Neuroinflammation and depression: A review

Romain Troubat1 | Pascal Barone1 | Samuel Leman1 | Thomas Desmidt1,2 | Arnaud Cressant1 | Boriana Atanasova1 | Bruno Brizard1 | Wissam El Hage1,2 | Alexandre Surget1 | Catherine Belzung1 | Vincent Camus1,2

1UMR 1253, iBrain, Université de Tours, Inserm, Tours, France
2CHRU 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, hypothalamus–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 monoxygenase; 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.

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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, & Khadaker, 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 immune 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, & Beck, 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 18F- or 11C-radiolabelled ligands to allow visualization of activated microglia including [11C]-PBR28, [11C]-PK11195 and [18F]-FEPPA. Since an initial negative result comparing [11C]-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 $^{[1]}$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 metabolotropic 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, & Meinel, 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-isoxazolopropionic 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 a member of the inflammasome family, a group of intracellular multi-protein 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 Th1 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 knock-out (KO) mice are less sensitive to stress and display a less pronounced behavioural depressive-like phenotype after LPS challenge (Csöllé 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 (Faroq 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 serotonergic 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 synthesized 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 monoxygenase (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 (Schwarz & Stone, 2017). KYN can also be metabolized via a “neuroprotective pathway” to kynurenic acid (KNA) by the enzyme kynurenine–amino-transferase, which is mainly expressed by astrocytes (Schwarcz et al., 2012). Unlike QUIN, KNA 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 synthesized 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...
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 plasma and CSF samples 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 cortico 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 KO—/- 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 (Laugeral 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 & Buttgerieg, 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 adrenocorticotrophic 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; Pariente, 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 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
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, Galiher-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 fulfill 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 (Rivet, 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 E2 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 neuro progenitor (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; Lachpak, 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 antimarial effect (Bai et al., 2019).

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 1  Clinical evidence of neuroinflammation hypothesis in major depressive disorder

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

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

<table>
<thead>
<tr>
<th>Physiopathology</th>
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<tbody>
<tr>
<td>Neuroinflammation (NI) is mainly supported by microglial cells and astrocytes</td>
</tr>
<tr>
<td>NI results from activation of immune cells through stimulation of Pattern Recognition Receptors (PRRs) such as Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) including Toll-like receptors, P2X7 receptors…</td>
</tr>
<tr>
<td>Specific Pathogen-Associated Molecular Patterns (PAMPs) like lipopolysaccharide can trigger pro-inflammatory cytokines and lead to “sickness behaviour”</td>
</tr>
<tr>
<td>NI alters serotonin synthesis in switching tryptophan (TRY) catabolism in favour of Kynurenine (KYN) synthesis which metabolite Quinolinic Acid increases Glutamate neurotransmission</td>
</tr>
<tr>
<td>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 Inflamasome</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>“Stere 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</td>
</tr>
</tbody>
</table>
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, 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 (Grönberg, 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 be 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

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