (Brannigan et al., 2019, 2020; Glover, 2011; Malaspina et al., 2008; Stein et al., 2014). Women
634 experiencing psychosocial stress/mental illness during gestation have altered HPA axis
635 function and increased circulating pro-inflammatory cytokines (Cheng and Pickler, 2014;
636 Corwin et al., 2013; Coussons-Read et al., 2007; O'Connor et al., 2014; Szpunar and Parry,
637 2018), although note that some studies have found no association between perceived maternal
638 stress/mental illness and cortisol (Rouse and Goodman, 2014). It is therefore hypothesised that
639 offspring in utero are exposed to abnormal levels of maternally derived stress hormones and
640 pro-inflammatory cytokines, which may interact to alter the development of biological systems,
641 including the brain (Elenkov et al., 2005). Maternal malnutrition and over-nutrition are also
642 associated with schizophrenia, autism and metabolic disorders in offspring, and here exposure
643 to inflammatory factors is hypothesised to play a role (Smith and Reyes 2017). Despite this,
644 there are very few human studies examining the lasting effects of prenatal stress on immune
645 function in offspring. One study demonstrated that monocytes from women whose mothers had
646 experienced psychosocial stress during pregnancy produced elevated levels of IL-6 and IL-10,
647 and a bias for T helper cytokine production resulting from an overproduction of IL-4 relative
648 to IFN γ (Entringer et al., 2008). Another found that maternal diets deficient in key nutrients

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

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

664

665 *Animals – prenatal & early postnatal*

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

673 communication, repetitive behaviours, altered sensorimotor gating, increased anxiety, impaired
674 working memory and cognitive flexibility (Bock et al., 2015; Nishi et al., 2014; Smith and
675 Reyes, 2017; Tractenberg et al., 2016). These are accompanied by structural changes in
676 hippocampus and PFC and altered dopamine and serotonin signalling (Estes and McAllister,
677 2016; Smith and Reyes, 2017). Enhanced immune signalling from the mother appears to be
678 one key mechanism underlying these changes - injection of IL-6 alone is capable of producing
679 many prenatal-stress induced behavioural, structural and molecular changes in the offspring
680 (Smith et al., 2007). Furthermore, co-injecting poly (I:C) with an antibody that blocks the
681 function of IL-6 or IL-17 partially rescues the phenotype (Choi, 2016; Smith et al., 2007). This
682 demonstrates that immune challenge in early life is causal in producing altered brain
683 development in offspring.

684 Alongside behavioural and neuronal changes, perinatal stress permanently alters
685 immune function peripherally and centrally in the offspring. Psychological stressors including
686 noise, light and restraint stress during gestation decrease the effectiveness of NKCs and B
687 lymphocyte proliferation in the periphery, and maternal malnutrition/high fat diet impair T and
688 B lymphocyte activity (Falcone et al., 2017; Kay et al., 1998; Liaudat et al., 2012; Verwaerde
689 et al., 2006) Maternal psychological stressors, MIA, maternal separation/deprivation and
690 dietary manipulations alter expression of numerous cytokines in plasma or brain, either at
691 baseline or following a subsequent immune challenge, and there are many excellent reviews
692 on these topics (Avitsur et al., 2006, 2013; Bekhbat and Neigh, 2018; Bergdolt and Dunaevsky,
693 2019; Dimatelis et al., 2012; Diz-Chaves et al., 2013; Falcone et al., 2017; Saavedra et al.,
694 2017; Smith and Reyes, 2017; Wieck et al., 2013). These changes often occur in an age and
695 region-specific pattern, and suggest that similar to MIA, psychosocial stress may alter brain
696 development via regulation of the immune system.

697 A wide range of perinatal stressors (e.g. MIA, maternal psychosocial stress, brief daily
698 separation, prenatal high fat diet and neonatal exposure to diesel particles) alter the
699 developmental trajectory, density and morphology of microglia and astrocytes throughout the
700 developing brain (Baldy et al., 2018; Banqueri et al., 2019; Bekhbat and Neigh, 2018; Bergdolt
701 and Dunaevsky, 2019; Bilbo and Tsang, 2010; Bland et al., 2010; Bolton et al., 2017; Catale et
702 al., 2020; Cohen et al., 2016; Delpech et al., 2016; Diz-Chaves et al., 2012, 2013; Edlow et al.,
703 2019; Gomez-Gonzalez and Escobar, 2010; Lopez-Gallardo et al., 2008; Makinson et al., 2017;
704 Matcovitch-Natan et al., 2016; Reus et al., 2019; Roque et al., 2016; Saavedra et al., 2017;
705 Smith and Reyes, 2017), although note that some studies find no change (Bergdolt and
706 Dunaevsky, 2019; Giovanoli et al., 2016). Some of these changes are transitory in nature, others
707 persist into adulthood, and effects are often exacerbated following a further immune challenge
708 in adulthood. Temporarily depleting microglia in the early neonatal period causes anxiety,
709 despair and working-memory deficits in adulthood, highlighting their importance for the
710 development of normal behaviour (Nelson and Lenz, 2017; VanRyzin et al., 2016). MIA alters
711 MHCII levels on microglia and MHC1 on neurons in the brains of offspring (Coiro et al., 2015;
712 Hadar et al., 2017). MHCI is involved in the regulation of synaptic pruning and circuits, is
713 regulated by cytokines and co-localises with C1q, which also plays a role in synaptic
714 elimination during early postnatal refinement of the functional visual system (Miyamoto et al.,
715 2013). Altered synaptogenesis and pruning have been suggested as potential mechanisms
716 contributing to neurodevelopmental disorders such as schizophrenia and autism spectrum
717 disorder (Habela et al., 2016; McCutcheon et al., 2020). Together, this suggests that
718 psychosocial stress during early life has profound effects on the immune system which
719 correlates with altered postnatal brain developmental processes.

720

721 **Childhood/pre-pubertal/adolescent stress**

722 *Humans*

723 Abuse, neglect, parental illness, death, abandonment, crime, divorce, war, displacement and
724 natural disaster in childhood are associated with psychiatric illnesses and suicide attempts
725 (Abel et al., 2014; Bjorkenstam et al., 2016; Green et al., 2010; Kessler et al., 2010; van Os et
726 al., 2010; Wang et al., 2020; Zatti et al., 2017). They are also associated with significant
727 changes in the immune system in childhood and adulthood, especially altered CRP, IL-6,
728 TNF α , fibrinogen, E-selectin (expressed on cells activated by cytokines) and nuclear factor
729 kappa-light-chain enhancer of activated B cells (NF κ B, controls cytokine production)
730 (Baumeister et al., 2014; Carpenter et al., 2010; Coelho et al., 2014; Copeland et al., 2014;
731 Danese and Lewis, 2017; Danese et al., 2007; Fagundes et al., 2013; Kiecolt-Glaser et al., 2011;
732 Kuhlman et al., 2019; Lacey et al., 2014; Levandowski et al., 2016; Miller and Chen, 2007,
733 2010; Pace et al., 2012; Slopen et al., 2013; Takizawa et al., 2015). Sometimes these effects
734 are only seen after exposure to a subsequent stressor. In humans, IL-6 increases in response to
735 a variety of acute stressors, and this response is exaggerated in adults that were exposed to
736 early life adversity (Carpenter et al., 2010; Pace et al., 2012). Effects of developmental stress
737 on immune expression are also often exacerbated in individuals with a psychiatric disorder.
738 For example, childhood adversity (CA) predicted increased levels of TNF α and IL-6 in patients
739 with schizophrenia, and higher levels of IL-6 following CA are predictive of PTSD (Dennison
740 et al., 2013; Pervanidou et al., 2007). In women at risk for depression, a transition to depression
741 was accompanied by increases in pro-inflammatory markers CRP and IL-6 only in those
742 exposed to CA (Miller and Cole, 2012). This suggests that in the future, inflammatory
743 phenotype may be a useful diagnostic for stratifying psychiatric populations and considering
744 treatment options.

745 Longitudinal studies demonstrate an association between CA and physical illnesses,
746 diabetes and metabolic disorders and obesity (Li et al., 2019; Lown et al., 2019; Scott et al.,
747 2011). There is a high rate of medical problems in those with mental illness, suggesting there
748 may be common inflammatory mechanisms at work (Agorastos et al., 2019; Ehlert, 2013). An
749 alternative explanation is that this association arises due to lifestyle factors. A study providing
750 support for the former notion followed 1037 people since birth and found that cumulative
751 developmental stress was associated with elevated inflammatory markers CRP, fibrinogen and
752 white cell counts 20 years later, and this was not explained by potential confounders (Danese
753 et al., 2007). Stronger evidence is again provided through animal studies.

754

755 *Animals*

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

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

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

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

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

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

810

811 **Positive environmental experience and the neuroimmune system**

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

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

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

842 and caregiver attachments, high family functioning, close parental monitoring, good social
843 support and cognitive behavioural therapy can mitigate and protect against the negative effects
844 of developmental stress, but again, effects on neuroimmune function are unknown (Brown et
845 al., 2017; Fritz et al., 2018; Kok et al., 2015; Masten et al., 2009; McGoron et al., 2012; Nelson
846 et al., 2014; Sciaraffa et al., 2018; Tiet et al., 1998). One area which has received investigation
847 across the life course is diet. We have seen that malnutrition and over-nutrition during
848 development can negatively impact immune function, cognition and emotion, conversely,
849 optimal diet can exert the opposite effects. Here, interactions between the gut-brain axis are
850 thought to be particularly influential (Rogers et al. 2016). For example, breastfed infants
851 display decreased inflammation, and the Mediterranean diet, which is high in vegetables, fish
852 and ‘healthy’ dietary fats is also associated with reduced inflammation (Childs et al., 2019).
853 Addition of anti-inflammatory dietary omega-3 polyunsaturated fatty acids (PUFA) via fish oil
854 to the maternal diet reduced neonatal responses to allergens (decreased IL-5, 13 and 10 and
855 INF γ) (Dunstan et al., 2003). PUFA in the form of docosahexaenoic acid (DHA) has also been
856 found to normalise immune reactions to stress in pregnant women with two or more adverse
857 childhood experiences (Hantsoo et al., 2019). Finally, supplementation of maternal diet with
858 nutrients including folate, iodine and vitamin D are associated with enhanced fetal immunity
859 and paralleled by a decreased incidence of psychiatric illness in adulthood (Marques et al.,
860 2013). This suggests that diet may be a promising, viable, modifiable target for prevention and
861 treatment of psychiatric illnesses, although more research is needed. All measures in humans
862 are necessarily peripheral, so we can again turn to animal models to investigate central
863 changes.

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

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

870

871 *Postnatal early stimulation*

872 Postnatal early stimulation (also called early neonatal handling, early postnatal handling, early
873 handling, enhanced postnatal care or brief handling stress) involves removing rodent pups from
874 their dam for a few minutes daily during the first few weeks of life. Unlike prolonged separation
875 during this period (a method of invoking developmental stress through deprivation of maternal
876 nutrition, warmth and littermates), postnatal early stimulation (PES) is thought to stimulate the
877 mother to pay increased attention to the pups upon their return (e.g. increased licking and
878 grooming), and provide an enriching experience which can mitigate many adverse effects of
879 prenatal stress, particularly with regards to HPA axis function (Levine, 2000). A handful of
880 studies demonstrate that PES can also improve immune function. In rodents, PES enhances
881 peripheral T and B lymphocyte proliferation, and within the brain increases baseline expression
882 of IL-10 in the nucleus accumbens, an effect which is maintained into adulthood via decreased
883 methylation of IL-10, specifically in microglia (Lown and Dukta, 1987; Schwarz et al., 2011).
884 Expression of pro-inflammatory cytokines and chemokines, including CXCR3, TLR2, IL1-
885 β and CLL2 are also decreased following PES in the nucleus accumbens (Lacagnina et al.,
886 2017). PES reduced anxiety in WT mice but not in those lacking expression of the
887 inflammation suppressing factor interferon regulatory factor 2 binding protein 2 (IRF2BP2) on
888 microglia, suggesting the anxiolytic effects of PES may work through suppressing microglial
889 inflammation (Hari et al., 2017). PES increases mast cell number in and around the
890 hippocampus: whether it can reverse the effects of perinatal stress on mast cells is unknown

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

899

900 *Environmental enrichment*

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

915 (including social stress and predator exposure) in adulthood (McQuaid et al., 2018; Scarola et
916 al., 2019). When given during adolescence, EE can reverse the effects of developmental stress
917 on the immune system. Animals subjected to prenatal restraint stress displayed decreased CD4
918 T lymphocytes, increased IL-1 β and IL-10 in spleen and brain, effects which were reversed by
919 EE (Laviola et al., 2004). Maternally separated rats display increased TNF α and TNF α :IL-10:
920 this was reversed by EE (do Prado et al., 2016). Those given short-term variable stress in the
921 post-weaning, pre-pubertal phase had higher levels of blood monocytes with an increase in
922 CCL2 and decrease in CCR2 following immunological challenge (peritoneal inflammation),
923 and peritoneal cells expressed less IL-10 after LPS challenge in vitro. In this case, EE did not
924 reverse monocyte number or CCL2/CCR2, but did normalise IL-10 expression (Shtoots et al.,
925 2018). Enrichment protocols last 3-5 weeks, but the minimal or optimal duration or time of
926 intervention for effects to be observed is unknown. Similarly, it is unknown whether a single
927 bout of enrichment is sufficient to rescue immunological changes, or whether continual
928 enrichment is required, and whether effects last beyond early adulthood.

929

930 *Exercise*

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

939 (cytokines and microglial activation) in models of Alzheimer's and Parkinson's disease, and
940 this is reviewed elsewhere (Svensson et al., 2015; van Praag, 2009). In general, exercise
941 reduces pro-inflammatory cytokines, increases anti-inflammatory cytokines and decreases the
942 inflammatory phenotype of microglia (Delpech et al., 2016; Kohman et al., 2013; Madore et
943 al., 2020; Svensson et al., 2015). In particular, exercise induces IL-6 in muscle, blood and
944 cerebrospinal fluid, and IL-6 can suppress TNF α and IL1- β , promoting an anti-inflammatory
945 phenotype (Kilic et al., 2014; Petersen and Pedersen, 2006). Exercise is also effective in
946 alleviating depressive-type behaviour and decreasing INF γ in the prefrontal cortex (Liu et al.,
947 2013). The evidence for exhaustive exercise is less clear. Some studies show this is detrimental
948 for immune function, leaving animals more susceptible to severe symptoms of infection, others
949 demonstrate a protective effect (Simpson et al., 2020).

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

955

956 *Diet*

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

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

980

981 **Sex differences**

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

987 arthritis, psoriasis and Alzheimer's disease, accounting for 78% of patients, and display 2-3
988 times higher rates of anxiety, affective disorders, post-traumatic stress disorder and major
989 depressive disorder (Desai and Brinton, 2019; Kessler et al., 1993, 2005; Remes et al., 2016).
990 There is evidence that men show a better therapeutic response to tricyclic antidepressants,
991 women to selective serotonin reuptake inhibitors (although interestingly this effect is abolished
992 post-menopause), and there is also evidence of sex differences in response to psychological
993 interventions (LeGates et al., 2019; Wade et al., 2016). As we have discussed, stress results in
994 increased inflammation associated with disease, and it has been hypothesised that this effect is
995 greater in women, leaving them more vulnerable to stress related psychopathologies such as
996 anxiety and depression (Bekhbat and Neigh, 2018). This is supported by studies showing that
997 $INF\alpha$ and antiviral treatment results in greater depressive symptoms in women (Koskinas et
998 al., 2002; Udina et al., 2012). However, the links between low grade inflammation and
999 psychiatric illness have been questioned: when sex is accounted for this relationship appears to
1000 be specific to men (Liukkonen et al., 2011; Ramsey et al., 2016). Although not well studied,
1001 sex differences in basal neuroimmune function and subsequent response to drugs and
1002 environmental experiences may help to explain these differences (Brodin and Davis, 2017). In
1003 humans, sex differences in the relationship between stress and neuroimmune function are hard
1004 to disentangle, as women and men may perceive and cope with stress in divergent manners, so
1005 again animal models can provide more closely controlled insights into underlying mechanisms.
1006 We will now briefly summarise sex differences in the neuroimmune system, and their
1007 subsequent responses to environmental experiences.

1008 A handful of studies have compared sex differences in stress-related immune changes
1009 in humans, relying on peripheral measures. One study found that laboratory induced stress
1010 (using the Stroop colour-word interference and cold pressor test) affects T lymphocytes in a
1011 similar manner in males and females, yet increases NKC's in women whilst decreasing them in

1012 men (Pehlivanoglu et al., 2012). Sex hormones are likely to play a role in these divergent
1013 responses. Estrogen and progesterone in particular suppress immune function at physiological
1014 levels, and women taking oral contraceptives demonstrate higher immune responses to
1015 laboratory stress tests than unmedicated females and males (leukocytes, neutrophils and
1016 CD19+ B lymphocytes (Maes et al., 1999)). Laboratory stress also induces greater expression
1017 of IL-6 in post-menopausal women and chronic stress appears to result in greater immune
1018 suppression in women (Endrighi et al., 2016; Flynn et al., 2009). In animals, male and female
1019 lymphocytes display different levels of progesterone receptors (De Leon-Nava et al., 2009).
1020 Ex-vivo, microglia and astrocytes from neonatal rodent males release more IL-1 β when given
1021 LPS: co-stimulation with estradiol suppresses this release in male yet enhances release in
1022 female cells (Loram et al., 2012). Sex based immune differences at baseline and in response to
1023 social, sound and restraint stress are observed in leukocytes, NKCs, neutrophils and microglia
1024 in adult animals (Aghajani et al., 2018; Baldwin et al., 1997; Bollinger et al., 2016; Stefanski
1025 and Gruner, 2006).

1026 In the brain, microglia and mast cells show sex differences in number, morphology and
1027 activity during development, and are influential in masculinizing neural circuits in the rodent
1028 preoptic area (Hanamsagar et al., 2018; Lenz and Nelson, 2018; Lenz et al., 2013; Osborne et
1029 al., 2018; Schwarz et al., 2012). Rodent males have more microglia in early postnatal
1030 development, whereas females have more microglia with an activated morphology from
1031 puberty through adulthood (Schwarz et al., 2012), and female microglia reach an adult
1032 phenotype earlier and have higher levels of phagocytosis and phagocytic gene expression
1033 (Bordeleau et al., 2019; Nelson et al., 2017). Such differences could result in divergent
1034 consequences of developmental stress, which could be altered in a sex-specific manner
1035 depending on the time of insult. A few animal studies provide support for this hypothesis.
1036 Prenatal administration of dexamethasone alters morphology of microglia, reducing and

1037 shortening their processes in females, lengthening and increasing them in males (Caetano et
1038 al., 2017). In the hippocampus, prenatal restraint stress increases the proportion of active
1039 microglial in the CA1 in males, the dentate gyrus in females, and maternal separation decreases
1040 glial cells in the substantia nigra and ventral tegmental area in males but not females (Chocyk
1041 et al., 2011; Diz-Chaves et al., 2012, 2013). Time of assessment is also likely to prove crucial
1042 in determining long-term consequences of developmental stress: MIA increases glia cell
1043 markers in PFC and hippocampus in both sexes at 30 days, whereas at 60 days this increase is
1044 only evident in male PFC (de Souza et al., 2015).

1045 In animals, developmental stress also alters expression of inflammation-related genes
1046 in a sex-dependent manner, and generally, effects appear more pronounced in males. Two
1047 studies in mice found that prenatal light/restraint stress increases TNF α and IL1- β in the
1048 hippocampus of males, but only IL1- β is increased in females (Diz-Chaves et al., 2012, 2013).
1049 Another study using rats found that a similar prenatal protocol reduced expression of IL-1 β in
1050 the male rat hippocampus with no change in females (Mandyam et al., 2008). Discrepancies
1051 likely arise due to exact protocols and species used, and age of adult assessment. Maternal
1052 separation/deprivation increases circulating TNF α and TNF α :IL-10 and increases IL-1 receptor
1053 type 1 expression in hippocampal synapses in males only (do Prado et al., 2016; Viviani et al.,
1054 2014), and MIA potentiates the expression of IL1- β , CXC ligand 10, TNF α and suppressor of
1055 cytokine signalling 3 in the adult male hypothalamus, amygdala and PFC in response to LPS
1056 stimulation (Makinson et al., 2017). A similar effect is seen in adolescence. Here, mixed
1057 modality stress (restraint and social defeat) enhances hippocampal expression of IL1- β , TNF α
1058 and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IkB α ,
1059 inhibits NF κ β transcription) in males following an LPS challenge, this is not observed in
1060 females (Pyter et al., 2013).

1061 Although our knowledge on even basal sex differences in immune function are
1062 incomplete, there is mounting evidence that the neuroimmunological consequences of stress
1063 can diverge significantly between males and females. This is an area ripe for further
1064 exploration, and increased knowledge will assist in tailoring sex-specific treatments for a range
1065 of stress related disorders.

1066

1067 **Conclusions & future directions**

1068 It is now well established that the immune system plays a key role in the normal development
1069 and function of the CNS. This neuroimmune system responds to a wide range of environmental
1070 stimuli in adulthood and during development. Positive and negative environmental experiences
1071 throughout development can permanently alter the developing neuroimmune system, with
1072 accompanying behavioural alterations. Chronic or intense acute stress results in an abnormal
1073 neuroimmunological phenotype, which may result in abnormal brain structure and function,
1074 predisposing individuals to psychiatric illness. Although less well studied, positive experiences
1075 may promote resilience and can reverse the effects of developmental stress on the
1076 neuroimmune system. This proposes the neuroimmune system as a therapeutic target for
1077 psychiatric illnesses, especially those related to stress, and suggest that restoration of the
1078 neuroimmune system may be necessary for restoring proper brain function. Going forward,
1079 greater emphasis should be placed on the protective and restorative role that exposure to
1080 positive environmental experiences may provide for neuroimmune function. In particular,
1081 unlike negative experiences, the persistence of neuroimmune effects resulting from positive
1082 environmental experiences are virtually unknown, as are the potential existence of critical
1083 periods for maximum benefits, particularly in reversing the effects of developmental stress.
1084 The majority of studies focus on male subjects, yet those including females often find striking

1085 sex differences not only in basal neuroimmune function but also in response to developmental
1086 experiences. Future studies should strive to include females in order to tailor treatments based
1087 on sex where necessary.

1088

1089 **Acknowledgements**

1090 We would like to thank Dr Kerrie Thomas for valuable comments on a draft version of this
1091 manuscript, and the Hodge Foundation who provide NB with Fellowship funding and JR with
1092 PhD funding.

1093

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2384 **Abbreviations**

2385 AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid); BBB (blood brain barrier); C3aR1
2386 (complement component C3a receptor 1); CA (childhood adversity); CCL2 (C-C motif chemokine
2387 ligand 2); CCL3 (C-C motif chemokine ligand 3); CCR2 (C-C motif chemokine receptor 2); CNS
2388 (central nervous system); CRP (c reactive protein); CXC (C-X-C motif); CX3CL1 (C-X3-C motif
2389 ligand 1, also known as fractalkine); CXCL2 (CXC ligand 2); CXCL12 (CXC chemokine 12); CXCR4
2390 (CXC chemokine receptor 4); DHA (docosahexaenoic acid); EE (environmental enrichment); FKBP5
2391 (FK506-binding protein 5); GC (glucocorticoid); HPA (hypothalamic-pituitary-adrenal); IFN
2392 (interferon); IL (interleukin); LPS (lipopolysaccharide); LTD (long term depression); LTP (long
2393 term potentiation); MHC (major histocompatibility complex); MIA (maternal immune
2394 activation); NE (norepinephrine); NF κ B (nuclear factor kappa-light-chain enhancer of activated
2395 B cells); NKC (natural killer cells); NMDA (N-methyl-D-aspartate); PES (postnatal early
2396 stimulation); PFC (prefrontal cortex); PTSD (post-traumatic stress disorder); PUFA
2397 (polyunsaturated fatty acids); SAM (sympathetic-adrenal-medullary); TLR (toll-like
2398 receptors); TNF (tumour necrosis factor).

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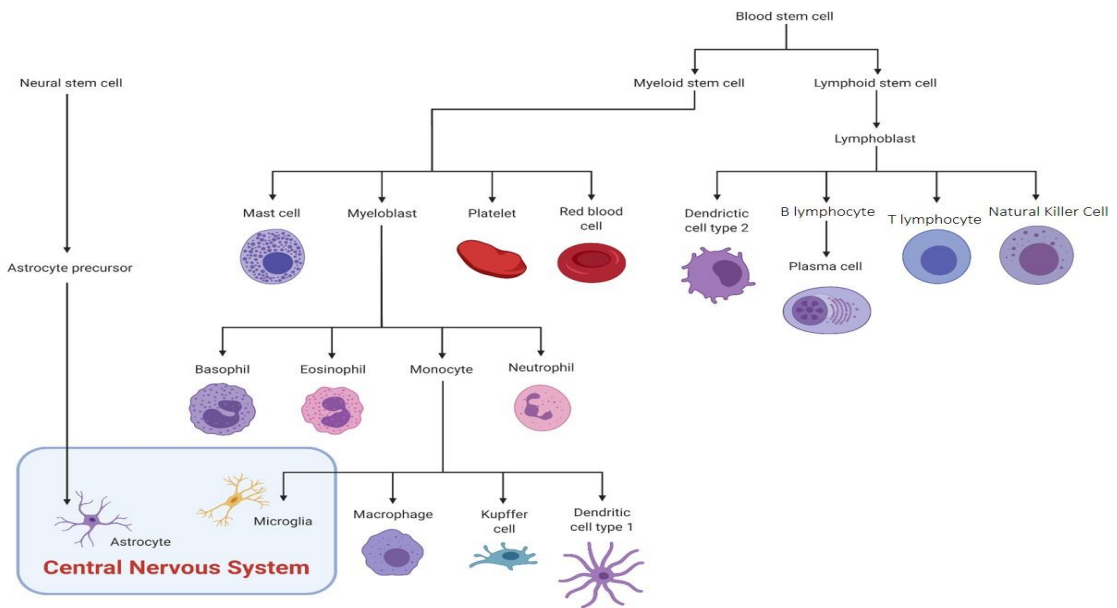


Figure 1: Developmental origins of immune cells in the periphery and central nervous system. Blood stem cells are bipotent stem cells that are the origin of all blood cell types, differentiating into either myeloid or lymphoid stems cells. Lymphoid stem cells differentiate into natural killer cells,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

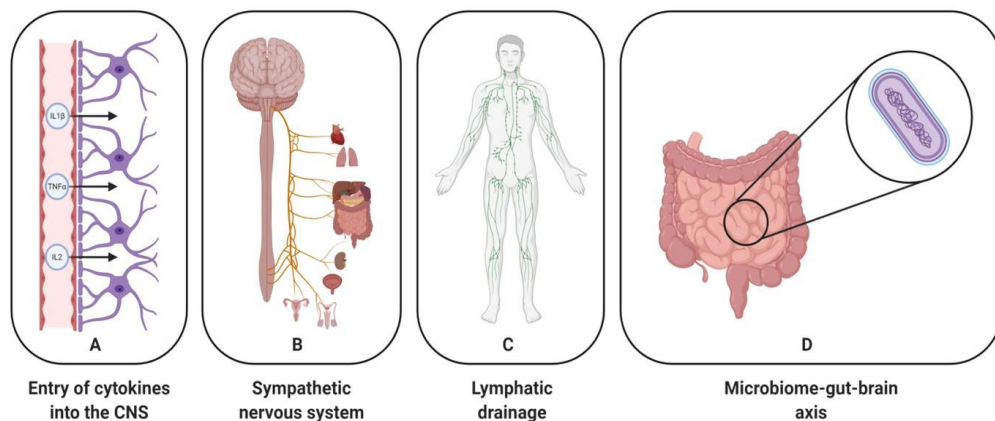
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Figure 2. Routes of peripheral immune system communication with the central nervous system (CNS). **A.** Cytokine diffusion (slow transmission): entry of cytokines into the brain through a disrupted or ‘leaky’ blood brain barrier and their active transport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

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Humans		Animals	
Positive	Negative	Negative	Positive
<p>Diet</p> <p>Neuroimmune effects Decreased inflammation Enhanced fetal immunity</p>	<p>Maternal immune activation Maternal autoimmune disease Maternal psychosocial stress Maternal mental illness</p> <p>Neuroimmune effects Altered cytokines T-helper cytokine production</p> <p>In utero (throughout gestation)</p>	<p>Maternal immune activation Synthetic stress hormones Pollution Dietary manipulations Psychological stress Maternal separation Limited nesting & bedding Poor maternal care</p> <p>Neuroimmune effects Effectiveness of natural killer cells B lymphocyte proliferation decreased Impaired T & B lymphocyte activity Range of cytokines increased & decreased Microglia/astrocyte – density, activity & morphology, major histocompatibility complex I & II</p> <p>Perinatal (throughout gestation – 3 weeks)</p>	<p>Postnatal early stimulation Diet</p> <p>Neuroimmune effects Leukocytes and lymphocytes Altered cytokines Microglial activity Decreased inflammation</p>
<p>Secure caregiving High family functioning Good social support Cognitive behavioural therapy Exercise Diet</p> <p>Neuroimmune effects Decreased inflammation</p>	<p>Abuse Neglect Parental illness Death Abandonment Crime Divorce War Natural disaster Displacement</p> <p>Neuroimmune effects Increased c-reactive protein, interleukin-6, tumour necrosis factor α, fibrinogen, E-selectin, nuclear factor-κB</p> <p>Childhood & Adolescence (0-18 years)</p>	<p>Social isolation Social defeat Unstable housing Short & long-term physical stressors</p> <p>Neuroimmune effects Microglia – number & activation Cytokines Blood monocytes & chemokine receptor 2 FK506-binding protein 5</p> <p>Childhood & Adolescence (3 weeks – 60 days)</p>	<p>Environmental enrichment Exercise Diet</p> <p>Neuroimmune effects Cytokines Lymphocytes</p>
<p>Exercise Mindfulness Stress-reduction & relaxation techniques Brief interventions to improve positive affect Diet</p> <p>Neuroimmune effects Altered cytokines C-reactive protein T lymphocyte proliferation Leukocyte number & efficiency Improved vaccine response Improved wound healing & response to psychophysiological challenges Immunoglobulin A Natural killer cells</p>	<p>Acute laboratory stress Caregiving stress Work stress Unemployment Poverty Death of loved one Marital problems Serious illness</p> <p>Neuroimmune effects Natural killer cells Cytokine alterations Lower immune response to vaccines</p> <p>Adulthood (18 years plus)</p>	<p>Social defeat Restraint Chronic variable stress</p> <p>Neuroimmune effects Monocytes Neutrophils Dendritic cells T lymphocytes Cytokines Microglia Mast cells</p> <p>Adulthood (60 days plus)</p>	<p>Environmental enrichment Exercise Diet</p> <p>Neuroimmune effects Enhance immune response to influenza A Microglia density Macrophage, lymphocyte & natural killer cell function & activity Cytokines</p>

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