HHS Public Access

Author manuscript

Nat Rev Immunol. Author manuscript; available in PMC 2017 August 03.

Published in final edited form as:

Nat Rev Immunol. 2016 January ; 16(1): 22–34. doi:10.1038/nri.2015.5.

The role of inflammation in depression: from evolutionary imperative to modern treatment target

Andrew H. Miller[1] and **Charles L. Raison**[2]

[1]Emory University School of Medicine, Winship Cancer Institute, Atlanta, 30322 Georgia, USA

[2]School of Human Ecology, University of Wisconsin–Madison, Madison, 53706 Wisconsin, USA

Abstract

Crosstalk between inflammatory pathways and neurocircuits in the brain can lead to behavioural responses, such as avoidance and alarm, that are likely to have provided early humans with an evolutionary advantage in their interactions with pathogens and predators. However, in modern times, such interactions between inflammation and the brain appear to drive the development of depression and may contribute to non-responsiveness to current antidepressant therapies. Recent data have elucidated the mechanisms by which the innate and adaptive immune systems interact with neurotransmitters and neurocircuits to influence the risk for depression. Here, we detail our current understanding of these pathways and discuss the therapeutic potential of targeting the immune system to treat depression.

Depression is a devastating disorder, afflicting up to 10% of the adult population in the United States and representing one of the leading causes of disability worldwide[1]. Although effective treatments are available, approximately one third of all patients with depression fail to respond to conventional antidepressant therapies[2], further contributing to the global burden of the disease. Accordingly, there is a pressing need for new conceptual frameworks for understanding the development of depression to develop better treatments. In this Review, we outline emerging data that point to the immune system — and, in particular, the inflammatory response — as a potentially important contributor to the pathophysiology of depression. We first consider the origins of this notion from an evolutionary perspective, examining the advantages of depressive behaviours in the context of host immune responses to pathogens, predators and conspecifics in ancestral environments. The pivotal role of psychosocial stress in the modern world are then examined, highlighting inflammasome activation and immune cell trafficking as novel mechanisms by which stress-induced inflammatory signals can be transmitted to the brain. Neurotransmitters and neurocircuits that are targets of the inflammatory response are also explored followed by an examination of brain–immune interactions as risk and resilience factors for depression. Finally, these interactions are discussed as a foundation for a new era of therapeutics that target the

Correspondence to: A.H.M., amill02@emory.edu.

Competing interests statement

The authors declare no competing interests.

immune system to treat depression, with a focus on how immunological biomarkers can be used to personalize care.

An evolutionary perspective

Data from humans and laboratory animals provide compelling evidence that stress-relevant neurocircuitry and immunity form an integrated system that evolved to protect organisms from a wide range of environmental threats. For example, in the context of a laboratory stressor that entails delivering a speech to a judgmental panel of supposed 'behavioural experts', subjects experience a classic 'fight or flight' response characterized by increases in heart rate and blood pressure as well as in cortisol and catecholamines. But something else happens within the body that demands a deeper explanation. The stressor activates key inflammatory pathways in peripheral blood mononuclear cells, including activation of the transcription factor nuclear factor–κB (NF-κB), and leads to marked increases in circulating levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6)[3,4]. In essence, the body mounts an immune response not against a pathogen, but against a threat to the subject's self-esteem. Moreover, individuals at high risk of developing depression (for example, those who have experienced early-life trauma) show increased inflammatory responses to such laboratory stressors compared with low-risk individuals[3]. Furthermore, the greater the inflammatory response to a psychosocial stressor, the more probable the subject is to develop depression over the ensuing months[5]. Two questions immediately present themselves: why should a stimulus devoid of any pathogen induce an inflammatory response, and why should this response promote the development of depression?

Pathogen host defence and depression

No coherent answer to these questions is apparent if immunity is viewed as merely another physiological system within the body. However, when seen against the back-drop of millions of years of co-evolution between mammals and the world of microorganisms and parasites, the human inflammatory bias exposed by laboratory stressors and reflected in the association between immune activation and depression not only makes imminent adaptive sense but also provides insight into a paradox deep within the heart of depression itself; namely, why are the genetic alleles that are most frequently associated with depression so common in the modern gene pool[6] (FIG. 1)?

Most adaptive theories of depression have focused on the potential benefits of depressive symptoms for relationships with other humans[7]. However, recent models have shifted the focus away from relationships with people, to relationships — both detrimental and beneficial — with pathogens[6,8]. These theories, which are supported by converging evidence (BOX 1), posit that modern humans have inherited a genomic bias towards inflammation because this response — and the depressive symptoms it promotes — enhanced host survival and reproduction in the highly pathogenic environments in which humans evolved[6]. From this theoretical perspective, at least some of the human vulnerability to depression evolved out of a behavioural repertoire — often referred to as 'sickness behaviour' — which promoted host survival in the face of infection. Indeed, it has been hypothesized that the social avoidance and anhedonia characteristic of depression serve to shunt energy resources

to fighting infection and wound healing, whereas the hypervigilance characteristic of anxiety disorders, commonly comorbid with depression, subserves protection from attack and subsequent pathogen exposure[6,9]. Even psychological stress can be understood from this theoretical perspective, given that the vast majority of stressors faced by mammals over evolutionary time boiled down to risks inherent in hunting, being hunted or competing for reproductive access or status. In all of these circumstances, the risk of pathogen invasion — and subsequent death from infection — was greatly increased as a result of wounding. In ancestral environments, the association between stress perception and risk of subsequent wounding was reliable enough that evolution favoured organisms that prepotently activated inflammatory systems in response to a wide array of environmental threats and challenges (including psychosocial stressors), even if this activation was often a ‘false alarm’ (REF. 6).

Box 1

Pathogen host defence hypothesis of depression

Several lines of evidence support the notion that the evolution and persistence of depression risk alleles and depressive symptoms in human populations are based on their relevance to ‘pathogen host defence’. This evidence includes:

- Until recently, approximately 50% of humans died from infectious causes before adulthood, thereby providing strong selective pressure for genetic alleles that enhance host defence[124].
- As a result of strong selective pressure, microbial interactions have been a primary driver of human evolution[125].
- Patterns of inflammatory activation associated with depression promote survival in highly pathogenic environments while increasing mortality in sanitary conditions common in the developed world[126].
- The best replicated risk alleles for depression have pro-inflammatory and/or anti-pathogen protective effects or have been implicated in social behaviours that are likely to reduce pathogen exposure[6].
- Environmental risk factors for the development of depression (that is, psychosocial stress, early life adversity, obesity and processed-food diet) are uniformly pro-inflammatory[13].
- Exposure to pro-inflammatory cytokines produces a sickness syndrome with symptoms that overlap considerably with those seen in depression and that can be ameliorated by treatment with antidepressants[23]. In addition, the onset of depression is often mistaken with development of sickness, and symptoms associated with infections are often mistaken with the onset of depression[127].
- Chronic cytokine exposure produces a combination of withdrawal and/or energy conservation, anxiety and/or hypervigilance behaviours and emotions that commonly coexist in depression[6,9].

- Symptoms shared by depression and sickness behaviour — such as hyperthermia and reduced iron availability — that lack any conceivable social value have potent anti-pathogen effects[6].

The ‘pathogen host defence’ hypothesis of depression may also provide insight into the twofold increase in depression in women compared to men, especially during the reproductive years[10]. Recent data indicate that women are more sensitive to the behavioural effects of inflammation, demonstrating greater increases in depressed mood than men following endotoxin exposure despite a similar magnitude in cytokine (IL-6 and tumour necrosis factor (TNF)) responses[11]. Women also exhibit a greater likelihood than men to develop depression in response to standardized doses of interferon-α (IFNα)[12]. By being more sensitive to inflammation-induced depressive symptoms, women may have benefited more from the protection provided by these symptoms in terms of fighting infection, healing wounds and avoiding subsequent pathogen exposure. Given the potentially negative impact of inflammation on reproductive success (for example, by reducing fertility and impairing lactation), the increase of depressive symptoms in women across evolutionary time may have given women of reproductive age an advantage in coping with and avoiding pathogens and the related inflammation, with increased depressive disorders being the ultimate trade-off in modern times.

Modern exaggeration of the inflammatory bias

The prevalence of autoimmune, allergic and inflammatory diseases has markedly increased in the past 100 years, and rates of these conditions follow a similar upward trajectory in societies transitioning from traditional (that is, rural) to modern (that is, urban) ways of life[13]. Increasing evidence suggests that this pattern of widespread immune dysregulation may result from disruptions in our relationship and/or contact with a variety of co-evolved, non-lethal immunoregulatory microorganisms and parasites, especially commensals and symbiotes in the microbiotas of the gut, skin and nasal and oral cavities, that were ubiquitous in the natural environments in which humans evolved[14]. Although widely disparate, these organisms (often referred to as ‘old friends’) share a tendency to reduce inflammation and suppress effector immune cells through the induction of IL-10 and transforming growth factor-β (TGFβ) while promoting the development of anti-inflammatory immune cell populations, such as alternatively activated (also referred to as ‘M2’) macrophages and regulatory T (T_{Reg}) cells and regulatory B cells[13,14] (FIG. 1). Owing to various cultural changes, including the loss of exposure to microbial diversity with the advent of sanitation practices, modern humans now lack this immunoregulatory input — especially during infancy and childhood. Consequently, we find ourselves in a condition of an exacerbated inflammatory bias, with the particular conditions afflicting any given individual largely the result of genetic predisposition and environmental (for example, psychosocial) exposures[13,14], ultimately accounting for the high co-morbidity between depression and autoimmune, allergic and inflammatory disorders[13,15].

Inflammation and depression

Data supporting the role of inflammation in depression are extensive and include findings that span experimental paradigms. Patients with major depressive disorder exhibit all of the cardinal features of an inflammatory response, including increased expression of pro-inflammatory cytokines and their receptors and increased levels of acute-phase reactants, chemokines and soluble adhesion molecules in peripheral blood and cerebrospinal fluid (CSF)[16,17]. Peripheral blood gene expression profiles consistent with a pro-inflammatory 'M1' macrophage phenotype and an over-representation of IL-6, IL-8 and type I IFN-induced signalling pathways have also been described[18–20]. In addition, increased expression of a variety of innate immune genes and proteins, including IL-1β, IL-6, TNF, Toll-like receptor 3 (TLR3) and TLR4, has been found in post-mortem brain samples from suicide victims that had depression[16,18,19,21]. Meta-analyses of the literature conclude that peripheral blood IL-1β, IL-6, TNF and C-reactive protein (CRP) are the most reliable biomarkers of inflammation in patients with depression[16]. Polymorphisms in inflammatory cytokine genes, including those encoding IL-1β, TNF and CRP, have also been associated with depression and its response to treatment[22]. Moreover, other genes implicated in depression derived from meta-analyses of genome-wide association studies have been linked to the immune response and the response to pathogens including TNF[6] (BOX 1). Administration of inflammatory cytokines (for example, IFNα) or their inducers (for example, endotoxin or typhoid vaccination) to otherwise non-depressed individuals causes symptoms of depression[23–26]. Furthermore, blockade of cytokines, such as TNF, or of inflammatory signalling pathway components, such as cyclooxygenase 2, has been shown to reduce depressive symptoms in patients with medical illnesses, including rheumatoid arthritis, psoriasis and cancer, as well as in patients with major depressive disorder[27–29].

As the field has matured, it has become increasingly apparent that inflammatory markers are elevated not only in a subgroup of patients with depression[30,31] but also in patients with other neuropsychiatric disorders including anxiety disorders and schizophrenia[32,33]. Moreover, as described below, it may be more accurate to characterize the impact of inflammation on behaviour as being associated not wholly with depression but with specific symptom dimensions across diagnoses that align with the Research Domain Criteria framework put forth by the National Institute of Mental Health (US Department of Health and Human Services). These symptoms, including positive and negative valence systems, relate to altered motivation and motor activity (anhedonia, fatigue and psychomotor impairment) and increased threat sensitivity (anxiety, arousal and alarm)[34]. Finally, inflammation has been associated with antidepressant treatment non-responsiveness[9,32,35–37]. For example, in a recent study, 45% of patients with non-response to conventional antidepressants exhibited a CRP >3 mg L^{-1} (REF. 30), which is considered indicative of a high level of inflammation on the basis of widely accepted cut-off points[38]. Of note, however, the percentage of patients with high CRP levels can vary as a function of the population being studied, with higher percentages in patients with depression and treatment resistance, childhood maltreatment, medical illnesses and metabolic syndrome.

Immune pathways involved in depression

Inflammasomes: stress in translation

Exposure to psychosocial stress is one of the most robust and reproducible predictors of developing depression in humans and is the primary experimental pathway to depressive-like behaviour in laboratory animals. Thus, the observation that exposure to a psychosocial laboratory stressor can activate an inflammatory response in humans was a major breakthrough in linking inflammation to depression[3,4]. An important question for the field, however, is by what mechanism is stress translated into inflammation? Although considerable attention has been paid to stress-induced neuroendocrine pathways, including the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), both of which have immunomodulatory functions[39], recent focus has been shifted towards inflammasomes, which may represent a crucial immunological interface between stress and inflammation[40] (FIG. 2). Inflammasomes are cytosolic protein complexes that form in myeloid cells in response to pathogenic microorganisms and non-pathogenic or ‘sterile’ stressors. Assembly of the inflammasome leads to activation of caspase 1, which then cleaves the precursor forms of IL-1β and IL-18 into the active cytokines[41]. Given the relatively sterile nature of psychosocial stress, primary interest has been directed towards understanding how inflammasome activation in depression may be triggered by endogenous damage-associated molecular patterns (DAMPs), including ATP, heat shock proteins (HSPs), uric acid, high mobility group box 1 (HMGB1) and a variety of molecules linked with oxidative stress. Indeed, all of these DAMPs are induced by the psychological and mixed (that is, psychological and physiological) stressors used in animal models of depression[42]; an effect that is in part mediated by stress-induced release of catecholamines[43]. Moreover, studies in laboratory animals indicate that chronic mild-stress activates the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, which is well-known to respond to DAMPs[44,45]. Blockade of NLRP3 reverses stress-induced increases in IL-1β in the peripheral blood and brain, while also abrogating depressive-like behaviour in mice[45]. Interestingly, NLRP3 inflammasome upregulation and caspase-mediated cleavage of the glucocorticoid receptor can cause resistance to the effects of glucocorticoids, which are among the most potent anti-inflammatory hormones in the body[46,47]. Stress-induced glucocorticoid resistance is a well-characterized biological abnormality in patients with major depressive disorder and has been associated with increased inflammation[48,49].

Supporting the potential role of the NLRP3 inflammasome in human depression are data demonstrating that increased expression of NLRP3 and caspase 1 in peripheral blood mononuclear cells of patients with depression is associated with increased blood concentrations of IL-1β and IL-18, which in turn correlate with depression severity[19,50]. In addition, DAMPs that are known to activate NLRP3 are increased in patients with mood disorders, with examples including HSPs, reactive oxygen species and other markers of oxidative stress such as xanthine oxidase, peroxides and F2-isoprostanes[51–53]. Finally, there is increasing interest in the potential role of the gut microbiome in mood regulation, which may be mediated in part by the inflammasomes[54]. Indeed, non-pathogenic commensal bacteria and derived microbial-associated molecular patterns (MAMPs) in the gut can leak into the peripheral circulation during stress and activate the inflammasomes[55], a process

mediated by the SNS and catecholamines[56] (FIG. 2). Of note, stress-induced increases in IL-1β and IL-18 were attenuated by treating animals with antibiotics or neutralizing lipopolysaccharide (LPS), demonstrating the importance of the composition of the gut microbiome and gut permeability in stress-induced inflammatory responses[55]. Taken together, these data support the notion that the inflammasome may be a key immunological point of integration of stress-induced danger signals that ultimately drive inflammatory responses relevant to depression.

Transmitting inflammatory signals to the brain

In addition to increased expression of innate immune cytokines and TLRs in post-mortem brain samples from suicide victims with depression, evidence of microglial and astroglial activation in several brain regions including frontal cortex, anterior cingulate cortex (ACC) and thalamus in post-mortem studies of patients with depression have been described[57–59,60]. Moreover, a well-controlled neuroimaging study using positron emission tomography (PET) and a radiolabelled tracer for the translocator protein (TSPO) — which is overexpressed in activated microglia, macrophages and astrocytes — revealed increased immune activation in the brains of patients with major depressive disorder compared with control subjects[61]. Of note, not all studies have revealed increased TSPO binding in patients with depression, possibly owing to effects of medication and/or a paucity of subjects with increased inflammation[61,62]. However, data from endotoxin administration to healthy volunteers indicates that radiolabelled TSPO ligands can readily identify cellular activation in several regions of the brain following a potent peripheral immune stimulus[63].

Work from laboratory animal studies has elucidated several pathways through which inflammatory signals can be transmitted from the periphery to the brain (FIG. 2). These data support the idea that inflammatory responses in peripheral tissues may drive inflammation in the brain leading to depression. Much of the early work focused on how inflammatory cytokines, which are relatively large molecules, could cross the blood–brain barrier (BBB) and influence brain function[64]. Two major pathways have been described: the ‘humoral pathway’, which involves cytokine passage through leaky regions in the BBB, such as the circumventricular organs, and the binding of cytokines to saturable transport molecules on the BBB; and the ‘neural pathway’, which involves the binding of cytokines to peripheral afferent nerve fibres, such as the vagus nerve, that in turn stimulate ascending catecholaminergic fibres in the brain and/or are translated back into central cytokine signals[16]. More recently, however, attention has shifted to a third pathway referred to as the ‘cellular pathway’, which involves the trafficking of activated immune cells, typically monocytes, to the brain vasculature and parenchyma. The details of this pathway have been elegantly dissected in the context of behavioural changes in mice that are associated with peripherally induced inflammation in the liver[65]. In these studies, the release of TNF from inflamed liver was found to stimulate microglial cell production of CC-chemokine ligand 2 (CCL2; also known as MCP1) that then attracted monocytes to the brain[65]. Blockade of monocyte infiltration to the brain using antibodies specific for the adhesion molecules P-selectin and α4 integrin abrogated depressive-like behaviour in this animal model[65]. Of note, cytokine-stimulated astrocytes also may be major producers of chemokines, such as CCL2 and CXC-chemokine ligand 1 (CXCL1), that attract immune cells to the brain[66]. The

cellular pathway additionally has been elucidated in the context of social defeat stress, whereby GFP-labelled monocytes coalesced in several regions of the brain associated with the detection of threat (for example, amygdala) — an effect that was dependent on CCL2 and was facilitated by mobilization of monocytes from the bone marrow as a result of stress-induced release of catecholamines[67,68] (FIG. 2). Of note, initial microglial activation during social defeat stress appeared to be a result of neuronal activation by catecholamines and decreased neuronal production of CX_3C-chemokine ligand 1 (CX_3CL1; also known as fractalkine), which maintains microglia in a quiescent state[67,68]. Interestingly, this cellular pathway has received intriguing support from post-mortem analyses of brain tissue from patients with depression who committed suicide that showed increased numbers of perivascular macrophages in association with increased gene expression of allograft inflammatory factor 1 (AIF1, also known as IBA1) and CCL2, which are associated with macrophage activation and cellular trafficking[59].

This evidence of peripheral myeloid cells trafficking to the brain during depression constitutes some of the first data supporting the existence of a central inflammatory response in human depression that is primarily driven by peripheral inflammatory events. Moreover, data demonstrate that antibodies that are specific for TNF but which do not cross the BBB, can block stress-induced depression in mice[69]. These findings indicate that peripheral inflammatory responses not only can provide important clues to the immunological mechanisms of inflammation in depression but also may serve as biomarkers and targets of immune-based therapies for depression. Protein biomarkers such as plasma CRP and TNF as well as immunotherapies targeting individual cytokines such as TNF, IL-1 and IL-6 may be most relevant in this regard. Of note, plasma CRP is a strong response predictor in anti-cytokine therapy[70].

Cytokines and neurotransmitters

Given the pivotal importance of neurotransmission to mood regulation, attention has been paid to the impact of inflammation and inflammatory cytokines on the monoamines serotonin, noradrenaline and dopamine, as well as on the excitatory amino acid glutamate (FIG. 3). There are several pathways through which inflammatory cytokines can lead to reduced synaptic availability of the monoamines, which is believed to be a fundamental mechanism in the pathophysiology of depression[71]. For example, IL-1β and TNF induction of p38 mitogen-activated protein kinase (MAPK) has been shown to increase the expression and function of the reuptake pumps for serotonin, leading to decreased synaptic availability of serotonin and depressive-like behaviour in laboratory animals[72]. Through the generation of reactive oxygen and nitrogen species, inflammatory cytokines have also been found to decrease the availability of tetrahydrobiopterin (BH4), a key enzyme co-factor in the synthesis of all monoamines that is highly sensitive to oxidative stress[73]. Indeed, CSF concentrations of BH4 have been shown to be negatively correlated with CSF levels of IL-6 in patients treated with the inflammatory cytokine IFNα[74]. In addition, the plasma phenylalanine to tyrosine ratio, an indirect measure of BH4 activity, was shown to correlate with CSF concentrations of dopamine as well as symptoms of depression in IFNα-treated patients[74]. Activation of the enzyme indoleamine 2,3-dioxygenase (IDO) is also believed to be involved in cytokine-induced neurotransmitter alterations, in part by diverting the

metabolism of tryptophan (the primary amino acid precursor of serotonin) into kynurenine, a compound that can be converted into the neurotoxic metabolite quinolinic acid by activated microglia and infiltrating monocytes and macrophages in the brain[75,76]. Of note, increased levels of quinolinic acid have been found in microglia in the ACC of suicide victims who suffered from depression[77]. Quinolinic acid directly activates receptors for glutamate (that is, *N*-methyl-D-aspartate (NMDA) receptors) while also stimulating glutamate release and blocking glutamate reuptake by astrocytes[78]. The effects of quinolinic acid on glutamate converge with the direct effects of pro-inflammatory cytokines on glutamate metabolism that include decreasing the expression of astrocyte glutamate reuptake pumps and stimulating astrocytic glutamate release[79], ultimately contributing to excessive glutamate both within and outside the synapse. The binding of glutamate to extrasynaptic NMDA receptors leads to increased excitotoxicity and decreased production of brain-derived neurotrophic factor (BDNF)[80]. BDNF fosters neurogenesis, an important prerequisite for an antidepressant response, and has been shown to be reduced by IL-1β and TNF and their downstream signalling pathways including NF-κB in stress-induced animal models of depression[81,82]. Increased levels of glutamate in the basal ganglia and dorsal ACC (dACC) — as measured by magnetic resonance spectroscopy (MRS) — have been described in patients receiving IFNα, and higher levels of glutamate correlated with an increase in depressive symptoms[83]. More recent data indicate that in patients with depression, increased inflammation as reflected by a CRP >3 mg L^{-1} is also associated with increased basal ganglia glutamate (compared with patients with a CRP <1 mg L^{-1}) that correlated with anhedonia and decreased psychomotor speed[84]. Interestingly, blocking glutamate receptors with ketamine or inhibiting IDO activity protects mice from LPS- or stress-induced depressive-like behaviour but leaves the inflammatory response intact[85,86]. These results indicate that increased activation of glutamate receptors by glutamate and/or quinolinic acid may be a common pathway through which inflammation causes depressive-like behaviour, suggesting that drugs that block glutamate receptor signalling and/or activation of the IDO pathway and its downstream metabolites might have unique applicability to patients with depression and increased inflammation. Importantly, conventional antidepressant medications act by increasing synaptic availability of monoamines and increasing neurogenesis through induction of BDNF[87]. Therefore, cytokines such as IL-1β and TNF serve to undermine these activities as they decrease the synaptic availability of monoamines while also decreasing BDNF and increasing extracellular glutamate, which is not a target of conventional antidepressant therapy. These cytokine-driven effects may explain the observations that increased inflammation is associated with less robust antidepressant treatment responses and that treatment-resistant patients exhibit increased inflammatory markers[88].

Effects of inflammation on neurocircuitry

Given the impact of cytokines on neurotransmitter systems that regulate the functional activity of neurocircuits throughout the brain, it is no surprise that neuroimaging studies have revealed cytokine-induced alterations in regional brain activity. Consistent with the evolutionary advantages of the partnership between the brain and the immune system, primary cytokine targets in the CNS involve those brain regions that regulate motivation and motor activity (promoting social avoidance and energy conservation) as well as arousal, anxiety and alarm (promoting hypervigilance and protection against attack) (FIG. 3).

Dopamine has a fundamental role in motivation and motor activity, and cytokines have been shown to decrease the release of dopamine in the basal ganglia in association with decreased effort-based motivation as well as reduced activation of reward circuitry in the basal ganglia, in particular the ventral striatum[89–91]. Inflammatory stimuli have been associated with reductions in reward responsiveness in the striatum across many neuroimaging platforms, demonstrating the validity and reproducibility of these cytokine-mediated effects on the brain in otherwise non-depressed individuals peripherally administered IFNα, endotoxin or typhoid vaccination and imaged by PET, functional magnetic resonance imaging (fMRI), MRS and quantitative magnetization transfer imaging[83,89,90,92,93]. Interestingly, recent fMRI studies suggest that inflammation-induced decreases in responsiveness to positive reward are also associated with increased sensitivity to aversive stimuli (that is, negative reinforcement) and reduced responsiveness to novelty in the substantia nigra (which is another dopamine-rich structure in the basal ganglia)[93,94]. Typhoid vaccination has also been shown to activate the subgenual ACC (sgACC), a brain region implicated in depression, and to decrease connectivity of the sgACC with the ventral striatum, an effect modulated by plasma IL-6 (REF. 26). These fMRI findings have recently been extended to patients with depression whose increased plasma CRP level is associated with decreased functional connectivity within reward-related circuits including the ventral striatum and the ventromedial prefrontal cortex that, in turn, mediates the relationship between CRP and anhedonia[95]. Indeed, patients with depression with a CRP >3 mg L^{-1} had little, if any, connectivity within reward-related circuits as measured by fMRI, whereas connectivity in patients with depression with a CRP <1 mg L^{-1} was similar to healthy controls[95]. Taken together, these data support the notion that the effect of cytokines on the brain in general and dopaminergic pathways in particular lead to a state of decreased motivation or anhedonia, which is a core symptom of depression.

fMRI studies have demonstrated that increased inflammation is also associated with increased activation of threat- and anxiety-related neurocircuitry, including the dACC as well as the insula and amygdala[26,96,97]. Of note, the dACC and amygdala are regions that exhibit increased activity in patients with high-trait anxiety and neuroticism[98], conditions that often accompany depression and are associated with increased inflammation. For example, increased concentrations of oral IL-6 and soluble TNF receptor 2 (also known as TNFRSF1B) in response to a public speaking stressor was significantly correlated with the response of the dACC to a social rejection task[97]. In addition, increased oral IL-6 expression in response to a social evaluation stressor was significantly correlated with activation of the amygdala, with subjects who exhibited the highest IL-6 responses to stress demonstrating the greatest connectivity within threat circuitry, including the amygdala and the dorsomedial prefrontal cortex, as measured by fMRI[99]. Interestingly, these data are consistent with the trafficking of monocytes to the amygdala during social defeat stress in mice[68].

Risk and resilience

Increased inflammation and the risk for depression

Consistent with the emerging recognition that inflammation may cause depression in certain subgroups of individuals, epidemiological studies on large community samples — as well as

smaller samples of medically ill individuals — have demonstrated that increased inflammation serves as a risk factor for the future development of depression. For example, increased peripheral blood CRP and IL-6 concentrations were found to significantly predict depressive symptoms after 12 years of follow up in the Whitehall II study of over 3,000 individuals, whereas no association was found between the presence of depressive symptoms and subsequent blood CRP and IL-6 levels[100]. Similar findings were reported in the English Longitudinal Study of Ageing in which a CRP >3 mg L^{-1} predicted depressive symptoms and not vice versa[101]. Of note, however, some studies have found no longitudinal relationship between depression and inflammation, and others have found that depression leads to increased inflammation[102]. Other factors known to be associated with increased peripheral inflammation, including childhood and adult trauma, have also been shown to be predictive of a greater risk of developing depression[103,104].

Both genetic and epigenetic mechanisms may explain why childhood or adult traumas can contribute to exaggerated or persistent inflammation and, ultimately, depression. For example, polymorphisms in *CRP* were associated not only with increased peripheral blood concentrations of CRP but also with symptoms of post-traumatic stress disorder, especially heightened arousal, in individuals exposed to civilian trauma[32]. Moreover, gene–environment interactions have been found to influence depression severity in response to chronic interpersonal stress: individuals carrying polymorphisms in *IL1B* that are associated with higher expression of peripheral IL-1β exhibited more severe depressive symptoms in the context of interpersonal stress than individuals without the *IL1B* risk allele[105]. Similarly, mice in which peripheral blood leukocytes produced high concentrations of LPS-induced IL-6 *ex vivo* before stress exposure showed decreased social exploration after social defeat stress, whereas mice that produced low levels of IL-6 before stress exposure exhibited no behavioural effects in response to social defeat[88]. Of note, adoptive transfer of bone marrow progenitor cells from mice producing high levels of IL-6 *ex vivo* to mice that produced low levels of IL-6 made these formerly stress-resilient animals sensitive to the depressive effects of social defeat[88].

Epigenetic changes in genes related to inflammation may also affect the risk for depression and anxiety in the context of psychosocial stress. Indeed, the well-documented association of childhood trauma with increased inflammation is linked to stress-induced epigenetic changes in *FKBP5*, a gene implicated in the development of depression and anxiety as well as in the sensitivity to glucocorticoids[106]. Allele-specific, childhood trauma-dependent DNA demethylation in functional glucocorticoid response elements of *FKBP5* were found to be associated with decreased sensitivity of peripheral blood immune cells to the inhibitory effects of the synthetic glucocorticoid dexamethasone on LPS-induced production of IL-6 *in vitro*[106]. Of note, decreased activation of glucocorticoid receptor-responsive genes in association with increased activation of genes regulated by NF-κB has been found to be a ‘fingerprint’ of the effects of chronic stress in several studies examining a variety of psychosocial stressors[39,107].

T cells and resilience to depression

Some of the most intriguing data regarding the role of the immune system in depression come from studies showing that T cells may protect against stress and depression in laboratory animals. For example, the adoptive transfer of T cells from animals exposed to chronic social defeat stress led to an antidepressant behavioural phenotype in stress-naive mice, which was associated with decreased pro-inflammatory cytokines in serum, a shift towards a neuroprotective M2 phenotype in microglia and increased neurogenesis in the hippocampus[108]. Similar results have been reported following acute stress in mice, in which effector T cell migration to the choroid plexus as a result of glucocorticoid induction of intercellular adhesion molecule 1 (ICAM1) expression in the choroid plexus was associated with reduced anxiety-like behaviour[109]. Mice with impaired release of glucocorticoids in response to stress were anxiety prone[109]. Immunization of anxiety-prone animals with a CNS-specific antigen restored T cell trafficking to the brain during stress and reversed anxiety-like behaviour in association with increased neurogenesis[109]. Immunization with a CNS-specific antigen also blocked stress-induced depression in mice[110]. The mechanism by which T cells influence resilience is believed to be related to their production of IL-4 within the meningeal space. Through as yet uncharacterized pathways, IL-4 then stimulates astrocytes to produce BDNF, and also promotes the conversion of meningeal monocytes and macrophages from a pro-inflammatory M1 phenotype to a less inflammatory M2 phenotype[111]. The movement of T cells throughout the brain, including the meningeal space, has become an area of special interest with the recent description of a brain lymphatic system that heretofore had gone unrecognized[112]. Data also indicate that T_{Reg} cells may have a role in reducing inflammation and supporting neuronal integrity during stress[113]. Similar reports have characterized T cells that are activated by vagal nerve stimulation to produce acetylcholine, which can inhibit NF-κB activation by binding to the α7 subunit of the nicotinic acetylcholine receptor[114].

Relevant to depression, however, peripheral T cell trafficking in response to glucocorticoids has been shown to be impaired in patients with depression, possibly owing to glucocorticoid resistance as a result of genetically mediated (for example, *FKBP5*) or inflammasome-mediated mechanisms targeting the glucocorticoid receptor[46,115]. In addition, inflammatory cytokines and their signalling pathways, including p38 MAPK, have direct inhibitory effects on glucocorticoid receptor function[116]. Moreover, patients with depression have been shown to have increased numbers of peripheral blood myeloid-derived suppressor cells, which inhibit T cell function[117]. Of note, activation of the NLRP3 inflammasome leads to increased accumulation of myeloid-derived suppressor cells[118]. Decreased numbers of peripheral blood T_{Reg} cells and reduced concentrations of anti-inflammatory cytokines in the blood, including TGFβ and IL-10, have also been reported in depression[119]. Thus, it appears that patients with depression may have impairments in neuroprotective and anti-inflammatory T cell responses.

These findings suggest that therapies that boost such T cell responses could be used in patients with depression. Examples include immunization strategies (with CNS antigens as discussed above) that attract T cells to the brain or administration of bacteria, such as *Mycobacterium vaccae,* or parasites that stimulate T_{Reg} cell responses or T cell production

of IL-4 (REFS 14,109,110,120). Indeed, colonization of pregnant dams with helminths attenuated the increase of hippocampal IL-1β in neonatal rats infected with bacteria and protected these animals from the subsequent development of microglial sensitization and cognitive dysfunction in adulthood. This effect was associated with increased *ex vivo* production of IL-4 and decreased production of IL-1β and TNF by splenic macrophages in response to LPS stimulation[120]. Finally, vagus nerve stimulation could be used to induce anti-inflammatory acetylcholine-producing T cells[121]. Although many strategies exist to activate anti-inflammatory T cell responses including the induction of T_{Reg} cells by administration of mesenchymal stem cells[122], the majority of the approaches discussed above have proof-of-concept data in animal models of depression. Nevertheless, the clinical relevance of these approaches has yet to be determined by randomized clinical trials in patients with depression.

Translational considerations

Our increasing understanding of how inflammatory processes contribute to depression, combined with the growing frustration over the lack of discovery of new antidepressants, have stimulated interest in the possibility that various classes of anti-inflammatory medications or other anti-inflammatory strategies (as discussed above) may hold promise as novel ‘all-purpose’ antidepressants. Unfortunately, it appears that anti-inflammatory agents may only demonstrate effective antidepressant activity in subgroups of patients who show evidence of increased peripheral inflammation, for example individuals with medical conditions including osteoarthritis and psoriasis that are characterized by increased levels of peripheral inflammation and patients with depression with increased inflammatory markers[29,30]. Moreover, in patients with depression who do not show elevated peripheral levels of inflammation, anti-inflammatory treatments may actually impair placebo responses that contribute to the effectiveness of all known antidepressant modalities[123]. In the only study to date examining the antidepressant effect of a cytokine antagonist in medically healthy adults with treatment-resistant depression, post hoc analysis revealed a dose-response relationship between baseline levels of peripheral inflammation and subsequent antidepressant response to the TNF inhibitor infliximab[30]. In patients with baseline plasma CRP concentrations ≥5 mg L^{-1}, infliximab outperformed placebo with an effect size similar to that observed in studies of standard antidepressants. Patients with a CRP >3 mg L^{-1}, the standard cut-off for high inflammation, also exhibited separation from placebo. Of note, this latter finding along with data demonstrating the relevance of a CRP >3 mg L^{-1} to altered reward circuitry and glutamate metabolism in depression as well as the prediction of subsequent depressive episodes (described above) aligns well with other diseases in which a CRP >3 mg L^{-1} is relevant to prediction and pathology including cardiovascular disease and diabetes. These data suggest that the cut-off for high inflammation in depression may be consistent with other disorders (BOX 2). Importantly, however, in patients with lower levels of inflammation, blockade of TNF with infliximab actually impaired the placebo response[30], suggesting that anti-inflammatory treatments in patients without inflammation may be detrimental, highlighting the growing recognition that the immune system has an important role in several processes central to neuronal integrity.

Box 2

Guidelines for anti-inflammatory clinical trials in depression

Based on the animal and human literature on the effects of cytokines on the brain, the following guidelines can inform clinical trials designed to test the cytokine hypothesis of depression.

Inflammation only occurs in subgroups of patients with depression[30]. Clinical trials should enrich for patient populations with evidence of increased inflammation, particularly those identified by a C-reactive protein (CRP) >3 mg L^{-1}, which has been shown to characterize patients with depression with altered reward circuitry and increased basal ganglia glutamate, as well as those who have shown a response to anti-cytokine therapy[30,84,95].

Anti-inflammatory drugs may harm patients without increased inflammation. Inflammatory cytokines and the innate immune response have pivotal roles in synaptic plasticity, neurogenesis, long-term potentiation (which is a fundamental process in learning and memory) and possibly antidepressant response[123,128].

Primary behavioural outcome variables should include measures of anhedonia and anxiety. Neuroimaging studies coupled with studies administering a variety of inflammatory stimuli, including the inflammatory cytokine interferon-α, endotoxin and typhoid vaccination, have revealed that inflammation targets neurocircuits in the brain that regulate motivation and reward as well as anxiety, arousal and alarm[35]. In addition, these symptoms have been shown to respond to anti-cytokine therapy in limited studies.

Drugs that specifically target inflammatory cytokines and/or their signalling pathways are preferable. The majority of clinical trials to date have used anti-inflammatory drugs (non-steroidal anti-inflammatory agents and minocycline, a tetracycline antibiotic) that have several off-target effects making the extant data relevant to testing the cytokine hypothesis of depression difficult to interpret[31].

Target engagement must be established in the periphery and ultimately the brain. Protein and gene expression markers of inflammation in the peripheral blood can serve as relevant proxies for inflammation in the brain[129], especially given evidence of trafficking of activated peripheral immune cells to the brain in stress-induced animal models of depression. Relevant therapeutic interventions should decrease peripheral inflammatory markers in concert with improvement of specific depressive symptoms. Translocator protein neuroimaging ligands may ultimately serve as direct measures of neuroinflammation and its inhibition by anti-inflammatory therapies in future clinical trials[61].

We conclude by offering the balanced perspective that anti-inflammatory therapies are unlikely to be all-purpose antidepressants. Perhaps we only think of standard antidepressants as all-purpose agents because we have never succeeded in developing predictive biomarkers that would reliably inform us of who will respond to any given agent. If so, then we view these agents as all-purpose, not because it is true but out of hope and ignorance. Thus,

instead of being a negative, perhaps the finding that baseline inflammatory biomarkers such as CRP can predict subsequent symptomatic response to anti-inflammatory strategies is, in fact, the most positive development thus far in our quest to understand how the immune system might be harnessed to improve the treatment of depression.

Conclusion

In ancestral times, integration of inflammatory responses and behaviours of avoidance and alarm provided an evolutionary advantage in managing the microbial world. In the absence of the temporizing influence of commensal organisms that were rife in environments in which humans evolved, the inflammatory bias of the human species in the civilized world has been increasingly engaged in the complex world of psychosocial interactions and the inevitable stress it engenders. Responding to these sterile insults with activation of the inflammasome and mobilization of myeloid cells to the brain, the resultant release of inflammatory cytokines impinges on neurotransmitters and neurocircuits to lead to behaviours that are poorly suited for functioning in modern society. This inevitability of our evolutionary past is apparent in the high rates of depression that are seen in society today. There is also an increasing recognition of mechanisms of resilience that derive from our emerging understanding of the neuroprotective effects of a variety of T cell responses ranging from effector T cells that produce IL-4 to T_{Reg} cells with anti-inflammatory properties. A better understanding of these neuroprotective pathways and of the inflammatory mechanisms — from inflammasome activation to cell trafficking to the brain — that operate in patients with depression may lead to the development of novel anti-depressant therapies.

Glossary

Conspecifics
Members of the same species.

Sickness behaviour
An adaptive response to illness, often precipitated by infection, that includes social withdrawal, decreased appetite, lethargy, impaired concentration, depressed mood, irritability, muscle aches and pain, and fever. This syndrome is believed to prioritize shifting of energy resources to fighting infection and wound healing.

Anhedonia
A lack of interest in usually pleasurable activities that represents a decrease in motivation, which can either represent a decrease in the response to reward or in the willingness to expend effort to obtain reward.

Major depressive disorder
A clinical syndrome of depression characterized by the primary symptoms of depressed mood and anhedonia, and diagnosed using criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Social defeat stress

A model of depression that entails repeated exposure to a conspecific animal screened for aggressive behaviour. The animals are placed together in the same cage where they are exposed to brief bouts of defeat lasting 5–10 minutes daily typically for 6–10 days.

Myeloid-derived suppressor cells

A heterogeneous population of cells of myeloid origin that rapidly expands during inflammation and can potently suppress T cell responses. They are now being explored as potential therapeutic targets to inhibit immune responses in autoimmune disease or transplant rejection.

Cytokine hypothesis of depression

A theoretical framework that suggests that cytokines have a primary role in alterations of neurotransmitter metabolism, neuroendocrine function, neuroplasticity, neurocircuitry and behaviour in a subgroup of patients with depression and increased inflammation.

References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 386:743–800. [PubMed: 26063472]
2. Rush AJ, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006; 163:1905–1917. [PubMed: 17074942]
3. Pace TW, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006; 163:1630–1633. [PubMed: 16946190]
4. Bierhaus A, et al. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci USA. 2003; 100:1920–1925. This study is one of the first demonstrations that a psychological stressor could activate fundamental inflammatory signalling pathways (that is, NF-κB) in human peripheral blood mononuclear cells. [PubMed: 12578963]
5. Aschbacher K, et al. Maintenance of a positive outlook during acute stress protects against pro-inflammatory reactivity and future depressive symptoms. Brain Behav Immun. 2012; 26:346–352. [PubMed: 22119400]
6. Raison CL, Miller AH. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol Psychiatry. 2013; 18:15–37. This theoretical treatise proposes that depression, rather than being a maladaptive response to psychosocial challenge, is the outgrowth of an evolutionary advantage provided by a crosstalk between the immune system and the brain to survive ancestral challenges from pathogens and predators. [PubMed: 22290120]
7. Watson PJ, Andrews PW. Toward a revised evolutionary adaptationist analysis of depression: the social navigation hypothesis. J Affect Disord. 2002; 72:1–14. [PubMed: 12204312]
8. Kinney DK, Tanaka M. An evolutionary hypothesis of depression and its symptoms, adaptive value, and risk factors. J Nerv Ment Dis. 2009; 197:561–567. [PubMed: 19684491]
9. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014; 140:774–815. [PubMed: 24417575]
10. Seedat S, et al. Cross-national associations between gender and mental disorders in the World Health Organization World Mental Health Surveys. Arch Gen Psychiatry. 2009; 66:785–795. [PubMed: 19581570]
11. Moieni M, et al. Sex differences in depressive and socioemotional responses to an inflammatory challenge: implications for sex differences in depression. Neuropsychopharmacology. 2015; 40:1709–1716. [PubMed: 25598426]
12. Udina M, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J Clin Psychiatry. 2012; 73:1128–1138. [PubMed: 22967776]

13. Raison CL, Lowry CA, Rook GA. Inflammation, sanitation, and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. Arch Gen Psychiatry. 2010; 67:1211–1224. [PubMed: 21135322]
14. Rook GA, Lowry CA, Raison CL. Hygiene and other early childhood influences on the subsequent function of the immune system. Brain Res. 2015; 1617:47–62. [PubMed: 24732404]
15. Yirmiya R, et al. Illness, cytokines, and depression. Ann NY Acad Sci. 2000; 917:478–487. [PubMed: 11268375]
16. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009; 65:732–741. [PubMed: 19150053]
17. Maes M. Major depression and activation of the inflammatory response system. Adv Exp Med Biol. 1999; 461:25–46. [PubMed: 10442165]
18. Brambilla P, et al. Increased M1/decreased M2 signature and signs of Th1/Th2 shift in chronic patients with bipolar disorder, but not in those with schizophrenia. Transl Psychiatry. 2014; 4:e406. [PubMed: 24984193]
19. Drago A, Crisafulli C, Calabro M, Serretti A. Enrichment pathway analysis. The inflammatory genetic background in bipolar disorder. J Affect Disord. 2015; 179:88–94. [PubMed: 25855618]
20. Mostafavi S, et al. Type I interferon signaling genes in recurrent major depression: increased expression detected by whole-blood RNA sequencing. Mol Psychiatry. 2013; 19:1267–1274. [PubMed: 24296977]
21. Maes M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry. 1995; 19:11–38. In contrast to previous theories that primarily focused on reduced T cell responses to mitogenic stimuli, this is one of the first papers to posit that an activated immune system may have a role in the aetiology of depression. [PubMed: 7708925]
22. Bufalino C, Hepgul N, Aguglia E, Pariante CM. The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. Brain Behav Immun. 2012; 31:31–47. [PubMed: 22580182]
23. Capuron L, et al. Neurobehavioral effects of interferon-α in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology. 2002; 26:643–652. [PubMed: 11927189]
24. Reichenberg A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry. 2001; 58:445–452. [PubMed: 11343523]
25. Bonaccorso S, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-α-based immunotherapy are related to interferon-α-induced changes in the serotonergic system. J Clin Psychopharmacol. 2002; 22:86–90. [PubMed: 11799348]
26. Harrison NA, et al. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry. 2009; 66:407–414. [PubMed: 19423079]
27. Tyring S, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet. 2006; 367:29–35. [PubMed: 16399150]
28. Abbott R, et al. Tumour necrosis factor-α inhibitor therapy in chronic physical illness: a systematic review and meta-analysis of the effect on depression and anxiety. J Psychosom Res. 2015; 79:175–84. [PubMed: 25935351]
29. Kohler O, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry. 2014; 71:1381–1391. [PubMed: 25322082]
30. Raison CL, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013; 70:31–41. This report describes the results of the first double-blind, placebo-controlled trial of a monoclonal antibody against TNF to treat major depression, indicating that only patients with depression that have high levels of inflammation respond to cytokine antagonism. [PubMed: 22945416]
31. Miller AH, Raison CL. Are anti-inflammatory therapies viable treatments for psychiatric disorders?: where the rubber meets the road. JAMA Psychiatry. 2015; 72:527–528. [PubMed: 25853989]

32. Michopoulos V, et al. Association of *CRP* genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. Am J Psychiatry. 2015; 172:353–362. [PubMed: 25827033]
33. Fernandes, BS., et al. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry. 2015. http://dx.doi.org/10.1038/mp.2015.87
34. Morris SE, Cuthbert BN. Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. Dialogues Clin Neurosci. 2012; 14:29–37. [PubMed: 22577302]
35. Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety. 2013; 30:297–306. [PubMed: 23468190]
36. Cattaneo A, et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology. 2013; 38:377–385. [PubMed: 22990943]
37. Eurelings LS, Richard E, Eikelenboom P, van Gool WA, Moll van Charante EP. Low-grade inflammation differentiates between symptoms of apathy and depression in community-dwelling older individuals. Int Psychogeriatr. 2015; 27:639–647. [PubMed: 25729001]
38. Pearson TA, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107:499–511. [PubMed: 12551878]
39. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol. 2011; 11:625–632. [PubMed: 21818124]
40. Iwata M, Ota KT, Duman RS. The inflammasome: pathways linking psychological stress, depression, and systemic illnesses. Brain Behav Immun. 2013; 31:105–114. [PubMed: 23261775]
41. Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. Nature. 2012; 481:278–286. [PubMed: 22258606]
42. Fleshner M. Stress-evoked sterile inflammation, danger associated molecular patterns (DAMPs), microbial associated molecular patterns (MAMPs) and the inflammasome. Brain Behav Immun. 2013; 27:1–7. [PubMed: 22964544]
43. Cox SS, et al. Adrenergic and glucocorticoid modulation of the sterile inflammatory response. Brain Behav Immun. 2014; 36:183–192. [PubMed: 24321216]
44. Pan Y, Chen XY, Zhang QY, Kong LD. Microglial NLRP3 inflammasome activation mediates IL-1β-related inflammation in prefrontal cortex of depressive rats. Brain Behav Immun. 2014; 41:90–100. [PubMed: 24859041]
45. Zhang Y, et al. NLRP3 inflammasome mediates chronic mild stress-induced depression in mice via neuroinflammation. Int J Neuropsychopharmacol. 2015; 18 pii: pyv006.
46. Paugh SW, et al. NALP3 inflammasome upregulation and CASP1 cleavage of the glucocorticoid receptor cause glucocorticoid resistance in leukemia cells. Nat Genet. 2015; 47:607–614. [PubMed: 25938942]
47. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med. 2005; 353:1711–1723. [PubMed: 16236742]
48. Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am J Psychiatry. 2003; 160:1554–1565. [PubMed: 12944327]
49. Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav Immun. 2007; 21:9–19. [PubMed: 17070667]
50. Alcocer-Gomez E, et al. NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. Brain Behav Immun. 2014; 36:111–117. This paper provides the first indication that activation of the inflammasome may contribute to elevated levels of inflammatory cytokines such as IL-1β and IL-18 in major depression, consistent with studies in laboratory animal models of depression that demonstrated that inhibition of NLRP3 can block the development of stress-induced depressive-like behaviour. [PubMed: 24513871]

51. Stertz L, et al. Damage-associated molecular patterns and immune activation in bipolar disorder. Acta Psychiatr Scand. 2015; 132:211–217. [PubMed: 25891376]
52. Rawdin BJ, et al. Dysregulated relationship of inflammation and oxidative stress in major depression. Brain Behav Immun. 2013; 31:143–152. [PubMed: 23201587]
53. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:676–692. [PubMed: 20471444]
54. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. J Neurosci. 2014; 34:15490–15496. [PubMed: 25392516]
55. Maslanik T, et al. Commensal bacteria and MAMPs are necessary for stress-induced increases in IL-1β and IL-18 but not IL-6, IL-10 or MCP-1. PLoS ONE. 2012; 7:e50636. [PubMed: 23236381]
56. Lyte M, Vulchanova L, Brown DR. Stress at the intestinal surface: catecholamines and mucosa-bacteria interactions. Cell Tissue Res. 2011; 343:23–32. [PubMed: 20941511]
57. Rao JS, Harry GJ, Rapoport SI, Kim HW. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry. 2010; 15:384–392. [PubMed: 19488045]
58. Steiner J, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. J Psychiatr Res. 2008; 42:151–157. [PubMed: 17174336]
59. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav Immun. 2014; 42:50–59. This study provides some of the most compelling evidence that neuroinflammation occurs in major depression by demonstrating that monocytes traffic to the brain of patients with depressive symptoms and assume a perivascular localization in association with chemoattractant molecules such as CCL2, which has been shown to attract monocytes to the brain in animal models of stress. [PubMed: 24858659]
60. Nagy C, et al. Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. Mol Psychiatry. 2015; 20:320–328. [PubMed: 24662927]
61. Setiawan E, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiatry. 2015; 72:268–275. [PubMed: 25629589]
62. Hannestad J, et al. The neuroinflammation marker translocator protein is not elevated in individuals with mild-to-moderate depression: a [^{11}C]PBR28 PET study. Brain Behav Immun. 2013; 33:131–138. [PubMed: 23850810]
63. Sandiego CM, et al. Imaging robust microglial activation after lipopolysaccharide administration in humans with PET. Proc Natl Acad Sci USA. 2015; 112:12468–12473. [PubMed: 26385967]
64. Quan N, Banks WA. Brain-immune communication pathways. Brain Behav Immun. 2007; 21:727–735. [PubMed: 17604598]
65. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factor-α signaling during peripheral organ inflammation. J Neurosci. 2009; 29:2089–2102. [PubMed: 19228962]
66. Hennessy E, Griffin EW, Cunningham C. Astrocytes are primed by chronic neurodegeneration to produce exaggerated chemokine and cell infiltration responses to acute stimulation with the cytokines IL-1β and TNF-α. J Neurosci. 2015; 35:8411–8422. [PubMed: 26041910]
67. Wohleb ES, et al. β-adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J Neurosci. 2011; 31:6277–6288. [PubMed: 21525267]
68. Wohleb ES, Powell ND, Godbout JP, Sheridan JF. Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. J Neurosci. 2013; 33:13820–13833. References 67 and 68 present a series of experiments that demonstrate a cellular pathway by which cytokines signals can be transmitted to the brain via trafficking of monocytes from the bone marrow to the brain parenchyma, a process mediated by catecholamines and CCL2. [PubMed: 23966702]

69. Krugel U, Fischer J, Radicke S, Sack U, Himmerich H. Antidepressant effects of TNF-α blockade in an animal model of depression. J Psychiatr Res. 2013; 47:611–616. [PubMed: 23394815]

70. Arends S, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-α blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther. 2011; 13:R94. [PubMed: 21689401]

71. Gillespie, CF., Garlow, SJ., Binder, EB., Schatzberg, AF., Nemeroff, CB. Textbook of Psychopharmacology. Schatzberg, AF., Nemeroff, CB., editors. America Psychiatric Publishing; 2009. p. 903-944.

72. Zhu CB, et al. Interleukin-1 receptor activation by systemic lipopolysaccharide induces behavioral despair linked to MAPK regulation of CNS serotonin transporters. Neuropsychopharmacology. 2010; 35:2510–2520. [PubMed: 20827273]

73. Neurauter G, et al. Chronic immune stimulation correlates with reduced phenylalanine turnover. Curr Drug Metab. 2008; 9:622–627. [PubMed: 18781914]

74. Felger JC, et al. Tyrosine metabolism during interferon-α administration: association with fatigue and CSF dopamine concentrations. Brain Behav Immun. 2013; 31:153–160. [PubMed: 23072726]

75. Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011; 35:702–721. [PubMed: 21185346]

76. Raison CL, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-α: relationship to CNS immune responses and depression. Mol Psychiatry. 2010; 15:393–403. [PubMed: 19918244]

77. Steiner J, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflamm. 2011; 8:94.

78. Tavares RG, et al. Quinolinic acid stimulates synaptosomal glutamate release and inhibits glutamate uptake into astrocytes. Neurochem Int. 2002; 40:621–627. [PubMed: 11900857]

79. Tilleux S, Hermans E. Neuroinflammation and regulation of glial glutamate uptake in neurological disorders. J Neurosci Res. 2007; 85:2059–2070. [PubMed: 17497670]

80. Hardingham GE, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nat Neurosci. 2002; 5:405–414. [PubMed: 11953750]

81. Koo JW, Russo SJ, Ferguson D, Nestler NJ, Duman RS. Nuclear factor-κB is a critical mediator of stress-impaired neurogenesis and depressive behavior. Proc Natl Acad Sci USA. 2010; 107:2669–2674. [PubMed: 20133768]

82. Goshen I, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Mol Psychiatry. 2008; 13:717–728. [PubMed: 17700577]

83. Haroon E, et al. IFN-α-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. Neuropsychopharmacology. 2014; 39:1777–1785. [PubMed: 24481242]

84. Haroon, E., et al. Conceptual convergence:increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. Mol Psychiatry. 2015. http://dx.doi.org/10.1038/mp.2015.206

85. Walker AK, et al. NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. Neuropsychopharmacology. 2013; 38:1609–1616. [PubMed: 23511700]

86. O'Connor JC, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry. 2009; 14:511–522. [PubMed: 18195714]

87. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006; 59:1116–1127. [PubMed: 16631126]

88. Hodes GE, et al. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc Natl Acad Sci USA. 2014; 111:16136–16141. This paper gives

compelling evidence in laboratory animals that individual differences in the behavioural response to a social stressor is mediated by individual differences in the production of the inflammatory cytokine IL-6, suggesting that genetic and/or environmental factors that regulate inflammatory responses can determine stress-induced depressive-like behaviour. [PubMed: 25331895]

89. Capuron L, et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon-α administration. Arch Gen Psychiatry. 2012; 69:1044–1053. Using multimodal neuroimaging, this report provides an integration of the impact of inflammatory cytokines on reward pathways and dopamine metabolism in the basal ganglia that leads to alterations in behaviours relevant to motivation and ultimately anhedonia — a core symptom of depression. [PubMed: 23026954]
90. Eisenberger NI, et al. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry. 2010; 68:748–754. [PubMed: 20719303]
91. Felger JC, et al. Chronic interferon-α decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates. Neuropsychopharmacology. 2013; 38:2179–2187. [PubMed: 23657438]
92. Dowell, NG., et al. Acute changes in striatal microstructure predict the development of interferon-α induced fatigue. Biol Psychiatry. 2015. http://dx.doi.org/10.1016/j.biopsych.2015.05.015
93. Harrison NA, Cercignani M, Voon V, Critchley HD. Effects of inflammation on hippocampus and substantia nigra responses to novelty in healthy human participants. Neuropsychopharmacology. 2015; 40:831–838. [PubMed: 25154706]
94. Harrison, NA., et al. A neuro-computational account of how inflammation enhances sensitivity to punishments versus rewards. Biol Psychiatry. 2015. http://dx.doi.org/10.1016/j.biopsych.2015.07.018
95. Felger, JC., et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry. 2015. http://dx.doi.org/10.1038/mp.2015.168This neuroimaging study is the first to demonstrate that the impact of immune stimuli (for example, IFNα, typhoid vaccination and endotoxin) on the brains of otherwise non-depressed individuals extended to patients with depression, whose increased inflammation was found to reduce functional connectivity in reward-related neurocircuitry leading to anhedonia, a core symptom of depression
96. Harrison NA, et al. Neural origins of human sickness in interoceptive responses to inflammation. Biol Psychiatry. 2009; 66:415–422. [PubMed: 19409533]
97. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. Proc Natl Acad Sci USA. 2010; 107:14817–14822. This manuscript provides one of the first and most detailed descriptions of the relationship between stress-induced activation of inflammatory responses and sensitivity to a psychosocial stressor, identifying key brain regions such as the dACC as a target of cytokines, leading to anxiety, arousal and alarm. [PubMed: 20679216]
98. Eisenberger NI, Lieberman MD. Why rejection hurts: a common neural alarm system for physical and social pain. Trends Cogn Sci. 2004; 8:294–300. [PubMed: 15242688]
99. Muscatell KA, et al. Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. Brain Behav Immun. 2015; 43:46–53. [PubMed: 25016200]
100. Gimeno D, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med. 2009; 39:413–423. [PubMed: 18533059]
101. Au B, Smith KJ, Gariepy G, Schmitz N. The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA). Int J Geriatr Psychiatry. 2015; 30:976–984. [PubMed: 25537199]
102. Duivis HE, et al. Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: prospective findings from the heart and soul study. Am J Psychiatry. 2011; 168:913–920. [PubMed: 21724664]
103. Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, CM., Mondelli, V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry. 2015. http://dx.doi.org/10.1038/mp.2015.67

104. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA. 2007; 104:1319–1324. [PubMed: 17229839]
105. Tartter M, Hammen C, Bower JE, Brennan PA, Cole S. Effects of chronic interpersonal stress exposure on depressive symptoms are moderated by genetic variation at IL6 and IL1β in youth. Brain Behav Immun. 2015; 46:104–111. [PubMed: 25596176]
106. Klengel T, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci. 2013; 16:33–41. [PubMed: 23201972]
107. Miller GE, et al. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling. Biol Psychiatry. 2008; 64:266–272. [PubMed: 18440494]
108. Brachman RA, Lehmann ML, Maric D, Herkenham M. Lymphocytes from chronically stressed mice confer antidepressant-like effects to naive mice. J Neurosci. 2015; 35:1530–1538. [PubMed: 25632130]
109. Lewitus GM, Cohen H, Schwartz M. Reducing post-traumatic anxiety by immunization. Brain Behav Immun. 2008; 22:1108–1114. [PubMed: 18562161]
110. Lewitus GM, et al. Vaccination as a novel approach for treating depressive behavior. Biol Psychiatry. 2009; 65:283–288. References 109 and 110 provide the first evidence that engaging T cells to traffic to the brain during stress can block depressive- and anxiety-like behaviour and induce growth factors and neurogenesis in the brain, representing an entirely novel approach to the treatment of depression that takes advantage of the capacity of T cells to support neuronal integrity. [PubMed: 18722594]
111. Derecki NC, et al. Regulation of learning and memory by meningeal immunity: a key role for IL-4. J Exp Med. 2010; 207:1067–1080. [PubMed: 20439540]
112. Louveau A, et al. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015; 523:337–341. [PubMed: 26030524]
113. Kim SJ, et al. $CD4^+CD25^+$ regulatory T cell depletion modulates anxiety and depression-like behaviors in mice. PLoS ONE. 2012; 7:e42054. [PubMed: 22860054]
114. Rosas-Ballina M, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011; 334:98–101. [PubMed: 21921156]
115. Bauer ME, et al. Dexamethasone-induced effects on lymphocyte distribution and expression of adhesion molecules in treatment-resistant depression. Psychiatry Res. 2002; 113:1–15. [PubMed: 12467941]
116. Wang X, Wu H, Miller AH. Interleukin 1α (IL-1α) induced activation of p38 mitogen-activated protein kinase inhibits glucocorticoid receptor function. Mol Psychiatry. 2004; 9:65–75. [PubMed: 14699442]
117. Wei J, Zhang M, Zhou J. Myeloid-derived suppressor cells in major depression patients suppress T-cell responses through the production of reactive oxygen species. Psychiatry Res. 2015; 228:695–701. [PubMed: 26165964]
118. van Deventer HW, et al. The inflammasome component NLRP3 impairs antitumor vaccine by enhancing the accumulation of tumor-associated myeloid-derived suppressor cells. Cancer Res. 2010; 70:10161–10169. [PubMed: 21159638]
119. Li Y, et al. Altered expression of $CD4^+CD25^+$ regulatory T cells and its $5\text{-}HT_{1a}$ receptor in patients with major depression disorder. J Affect Disord. 2010; 124:68–75. [PubMed: 19900711]
120. Williamson LL, et al. Got worms? Perinatal exposure to helminths prevents persistent immune sensitization and cognitive dysfunction induced by early-life infection. Brain Behav Immun. 2015
121. Olofsson PS, Rosas-Ballina M, Levine YA, Tracey KJ. Rethinking inflammation: neural circuits in the regulation of immunity. Immunol Rev. 2012; 248:188–204. [PubMed: 22725962]
122. Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nat Immunol. 2014; 15:1009–1016. [PubMed: 25329189]

123. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ, Greengard P. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflammatory drugs in mice and humans. Proc Natl Acad Sci USA. 2011; 108:9262–9267. [PubMed: 21518864]

124. Gurven M, Kaplan H. Longevity among hunter-gatherers: a cross-cultural examination. Popul Dev Rev. 2007; 33:321–365.

125. Fumagalli M, et al. Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. PLoS Genet. 2011; 7:e1002355. [PubMed: 22072984]

126. Kuningas M, et al. Selection for genetic variation inducing pro-inflammatory responses under adverse environmental conditions in a Ghanaian population. PLoS ONE. 2009; 4:e7795. [PubMed: 19907653]

127. Ratcliffe M. A bad case of the flu?: the comparative phenomenology of depression and somatic illness. J Conscious Studies. 2013; 20:198–218.

128. Marin I, Kipnis J. Learning and memory… and the immune system. Learn Mem. 2013; 20:601–606. [PubMed: 24051097]

129. Mehta D, et al. Transcriptional signatures related to glucose and lipid metabolism predict treatment response to the tumor necrosis factor antagonist infliximab in patients with treatment-resistant depression. Brain Behav Immun. 2013; 31:205–215. [PubMed: 23624296]

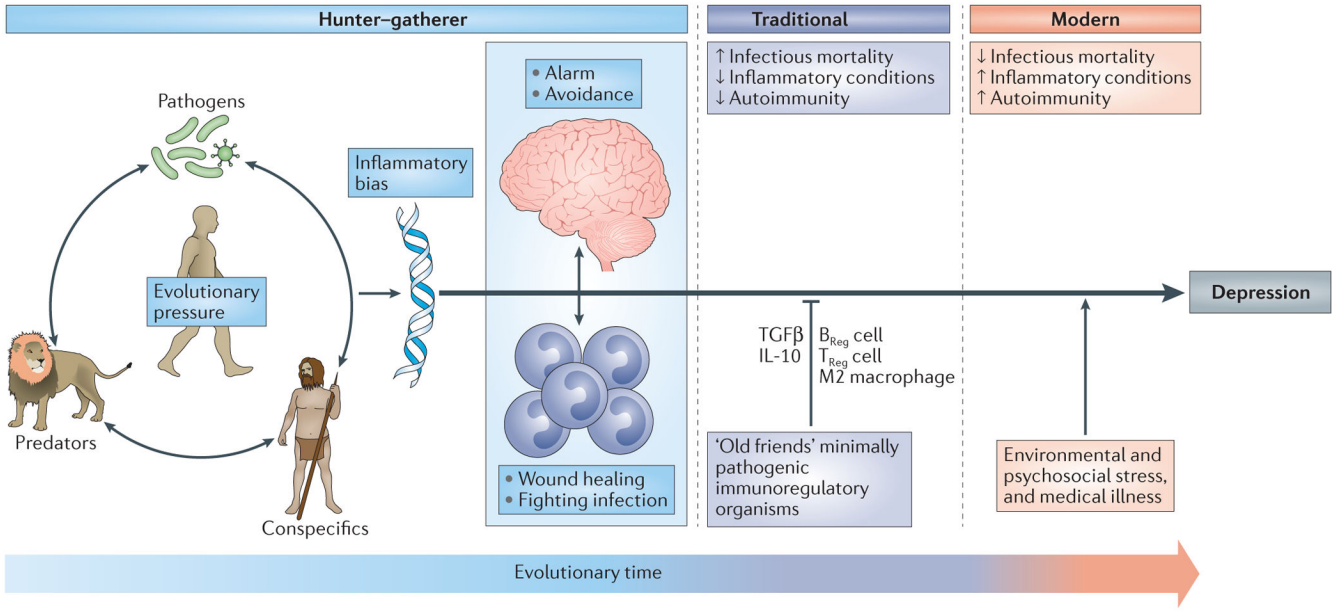

Figure 1. Evolutionary legacy of an inflammatory bias

Early evolutionary pressures derived from human interactions with pathogens, predators and human conspecifics (such as rivals) resulted in an inflammatory bias that included an integrated suite of immunological and behavioural responses that conserved energy for fighting infection and healing wounds, while maintaining vigilance against attack. This inflammatory bias is believed to have been held in check during much of human evolution by exposure to minimally pathogenic, tolerogenic organisms in traditional (that is, rural) environments that engendered immunological responses characterized by the induction of regulatory T (T_{Reg}) cells, regulatory B (B_{Reg}) cells and immunoregulatory M2 macrophages as well as the production of the anti-inflammatory cytokines interleukin-10 (IL-10) and transforming growth factor-β (TGFβ). In modern times, sanitized urban environments of more developed societies are rife with psychological challenges but generally lacking in the types of infectious challenges that were primary sources of morbidity and mortality across most of human evolution. In the absence of traditional immunological checks and balances, the psychological challenges of the modern world instigate ancestral immunological and behavioural repertoires that represent a decided liability, such as high rates of various inflammation-related disorders including depression.

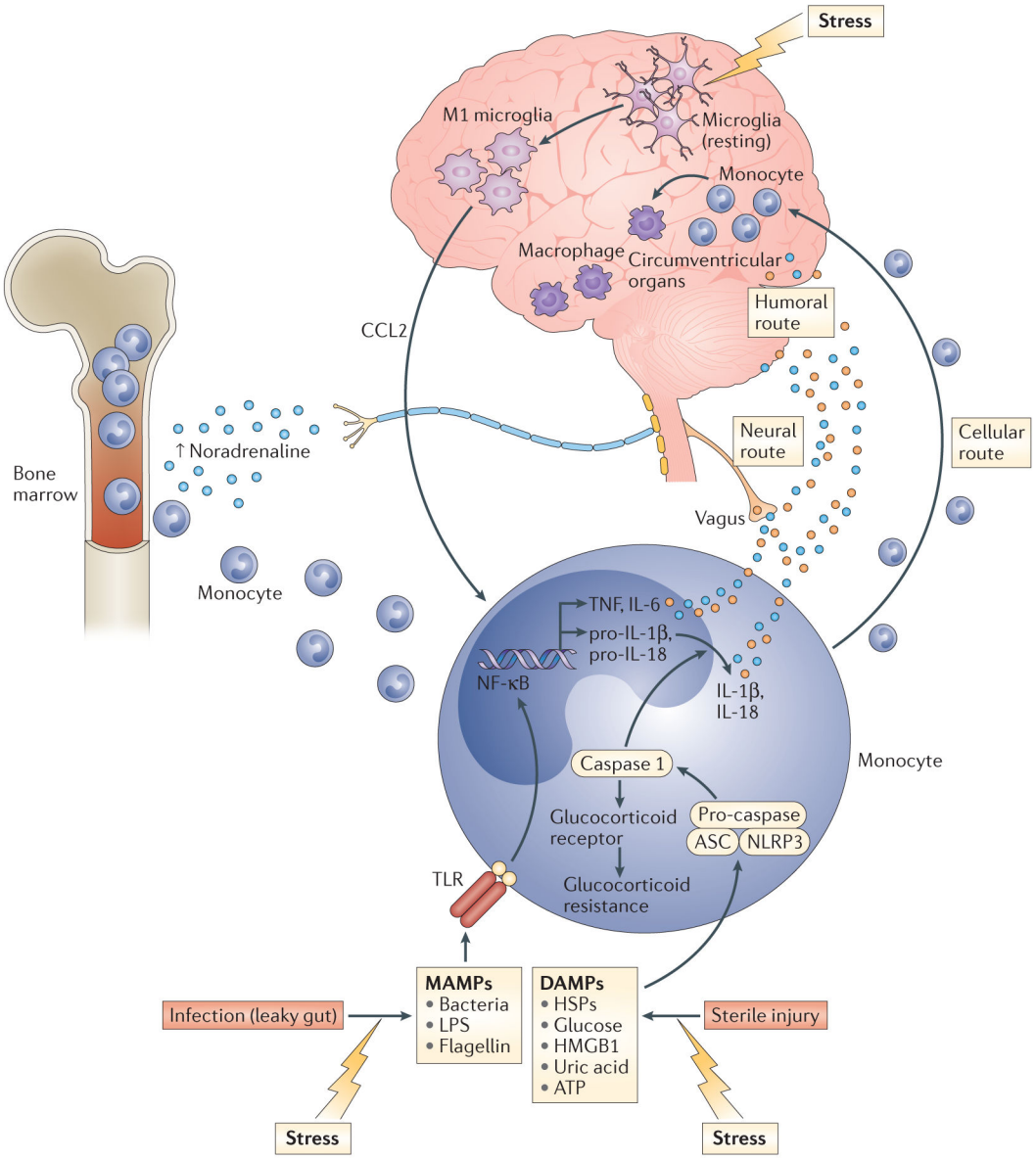

Figure 2. Transmitting stress-induced inflammatory signals to the brain

In the context of psychosocial stress, catecholamines (such as noradrenaline) released by activated sympathetic nervous system fibres stimulate bone marrow production and the release of myeloid cells (for example, monocytes) that enter the periphery where they encounter stress-induced damage-associated molecular patterns (DAMPs), bacteria and bacterial products such as microbial-associated molecular patterns (MAMPs) leaked from the gut. These DAMPs and MAMPs subsequently activate inflammatory signalling pathways such as nuclear factor-κB (NF-κB) and the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome. Stimulation of NLRP3 in turn activates caspase 1, which leads to the production of mature interleukin-1β (IL-1β) and IL-18 while also cleaving the glucocorticoid receptor contributing to glucocorticoid resistance. Activation of NF-κB stimulates the release of other pro-inflammatory cytokines including

tumour necrosis factor (TNF) and IL-6, which together with IL-1β and IL-18 can access the brain through humoral and neural routes. Psychosocial stress can also lead to the activation of microglia to a M1 pro-inflammatory phenotype, which release CC-chemokine ligand 2 (CCL2) that in turn attracts activated myeloid cells to the brain via a cellular route. Once in the brain, activated macrophages can perpetuate central inflammatory responses. ASC, apoptosis-associated speck-like protein containing a CARD; HMGB1, high mobility group box 1; HSP, heat shock protein; LPS, lipopolysaccharide; TLR, Toll-like receptor.

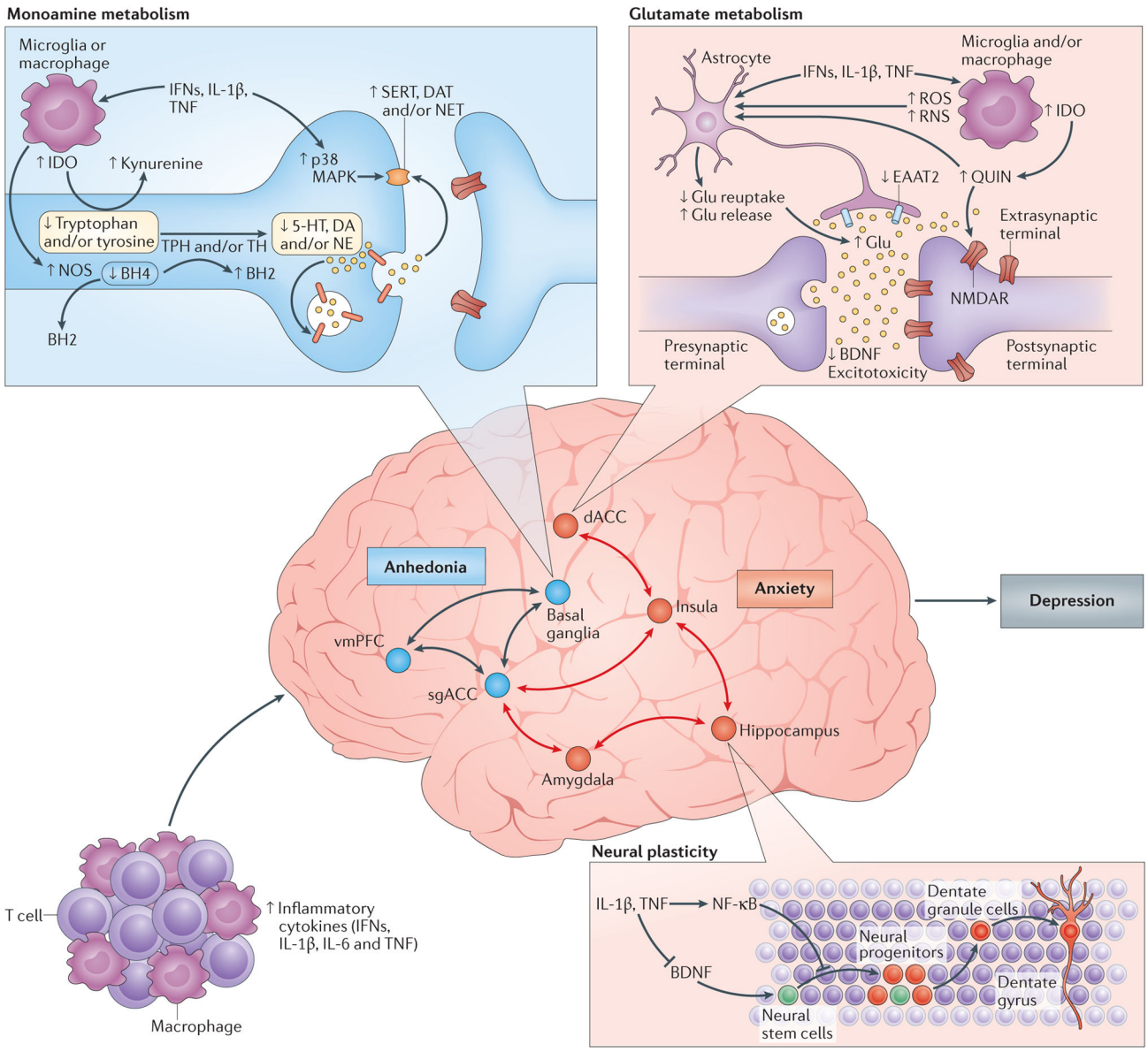

Figure 3. Cytokine targets in the brain: neurotransmitters and neurocircuits

Once in the brain, the inflammatory response can affect metabolic and molecular pathways influencing neurotransmitter systems that can ultimately affect neurocircuits that regulate behaviour, especially behaviours relevant to decreased motivation (anhedonia), avoidance and alarm (anxiety), which characterize several neuropsychiatric disorders including depression. On a molecular level, pro-inflammatory cytokines including type I and II interferons (IFNs), interleukin-1β (IL-1β) and tumour necrosis factor (TNF) can reduce the availability of monoamines — serotonin (5-HT), dopamine (DA) and noradrenaline (NE) — by increasing the expression and function of the presynaptic reuptake pumps (transporters) for 5-HT, DA and NE through activation of mitogen-activated protein kinase (MAPK) pathways and by reducing monoamine synthesis through decreasing enzymatic co-factors such as tetrahydrobiopterin (BH4), which is highly sensitive to cytokine-induced oxidative

stress and is involved in the production of nitric oxide (NO) by NO synthase (NOS). Many cytokines, including IFNγ, IL-1β and TNF, can also decrease relevant monoamine precursors by activating the enzyme indoleamine 2,3-dioxygenase (IDO), which breaks down tryptophan, the primary precursor for serotonin, into kynurenine. Activated microglia can convert kynurenine into quinolinic acid (QUIN), which binds to the *N*-methyl-D-aspartate receptor (NMDAR), a glutamate (Glu) receptor, and together with cytokine-induced reduction in astrocytic Glu reuptake and stimulation of astrocyte Glu release, in part by induction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), can lead to excessive Glu, an excitatory amino acid neurotransmitter. Excessive Glu, especially when binding to extrasynaptic NMDARs, can in turn lead to decreased brain-derived neurotrophic factor (BDNF) and excitotoxicity. Inflammation effects on growth factors such as BDNF in the dentate gyrus of the hippocampus can also affect fundamental aspects of neuronal integrity including neurogenesis, long-term potentiation and dendritic sprouting, ultimately affecting learning and memory. Cytokine effects on neurotransmitter systems, especially DA, can inhibit several aspects of reward motivation and anhedonia in corticostriatal circuits involving the basal ganglia, ventromedial prefrontal cortex (vmPFC) and subgenual and dorsal anterior cingulate cortex (sgACC and dACC, respectively), while also activating circuits regulating anxiety, arousal, alarm and fear including the amygdala, hippocampus, dACC and insula. BH2, dihydrobiopterin; DAT, dopamine transporter; EAAT2, excitatory amino acid transporter 2; NET, noradrenaline transporter; NF-κB, nuclear factor-κB; SERT, serotonin transporter; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase. Copyrighted 2015. Advanstar. 120580:1115BN.