Received: 24 August 2019 | Revised: 20 February 2020 | Accepted: 3 March 2020

DOI: 10.1111/ejn.14720

SPECIAL ISSUE REVIEW

EJN European Journal of Neuroscience FENS WILEY

Neuroinflammation and depression: A review

Romain Troubat[1] | **Pascal Barone**[1] | **Samuel Leman**[1] | **Thomas Desmidt**[1,2] | **Arnaud Cressant**[1] | **Boriana Atanasova**[1] | **Bruno Brizard**[1] | **Wissam El Hage**[1,2] | **Alexandre Surget**[1] | **Catherine Belzung**[1] | **Vincent Camus**[1,2]

[1]UMR 1253, iBrain, Université de Tours, Inserm, Tours, France

[2]CHRU de Tours, Tours, France

Correspondence
Catherine Belzung, UMR 1253, iBrain, UFR Sciences et Techniques, Parc Grandmont, F-37200 Tours, France.
Email: catherine.belzung@univ-tours.fr

Abstract

Some recent clinical and preclinical evidence suggests that neuroinflammation is a key factor that interacts with the three neurobiological correlates of major depressive disorder: depletion of brain serotonin, dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus. This review discusses the main players in brain immunity as well as how inflammation interacts with the above three mechanisms. It is reported that kynurenine (KYN) pathway alteration in favour of its excitotoxic component and HPA axis dysregulation have the common effect of increasing extracellular glutamate levels and glutamate neurotransmission, which can impact hippocampal neurogenesis. This pathophysiological cascade appears to be triggered or sustained and reinforced by any chronic inflammatory condition involving increased circulating markers of inflammation that are able to cross the blood–brain barrier and activate microglia; it can also be the consequence of primary brain neuroinflammation, such as in neurodegenerative disorders with early manifestations that are frequently depressive symptoms. Further recent data indicate that primary microglial activation may also result from a direct impact of chronic stress on vascular function. The intricated dynamic crosstalk between neuroinflammation and other relevant neurobiological correlates of depression add to evidence

Abbreviations: 3-HK, 3-hydroxy-kynurenine; 5-HT, 5-hydroxytryptamine, serotonin; ACTH, adrenocorticotropic hormone; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; AP-1, activator protein 1; ATP, adenosine triphosphate; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CCL2, chemokine (C-C motif) ligand 2; CCR2, C-C chemokine receptor type 2; CNS, central nervous system; COX, cyclooxygenase; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; CSF, cerebrospinal fluid; CX3CR1, CX3C chemokine receptor 1; DAMPs, damage-associated molecular patterns; GRs, glucocorticoid receptors; HPA, hypothalamic–pituitary–adrenal; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; IL-1R1, IL-1 type 1 receptor; ISG15, interferon-stimulated gene 15; KAT, kynurenine amino-transferase; KMO, kynurenine monooxygenase; KO, knockout; KYN, kynurenine; KYNA, kynurenic acid; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MDD, major depressive disorder; MKP-1, MAPK phosphatase 1; MRI, magnetic resonance imaging; MyD88, myeloid differentiation primary response 88; NAD+, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa B; NI, neuroinflammation; NLRP3, NOD-like receptor pyrin domain-containing -3; NMDA, N-methyl-D-aspartate; NPCs, neural precursor cells; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMPs, pathogen-associated molecular patterns; PET, positron emission tomography; PRRs, pattern recognition receptors; QUIN, quinolinic acid; rNSCs, radial neural stem cells; STAT3, signal transducer and activator of transcription 3; TDO, tryptophan 2,3-dioxygenase; TGF, transforming growth factor; Th17, T helper 17 cells; TLRs, Toll-Like receptors; TNF-α, Tumour necrosis factor-α; TRY, tryptophan; UCMS, unpredictable chronic mild stress; USP18, ubiquitin-specific peptidase 18.

Belzung and Camus authors contributed equally to this work.

Edited by Michel Barrot.

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.14720

that neuroinflammation may be a key therapeutic target for future therapeutic strategies in major depressive disorder.

KEYWORDS

cytokines, depression, hippocampal neurogenesis, HPA axis, kynurenine, microglia, neuroinflammation, serotonin

1 | INTRODUCTION

Major depressive disorder (MDD) is one of the most frequent and severe psychiatric conditions, with an estimated prevalence reaching 15% in the general population (Andrade et al., 2003). MDD is twice as prevalent in women compared to men (Grigoriadis & Robinson, 2007). MDD is known to dramatically increase the risk of premature death by suicide (Cheng, Chen, Chen, & Jenkins, 2000) or other general medical conditions (Jeong et al., 2013), such as vascular diseases (Brown, Stewart, Stump, & Callahan, 2011). Our understanding of the neurobiology of depression originates with the serendipitous discovery of the antidepressant properties of drugs that enhance the neurotransmission of brain monoamines (Pereira & Hiroaki-Sato, 2018). This knowledge was enriched by the discovery of two other key mechanisms of depression: alteration in the regulation of the hypothalamus–pituitary–adrenal (HPA) axis (Bao & Swaab, 2019) and the possible role of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus (Eliwa, Belzung, & Surget, 2017). However, considering that only one-third of patients suffering from MDD achieve complete remission of symptoms after a single antidepressant treatment (Trivedi et al., 2006) and that the remission rate increases up to 60% after two different antidepressant trials (Rush et al., 2006), it can be deduced that the neurobiological mechanisms of depression cannot be solely explained as the consequence of these three mechanisms. Among the other potential biological correlates, neuroinflammation (NI), which is known to be associated with several neurologic disorders such as multiple sclerosis or neurodegenerative disorders such as Alzheimer's disease (Heneka et al., 2015), has received increasing attention because animal and human studies have demonstrated that immune challenges can induce depressive-like "sickness behaviour" (Raison, Capuron, & Miller, 2006). Moreover, since the initial descriptions by Maes (Maes et al., 1995) and Levine (Levine et al., 1999), numerous studies have described the existence of a strong association between depression and peripheral markers of inflammation in both blood and cerebrospinal fluid (CSF). For example, a recent cumulative meta-analysis reported interleukin-6 (IL-6) and C-reactive protein (CRP) to be most strongly associated with depression among markers of inflammation (Haapakoski, Mathieu, Ebmeier, Alenius, & Kivimäki, 2015), with a high correlation with anhedonia and psychomotor retardation symptoms (Felger et al., 2018). Pharmacovigilance data provide additional evidence regarding the use of interferon (IFN) in the treatment of cancers or chronic viral diseases. The IFN family of proteins secreted by immune cells have immunoregulatory, anti-viral, anti-apoptotic and anti-proliferative proprieties. IFN-β has an inhibitory effect on pro-inflammatory cytokines, whereas IFN-α mainly exerts anti-viral and pro-inflammatory effects, and IFN-α has been shown as a side effect to be associated with a high rate of MDD (Capuron et al., 2002; Miyaoka et al., 1999). Further support for a link between neuroinflammation and depression, recent clinical findings report that numerous anti-inflammatory agents may have antidepressant effects. One meta-analysis pooling data from 4 randomized controlled studies investigating the effects of pro-inflammatory cytokine inhibitors against placebo, (2 with adalimumab and 2 with etanercept), showed that both treatments significantly improved depressive symptoms (Kappelmann, Lewis, Dantzer, Jones, & Khandaker, 2018). Although a randomized controlled study of the effect of infliximab against placebo failed to demonstrate any antidepressant effects, the findings suggested that a potential antidepressant response might be higher in patients with the highest level of high sensitivity-C-reactive protein (high sensitivity-CRP > 5 mg/L) at baseline. The study also found motor retardation, work and activity, suicidal thoughts and depressive mood to be the clinical symptoms that were significantly improved in the infliximab group (McIntyre et al., 2019). Another meta-analysis (Köhler-Forsberg et al., 2019) identified 36 studies including almost 10,000 patients and assessed the effects of nonsteroidal anti-inflammatory drugs (NSAIDs), cytokine inhibitors (adalimumab, ustekinumab, etanercept, ixekizumab), statins, minocycline, pioglitazone and glucocorticoids. The pooled data suggested that with the exception of pioglitazone, all anti-inflammatory drugs improved depressive symptomatology, with a good tolerability profile. Finally, another meta-analysis that pooled data from 26 randomized controlled trials involving 1,610 participants confirmed that NSAIDS, omega-3 fatty acids, statins, minocycline and modafinil all have significant antidepressant effects (Bai et al., 2019). However, the exact

mechanism by which neuroinflammation interacts with the known neurobiological mechanisms of depression remains unclear.

The aim of this review is to describe the main components of neuroinflammation and to discuss associations between neuroinflammation and the most relevant neurobiological correlates of depression: serotonin neurotransmission, HPA axis hyperactivity and hippocampal neurogenesis.

2 | IMMUNITY, CENTRAL NERVOUS SYSTEM AND NEUROINFLAMMATION

2.1 | Brain immune privilege

Immunity can be understood as a "several lines of defence" system that blocks microbial invasion or limits microbial pathogenicity, limits cancer growth and drives rejection of transplanted tissues. Through evolution, mammals have progressively acquired several types of defence systems: mechanical barriers such as the skin, epithelium or blood–brain barrier (BBB), an innate immune system that drives a non-specific early inflammatory response to infection or tissue damage through the activation of white blood cells (Turvey & Broide, 2010), and an adaptive immunity system that involves T and B lymphocytes interacting with specific unique and distinct molecular targets, that is, antigens and operating immunological memory within the lymphatic system (Anderson, Buffone, & Hammer, 2019; Bonilla & Oettgen, 2010).

The brain tissue is supposed to be protected from any entry of pathogenic agents and immune cells because of the BBB. This “immune privilege” of the brain was initially understood as a consequence of the lack of any lymphatic drainage of this organ (Cserr, Harling-Berg, & Knopf, 1992; Louveau, Harris, & Kipnis, 2015). Since then, the brain has been considered a “lawless zone” with regard to peripheral immunity influences and consequently as having its own cellular players to support immunity: oligodendrocytes, which provide support and insulation to axons of myelinated neurons; microglial cells, which act as resident innate immune response cells in the brain by scavenging damaged brain tissue and pathogenic agents; and astrocytes which are closely associated with both pericytes of the BBB and synapses of neurons, with an important role in regulating the extracellular levels of glutamate and in the dynamic control of brain microcirculation (Engelhardt, Vajkoczy, & Weller, 2017). Cells of adaptive immunity such as B and T lymphocytes appear to be limited to the CSF in brain meninges but can infiltrate brain tissue in pathological conditions by expressing chemoattractant and adhesion molecules that guide activated T cells to roll, adhere and extravasate into the perivascular space (Congdon, Sanchez-Perez, & Sampson, 2019).

2.2 | Microglial cells as support for brain innate immunity

Microglia originate in the yolk sac during the embryonal period and derive from erythro-myeloid colony stimulating factor 1 receptor precursors cells and then populate the neuroepithelium. Microglial cells share a common origin with peripheral macrophages, unlike other brain cells, and have a strong regenerative capacity to maintain sufficient numbers to carry out their functions (Czeh, Gressens, & Kaindl, 2011). These cells undergo morphological transformations with regard to their functional state. At rest and in the sentinel state, microglial cells are ramified. Microglia move towards the activated phenotype (i.e. M1 microglia), in which the activation of the NOD-like receptor pyrin domain-containing-3 (NLRP3) inflammasome stimulates secretion of chemokines and cytokines (Ślusarczyk et al., 2018), such as IL-1β, IL-6 and tumour necrosis factor-α (TNF-α), as well as other mediators of inflammation such as inducible nitric oxide synthase, cyclooxygenase (COX) and matrix metalloproteinase (Lively & Schlichter, 2018). Microglial cells also recruit additional microglia to the site of infection or brain damage for a more efficient response (Franco & Fernández-Suárez, 2015; Kumar, 2019). The other microglia phenotype, called M2 microglia, prevents M1-induced damage and neurotoxicity. The M2 phenotype is induced via uptake of apoptotic cells or myelin debris exposure as well as by anti-inflammatory cytokines (IL-4, IL-10 and transforming growth factor–TGF). M2 cells promote anti-inflammation, tissue repair and extracellular reconstruction (Tang & Le, 2016) as well as neurogenesis (Yuan et al., 2017). Confirmation that activated microglia are associated with depression was first obtained from animal studies. In particular, it has been shown that CD11b, known to be expressed by peripheral immune cells and microglia (Hoogland, Houbolt, Westerloo, Gool, & Beek, 2015), is increased in several brain structures implicated in depression, such as the hippocampus and amygdala, in mice exposed to unpredictable chronic mild stress (UCMS) (Farooq et al., 2012). This CD11b over-expression was found to be reversed by an antidepressant treatment (fluoxetine) in parallel with normalization of the behavioural and neuroendocrine changes induced by UCMS (Farooq et al., 2018). Similar results were obtained in human studies using positron emission tomography (PET) with ^{18}F- or ^{11}C-radiolabelled ligands to allow visualization of activated microglia including [^{11}C]-PBR28, [^{11}C]-PK11195 and [^{18}F]-FEPPA. Since an initial negative result comparing [^{11}C]-PBR28 PET ligand binding in 10 depressed subjects and 10

controls (Hannestad et al., 2013), a more recent study using the same ligand found that depressed subjects exhibited increased neuroinflammation compared with controls, mostly in the prefrontal and anterior cingulate cortices and in the hippocampus (Richards et al., 2018). Studies utilizing other PET ligands have reported higher [^{11}C]-PK11195 uptake in the prefrontal cortex, insula and anterior cingulate cortex in depressed drug-free patients than in healthy controls (Holmes et al., 2018). Furthermore, uptake correlated highly with the level of circulating CRP (Su et al., 2016), but [^{18}F]-FEPPA uptake correlated with the duration of untreated depression (Setiawan et al., 2018) and may be decreased by psychotherapeutic interventions in parallel with symptom improvement (Li, Sagar, & Kéri, 2018).

2.3 | Astrocytes and the blood–brain barrier

Astrocytes are the most numerous cells in the central nervous system (CNS). Long considered simple support cells for neurons, it has now been established that astrocytes ensure proper functioning of synapses and propagation of action potentials along axons (Deemyad, Lüthi, & Spruston, 2018). Similar to microglial cells, astrocytes express common pattern recognition receptors (PRRs) to combat CNS threats and are able to switch to an activated state (Guttenplan & Liddelow, 2019), for example, through lipopolysaccharide (LPS) challenge (Okada et al., 2006). Once activated, astrocytes undergo morphological changes and become hypertrophied cells able to secrete pro-inflammatory cytokines (Liddelow & Barres, 2017). These cytokines are even more relevant to neurons, as astrocytes maintain close contact with synaptic terminals and modify neuronal excitability and metabolism as well as neurotransmission. Astrocytes can also respond positively to neuroinflammation, especially to IL-1β, by secreting neurotrophic factors such as TGF-β to facilitate neuronal survival, regulate remyelination and enhance the extracellular matrix (Bélanger & Magistretti, 2009).

Astrocytes serve as major components of communication between blood microcirculation and brain tissue due to the close contact they have with the endothelial cells, pericytes and tight junctions that constitute the BBB. Activated astrocytes exhibit a decrease in glutamate internalization that negatively impacts the production of connexin 43, a major constituent of gap junctions (Gimsa, Mitchison, & Brunner-Weinzierl, 2013). Under metabotropic glutamate receptor-1 stimulation, an increase in intracellular levels of Ca^{2+} at the perivascular endfeet triggers arteriolar dilation (Cauli & Hamel, 2018; Zonta et al., 2003), ultimately enhancing BBB permeability. In particular, astrocytes can activate T lymphocytes in the blood via immunoregulatory receptor cytotoxic T-lymphocyte-associated protein 4 and induce apoptosis in defence cells via constitutive expression of Fas ligand (a transmembrane protein belonging to the TNF family). After chronic activation, astrocytes produce chemokines in high levels, such as chemokine (C-C motif) ligand 2 (CCL2), which fix peripheral immune cell receptors (CCR2) to induce extravasation and infiltration of macrophages and monocytes from the circulation (Farina, Aloisi, & Meinl, 2007; Gimsa et al., 2013).

One of the other key functions of astrocytes is to provide glucose and glutamine to neurons, both of which are precursors for glutamate synthesis, and to contribute to the reuptake of glutamate from the synaptic cleft and its degradation or recycling. Through these functions, astrocytes can significantly modulate synaptic concentration of glutamate and influence glutamate-depend functions (Malarkey & Parpura, 2008). After its release into the extracellular space, glutamate binds to ionotropic glutamate receptors (N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs)) and to metabotropic glutamate receptors on the membrane of both presynaptic and postsynaptic neurons (Popoli, Yan, McEwen, & Sanacora, 2011). Interestingly, NMDA receptor antagonism with drugs such as ketamine has strong and rapid antidepressant effects (Lener et al., 2017), suggesting that glutamate neurotransmission may have a major role in the pathophysiology of depression (Sanacora, Treccani, & Popoli, 2012). Finally, astrocytes are also key providers of adenosine triphosphate (ATP), which has been shown to be released by astrocytes (Lalo et al., 2014) following exposure to various stimuli, such as mechanical stress (Maneshi et al., 2017).

2.4 | The P2x7-Nlrp3 inflammasome cascade is a key mechanism in depression

The recognition of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) by cell-surface receptors activates several intracellular signalling pathways, such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), which control induction of pro-inflammatory cytokine synthesis, and the NLRP3 inflammasome, which cleaves pro-IL-1β and pro-IL-18 cytokines into their mature forms (Tang, Kang, Coyne, Zeh, & Lotze, 2012). NLRP3 is member of the inflammasome family, a group of intracellular multiprotein oligomer complexes that are involved in activating pro-caspase-1, which cleaves multiple substrates implicated in inflammation or cell death (Place & Kanneganti, 2018). NLRP3 is expressed in both microglial cells and peripheral immune cells. Under physiological conditions, inflammasome-induced IL-1β expression is essential as trophic support to promote long-term potentiation and memory formation (Yirmiya, Winocur, & Goshen, 2002). However, at high levels, IL-1β becomes excitotoxic, alters synaptic activity (Huang, Smith, Ibáñez-Sandoval, Sims, & Friedman, 2011)

and modulates monoaminergic and glutamatergic synaptic transmission (Hu, Sheng, Ehrlich, Peterson, & Chao, 2000; Ramamoorthy et al., 1995; Yang et al., 2019). Interestingly, it has been suggested that the antidepressant effect of ketamine that reverses LPS-induced depressive-like behaviours in mice correlates with hippocampal over-expression of NLRP3 and IL-1β (Li et al., 2019). NLRP3 activation in peripheral immune cells also induces IL-1β expression, which engages the polarization of undifferentiated CD4 + T cells into T helper 17 (Th17) lymphocytes, among other effects (Acosta-Rodriguez, Napolitani, Lanzavecchia, & Sallusto, 2007). Th17 cells can specifically release IL-17 and IL-23 to weaken BBB endothelial tight junctions and promote BBB permeability (Kebir et al., 2007).

Although LPS- or cell debris-induced inflammation is mainly mediated through activation of Toll-like receptors (TLRs) by PAMPs or DAMPs, it appears that activation of the NLRP3 inflammasome in microglial cells is mediated by potassium efflux resulting from the binding of ATP to the purinergic P2X7 receptor (Cassel & Sutterwala, 2010). The P2X7 receptor is a member of the ionotropic P2X receptor family, which are key constituents mediating the extracellular ATP signalling pathway (Jiang, Baldwin, Roger, & Baldwin, 2013). Genetic polymorphisms in the gene encoding the P2X7 receptor have been suggested to increase the risk of developing major depression or bipolar disorder (Roger et al., 2010). In accordance with this clinical observation, P2X7R knockout (KO) mice are less sensitive to stress and display a less pronounced behavioural depressive-like phenotype after LPS challenge (Csölle et al., 2013). Moreover, Blue-Brilliant-G, a non-specific antagonist of P2X7 receptors, exhibits antidepressant properties in mice in both LPS challenge (Ma, Ren, Zhang, & Hashimoto, 2014) and UCMS (Farooq et al., 2018) model of depression. Taken together, these data suggest that the non-pathogen-associated mechanism of microglial activation – so-called "sterile inflammation" – via activation of the P2X7-NLRP3 inflammasome cascade is a key neurobiological process in the pathophysiology of depression (Ratajczak et al., 2019). Nonetheless, the relevance of this process to the three best-known neurobiological correlates of depression (aminergic neurotransmission, HPA axis hyperactivation and hippocampal neurogenesis) remains to be determined.

3 | NEUROINFLAMMATION AND MAIN NEUROBIOLOGICAL MECHANISMS OF DEPRESSION

3.1 | Serotonin neurotransmission and the serotonin-kynurenine hypothesis of depression

The serotoninergic hypothesis of depression was based on data showing that serotonin metabolism is reduced in depression (Hirschfeld, 2000). According to preclinical and clinical experiments, antidepressants enhance the bio-availability of cerebral serotonin (Blier, Montigny, & Chaput, 1990; Schmidt, Fuller, & Wong, 1988; Shulman, Herrmann, & Walker, 2013). Clinical experiments have also reported that serotonin metabolism is reduced in depressed suicide subjects (Asberg, 1997) and that acute tryptophan (TRY) depletion induces mild depressive symptoms in patients who recovered from depression (Moreno et al., 2010). 5-Hydroxytryptamine (5-HT), also called serotonin, is synthetized from the amino acid tryptophan by the enzyme tryptophan hydroxylase. However, another TRY catabolism pathway involves indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), which metabolize TRY into KYN (Figure 1) (Badawy, 2017; Guillemin, 2012). The switch of TRY catabolism from pathway allowing serotonin synthesis to the KYN pathway seems to be strongly related to inflammation, as IDO, which exhibits low activity under basal conditions, was shown to be inducible by pro-inflammatory cytokines (O'Connor et al., 2009). KYN is catabolized into metabolites belonging to either an "excitotoxic pathway" or a "neuroprotective pathway". The former includes metabolites such as 3-hydroxy-kynurenine (3-HK), 3-hydroxy-anthralinic acid and quinolinic acid (QUIN), a glutamate NMDA receptor agonist and the end-point co-enzyme nicotinamide adenine dinucleotide (NAD+) as end-point. These last two molecules have strong neurotoxic properties: QUIN due to its potent agonistic effect on glutamatergic neurotransmission and NAD + as a potent pro-oxidative compound (Guillemin, 2012; Schwarcz, Bruno, Muchowski, & Wu, 2012). The kynurenine monooxygenase (KMO) enzyme that converts KYN to 3-HK is weakly expressed in neurons (Guillemin et al., 2007) but is predominantly expressed in immunocompetent cells: macrophages, monocytes and microglial cells (Guillemin, Smythe, Takikawa, & Brew, 2005). It is generally accepted that the "excitotoxic pathway" is weakly active under normal conditions but strongly induced during inflammation (Schwarcz & Stone, 2017). KYN can also be metabolized via a "neuroprotective pathway" to kynurenic acid (KYNA) by the enzyme kynurenine–amino-transferase, which is mainly expressed by astrocytes (Schwarcz et al., 2012). Unlike QUIN, KYNA has neuroprotective effects (Jhamandas, Boegman, Beninger, Miranda, & Lipic, 2000) through the same glutamatergic targets but with an opposing effect. Indeed, it exerts its protective effect by its antagonistic action on NMDA glutamatergic receptors and by reducing extracellular release of glutamate (Konradsson-Geuken et al., 2010; Wu et al., 2010). Therefore, it has been proposed that the homoeostasis of glutamatergic neurotransmission can be dynamically regulated by the ratio QUIN/KYNA, respectively synthetized by microglial cells and astrocytes (Barone, 2019; Schwarcz & Stone, 2017).

Activation of the KYN pathway by inflammation has been demonstrated in both clinical human and preclinical animal

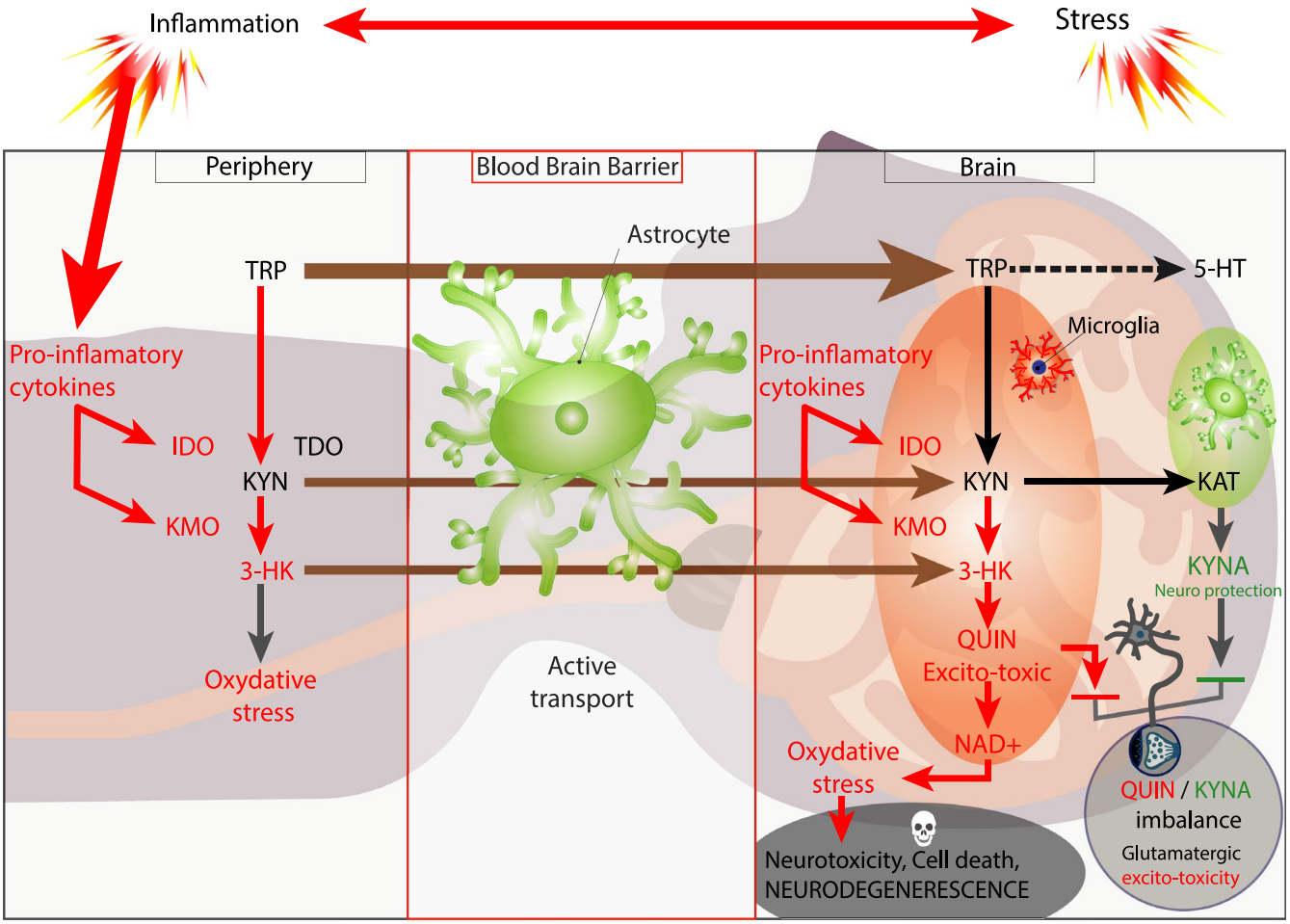

FIGURE 1 A first catabolic step of the kynurenine pathway is mediated by the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) which metabolize TRY into KYN. KYN is subsequently converted into metabolites having modulatory effects on glutamatergic neurotransmission: either the "excitotoxic" branch or the "neuroprotective" branch. In the excitotoxic branch, 3-hydroxy-kynurenine (3-hydroxy-kynurenine) is metabolized into quinolinic acid (QUIN) by the enzyme kynurenine 3-monooxygenase (KMO), and subsequently to 3-Hydroxy-Anthralinic acid by kynureninase, then to quinolinic acid (QUIN) and the end-point metabolite NAD+. In the neuroprotective branch, KYN is metabolized into kynurenic acid (KYNA) by the enzyme kynurenine amino-transferase (KAT). In the brain, the generally accepted view holds that brain KP is mainly glial rather than neuronal

studies. Excitotoxic metabolites and/or reductions in neuroprotective metabolites in plasma or CSF samples have been reported for patients with MDD (Ogawa et al., 2014) and suicide attempters (Messaoud et al., 2018; Sublette et al., 2011). In addition, the KYN/TRY ratio (an indicator of the activation of the first step of the KYN pathway) was found to be increased in the plasma and CSF of patients having received IFN-α and to correlate with the intensity of depressive symptoms (Raison et al., 2010). In suicide attempters, a long-term dysregulation of the KYN pathway towards the excitotoxic component was also observed, and the symptom intensity was coupled to an increased inflammatory load (Bay-Richter et al., 2015). Activation of the KYN pathway also occurs in various depression subtypes such as immunotherapy-related depression (Capuron et al., 2002), post-partum depression (Kohl et al., 2005), cardiovascular disease-related depression (Swardfager et al., 2009), depression episodes in bipolar disorders (Wurfel et al., 2017), depression in patients with suicidal behaviour (Brundin, Bryleva, & Thirtamara Rajamani, 2017) and depression resistant to antidepressant drugs (Serafini et al., 2017). Results from post-mortem studies have provided evidence to support these clinical data. A reduction in KYN pathway metabolism in the prefrontal cortex of patients with MDD (Clark et al., 2016) and a reduction in QUIN in the hippocampus (right CA1) of depressed subjects (Busse et al., 2015) have been shown. Moreover, severe depression was associated with increased microglial QUIN in the anterior cingulate gyrus of depressed subjects (Busse et al., 2015), suggesting activation of the excitotoxic branch of the KYN pathway in MDD patients with suicide behaviours. Finally, the link between inflammation, KYN pathway excitotoxic component imbalance and morphological brain abnormalities found in depressed patients has been strengthened by an advanced study reporting that imbalance in neuroprotection/neurotoxicity may explain,

at least partially, the morphologic reductions in the prefrontal cortical thickness in MDD patients and that these changes may be strongly associated with the levels of neuroactive KYN metabolites (Meier et al., 2016).

Preclinical studies have confirmed that the KYN pathway is activated by inflammatory challenge, and both IDO (Dostal, Carson Sulzer, Kelley, Freund, & McCusker, 2017) and KMO (Connor, Starr, O'Sullivan, & Harkin, 2008) are activated by pro-inflammatory cytokines. LPS challenge activates the enzyme IDO (Dobos et al., 2012) as well as the microglial enzyme KMO (Walker et al., 2013), strengthening the bias of the KYN pathway towards its deleterious excitotoxic component. Transgenic KMO−/− mice were shown to not develop LPS-induced depressive-like behaviours, whereas direct administration of the QUIN precursor 3-HK caused these depression-like behaviours (Parrott et al., 2016). In addition, pharmacological blockade of IDO by peripheral administration of the IDO inhibitor 1-methyl tryptophan suppressed depressive-like behaviour in mice induced by both LPS challenge (Dobos et al., 2012; O'Connor et al., 2009) and chronic stress (Laugeray et al., 2016).

3.2 | HPA axis

It has been known for decades that one of the strongest biological correlates of MDD is dysregulation of the HPA axis, including glucocorticoid hypersecretion and alterations in its negative feedback (Nemeroff & Evans, 1984; Vreeburg et al., 2009). These findings are particularly relevant for the discussion, as there are manifold mutual interactions between the HPA axis, inflammation and the immune system.

3.2.1 | HPA axis dysfunction in MDD

The HPA axis represents the canonical stress hormone system that orchestrates the release of glucocorticoids by the adrenal glands in response to environmental or endogenous stressors. Once released, glucocorticoids can function in virtually all parts of the body and regulate a broad range of physiological processes through the genomic and non-genomic effects of glucocorticoid receptors (GRs) (Stahn & Buttgereit, 2008). Among these effects, glucocorticoids are able to influence metabolic, cardiovascular, immunological and cognitive functions. This system is therefore pivotal in the response to stress and in homoeostasis regulation. In addition to these physiological actions, glucocorticoids can instigate negative feedback on the HPA axis at multiple levels: directly on the components of the axis and indirectly via brain structures such as the hippocampus, prefrontal cortex and amygdala (Ulrich-Lai & Herman, 2009).

HPA axis abnormalities have been observed in a significant proportion of depressed patients, ranging from 35% to 65%, and are essentially characterized by exaggerated glucocorticoid release and/or increased expression of the adrenocorticotropic hormone (ACTH) secretagogue corticotropin-releasing hormone (Holsboer, 2000; Swaab, Bao, & Lucassen, 2005). These findings are supported by data demonstrating higher plasma, salivary and urinary glucocorticoid concentrations in depressed patients, changes in GR expression or in their functional effects, and higher weight and sensitivity of the adrenal glands to ACTH (leading to higher glucocorticoid release) (Gillespie & Nemeroff, 2005; Holsboer, 2000; Pariante, 2003, 2017). Most such HPA axis dysregulation is believed to be primarily driven by disruptions of the GR-dependent negative feedback of the HPA axis (i.e. GR resistance) because in a large proportion of MDD case, a reduced capacity to decrease glucocorticoid secretion in response to dexamethasone, a GR agonist, is observed. Interestingly, dexamethasone suppression is restored after effective antidepressant therapies (Ising et al., 2007), and this effect appears to be critical for antidepressant effects, given that the negative feedback improvements precede remission of depressed patients with HPA axis abnormalities. Moreover, normalization of HPA axis hyperactivity occurs after successful electroconvulsive therapy (Kling et al., 1994).

3.2.2 | Interactions between the HPA axis and immune system

The HPA axis exploits of the versatile effects of glucocorticoids to help organisms cope with any situation that might challenge homoeostasis. Among these effects, the immunomodulatory actions of glucocorticoids are essential for maintaining balance, even in high-risk situations. Glucocorticoid immunomodulatory effects are widespread, complex and multifaceted, targeting nearly all cell types and functions of immune systems (Bellavance & Rivest, 2014; Busillo & Cidlowski, 2013).

Anti-inflammatory properties of glucocorticoids

The anti-inflammatory and immunosuppressive effects of glucocorticoids have been known for decades, and accordingly, synthetic glucocorticoids such as prednisone or dexamethasone have been widely used to treat several pathological chronic inflammation conditions (Becker, 2013). These effects are believed to be underpinned by a series of genomic and non-genomic GR actions on factors involved in inflammation activation, maintenance and regulation of both innate and adaptive immune responses. Specifically, the anti-inflammatory effects of glucocorticoids are primarily elicited via GR-mediated trans-repression of key inflammatory transcription factors such as the NF-κB activator protein 1 (AP-1) pathway (De Bosscher, Vanden Berghe, & Haegeman, 2003; Newton & Holden, 2007), resulting in reduced expression of pro-inflammatory genes including chemokines and cytokines such as IL-1β, IL-6 and TNF-α (Cruz-Topete

& Cidlowski, 2015; Tuckermann et al., 2007). The mechanisms underlying these genomic effects include the following: (a) GR binding to glucocorticoid response elements in the promoter region of pro-inflammatory genes, negatively modulating AP-1 transcriptional activity; (b) direct GR interaction (tethering) with p65 and c-jun, subunit elements of NF-κB and AP-1, respectively, resulting in repression of their transcriptional activity; and (c) recruitment of histone deacetylases to NF-κB-dependent promoters. Moreover, other genomic actions of GR can occur through activation of anti-inflammatory genes. For instance, glucocorticoids have been shown to promote tristetraprolin, which is able to destabilize the mRNA of many pro-inflammatory cytokines (Carrick, Lai, & Blackshear, 2004; Smoak & Cidlowski, 2006). Immunosuppressive activities of glucocorticoids also include non-genomic activities based on direct interaction with membrane proteins and negative regulation of pro-inflammatory signalling pathways, such as GR-mediated activation of MAPK phosphatase 1 (MKP-1), inhibiting MAPK signalling and preventing expression of many pro-inflammatory factors (Ayroldi et al., 2012; Busillo & Cidlowski, 2013). Taken together, these effects can impact the immune response at physiological and cellular levels. In particular, the immunosuppressive effects of glucocorticoids can induce apoptosis in immune cells such as T lymphocytes, neutrophils, basophils and eosinophils (Sorrells & Sapolsky, 2007).

Regardless, one important question is how do the anti-inflammatory effects of glucocorticoids interact with HPA axis abnormalities and glucocorticoid hypersecretion in patients with MDD, particularly in the light of the neuroinflammation hypothesis of depression. At first glance, both effects may seem irreconcilable, but several mechanisms and observations may actually provide explanations for these apparent discrepancies in glucocorticoid functions in patients with MDD, especially when considering the potential pro-inflammatory effects of glucocorticoids, as described below.

Pro-inflammatory properties of glucocorticoids

In addition to well-established anti-inflammatory actions, accumulating evidence indicates that glucocorticoids exhibit pro-inflammatory properties (for a review see Cruz-Topete & Cidlowski, 2015). At least three mechanisms that putatively support such pro-inflammatory glucocorticoid actions have been proposed to date. All of them focus on the genomic effects of GRs and on the induced expression of immune-related genes promoting pro-inflammatory responses (Chinenov & Rogatsky, 2007; Galon et al., 2002).

First, glucocorticoids have been shown to activate TLR pathways and to increase expression of several members of the TLR family critical for inflammation induction, including TLR2 and TLR4 (Chinenov & Rogatsky, 2007; Hermoso, Matsuguchi, Smoak, & Cidlowski, 2004; Homma et al., 2004). These findings are remarkable considering that glucocorticoid actions have generally been associated with TLR attenuation (rather than activation), notably via GR-mediated MKP-1 activation. Furthermore, it appears that pro-inflammatory glucocorticoid effects can be strongly potentiated in the presence of pro-inflammatory cytokines such as TNF-α and leukaemia inhibitory factor, a cytokine related to the IL-6 family. A synergistic action between glucocorticoids and these cytokines has been shown to stimulate pro-inflammatory pathways, including the induction of factors such as TLR2, TLR4, SerpinA3 and signal transducer and activator of transcription 3 (STAT3) target genes (Bornstein et al., 2004; Langlais, Couture, Balsalobre, & Drouin, 2008; Lannan, Galliher-Beckley, Scoltock, & Cidlowski, 2012).

Second, glucocorticoids have been reported to promote expression of P2Y2 purinergic receptors, activation of which by ATP leads to IL-6 secretion by endothelial cells, contributing to inflammation and the immune response (Ding, Gao, Jacobson, & Suffredini, 2010).

A third putative mechanism involves inflammasome regulation through genomic actions of GR. Specifically, glucocorticoids promote expression of the NLRP3 gene. By facilitating NLRP3 induction and inflammasome formation, glucocorticoids promote activation of the inflammatory response and the release of pro-inflammatory cytokines such as IL-1β (Busillo, Azzam, & Cidlowski, 2011).

Chronic stress and depression promote the pro-inflammatory action of glucocorticoids

One circumstance under which the pro-inflammatory properties of glucocorticoids seem privileged is stress. Indeed, the pro-inflammatory actions of glucocorticoids appear to be exacerbated in animals exposed to acute or chronic stress, indicating that distinct glucocorticoid effects on inflammation may depend on circumstances (Bellavance & Rivest, 2014). The fact that the pro-inflammatory effects of glucocorticoids may surpass their anti-inflammatory effects within the context of stress (Dantzer, 2018) is particularly relevant for patients with MDD, as stress is a major risk factor for MDD. Chronic stress has reliably been associated with HPA axis abnormalities along with the salient features of inflammation in patients and animal models (Espinosa-Oliva et al., 2011; Farooq et al., 2018; Laugeray et al., 2016; Pariante, 2017; Surget et al., 2011). This, may at least partly explain why HPA axis hyperactivity and inflammation can coexist in patients with MDD, leading to high levels of glucocorticoids along with inflammatory markers such as IL-1, IL-6, TNF-α and CRP and microglial activation in the same patients (Cattaneo et al., 2013).

Another aspect of the relationship between the HPA axis and inflammation in MDD is linked to the GR deficiency observed in patients and animal models (Pariante, 2017). Indeed, disruption of HPA axis negative feedback in those with MDD has been attributed to impaired GR functions caused by GR

desensitization and defective responsivity. As such, even under high levels of glucocorticoid, GR is unable to fulfil its regulatory control over HPA axis activity and therefore to reduce glucocorticoid release (Surget et al., 2011). Hence, it is possible that such GR functional deficits apply not only to their regulatory role with regard to the HPA axis but also to other GR functions, including immunomodulatory actions. In this case, GRs may also become unable to exert their anti-inflammatory actions even under high glucocorticoid levels, resulting in the elevation of pro-inflammatory cytokines and neuroinflammation in those with MDD. This possibility has indeed been supported by several clinical results showing, for example, that (1) elevated glucocorticoid levels and inflammation may occur in the same depressed patients and (2) GR resistance is observed in these patients and applies to both the HPA axis and inflammatory responses (Carvalho, Garner, Dew, Fazakerley, & Pariante, 2010; Cattaneo et al., 2013).

Reciprocal interactions exist between the hpa axis and immune systems

Finally, if the HPA axis and glucocorticoids are generally considered to regulate the immune response, diverse mediators of the immune system can similarly modulate HPA axis activity. More specifically, pro-inflammatory cytokines have been shown to promote activation of the HPA axis and elicit glucocorticoid release (Rivest, 2010). This is the case when pro-inflammatory cytokines are produced in the brain during neuroinflammation and can therefore directly trigger activation of the HPA axis by their effects on hypothalamic cells. Peripheral, circulating inflammatory mediators also affect HPA axis activity, reaching the hypothalamus directly through the endothelium of the circumventricular organs or an altered BBB (Bellavance & Rivest, 2014) or indirectly through afferent fibres from the vagus nerve conveying information about peripheral inflammation (Sternberg, 2006; Tracey, 2009). Alternatively, findings indicate that peripheral inflammatory mediators also lead to parenchymal release from brain capillaries involving myeloid differentiation primary response88 (MyD88), COX-1, COX-2 and prostaglandin E_2 and relaying stimulatory signals to the HPA axis (Elander et al., 2009; García-Bueno, Serrats, & Sawchenko, 2009; Serrats et al., 2010).

3.3 | Neurogenesis and neuroplasticity

3.3.1 | Adult hippocampal neurogenesis

It is now well established that neurogenesis persists during adulthood. However, the generation of new-born neurons in adults is restricted to some brain areas known as adult neurogenic niches, namely, the subventricular zone of the lateral ventricles and the sub-granular zone of the dentate gyrus of the hippocampus (Altman, 1962; Altman & Das, 1965; Eriksson et al., 1998). There has been some debate regarding the persistence of this phenomenon in the hippocampus of humans during adulthood, with some authors claiming that it is limited to childhood/early adolescence (Sorrells et al., 2018). Nevertheless, convincing data now strongly support the idea that this process is still present in adults (Boldrini et al., 2018, 2019; Moreno-Jiménez et al., 2019; Spalding et al., 2013). The birth of new neurons during adulthood undergoes a sequential process, starting with radial neural stem cells (rNSCs), which produce a copy of themselves together with neuroprogenitor (also known as type 2 cells) amplification (Bonaguidi et al., 2011; Encinas et al., 2011). Type 2 cells divide and differentiate into neuroblasts that generate immature neurons, which become mature granule cells. In total, the entire process takes approximately 8 weeks (Toda, Parylak, Linker, & Gage, 2019) and is strongly stimulated by brain-derived neurotrophic factor (BDNF) (Li, Jiang, Zhang, & Chen, 2009), a neurotrophic factor expressed in various brain regions that also has significant effects on neuronal plasticity (Cheng et al., 2011; Wang et al., 2015).

3.3.2 | Adult neurogenesis, depression and antidepressants

Several findings have led to the idea that adult hippocampal neurogenesis may be crucial in the pathophysiology of depression as well as in its aetiology and in the effects of antidepressant drugs (see Eisch & Petrik, 2012; Eliwa et al., 2017; Tanti & Belzung, 2013a, 2013b for extensive reviews). This claim is supported by the following findings: (a) adult hippocampal neurogenesis is decreased both in animal models of depression and in human subjects undergoing a depressive episode; (b) chronic antidepressant drugs induce an increase in adult hippocampal neurogenesis; (c) an experimentally induced increase in adult hippocampal neurogenesis dampens the ability of stress to induce a depressive-like phenotype, whereas a decrease in adult neurogenesis alters stress sensitivity; and (d) ablation of hippocampal neurogenesis prevents the ability of antidepressants to induce remission. It should be noted, however, that the picture is more complex, as remission can also be induced independently from neurogenesis suggesting that the lack of neurogenesis does not elicit depression in a direct/linear way. Thus, any factor that decreases adult hippocampal neurogenesis might induce depressive-like behaviour. Neuroinflammation is one such factor.

3.3.3 | Neuroinflammation and neurogenesis

In fact, adult hippocampal neurogenesis is altered by several factors that induce neuroinflammation related depressive-like

behaviours, including LPS or IFN-α. LPS, which elicits depressive-like behaviours as well as neuroinflammation, attenuates adult hippocampal neurogenesis in rodents (Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003; Fujioka & Akema, 2010; Monje, Toda, & Palmer, 2003; Wu et al., 2007; Zonis et al., 2013) together with a decrease in BDNF expression (Guan & Fang, 2006; Lapchak, Araujo, & Hefti, 1993). More precisely, chronic LPS reduces the dendritic length and postsynaptic cluster density of immature new-born granule cells in the hippocampus in mice (Llorens-Martín et al., 2014). This is also observed after IFN-α injection, which alters hippocampal cell proliferation (Cai et al., 2019; Kaneko et al., 2006; Zheng et al., 2014), survival (Cai et al., 2019) and neuronal differentiation (Zheng et al., 2014) in both rats and mice.

3.3.4 | Neurogenesis and microglia

How can neuroinflammation induced decreases in adult hippocampal neurogenesis be explained? Microglial cells seem to be key players, as LPS-induced microglial activation inhibits hippocampal neurogenesis (Ekdahl et al., 2003; Monje et al., 2003). Adult new-born neurons are regulated by different components of the neurogenic niche, including microglia and astrocytes (Gonçalves et al., 2016; Hanisch & Kettenmann, 2007; de Miranda, Zhang, Katsumoto, & Teixeira, 2017; Sofroniew, 2015). Interestingly, within the neurogenic niche, microglia establish close contacts with all cells involved in the generation of new neurons, from rNSCs to neuroblasts and adult-born neurons themselves (Sierra et al., 2010). More precisely, microglia eliminate apoptotic adult adult-born neurons and neuroblasts through phagocytosis (Sierra et al., 2010). Furthermore, the survival of adult new-born cells requires that they become assimilated into a functional network, developing axonal and dendritic contacts. Several animal studies have suggested that microglia are involved in dendritic tree sprouting and in shaping the axonal terminals of adult-born granule cells as well as in the generation and elimination of the excess of synaptic contacts established by maturing granule cells from 2 to 8 weeks, a time when these cells undergo structural synaptic remodelling (Bolós et al., 2018). Thus, microglia participate in modulating adult-born neurons as well as mature granule cell connectivity. Regarding molecular mechanisms underlying these effects, a candidate process involves CX3C chemokine receptor 1 (CX3CR1), also known as fractalkine receptor or G-protein coupled receptor 13. For instance, neurogenesis is decreased in CX3CR1 KO mice (Rogers et al., 2011); more precisely, the density of dendritic spines of hippocampal adult-born granule cells is reduced in CX3CR1 KO mice (Bolós et al., 2018).

3.3.5 | Cell and molecular underpinnings of neuroinflammation-induced neurogenesis alteration

Inflammation might affect neurogenesis via several putative pathways. The main contributor to inflammatory-related decreases in adult hippocampal neurogenesis is related to microglia-induced release of pro-inflammatory cytokines, including TNF-α, IFN-α, IL-1β and IL6. Specifically, in 2003, Monje and colleagues showed that LPS-induced inflammation inhibits adult hippocampal neurogenesis via microglial release of IL-6 and TNF-α in rats (Monje et al., 2003). This was because the neurogenic lineage displayed higher sensitivity to pro-inflammatory agents than did the gliogenic lineage (Monje et al., 2003). The mechanisms underlying the effects of IFN-α were also elucidated, with IFN-α increasing interferon-stimulated gene 15 (ISG15), ubiquitin-specific peptidase 18 (USP18), and IL-6 expression. Co-treatment with a combination of ISG15, USP18 and IL-6 is sufficient to reduce neurogenesis on human hippocampal progenitor cell line (Borsini et al., 2018); therefore, this mechanism explains the anti-neurogenic effects of IFN-α. However, most efforts have concentrated on the molecular cascade underlying the effects of IL-1β. Indeed, direct exposure to IL-1β or to its inducers LPS and IFN-α decrease hippocampal neurogenesis and promote depressive-like behaviours in mice (Goshen et al., 2008; Koo & Duman, 2008) and rats (Kaneko et al., 2006; Monje et al., 2003), as found to occur after both acute in vitro injection (Green & Nolan, 2012; Ryan, O'Keeffe, O'Connor, Keeshan, & Nolan, 2013; Zunszain et al., 2012) or acute in vivo administration (Goshen et al., 2008; McPherson, Aoyama, & Harry, 2011) of IL-1β. Conversely, chronic IL-1β infusion into the dorsal hippocampus of mice for 4 weeks via osmotic mini-pumps decreased the number of hippocampal immature new-born neurons (Goshen et al., 2008). Similarly, transgenic over-expression of IL-1β in the dentate gyrus reduced immature granule cell levels (Wu et al., 2012), which was also found in a human hippocampal progenitor cell line (Borsini et al., 2018). Furthermore, it has been shown that chronic IL-1β over-expression impairs the complexity of neurites of immature new-born neurons of adult male rats (Hueston et al., 2018) and that IL-1β regulates both proliferation and differentiation of neural precursor cells (NPCs) from rat brain (Wang et al., 2007). Interestingly, the detrimental effects of IL-1β on neurogenesis can be counteracted by antidepressants, as it was found that sertraline and venlafaxine dampen the reduction in immature granule cells elicited by IL-1β (Borsini et al., 2018). These effects of IL-1β may be related to the fact that the cytokine is expressed at high levels within the hippocampus (Ban, Milon, Prudhomme, Fillion, & Haour, 1991; Parnet et al., 1994), possibly mediated through the IL-1 type 1 receptor (IL-1R1). In fact, NPCs express IL-1R1, suggesting that IL-1β may act

directly on these cells (Green et al., 2012; Ryan et al., 2013), and it has been shown in a mouse model of viral encephalitis recovery that the detrimental effect of IL-1β on neurogenesis can be prevented by IL-1R1 antagonism (Garber et al., 2019). Others have explored the molecular mechanisms underlying the effects of IL-1β, showing that IL-1β activates STAT3 in NPCs, leading to a decrease in cell differentiation (Chen et al., 2013). Additionally, inhibition of the STAT3 pathway rescues neuronal differentiation in vitro, suggesting that this molecular pathway might be causal (Chen et al., 2013).

4 | DISCUSSION

As reviewed above, both preclinical and clinical data show that neuroinflammation is strongly associated with depression (main findings are recapitulated in Tables 1 and 2). Interestingly, inflammation may be one of causes for the higher prevalence of depression in women, as the prevalence of autoimmune diseases (Whitacre, 2001) like depression (Grigoriadis & Robinson, 2007) is twice as high in women than in men, and these findings may reflect gender differences in basal immune activity (Chapman et al., 2009). The gender difference in terms of prevalence of MDD begins in adolescence and does not appear to be related to sex hormones (Kessler, 2003) but rather to higher sensitivity to stressful life events (Kendler, Thornton, & Prescott, 2001) or childhood psychosocial stress (Takizawa, Danese, Maughan, & Arseneault, 2015), which may be attributed to inflammation. In support of this hypothesis, women exposed to an experimental endotoxin challenge (single injection of a low dose of endotoxin from *Escherichia coli*) displayed increased levels of depressed mood and feeling of social disconnection compared to those who received placebo (Moieni et al., 2015). However, other clinical data did not confirm the potential role of this inflammatory component, as anti-inflammatory compounds (and particularly celecoxib and omega-3 fatty acids in monotherapy) were found to have no significant antidepressant effects in women, as might have been expected (Bai et al., 2019).

TABLE 1 Clinical evidence of neuroinflammation hypothesis in major depressive disorder

Clinical evidence
Increased circulating pro-inflammatory cytokines found in patient with treatment resistance depression
Cytokines therapy in cancer patient and interferon therapy in patient with hepatitis C can induce depressive symptoms
Imbalance in kynurenine metabolites pathways found in blood of depressed patient
Anti-inflammatory compounds have antidepressant effects
PET imaging shows activated microglia is depressed subject

Nonetheless, attempts to integrate together the different lines of evidence supporting the association of neuroinflammation, serotonin/kynurenine pathways, HPA axis and depression result in an incomplete picture. As an example, in response to the question of how inflammation may reduce serotonin brain availability, an initial "kynurenine" hypothesis of depression was proposed (Lapin, 2003) that suggested the existence of a shunt of the TRY catabolism pathway in favour of the KYN pathway. Subsequently, a "new 5-HT hypothesis of depression" put forward (Maes, Leonard, Myint, Kubera, & Verkerk, 2011), whereby increased levels of glucocorticoids, systemic inflammation and cell-mediated immune activation preferentially displace TRY catabolism towards the KYN pathway through a stimulating effect on TDO/IDO enzymes. Therefore, the serotoninergic hypothesis has been reconsidered within a serotonin-kynurenine-inflammatory hypothesis of depression, with the kynurenine pathway being connected with a more general "inflammatory hypothesis" of depression (Savitz, 2019). In addition, clarifying whether neuroinflammation is a consequence of MDD or a key aetiological factor causing depression appears to be a chicken-or-egg dilemma. For instance, the TRY catabolism pathway may be displaced towards its KYN pathway by inflammation,

TABLE 2 Roles of neuroinflammation in the physiopathology of major depressive disorder

Physiopathology
Neuroinflammation (NI) is mainly supported by microglial cells and astrocytes
NI results from activation of immune cells through stimulation of Pattern Recognition Receptors (PRR) such as Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) including Toll-like receptors, P2X7 receptors…
Specific Pathogen-Associated Molecular Patterns (PAMPs) like lipopolysaccharide can trigger pro-inflammatory cytokines and lead to "sickness behaviour"
NI alters serotonin synthesis in switching tryptophan (TRY) catabolism in favour of Kynurenine (KYN) synthesis which metabolite Quinolinic Acid increases Glutamate neurotransmission
Chronic stress may switch Glucocorticoids (GCs) towards pro-inflammatory effects by activation of Toll-like receptors or ATP gated Purinergic receptors and increased expression of NLRP3 Inflammasome
Chronic stress induced altered hippocampal neurogenesis is mediated by NI through activation of IL1 receptor of progenitor cells and alteration of the Brain-Derived Neurotrophic Factor (BDNF) expression
"Sterile inflammation" may be triggered by ATP stimulation of P2X7 receptor and activation of the P2X7 inflammasome pathway in particular through mechanical stress due to the impact of chronic stress on vascular function

yet its excitotoxic branch contributes, in turn, to enhance the inflammatory process.

Regarding the role of glucocorticoids in MDD, we cannot exclude the possibility that neuroinflammation in MDD is fuelled by HPA axis abnormalities and glucocorticoid hypersecretion; however, it is also possible that HPA axis abnormalities originate directly from neuroinflammation. It is clear from recent findings that glucocorticoid actions on immune systems are not limited to a monolithic anti-inflammatory effect, as previously believed (Busillo & Cidlowski, 2013). Instead, they provide elaborate regulation of the immune system with the possibility of finely tuning levels of anti-inflammatory and pro-inflammatory factors depending on circumstances, and glucocorticoids interact with other immunological molecules. It has been proposed that these apparently opposite dual actions of glucocorticoids act in concert to prepare the immune system to react to stressors through pro-inflammatory effects and to restore homoeostasis through its anti-inflammatory effects (Busillo & Cidlowski, 2013). Regardless, this suggestion is speculative, and it is therefore important to better understand how these two properties of glucocorticoids are dynamically balanced during immune responses and under stressors and to identify what circumstances may favour one or the other of the glucocorticoid actions. Considering the crosstalk between these HPA axis and immune response systems, it remains likely that the dysregulation of one will affect the other and that abnormalities in both systems may fuel each other in disorders such as depression.

In a similar manner, two different pathways may link neurogenesis, neuroinflammation and depression: (a) a direct pathway, in which neuroinflammation directly causes a reduction in neurogenesis, which in turn leads to depressive-like behaviours; and (b) an alternative pathway, according to which neuroinflammation and neurogenesis loss each independently contribute to the occurrence of depression. Abundant literature provides a large amount of evidence for the first proposal. Accordingly, neuroinflammation and the associated pro-inflammatory cytokines TNF-α, IL-1β and IL-6 cause a loss of hippocampal neurogenesis, which may promote depressive-like behaviours (Borsini et al., 2018; Monje et al., 2003). However, as mentioned above, neurogenesis loss does not always linearly induce depressive-like phenotypes. Thus, it may be that other factors triggered by neuroinflammation, including activation of the kynurenine pathway and excess glucocorticoids, synergize with neurogenesis loss, producing a depressive-like state. In this case, the neuroinflammation related decrease in adult neurogenesis would not be sufficient to induce depression but would act together with these other factors in a cumulative way. In this sense, one might propose that depression is not a unitary phenomenon. Indeed, some forms of depression would be caused by accumulation of (a) the activation of the excitotoxic branch of the kynurenine pathway; plus (b) dysfunction of the HPA axis regulation; plus (c) decrease of hippocampal neurogenesis, whereas others might, for example, be related to another combination, including neurogenesis reductions with, for example, increased activity of brain areas associated to depression like the ventromedial prefrontal cortex, cingulate cortex or insula (Savitz, 2017; Thomson & Craighead, 2008). These different forms would potentially be alleviated via different therapeutic options.

At this stage, a picture emerges in which an altered KYN pathway in favour of its excitotoxic component and HPA axis dysregulation have the common effect of increasing extracellular glutamate and glutamate neurotransmission, which in turn can alter neurogenesis. This pathophysiological cascade seems to be triggered or sustained and reinforced by any chronic inflammatory conditions with increased circulating markers of inflammation being able to cross the BBB and activate microglia. One of the most convincing arguments in favour of peripheral inflammation as a causative factor of depression is the temporal relationship between the two phenomena. Several pathological chronic inflammatory conditions, such as cancer, cardiovascular diseases, obesity and type II diabetes, have been shown to be risk factors for depression, and this risk appears to be related to high levels of circulating CRP, IL-1 or IL-6 (Howren, Lamkin, & Suls, 2009). Additionally, gut dysbiosis, resulting from the interruption in the balance of microbiota, has been suggested to favour neuropsychiatric disorders such as Alzheimer's disease or depression (Luca, Mauro, Mauro, & Luca, 2019; Petersen & Round, 2014). Indeed, the BBB protects the brain tissue from any contact with peripheral immune cells, but under pathological conditions such as ischaemia (Ju et al., 2018) or chronic inflammation associated with ageing (Elahy et al., 2015) or chronic pain (Brooks, Hawkins, Huber, Egleton, & Davis, 2005), alterations in the BBB and blood/CSF permeability allow immune cells to penetrate the brain (Grønberg, Johansen, Kristiansen, & Hasseldam, 2013; Hickey, Hsu, & Kimura, 1991; Price et al., 2004). Moreover, it has been demonstrated that peripheral LPS challenge induces TNF-α synthesis in the liver and increases serum TNF-α, which then crosses the BBB to activate brain microglia and induce cytokines and other pro-inflammatory factors (Qin et al., 2007).

Despite strong evidence to suggest that peripheral inflammation can trigger or strengthen the pathophysiological cascades causing neuroinflammation, it is more difficult to understand how depression can be initiated by a primary neuroinflammation that secondarily triggers and/or sustains the pathophysiological cascades and increases peripherally circulating inflammatory factors. One possible explanation is to consider neuroinflammation as the consequence of a brain disease such as a neurodegenerative disorder or cerebrovascular disease. A very large amount of data suggest that depression might be a risk factor or precede the clinical symptoms of both Alzheimer's disease (Tan et al., 2019)

and Parkinson's disease (Wang, Mao, Xiang, & Fang, 2018); moreover, both neurodegenerative disorders that have been shown to be associated with microglial activation (Ghadery et al., 2019; Hamelin et al., 2018). Similarly, depression, particularly depression in old age, has been suggested to be related to vascular abnormalities, as revealed by magnetic resonance imaging white matter hyperintensities (van Agtmaal, Houben, Pouwer, Stehouwer, & Schram, 2017) that correlate with inflammatory markers (Frodl & Amico, 2014). It is also possible to consider the potential role of "sterile neuroinflammation" in the absence of any neurodegenerative or cerebrovascular disease. A possible explanation arises from considering the impact of chronic stress on vascular function and the critical role of the neurovascular unit. For example, mice experiencing UCMS-induced behavioural changes that were reversed by the antidepressant fluoxetine exhibited subsequent changes in vascular reactivity and endothelial dysfunction that were independent of those attributable to ageing (Isingrini, Belzung, d'Audiffret, & Camus, 2011). In fact, these changes were related to a nitric oxide-dependent vasorelaxation mechanism (Isingrini, Belzung, Freslon, Machet, & Camus, 2012), which is known to be mediated by NMDA receptor activation (Garthwaite, Charles, & Chess-Williams, 1988). Chronic stress also reduces expression of claudin-5 in the nucleus accumbens, which alters BBB permeability and facilitates entry of IL-6 into the brain (Menard et al., 2017). Similarly, endothelial cells reportedly mediate communication between circulating monocytes and microglial cells in mice exposed to a repeated social defeat protocol that induced neuronal activation, cell adhesion expression, recruitment of circulating monocytes and microglial activation, all of which were prevented by prior administration of clonazepam (McKim et al., 2018). A similar study suggested that this notion that monocyte recruitment is needed to direct the impact of astrocytes on arteriolar dilation may also been considered as a potential factor of blood and brain communication and a key component of glucose transport from blood circulation to astrocytes and neurons. This vasodilatation effect was shown to be mediated by glutamate (Zonta et al., 2003), although there is less evidence regarding how vascular arteriolar dynamics affect glial and neural functioning. However, mechanical stimulation of brain cells may have functional implications: for example, it was possible to observe, in a cellular model expressing P2X7 receptors, mechanical stimulation promoted the release of extracellular ATP and consequently induced interleukin production (Lim, Lu, Beckel, & Mitchell, 2016). At a macroscopic level, the brain tissue is continuously under physical strain, which can now be well documented by ultrasound or magnetic resonance imaging (MRI) techniques and is described as brain tissue pulsatility. Brain tissue pulsatility is understood as brain structure motion and strain under perfusion and vascular function (Wagshul, Eide, & Madsen, 2011). Brain pulsatility correlates well with electrophysiology and cognitive performance (Angel et al., 2018), and it has been shown to be increased in depressed patients (Desmidt et al., 2017). Therefore, it may be hypothesized that an increase in brain tissue pulsatility is associated with microglial activation through activation of the P2X7-inflammasome axis. In line with this hypothesis, endothelial shear stress can induce ATP release by both microglial cells (Green et al., 2018) and astrocytes (Lalo et al., 2014) and consequently activate P2X7-mediated inflammation. In addition, a recent study showed that mice chronically exposed to unpredictable alternating frequencies of ultrasound stimulations exhibit depressive-like behaviours associated with decreased neurogenesis and BDNF expression and neuroinflammation (Pavlov et al., 2019). These preliminary results offer new understanding of how chronic stress may lead to depression through the activation of complex mechanisms that integrate changes in monoamine and glutamate neurotransmission, HPA axis dysregulation and altered neurogenesis via a neuroinflammatory process that originates in the blood–brain communication system represented by the brain microcirculation and its close contact with glial and neuronal cells.

CONFLICT OF INTEREST

WEH reports consulting fees from Eisai, Janssen, Lundbeck, Otsuka, and UCB.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the manuscript.

ORCID

Romain Troubat https://orcid.org/0000-0002-9657-4222
Samuel Leman https://orcid.org/0000-0002-0999-9979
Thomas Desmidt https://orcid.org/0000-0003-0949-8389
Boriana Atanasova https://orcid.org/0000-0002-5877-4645
Bruno Brizard https://orcid.org/0000-0002-0110-822X
Wissam El Hage https://orcid.org/0000-0003-3877-0855
Alexandre Surget https://orcid.org/0000-0002-0333-4634
Catherine Belzung https://orcid.org/0000-0001-6095-5974
Vincent Camus https://orcid.org/0000-0002-6845-221X

REFERENCES

Acosta-Rodriguez, E. V., Napolitani, G., Lanzavecchia, A., & Sallusto, F. (2007). Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. *Nature Immunology*, *8*, 942–949.

Altman, J. (1962). Are new neurons formed in the brains of adult mammals? *Science*, *135*, 1127–1128.

Altman, J., & Das, G. D. (1965). Post-natal origin of microneurones in the rat brain. *Nature*, *207*, 953–956.

Anderson, N. R., Buffone, A., & Hammer, D. A. (2019). T lymphocytes migrate upstream after completing the leukocyte adhesion cascade. *Cell Adhesion & Migration*, *13*(1), 1–6.

Andrade, L., Caraveo-Anduaga, J. J., Berglund, P., Bijl, R. V., de Graaf, R., Vollebergh, W., … Wittchen, H. U. (2003). The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. *International Journal of Methods in Psychiatric Research*, *12*, 3–21.

Angel, L., Bouazzaoui, B., Isingrini, M., Fay, S., Taconnat, L., Vanneste, S., … Remenieras, J.-P. (2018). Brain tissue pulsatility mediates cognitive and electrophysiological changes in normal aging: Evidence from ultrasound tissue pulsatility imaging (TPI). *Brain and Cognition*, *123*, 74–80.

Asberg, M. (1997). Neurotransmitters and suicidal behavior. The evidence from cerebrospinal fluid studies. *Annals of the New York Academy of Sciences*, *836*, 158–181.

Ayroldi, E., Cannarile, L., Migliorati, G., Nocentini, G., Delfino, D. V., & Riccardi, C. (2012). Mechanisms of the anti-inflammatory effects of glucocorticoids: Genomic and nongenomic interference with MAPK signaling pathways. *The FASEB Journal*, *26*, 4805–4820.

Badawy, A.- A.-B. (2017). Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects. *International Journal of Tryptophan Research*, *10*, 1178646917691938.

Bai, S., Guo, W., Feng, Y., Deng, H., Li, G., Nie, H., … Tang, Z. (2019). Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: A systematic review and meta-analysis of randomised controlled trials. *Journal of Neurology, Neurosurgery and Psychiatry*, *91*(1), 21–32.

Ban, E., Milon, G., Prudhomme, N., Fillion, G., & Haour, F. (1991). Receptors for interleukin-1 (alpha and beta) in mouse brain: Mapping and neuronal localization in hippocampus. *Neuroscience*, *43*, 21–30.

Bao, A.-M., & Swaab, D. F. (2019). The human hypothalamus in mood disorders: The HPA axis in the center. *IBRO Rep*, *6*, 45–53.

Barone, P. (2019). The "Yin" and the "Yang" of the kynurenine pathway: Excitotoxicity and neuroprotection imbalance in stress-induced disorders. *Behavioural Pharmacology*, *30*, 163–186.

Bay-Richter, C., Linderholm, K. R., Lim, C. K., Samuelsson, M., Träskman-Bendz, L., Guillemin, G. J., … Brundin, L. (2015). A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. *Brain, Behavior, and Immunity*, *43*, 110–117.

Becker, D. E. (2013). Basic and clinical pharmacology of glucocorticosteroids. *Anesthesia Progress*, *60*, 25–32.

Bélanger, M., & Magistretti, P. J. (2009). The role of astroglia in neuroprotection. *Dialogues in Clinical Neuroscience*, *11*, 281–295.

Bellavance, M.-A., & Rivest, S. (2014). The HPA – Immune axis and the immunomodulatory actions of glucocorticoids in the brain. *Frontiers in Immunology*, *5*, 136.

Blier, P., de Montigny, C., & Chaput, Y. (1990). A role for the serotonin system in the mechanism of action of antidepressant treatments: Preclinical evidence. *Journal of Clinical Psychiatry*, *51*(Suppl), 14–20; discussion 21.

Boldrini, M., Fulmore, C. A., Tartt, A. N., Simeon, L. R., Pavlova, I., Poposka, V., … Mann, J. J. (2018). Human hippocampal neurogenesis persists throughout aging. *Cell Stem Cell*, *22*, 589–599.e5.

Boldrini, M., Galfalvy, H., Dwork, A. J., Rosoklija, G. B., Trencevska-Ivanovska, I., Pavlovski, G., … Mann, J. J. (2019). Resilience is associated with larger dentate gyrus, while suicide decedents with major depressive disorder have fewer granule neurons. *Biological Psychiatry*, *85*, 850–862.

Bolós, M., Perea, J. R., Terreros-Roncal, J., Pallas-Bazarra, N., Jurado-Arjona, J., Ávila, J., & Llorens-Martín, M. (2018). Absence of microglial CX3CR1 impairs the synaptic integration of adult-born hippocampal granule neurons. *Brain, Behavior, and Immunity*, *68*, 76–89.

Bonaguidi, M. A., Wheeler, M. A., Shapiro, J. S., Stadel, R. P., Sun, G. J., Ming, G., & Song, H. (2011). In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. *Cell*, *145*, 1142–1155.

Bonilla, F. A., & Oettgen, H. C. (2010). Adaptive immunity. *Journal of Allergy and Clinical Immunology*, *125*, S33–S40.

Bornstein, S. R., Zacharowski, P., Schumann, R. R., Barthel, A., Tran, N., Papewalis, C., … Zacharowski, K. (2004). Impaired adrenal stress response in Toll-like receptor 2-deficient mice. *Proceedings of the National Academy of Sciences*, *101*, 16695–16700.

Borsini, A., Cattaneo, A., Malpighi, C., Thuret, S., Harrison, N. A., Zunszain, P. A., & Pariante, C. M.; MRC ImmunoPsychiatry Consortium (2018). Interferon-alpha reduces human hippocampal neurogenesis and increases apoptosis via activation of distinct stat1-dependent mechanisms. *International Journal of Neuropsychopharmacology*, *21*, 187–200.

Brooks, T. A., Hawkins, B. T., Huber, J. D., Egleton, R. D., & Davis, T. P. (2005). Chronic inflammatory pain leads to increased blood-brain barrier permeability and tight junction protein alterations. *American Journal of Physiology. Heart and Circulatory Physiology*, *289*, H738–H743.

Brown, J. M., Stewart, J. C., Stump, T. E., & Callahan, C. M. (2011). Risk of coronary heart disease events over 15 years among older adults with depressive symptoms. *The American Journal of Geriatric Psychiatry*, *19*, 721–729.

Brundin, L., Bryleva, E. Y., & Thirtamara Rajamani, K. (2017). Role of inflammation in suicide: from mechanisms to treatment. *Neuropsychopharmacology*, *42*, 271–283.

Busillo, J. M., Azzam, K. M., & Cidlowski, J. A. (2011). Glucocorticoids sensitize the innate immune system through regulation of the NLRP3 inflammasome. *Journal of Biological Chemistry*, *286*, 38703–38713.

Busillo, J. M., & Cidlowski, J. A. (2013). The five Rs of glucocorticoid action during inflammation: Ready, reinforce, repress, resolve, and restore. *Trends in Endocrinology & Metabolism*, *24*, 109–119.

Busse, M., Busse, S., Myint, A. M., Gos, T., Dobrowolny, H., Müller, U. J., … Steiner, J. (2015). Decreased quinolinic acid in the hippocampus of depressive patients: Evidence for local anti-inflammatory and neuroprotective responses? *European Archives of Psychiatry and Clinical Neuroscience*, *265*, 321–329.

Cai, B., Seong, K.-J., Bae, S.-W., Kook, M. S., Chun, C., Lee, J. H., … Kim, W.-J. (2019). Water-soluble arginyl–diosgenin analog attenuates hippocampal neurogenesis impairment through blocking microglial activation underlying NF-κB and JNK MAPK signaling in adult mice challenged by LPS. *Molecular Neurobiology*, *56*(9), 6218–6238.

Capuron, L., Gumnick, J. F., Musselman, D. L., Lawson, D. H., Reemsnyder, A., Nemeroff, C. B., & Miller, A. H. (2002). Neurobehavioral effects of interferon-α in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology*, *26*, 643–652.

Carrick, D. M., Lai, W. S., & Blackshear, P. J. (2004). The tandem CCCH zinc finger protein tristetraprolin and its relevance to cytokine mRNA turnover and arthritis. *Arthritis Research & Therapy*, *6*, 1–17.

Carvalho, L. A., Garner, B. A., Dew, T., Fazakerley, H., & Pariante, C. M. (2010). Antidepressants, but not antipsychotics, modulate GR function in human whole blood: An insight into molecular mechanisms. *European Neuropsychopharmacology*, *20*, 379–387.

Cassel, S. L., & Sutterwala, F. S. (2010). Sterile inflammatory responses mediated by the NLRP3 inflammasome. *European Journal of Immunology*, *40*, 607–611.

Cattaneo, A., Gennarelli, M., Uher, R., Breen, G., Farmer, A., Aitchison, K. J., … Pariante, C. M. (2013). Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology*, *38*, 377–385.

Cauli, B., & Hamel, E. (2018). Brain perfusion and astrocytes. *Trends in Neurosciences*, *41*, 409–413.

Chapman, B. P., Khan, A., Harper, M., Stockman, D., Fiscella, K., Walton, J., … Moynihan, J. (2009). Gender, race/ethnicity, personality, and interleukin-6 in urban primary care patients. *Brain, Behavior, and Immunity*, *23*, 636–642.

Chen, E., Xu, D., Lan, X., Jia, B., Sun, L., Zheng, J. C., & Peng, H. (2013). A novel role of the STAT3 pathway in brain inflammation-induced human neural progenitor cell differentiation. *Current Molecular Medicine*, *13*, 1474–1484.

Cheng, A. T., Chen, T. H., Chen, C. C., & Jenkins, R. (2000). Psychosocial and psychiatric risk factors for suicide. Case-control psychological autopsy study. *British Journal of Psychiatry*, *177*, 360–365.

Cheng, P.-L., Song, A.-H., Wong, Y.-H., Wang, S., Zhang, X., & Poo, M.-M. (2011). Self-amplifying autocrine actions of BDNF in axon development. *Proceedings of the National Academy of Sciences*, *108*, 18430–18435.

Chinenov, Y., & Rogatsky, I. (2007). Glucocorticoids and the innate immune system: Crosstalk with the Toll-like receptor signaling network. *Molecular and Cellular Endocrinology*, *275*, 30–42.

Clark, S. M., Pocivavsek, A., Nicholson, J. D., Notarangelo, F. M., Langenberg, P., McMahon, R. P., … Tonelli, L. H. (2016). Reduced kynurenine pathway metabolism and cytokine expression in the prefrontal cortex of depressed individuals. *Journal of Psychiatry & Neuroscience*, *41*, 386–394.

Congdon, K. L., Sanchez-Perez, L. A., & Sampson, J. H. (2019). Effective effectors: How T cells access and infiltrate the central nervous system. *Pharmacology & Therapeutics*, *197*, 52–60.

Connor, T. J., Starr, N., O'Sullivan, J. B., & Harkin, A. (2008). Induction of indolamine 2,3-dioxygenase and kynurenine 3-monooxygenase in rat brain following a systemic inflammatory challenge: A role for IFN-gamma? *Neuroscience Letters*, *441*, 29–34.

Cruz-Topete, D., & Cidlowski, J. A. (2015). One hormone, two actions: Anti- and pro-inflammatory effects of glucocorticoids. *NeuroImmunoModulation*, *22*, 20–32.

Cserr, H. F., Harling-Berg, C. J., & Knopf, P. M. (1992). Drainage of brain extracellular fluid into blood and deep cervical lymph and its immunological significance. *Brain Pathology*, *2*, 269–276.

Csölle, C., Baranyi, M., Zsilla, G., Kittel, A., Gölöncsér, F., Illes, P., … Sperlágh, B. (2013). Neurochemical changes in the mouse hippocampus underlying the antidepressant effect of genetic deletion of P2X7 receptors. *PLoS ONE*, *8*, e66547.

Czeh, M., Gressens, P., & Kaindl, A. M. (2011). The yin and yang of microglia. *Developmental Neuroscience*, *33*, 199–209.

Dantzer, R. (2018). Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiological Reviews*, *98*, 477–504.

De Bosscher, K., Vanden Berghe, W., & Haegeman, G. (2003). The interplay between the glucocorticoid receptor and nuclear factor-κB or activator protein-1: Molecular mechanisms for gene repression. *Endocrine Reviews*, *24*, 488–522.

de Miranda, A. S., Zhang, C.-J., Katsumoto, A., & Teixeira, A. L. (2017). Hippocampal adult neurogenesis: Does the immune system matter? *Journal of the Neurological Sciences*, *372*, 482–495.

Deemyad, T., Lüthi, J., & Spruston, N. (2018). Astrocytes integrate and drive action potential firing in inhibitory subnetworks. *Nature Communications*, *9*, 1–13.

Desmidt, T., Brizard, B., Dujardin, P. A., Ternifi, R., Remenieras, J. P., Patat, F., … Camus, V. (2017). Brain tissue pulsatility is increased in midlife depression: A comparative study using ultrasound tissue pulsatility imaging. *Neuropsychopharmacology*, *42*, 2575–2582.

Ding, Y., Gao, Z.-G., Jacobson, K. A., & Suffredini, A. F. (2010). Dexamethasone enhances ATP-induced inflammatory responses in endothelial cells. *Journal of Pharmacology and Experimental Therapeutics*, *335*, 693–702.

Dobos, N., de Vries, E. F. J., Kema, I. P., Patas, K., Prins, M., Nijholt, I. M., … Eisel, U. L. M. (2012). The role of indoleamine 2,3-dioxygenase in a mouse model of neuroinflammation-induced depression. *Journal of Alzheimer's Disease*, *28*, 905–915.

Dostal, C. R., Carson Sulzer, M., Kelley, K. W., Freund, G. G., & McCusker, R. H. (2017). Glial and tissue-specific regulation of Kynurenine Pathway dioxygenases by acute stress of mice. *Neurobiological Stress*, *7*, 1–15.

Eisch, A. J., & Petrik, D. (2012). Depression and hippocampal neurogenesis: A road to remission? *Science*, *338*, 72–75.

Ekdahl, C. T., Claasen, J.-H., Bonde, S., Kokaia, Z., & Lindvall, O. (2003). Inflammation is detrimental for neurogenesis in adult brain. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 13632–13637.

Elahy, M., Jackaman, C., Mamo, J. C., Lam, V., Dhaliwal, S. S., Giles, C., … Takechi, R. (2015). Blood-brain barrier dysfunction developed during normal aging is associated with inflammation and loss of tight junctions but not with leukocyte recruitment. *Immunity & Ageing*, *12*, 2.

Elander, L., Engström, L., Ruud, J., Mackerlova, L., Jakobsson, P.-J., Engblom, D., … Blomqvist, A. (2009). Inducible prostaglandin E2 synthesis interacts in a temporally supplementary sequence with constitutive prostaglandin-synthesizing enzymes in creating the hypothalamic–pituitary–adrenal axis response to immune challenge. *Journal of Neuroscience*, *29*, 1404–1413.

Eliwa, H., Belzung, C., & Surget, A. (2017). Adult hippocampal neurogenesis: Is it the alpha and omega of antidepressant action? *Biochemical Pharmacology*, *141*, 86–99.

Encinas, J. M., Michurina, T. V., Peunova, N., Park, J.-H., Tordo, J., Peterson, D. A., … Enikolopov, G. (2011). Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. *Cell Stem Cell*, *8*, 566–579.

Engelhardt, B., Vajkoczy, P., & Weller, R. O. (2017). The movers and shapers in immune privilege of the CNS. *Nature Immunology*, *18*, 123–131.

Eriksson, P. S., Perfilieva, E., Björk-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A., & Gage, F. H. (1998). Neurogenesis in the adult human hippocampus. *Nature Medicine*, *4*, 1313–1317.

Espinosa-Oliva, A. M., de Pablos, R. M., Villarán, R. F., Argüelles, S., Venero, J. L., Machado, A., & Cano, J. (2011). Stress is critical for LPS-induced activation of microglia and damage in the rat hippocampus. *Neurobiology of Aging*, *32*, 85–102.

Farina, C., Aloisi, F., & Meinl, E. (2007). Astrocytes are active players in cerebral innate immunity. *Trends in Immunology*, *28*, 138–145.

Farooq, R. K., Isingrini, E., Tanti, A., Le Guisquet, A.-M., Arlicot, N., Minier, F., … Camus, V. (2012). Is unpredictable chronic mild stress (UCMS) a reliable model to study depression-induced neuroinflammation? *Behavioral Brain Research*, *231*, 130–137.

Farooq, R. K., Tanti, A., Ainouche, S., Roger, S., Belzung, C., & Camus, V. (2018). A P2X7 receptor antagonist reverses behavioural alterations, microglial activation and neuroendocrine dysregulation in an unpredictable chronic mild stress (UCMS) model of depression in mice. *Psychoneuroendocrinology*, *97*, 120–130.

Franco, R., & Fernández-Suárez, D. (2015). Alternatively activated microglia and macrophages in the central nervous system. *Progress in Neurobiology*, *131*, 65–86.

Frodl, T., & Amico, F. (2014). Is there an association between peripheral immune markers and structural/functional neuroimaging findings? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *48*, 295–303.

Fujioka, H., & Akema, T. (2010). Lipopolysaccharide acutely inhibits proliferation of neural precursor cells in the dentate gyrus in adult rats. *Brain Research*, *1352*, 35–42.

Galon, J., Franchimont, D., Hiroi, N., Frey, G., Boettner, A., Ehrhart-Bornstein, M., Oshea, J. J., Chrousos, G. P., & Bornstein, S. R. (2002). Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. *The FASEB Journal*, *16*, 61–71.

Garber, C., Soung, A., Vollmer, L. L., Kanmogne, M., Last, A., Brown, J., & Klein, R. S. (2019). T cells promote microglia-mediated synaptic elimination and cognitive dysfunction during recovery from neuropathogenic flaviviruses. *Nature Neuroscience*, *22*(8), 1276–1288.

García-Bueno, B., Serrats, J., & Sawchenko, P. E. (2009). Cerebrovascular cyclooxygenase-1 expression, regulation, and role in hypothalamic-pituitary-adrenal axis activation by inflammatory stimuli. *Journal of Neuroscience*, *29*, 12970–12981.

Garthwaite, J., Charles, S. L., & Chess-Williams, R. (1988). Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. *Nature*, *336*, 385.

Ghadery, C., Koshimori, Y., Christopher, L., Kim, J., Rusjan, P., Lang, A. E., … Strafella, A. P. (2019). The interaction between neuroinflammation and β-amyloid in cognitive decline in Parkinson's disease. *Molecular Neurobiology*, *57*(1), 492–501.

Gillespie, C. F., & Nemeroff, C. B. (2005). Hypercortisolemia and depression. *Psychosomatic Medicine*, *67*(Suppl 1), S26–28.

Gimsa, U., Mitchison, N. A., & Brunner-Weinzierl, M. C. (2013). Immune privilege as an intrinsic CNS property: Astrocytes protect the CNS against T-cell-mediated neuroinflammation. *Mediators of Inflammation*, *2013*, 320519.

Gonçalves, A., Lin, C.-M., Muthusamy, A., Fontes-Ribeiro, C., Ambrósio, A. F., Abcouwer, S. F., … Antonetti, D. A. (2016). Protective effect of a GLP-1 analog on ischemia-reperfusion induced blood-retinal barrier breakdown and inflammation. *Investigative Ophthalmology & Visual Science*, *57*, 2584–2592.

Goshen, I., Kreisel, T., Ben-Menachem-Zidon, O., Licht, T., Weidenfeld, J., Ben-Hur, T., & Yirmiya, R. (2008). Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. *Molecular Psychiatry*, *13*, 717–728.

Green, H. F., & Nolan, Y. M. (2012). Unlocking mechanisms in interleukin-1β-induced changes in hippocampal neurogenesis–a role for GSK-3β and TLX. *Transl. Psychiatry*, *2*, e194.

Green, H. F., Treacy, E., Keohane, A. K., Sullivan, A. M., O'Keeffe, G. W., & Nolan, Y. M. (2012). A role for interleukin-1β in determining the lineage fate of embryonic rat hippocampal neural precursor cells. *Molecular and Cellular Neurosciences*, *49*, 311–321.

Green, J. P., Souilhol, C., Xanthis, I., Martinez-Campesino, L., Bowden, N. P., Evans, P. C., & Wilson, H. L. (2018). Atheroprone flow activates inflammation via endothelial ATP-dependent P2X7-p38 signalling. *Cardiovascular Research*, *114*, 324–335.

Grigoriadis, S., & Robinson, G. E. (2007). Gender issues in depression. *Annals of Clinical Psychiatry*, *19*, 247–255.

Grønberg, N. V., Johansen, F. F., Kristiansen, U., & Hasseldam, H. (2013). Leukocyte infiltration in experimental stroke. *Journal of Neuroinflammation*, *10*, 892.

Guan, Z., & Fang, J. (2006). Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. *Brain, Behavior, and Immunity*, *20*, 64–71.

Guillemin, G. J. (2012). Quinolinic acid, the inescapable neurotoxin. *FEBS Journal*, *279*, 1356–1365.

Guillemin, G. J., Cullen, K. M., Lim, C. K., Smythe, G. A., Garner, B., Kapoor, V., … Brew, B. J. (2007). Characterization of the kynurenine pathway in human neurons. *Journal of Neurochemistry*, *27*, 12884–12892.

Guillemin, G. J., Smythe, G., Takikawa, O., & Brew, B. J. (2005). Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia*, *49*, 15–23.

Guttenplan, K. A., & Liddelow, S. A. (2019). Astrocytes and microglia: Models and tools. *Journal of Experimental Medicine*, *216*, 71–83.

Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2015). Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain, Behavior, and Immunity*, *49*, 206–215.

Hamelin, L., Lagarde, J., Dorothée, G., Potier, M. C., Corlier, F., Kuhnast, B., … Sarazin, M. (2018). Distinct dynamic profiles of microglial activation are associated with progression of Alzheimer's disease. *Brain*, *141*, 1855–1870.

Hanisch, U.-K., & Kettenmann, H. (2007). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience*, *10*, 1387–1394.

Hannestad, J., DellaGioia, N., Gallezot, J.-D., Lim, K., Nabulsi, N., Esterlis, I., … Carson, R. E. (2013). The neuroinflammation marker translocator protein is not elevated in individuals with mild-to-moderate depression: A [^{11}C]PBR28 PET study. *Brain, Behavior, and Immunity*, *33*, 131–138.

Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. *Lancet Neurology*, *14*, 388–405.

Hermoso, M. A., Matsuguchi, T., Smoak, K., & Cidlowski, J. A. (2004). Glucocorticoids and tumor necrosis factor alpha cooperatively regulate toll-like receptor 2 gene expression. *Molecular and Cellular Biology*, *24*, 4743–4756.

Hickey, W. F., Hsu, B. L., & Kimura, H. (1991). T-lymphocyte entry into the central nervous system. *Journal of Neuroscience Research*, *28*, 254–260.

Hirschfeld, R. M. (2000). History and evolution of the monoamine hypothesis of depression. *Journal of Clinical Psychiatry*, *61*(Suppl 6), 4–6.

Holmes, S. E., Hinz, R., Conen, S., Gregory, C. J., Matthews, J. C., Anton-Rodriguez, J. M., … Talbot, P. S. (2018). Elevated translocator protein in anterior cingulate in major depression and a role for inflammation in suicidal thinking: A positron emission tomography study. *Biological Psychiatry*, *83*, 61–69.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, *23*, 477–501.

Homma, T., Kato, A., Hashimoto, N., Batchelor, J., Yoshikawa, M., Imai, S., … Matsumoto, K. (2004). Corticosteroid and cytokines synergistically enhance toll-like receptor 2 expression in respiratory epithelial cells. *American Journal of Respiratory Cell and Molecular Biology*, *31*, 463–469.

Hoogland, I. C. M., Houbolt, C., van Westerloo, D. J., van Gool, W. A., & van de Beek, D. (2015). Systemic inflammation and microglial activation: Systematic review of animal experiments. *Journal of Neuroinflammation*, *12*, 114.

Howren, M., Lamkin, D., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine*, *71*, 171–186.

Hu, S., Sheng, W. S., Ehrlich, L. C., Peterson, P. K., & Chao, C. C. (2000). Cytokine effects on glutamate uptake by human astrocytes. *NeuroImmunoModulation*, *7*, 153–159.

Huang, Y., Smith, D. E., Ibáñez-Sandoval, O., Sims, J. E., & Friedman, W. J. (2011). Neuron-specific effects of interleukin-1β are mediated by a novel isoform of the IL-1 receptor accessory protein. *Journal of Neuroscience*, *31*, 18048–18059.

Hueston, C. M., O'Leary, J. D., Hoban, A. E., Kozareva, D. A., Pawley, L. C., O'Leary, O. F., … Nolan, Y. M. (2018). Chronic interleukin-1β in the dorsal hippocampus impairs behavioural pattern separation. *Brain, Behavior, and Immunity*, *74*, 252–264.

Ising, M., Horstmann, S., Kloiber, S., Lucae, S., Binder, E. B., Kern, N., … Holsboer, F. (2007). Combined dexamethasone/corticotropin releasing hormone test predicts treatment response in major depression – a potential biomarker? *Biol. Psychiatry*, *62*, 47–54.

Isingrini, E., Belzung, C., d'Audiffret, A., & Camus, V. (2011). Early and late-onset effect of chronic stress on vascular function in mice: a possible model of the impact of depression on vascular disease in aging. *American Journal of Geriatric Psychiatry*, *19*, 335–346.

Isingrini, E., Belzung, C., Freslon, J.-L., Machet, M.-C., & Camus, V. (2012). Fluoxetine effect on aortic nitric oxide-dependent vasorelaxation in the unpredictable chronic mild stress model of depression in mice. *Psychosomatic Medicine*, *74*, 63–72.

Jeong, H.-G., Lee, J. J., Lee, S. B., Park, J. H., Huh, Y., Han, J. W., … Kim, K. W. (2013). Role of severity and gender in the association between late-life depression and all-cause mortality. *International Psychogeriatrics*, *25*, 677–684.

Jhamandas, K. H., Boegman, R. J., Beninger, R. J., Miranda, A. F., & Lipic, K. A. (2000). Excitotoxicity of quinolinic acid: Modulation by endogenous antagonists. *Neurotoxicity Research*, *2*, 139–155.

Jiang, L.-H., Baldwin, J., Roger, S., & Baldwin, S. (2013). Insights into the molecular mechanisms underlying mammalian P2X7 receptor functions and contributions in diseases, revealed by structural modeling and single nucleotide polymorphisms. *Frontiers in Pharmacology*, *4*, 55.

Ju, F., Ran, Y., Zhu, L., Cheng, X., Gao, H., Xi, X., … Zhang, S. (2018). Increased BBB permeability enhances activation of microglia and exacerbates loss of dendritic spines after transient global cerebral ischemia. *Frontiers in Cellular Neuroscience*, *12*, 236.

Kaneko, N., Kudo, K., Mabuchi, T., Takemoto, K., Fujimaki, K., Wati, H., … Kanba, S. (2006). Suppression of cell proliferation by interferon-alpha through interleukin-1 production in adult rat dentate gyrus. *Neuropsychopharmacology*, *31*, 2619–2626.

Kappelmann, N., Lewis, G., Dantzer, R., Jones, P. B., & Khandaker, G. M. (2018). Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Molecular Psychiatry*, *23*, 335–343.

Kebir, H., Kreymborg, K., Ifergan, I., Dodelet-Devillers, A., Cayrol, R., Bernard, M., … Prat, A. (2007). Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nature Medicine*, *13*, 1173–1175.

Kendler, K. S., Thornton, L. M., & Prescott, C. A. (2001). Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. *American Journal of Psychiatry*, *158*, 587–593.

Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders*, *74*, 5–13.

Kling, M. A., Geracioti, T. D., Licinio, J., Michelson, D., Oldfield, E. H., & Gold, P. W. (1994). Effects of electroconvulsive therapy on the CRH-ACTH-cortisol system in melancholic depression: Preliminary findings. *Psychopharmacology Bulletin*, *30*, 489–494.

Kohl, C., Walch, T., Huber, R., Kemmler, G., Neurauter, G., Fuchs, D., … Sperner-Unterweger, B. (2005). Measurement of tryptophan, kynurenine and neopterin in women with and without postpartum blues. *Journal of Affective Disorders*, *86*, 135–142.

Köhler-Forsberg, O., Lydholm, C. N., Hjorthøj, C., Nordentoft, M., Mors, O., & Benros, M. E. (2019). Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: Meta-analysis of clinical trials. *Acta Psychiatrica Scandinavica*, *139*, 404–419.

Konradsson-Geuken, A., Wu, H. Q., Gash, C. R., Alexander, K. S., Campbell, A., Sozeri, Y., … Bruno, J. P. (2010). Cortical kynurenic acid bi-directionally modulates prefrontal glutamate levels as assessed by microdialysis and rapid electrochemistry. *Neuroscience*, *169*, 1848–1859.

Koo, J. W., & Duman, R. S. (2008). IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 751–756.

Kumar, V. (2019). Toll-like receptors in the pathogenesis of neuroinflammation. *Journal of Neuroimmunology*, *332*, 16–30.

Lalo, U., Palygin, O., Rasooli-Nejad, S., Andrew, J., Haydon, P. G., & Pankratov, Y. (2014). Exocytosis of ATP from astrocytes modulates phasic and tonic inhibition in the neocortex. *PLoS Biology*, *12*, e1001747.

Langlais, D., Couture, C., Balsalobre, A., & Drouin, J. (2008). Regulatory network analyses reveal genome-wide potentiation of LIF signaling by glucocorticoids and define an innate cell defense response. *PLoS Genetics*, *4*, e1000224.

Lannan, E. A., Galliher-Beckley, A. J., Scoltock, A. B., & Cidlowski, J. A. (2012). Proinflammatory actions of glucocorticoids: glucocorticoids and TNFα coregulate gene expression in vitro and in vivo. *Endocrinology*, *153*, 3701–3712.

Lapchak, P. A., Araujo, D. M., & Hefti, F. (1993). Systemic interleukin-1 beta decreases brain-derived neurotrophic factor messenger RNA expression in the rat hippocampal formation. *Neuroscience*, *53*, 297–301.

Lapin, I. P. (2003). Neurokynurenines (NEKY) as common neurochemical links of stress and anxiety. *Advances in Experimental Medicine and Biology*, *527*, 121–125.

Laugeray, A., Launay, J.-M., Callebert, J., Mutlu, O., Guillemin, G. J., Belzung, C., & Barone, P. R. (2016). Chronic treatment with the IDO1 inhibitor 1-methyl-D-tryptophan minimizes the behavioural and biochemical abnormalities induced by unpredictable chronic mild stress in mice – comparison with fluoxetine. *PLoS ONE*, *11*, e0164337.

Lener, M. S., Niciu, M. J., Ballard, E. D., Park, M., Park, L. T., Nugent, A. C., & Zarate, C. A. (2017). Glutamate and gamma-aminobutyric acid systems in the pathophysiology of major depression and antidepressant response to ketamine. *Biological Psychiatry*, *81*, 886–897.

Levine, J., Barak, Y., Chengappa, K. N., Rapoport, A., Rebey, M., & Barak, V. (1999). Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology*, *40*, 171–176.

Li, H., Sagar, A. P., & Kéri, S. (2018). Translocator protein (18kDa TSPO) binding, a marker of microglia, is reduced in major depression during cognitive-behavioral therapy. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *83*, 1–7.

Li, J.-M., Liu, L.-L., Su, W.-J., Wang, B., Zhang, T., Zhang, Y., & Jiang, C.-L. (2019). Ketamine may exert antidepressant effects via suppressing NLRP3 inflammasome to upregulate AMPA receptors. *Neuropharmacology*, *146*, 149–153.

Li, T., Jiang, L., Zhang, X., & Chen, H. (2009). In-vitro effects of brain-derived neurotrophic factor on neural progenitor/stem cells from rat hippocampus. *NeuroReport*, *20*, 295.

Liddelow, S. A., & Barres, B. A. (2017). Reactive astrocytes: production, function, and therapeutic potential. *Immunity*, *46*, 957–967.

Lim, J. C., Lu, W., Beckel, J. M., & Mitchell, C. H. (2016). Neuronal release of cytokine IL-3 triggered by mechanosensitive autostimulation of the P2X7 receptor is neuroprotective. *Frontiers in Cellular Neuroscience*, *10*, 270.

Lively, S., & Schlichter, L. C. (2018). Microglia responses to pro-inflammatory stimuli (LPS, IFNγ+TNFα) and reprogramming by resolving cytokines (IL-4, IL-10). *Frontiers in Cellular Neuroscience*, *12*, 215.

Llorens-Martín, M., Jurado-Arjona, J., Fuster-Matanzo, A., Hernández, F., Rábano, A., & Ávila, J. (2014). Peripherally triggered and GSK-3β-driven brain inflammation differentially skew adult hippocampal neurogenesis, behavioral pattern separation and microglial activation in response to ibuprofen. *Translational Psychiatry*, *4*, e463.

Louveau, A., Harris, T. H., & Kipnis, J. (2015). Revisiting the Mechanisms of CNS Immune Privilege. *Trends in Immunology*, *36*, 569–577.

Luca, M., Di Mauro, M., Di Mauro, M., & Luca, A. (2019). Gut microbiota in Alzheimer's disease, depression, and type 2 diabetes mellitus: the role of oxidative stress. *Oxidative Medicine and Cellular Longevity*, *2019*, 4730539.

Ma, M., Ren, Q., Zhang, J.-C., & Hashimoto, K. (2014). Effects of brilliant blue G on serum tumor necrosis factor-α levels and depression-like behavior in mice after lipopolysaccharide administration. *Clinical Psychopharmacology and Neuroscience*, *12*, 31–36.

Maes, M., Leonard, B. E., Myint, A. M., Kubera, M., & Verkerk, R. (2011). 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. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*, 702–721.

Maes, M., Meltzer, H. Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., & Desnyder, R. (1995). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *Journal of Affective Disorders*, *34*, 301–309.

Malarkey, E. B., & Parpura, V. (2008). Mechanisms of glutamate release from astrocytes. *Neurochemistry International*, *52*, 142–154.

Maneshi, M. M., Maki, B., Gnanasambandam, R., Belin, S., Popescu, G. K., Sachs, F., & Hua, S. Z. (2017). Mechanical stress activates NMDA receptors in the absence of agonists. *Scientific Reports*, *7*(1).

McIntyre, R. S., Subramaniapillai, M., Lee, Y., Pan, Z., Carmona, N. E., Shekotikhina, M., … Mansur, R. B. (2019). Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: a randomized clinical trial. *JAMA Psychiatry*, *76*(8), 783.

McKim, D. B., Weber, M. D., Niraula, A., Sawicki, C. M., Liu, X., Jarrett, B. L., … Godbout, J. P. (2018). Microglial recruitment of IL-1β-producing monocytes to brain endothelium causes stress-induced anxiety. *Molecular Psychiatry*, *23*, 1421–1431.

McPherson, C. A., Aoyama, M., & Harry, G. J. (2011). Interleukin (IL)-1 and IL-6 regulation of neural progenitor cell proliferation with hippocampal injury: Differential regulatory pathways in the subgranular zone (SGZ) of the adolescent and mature mouse brain. *Brain, Behavior, and Immunity*, *25*, 850–862.

Meier, T. B., Drevets, W. C., Wurfel, B. E., Ford, B. N., Morris, H. M., Victor, T. A., … Savitz, J. (2016). Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder. *Brain, Behavior, and Immunity*, *53*, 39–48.

Menard, C., Pfau, M. L., Hodes, G. E., Kana, V., Wang, V. X., Bouchard, S., … Russo, S. J. (2017). Social stress induces neurovascular pathology promoting depression. *Nature Neuroscience*, *20*, 1752.

Messaoud, A., Mensi, R., Douki, W., Neffati, F., Najjar, M. F., Gobbi, G., … Comai, S. (2018). Reduced peripheral availability of tryptophan and increased activation of the kynurenine pathway and cortisol correlate with major depression and suicide. *The World Journal of Biological Psychiatry*, 1–9.

Miyaoka, H., Otsubo, T., Kamijima, K., Ishii, M., Onuki, M., & Mitamura, K. (1999). Depression from interferon therapy in patients with hepatitis C. *American Journal of Psychiatry*, *156*, 1120.

Moieni, M., Irwin, M. R., Jevtic, I., Olmstead, R., Breen, E. C., & Eisenberger, N. I. (2015). Sex differences in depressive and socioemotional responses to an inflammatory challenge: implications for sex differences in depression. *Neuropsychopharmacology*, *40*, 1709–1716.

Monje, M. L., Toda, H., & Palmer, T. D. (2003). Inflammatory blockade restores adult hippocampal neurogenesis. *Science*, *302*, 1760–1765.

Moreno, F. A., Parkinson, D., Palmer, C., Castro, W. L., Misiaszek, J., El Khoury, A., … Delgado, P. L. (2010). CSF neurochemicals during tryptophan depletion in individuals with remitted depression and healthy controls. *European Neuropsychopharmacology*, *20*, 18–24.

Moreno-Jiménez, E. P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarra, N., … Llorens-Martín, M. (2019). Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nature Medicine*, *25*, 554–560.

Nemeroff, C. B., & Evans, D. L. (1984). Correlation between the dexamethasone suppression test in depressed patients and clinical response. *American Journal of Psychiatry*, *141*, 247–249.

Newton, R., & Holden, N. S. (2007). Separating transrepression and transactivation: a distressing divorce for the glucocorticoid receptor? *Molecular Pharmacology*, *72*, 799–809.

O'Connor, J. C., André, C., Wang, Y., Lawson, M. A., Szegedi, S. S., Lestage, J., … Dantzer, R. (2009). Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. *Journal of Neuroscience*, *29*, 4200–4209.

Ogawa, S., Fujii, T., Koga, N., Hori, H., Teraishi, T., Hattori, K., … Kunugi, H. (2014). Plasma L-tryptophan concentration in major depressive disorder: New data and meta-analysis. *Journal of Clinical Psychiatry*, *75*, e906–915.

Okada, S., Nakamura, M., Katoh, H., Miyao, T., Shimazaki, T., Ishii, K., … Okano, H. (2006). Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. *Nature Medicine*, *12*, 829–834.

Pariante, C. M. (2003). Depression, stress and the adrenal axis. *Journal of Neuroendocrinology*, *15*, 811–812.

Pariante, C. M. (2017). Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. *European Neuropsychopharmacology*, *27*, 554–559.

Parnet, P., Amindari, S., Wu, C., Brunke-Reese, D., Goujon, E., Weyhenmeyer, J. A., … Kelley, K. W. (1994). Expression of type I and type II interleukin-1 receptors in mouse brain. *Brain Research*, *27*, 63–70.

Parrott, J. M., Redus, L., Santana-Coelho, D., Morales, J., Gao, X., & O'Connor, J. C. (2016). Neurotoxic kynurenine metabolism is increased in the dorsal hippocampus and drives distinct depressive behaviors during inflammation. *Translational Psychiatry*, *6*, e918.

Pavlov, D., Bettendorff, L., Gorlova, A., Olkhovik, A., Kalueff, A. V., Ponomarev, E. D., … Strekalova, T. (2019). Neuroinflammation and aberrant hippocampal plasticity in a mouse model of emotional stress evoked by exposure to ultrasound of alternating frequencies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *90*, 104–116.

Pereira, V. S., & Hiroaki-Sato, V. A. (2018). A brief history of antidepressant drug development: From tricyclics to beyond ketamine. *Acta Neuropsychiatrica*, , *30*(6), 307–322.

Petersen, C., & Round, J. L. (2014). Defining dysbiosis and its influence on host immunity and disease. *Cellular Microbiology*, *16*, 1024–1033.

Place, D. E., & Kanneganti, T.-D. (2018) Recent advances in inflammasome biology. *Current Opinion in Immunology 50*, 32–38.

Popoli, M., Yan, Z., McEwen, B. S., & Sanacora, G. (2011). The stressed synapse: The impact of stress and glucocorticoids on glutamate transmission. *Nature Reviews Neuroscience*, *13*, 22–37.

Price, C. J. S., Menon, D. K., Peters, A. M., Ballinger, J. R., Barber, R. W., Balan, K. K., … Warburton, E. A. (2004). Cerebral neutrophil recruitment, histology, and outcome in acute ischemic stroke. *Stroke*, *35*, 1659–1664.

Qin, L., Wu, X., Block, M. L., Liu, Y., Breese, G. R., Hong, J.-S., … Crews, F. T. (2007). Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia*, *55*, 453–462.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*, 24–31.

Raison, C. L., Dantzer, R., Kelley, K. W., Lawson, M. A., Woolwine, B. J., Vogt, G., … Miller, A. H. (2010). CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: Relationship to CNS immune responses and depression. *Molecular Psychiatry*, *15*, 393–403.

Ramamoorthy, S., Ramamoorthy, J. D., Prasad, P. D., Bhat, G. K., Mahesh, V. B., Leibach, F. H., & Ganapathy, V. (1995). Regulation of the human serotonin transporter by interleukin-1 beta. *Biochemical and Biophysical Research Communications*, *216*, 560–567.

Ratajczak, M. Z., Mack, A., Bujko, K., Domingues, A., Pedziwiatr, D., Kucia, M., … Samochowiec, J. (2019). ATP-Nlrp3 inflammasome-complement cascade axis in sterile brain inflammation in psychiatric patients and its impact on stem cell trafficking. *Stem Cell Reviews and Reports*, *15*, 497–505.

Richards, E. M., Zanotti-Fregonara, P., Fujita, M., Newman, L., Farmer, C., Ballard, E. D., … Zarate, C. A. Jr (2018). PET radioligand binding to translocator protein (TSPO) is increased in unmedicated depressed subjects. *EJNMMI Research*, *8*, 57.

Rivest, S. (2010). Interactions between the immune and neuroendocrine systems. *Progress in Brain Research*, *181*, 43–53.

Roger, S., Mei, Z. Z., Baldwin, J. M., Dong, L., Bradley, H., Baldwin, S. A., … Jiang, L. H. (2010). Single nucleotide polymorphisms that were identified in affective mood disorders affect ATP-activated P2X7 receptor functions. *Journal of Psychiatric Research*, *44*, 347–355.

Rogers, J. T., Morganti, J. M., Bachstetter, A. D., Hudson, C. E., Peters, M. M., Grimmig, B. A., … Gemma, C. (2011). CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. *Journal of Neuroscience*, *31*, 16241–16250.

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry*, *163*, 1905–1917.

Ryan, S. M., O'Keeffe, G. W., O'Connor, C., Keeshan, K., & Nolan, Y. M. (2013). Negative regulation of TLX by IL-1β correlates with an inhibition of adult hippocampal neural precursor cell proliferation. *Brain, Behavior, and Immunity*, *33*, 7–13.

Sanacora, G., Treccani, G., & Popoli, M. (2012). Towards a glutamate hypothesis of depression. *Neuropharmacology*, *62*, 63–77.

Savitz, J. (2017). Role of Kynurenine metabolism pathway activation in major depressive disorders. *Current Topics in Behavioral Neurosciences*, *31*, 249–267.

Savitz, J. (2019). The kynurenine pathway: a finger in every pie. *Molecular Psychiatry*, *25*, 131–147.

Schmidt, M. J., Fuller, R. W., & Wong, D. T. (1988). Fluoxetine, a highly selective serotonin reuptake inhibitor: A review of preclinical studies. *British Journal of Psychiatry*, *153*(S3), 40–46.

Schwarcz, R., Bruno, J. P., Muchowski, P. J., & Wu, H.-Q. (2012). Kynurenines in the mammalian brain: When physiology meets pathology. *Nature Reviews Neuroscience*, *13*, 465–477.

Schwarcz, R., & Stone, T. W. (2017). The kynurenine pathway and the brain: Challenges, controversies and promises. *Neuropharmacology*, *112*, 237–247.

Serafini, G., Adavastro, G., Canepa, G., Capobianco, L., Conigliaro, C., Pittaluga, F., … Amore, M. (2017). Abnormalities in kynurenine pathway metabolism in treatment-resistant depression and suicidality: A systematic review. *CNS & Neurological Disorders: Drug Targets*, *16*, 440–453.

Serrats, J., Schiltz, J. C., García-Bueno, B., van Rooijen, N., Reyes, T. M., & Sawchenko, P. E. (2010). Dual roles for perivascular macrophages in immune-to-brain signaling. *Neuron*, *65*, 94–106.

Setiawan, E., Attwells, S., Wilson, A. A., Mizrahi, R., Rusjan, P. M., Miler, L., … Meyer, J. H. (2018). Association of translocator protein total distribution volume with duration of untreated major depressive disorder: A cross-sectional study. *Lancet Psychiatry*, *5*, 339–347.

Shulman, K. I., Herrmann, N., & Walker, S. E. (2013). Current place of monoamine oxidase inhibitors in the treatment of depression. *CNS Drugs*, *27*, 789–797.

Sierra, A., Encinas, J. M., Deudero, J. J. P., Chancey, J. H., Enikolopov, G., Overstreet-Wadiche, L. S., … Maletic-Savatic, M. (2010).

Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, *7*, 483–495.

Ślusarczyk, J., Trojan, E., Głombik, K., Piotrowska, A., Budziszewska, B., Kubera, M., … Basta-Kaim, A. (2018). Targeting the NLRP3 inflammasome-related pathways via tianeptine treatment-suppressed microglia polarization to the m1 phenotype in lipopolysaccharide-stimulated cultures. *International Journal of Molecular Sciences*, *19*, E1965.

Smoak, K., & Cidlowski, J. A. (2006). Glucocorticoids regulate tristetraprolin synthesis and posttranscriptionally regulate tumor necrosis factor alpha inflammatory signaling. *Molecular and Cellular Biology*, *26*, 9126–9135.

Sofroniew, M. V. (2015). Astrocyte barriers to neurotoxic inflammation. *Nature Reviews Neuroscience*, *16*, 249–263.

Sorrells, S. F., Paredes, M. F., Cebrian-Silla, A., Sandoval, K., Qi, D., Kelley, K. W., … Alvarez-Buylla, A. (2018). Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature*, *555*, 377–381.

Sorrells, S. F., & Sapolsky, R. M. (2007). An inflammatory review of glucocorticoid actions in the CNS. *Brain, Behavior, and Immunity*, *21*, 259–272.

Spalding, K. L., Bergmann, O., Alkass, K., Bernard, S., Salehpour, M., Huttner, H. B., … Frisén, J. (2013). Dynamics of hippocampal neurogenesis in adult humans. *Cell*, *153*, 1219–1227.

Stahn, C., & Buttgereit, F. (2008). Genomic and nongenomic effects of glucocorticoids. *Nature Reviews Rheumatology*, *4*, 525–533.

Sternberg, E. M. (2006). Neural regulation of innate immunity: A coordinated nonspecific host response to pathogens. *Nature Reviews Immunology*, *6*, 318–328.

Su, L., Faluyi, Y. O., Hong, Y. T., Fryer, T. D., Mak, E., Gabel, S., … O'Brien, J. T. (2016). Neuroinflammatory and morphological changes in late-life depression: The NIMROD study. *British Journal of Psychiatry*, *209*, 525–526.

Sublette, M. E., Galfalvy, H. C., Fuchs, D., Lapidus, M., Grunebaum, M. F., Oquendo, M. A., … Postolache, T. T. (2011). Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. *Brain, Behavior, and Immunity*, *25*, 1272–1278.

Surget, A., Tanti, A., Leonardo, E. D., Laugeray, A., Rainer, Q., Touma, C., … Belzung, C. (2011). Antidepressants recruit new neurons to improve stress response regulation. *Molecular Psychiatry*, *16*, 1177–1188.

Swaab, D. F., Bao, A.-M., & Lucassen, P. J. (2005). The stress system in the human brain in depression and neurodegeneration. *Ageing Research Reviews*, *4*, 141–194.

Swardfager, W., Herrmann, N., Dowlati, Y., Oh, P. I., Kiss, A., Walker, S. E., & Lanctôt, K. L. (2009). Indoleamine 2,3-dioxygenase activation and depressive symptoms in patients with coronary artery disease. *Psychoneuroendocrinology*, *34*, 1560–1566.

Takizawa, R., Danese, A., Maughan, B., & Arseneault, L. (2015). Bullying victimization in childhood predicts inflammation and obesity at mid-life: A five-decade birth cohort study. *Psychological Medicine*, *45*, 2705–2715.

Tan, E. Y. L., Köhler, S., Hamel, R. E. G., Muñoz-Sánchez, J. L., Verhey, F. R. J., & Ramakers, I. H. G. B. (2019). Depressive symptoms in mild cognitive impairment and the risk of dementia: a systematic review and comparative meta-analysis of clinical and community-based studies. *Journal of Alzheimer's Disease*, *67*, 1319–1329.

Tang, D., Kang, R., Coyne, C. B., Zeh, H. J., & Lotze, M. T. (2012). PAMPs and DAMPs: Signal 0s that Spur autophagy and immunity. *Immunological Reviews*, *249*, 158–175.

Tang, Y., & Le, W. (2016). Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Molecular Neurobiology*, *53*, 1181–1194.

Tanti, A., & Belzung, C. (2013a). Hippocampal neurogenesis: A biomarker for depression or antidepressant effects? Methodological considerations and perspectives for future research. *Cell and Tissue Research*, *354*, 203–219.

Tanti, A., & Belzung, C. (2013b). Neurogenesis along the septo-temporal axis of the hippocampus: Are depression and the action of antidepressants region-specific? *Neuroscience*, *252*, 234–252.

Thomson, F., & Craighead, M. (2008). Innovative approaches for the treatment of depression: Targeting the HPA axis. *Neurochemical Research*, *33*, 691–707.

Toda, T., Parylak, S. L., Linker, S. B., & Gage, F. H. (2019). The role of adult hippocampal neurogenesis in brain health and disease. *Molecular Psychiatry*, *24*, 67–87.

Tracey, K. J. (2009). Reflex control of immunity. *Nature Reviews Immunology*, *9*, 418–428.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., … Fava, M. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *American Journal of Psychiatry*, *163*, 28–40.

Tuckermann, J. P., Kleiman, A., Moriggl, R., Spanbroek, R., Neumann, A., Illing, A., … Schütz, G. (2007). Macrophages and neutrophils are the targets for immune suppression by glucocorticoids in contact allergy. *Journal of Clinical Investigation*, *117*, 1381–1390.

Turvey, S. E., & Broide, D. H. (2010) Chapter 2: Innate immunity. *Journal of Allergy and Clinical Immunology*, *125*, S24–S32.

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, *10*, 397–409.

van Agtmaal, M. J. M., Houben, A. J. H. M., Pouwer, F., Stehouwer, C. D. A., & Schram, M. T. (2017). Association of microvascular dysfunction with late-life depression: A systematic review and meta-analysis. *JAMA Psychiatry*, *74*, 729–739.

Vreeburg, S. A., Hoogendijk, W. J., van Pelt, J., Derijk, R. H., Verhagen, J. C., van Dyck, R., … Penninx, B. W. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: Results from a large cohort study. *Archives of General Psychiatry*, *66*, 617–626.

Wagshul, M. E., Eide, P. K., & Madsen, J. R. (2011). The pulsating brain: A review of experimental and clinical studies of intracranial pulsatility. *Fluids Barriers CNS*, *8*, 5.

Walker, A. K., Budac, D. P., Bisulco, S., Lee, A. W., Smith, R. A., Beenders, B., … Dantzer, R. (2013). NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology*, *38*, 1609–1616.

Wang, L., Chang, X., She, L., Xu, D., Huang, W., & Poo, M. (2015). Autocrine action of BDNF on dendrite development of adult-born hippocampal neurons. *Journal of Neuroscience*, *35*, 8384–8393.

Wang, S., Mao, S., Xiang, D., & Fang, C. (2018). Association between depression and the subsequent risk of Parkinson's disease: A meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *86*, 186–192.

Wang, X., Fu, S., Wang, Y., Yu, P., Hu, J., Gu, W., … Lu, P. (2007). Interleukin-1beta mediates proliferation and differentiation of multipotent neural precursor cells through the activation of SAPK/JNK pathway. *Molecular and Cellular Neurosciences*, *36*, 343–354.

Whitacre, C. C. (2001). Sex differences in autoimmune disease. *Nature Immunology*, *2*, 777–780.

Wu, C.-W., Chen, Y.-C., Yu, L., Chen, H., Jen, C. J., Huang, A.-M., … Kuo, Y.-M. (2007). Treadmill exercise counteracts the suppressive effects of peripheral lipopolysaccharide on hippocampal neurogenesis and learning and memory. *Journal of Neurochemistry*, *103*, 2471–2481.

Wu, H.-Q., Pereira, E. F. R., Bruno, J. P., Pellicciari, R., Albuquerque, E. X., & Schwarcz, R. (2010). The astrocyte-derived alpha7 nicotinic receptor antagonist kynurenic acid controls extracellular glutamate levels in the prefrontal cortex. *Journal of Molecular Neuroscience*, *40*, 204–210.

Wu, M. D., Hein, A. M., Moravan, M. J., Shaftel, S. S., Olschowka, J. A., & O'Banion, M. K. (2012). Adult murine hippocampal neurogenesis is inhibited by sustained IL-1β and not rescued by voluntary running. *Brain, Behavior, and Immunity*, *26*, 292–300.

Wurfel, B. E., Drevets, W. C., Bliss, S. A., McMillin, J. R., Suzuki, H., Ford, B. N., … Savitz, J. B. (2017). Serum kynurenic acid is reduced in affective psychosis. *Translational Psychiatry*, *7*, e1115.

Yang, S.-J., Han, A. R., Kim, E.-A., Yang, J. W., Ahn, J.-Y., Na, J.-M., & Cho, S.-W. (2019). KHG21834 attenuates glutamate-induced mitochondrial damage, apoptosis, and NLRP3 inflammasome activation in SH-SY5Y human neuroblastoma cells. *European Journal of Pharmacology*, *856*, 172412.

Yirmiya, R., Winocur, G., & Goshen, I. (2002). Brain interleukin-1 is involved in spatial memory and passive avoidance conditioning. *Neurobiology of Learning and Memory*, *78*, 379–389.

Yuan, J., Ge, H., Liu, W., Zhu, H., Chen, Y., Zhang, X., … Lin, J. (2017). M2 microglia promotes neurogenesis and oligodendrogenesis from neural stem/progenitor cells via the PPARγ signaling pathway. *Oncotarget*, *8*, 19855–19865.

Zheng, L.-S., Hitoshi, S., Kaneko, N., Takao, K., Miyakawa, T., Tanaka, Y., … Sawamoto, K. (2014). Mechanisms for interferon-α-induced depression and neural stem cell dysfunction. *Stem Cell Reports*, *3*, 73–84.

Zonis, S., Ljubimov, V. A., Mahgerefteh, M., Pechnick, R. N., Wawrowsky, K., & Chesnokova, V. (2013). p21Cip restrains hippocampal neurogenesis and protects neuronal progenitors from apoptosis during acute systemic inflammation. *Hippocampus*, *23*, 1383–1394.

Zonta, M., Angulo, M. C., Gobbo, S., Rosengarten, B., Hossmann, K.-A., Pozzan, T., & Carmignoto, G. (2003). Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nature Neuroscience*, *6*, 43.

Zunszain, P. A., Anacker, C., Cattaneo, A., Choudhury, S., Musaelyan, K., Myint, A. M., … Pariante, C. M. (2012). Interleukin-1β: A new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology*, *37*, 939–949.

How to cite this article: Troubat R, Barone P, Leman S, et al. Neuroinflammation and depression: A review. *Eur J Neurosci*. 2021;53:151–171. https://doi.org/10.1111/ejn.14720