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## How Inflammation Affects the Brain in Depression: A Review of Functional and Structural MRI Studies

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This narrative review discusses how peripheral and central inflammation processes affect brain function and structure in depression, and reports on recent peripheral inflammatory marker-based functional and structural magnetic resonance imaging (MRI) studies from the perspective of neural-circuit dysfunction in depression. Chronic stress stimulates the activity of microglial cells, which increases the production of pro-inflammatory cytokines in the brain. In addition, microglial activation promotes a shift from the synthesis of serotonin to the synthesis of neurotoxic metabolites of the kynurenine pathway, which induces glutamatemediated excitotoxicity in neurons. Furthermore, the region specificity of microglial activation is hypothesized to contribute to the vulnerability of specific brain regions in the depressionrelated neural circuits to inflammation-mediated brain injury. MRI studies are increasingly investigating how the blood levels of inflammatory markers such as C-reactive protein, interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  are associated with functional and structural neuroimaging markers in depression. Functional MRI studies have found that peripheral inflammatory markers are associated with aberrant activation patterns and altered functional connectivity in neural circuits involved in emotion regulation, reward processing, and cognitive control in depression. Structural MRI studies have suggested that peripheral inflammatory markers are related to reduced cortical gray matter and subcortical volumes, cortical thinning, and decreased integrity of white matter tracts within depression-related neural circuits. These neuroimaging findings may improve our understanding of the relationships between neuroinflammatory processes at the molecular level and macroscale in vivo neuralcircuit dysfunction in depression.

**Keywords** depression; major depressive disorder; inflammation; magnetic resonance imaging; neuroimaging.

## **INTRODUCTION**

Depression is a common debilitating disease worldwide that affects one in six adults during their lifetime.<sup>1</sup> It is the second-most-important contributor to the global disease burden quantified as disability-adjusted life years.<sup>2</sup> Depression is also associated with low job productivity,<sup>3</sup> poor health-related quality of life,<sup>4</sup> and increased health-care utilization and costs,<sup>5</sup> and has a high mortality rate.<sup>6</sup> The main clinical features of depression are persistent low mood, anhedonia, cognitive bias (e.g., negative thoughts and feelings of worthlessness and guilt), fatigue, changes in appetite and weight, sleep disturbance, psychomotor retardation and agitation, suicidal thoughts and attempts, and cognitive impairment.<sup>7</sup>

Advances in the understanding of the pathophysiology of depression have revealed multifaceted neurobiological characteristics of the disease, including a genetic predisposition, monoaminergic deficiency (e.g., serotonin, norepinephrine, and dopamine), dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, decreased neuroplasticity, disruption of

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circadian rhythm, and cerebrovascular disease.<sup>7-12</sup> Recent advances in neuroimaging analysis techniques have led to the hypothesis found that the aforementioned etiological factors lead to the development of depression via dysfunction of the neural circuits involved in emotion, reward, and cognitive processing.<sup>13</sup> Furthermore, evidence has accumulated over the past 3 decades that neural–immune interactions contribute to the pathogenesis of depression.<sup>14,15</sup>

The findings of numerous studies support the hypothesis that heightened inflammatory responses in the brain play a pivotal role in the development of depression.<sup>16</sup> Clinically there is a high rate of comorbidity between depression and inflammation-related medical conditions such as inflammatory bowel disease,<sup>17</sup> asthma,<sup>18</sup> rheumatoid arthritis,<sup>19</sup> diabetes mellitus,<sup>20</sup> and cancer.<sup>21</sup> Inflammation is also involved in the pathophysiology of several neurological disorders that have high rates of comorbidity with depression, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease, stroke, and migraine.<sup>22-29</sup> The systemic administration of interferon (IFN)-a or interleukin (IL)-2 (which exert proinflammatory exerts) to boost antitumor responses or amplify antiviral immunity has been reported to induce depression in 20%-50% of patients.<sup>15,30</sup> This clinical evidence supports the hypothesis that inflammation is closely involved in the pathophysiology of depression. Recent meta-analyses have provided further support for this hypothesis, by finding that the peripheral levels of inflammatory markers such as C-reactive protein (CRP), IL-6, IL-10, IL-12, tumor necrosis factor-a (TNF-a), soluble IL-2 receptor (sIL-2R), and IL-1 receptor antagonist are significantly higher in patients with depression than in healthy controls.31-33 Furthermore, the findings of numerous animal and human studies suggest that the inflammatory response to an immune challenge induces depression-like sickness behavior,<sup>34</sup> whereas knocking out inflammation-related receptors (e.g., TNF-a or IL-6) provides resilience to depressive-like behavior in a chronic stress condition in animal models.<sup>35,36</sup>

While it is unclear how the inflammatory response affects brain networks involved in the psychopathology of depression, it has been suggested that proinflammatory cytokines and several metabolites from inflammatory processes in the central nervous system (CNS) exert direct neurotoxic effects on the brain.<sup>37</sup> These effects may lead to dysfunction of the neural circuits involved in emotion regulation and reward or cognitive processing, which is associated with overwhelming low mood, failure of top-down emotion regulation, decreased motivation and anhedonia, and cognitive impairment in depression.<sup>13</sup> Recent studies have investigated the complex relationship between the inflammatory state—as measured by peripheral inflammatory markers—and dysfunction and structural alterations of the brain using neuroimaging tools such as functional and structural magnetic resonance imaging (MRI), which has revealed that a heightened inflammatory response may affect depression-related neural-circuit dysfunction.<sup>38,39</sup>

This narrative review article discusses how peripheral and central inflammation processes affect brain function and structure in depression, and reports on recent peripheral inflammatory marker-based functional and structural MRI studies from the perspective of neural-circuit dysfunction in depression.

## HOW PERIPHERAL AND CENTRAL INFLAMMATION PROCESSES AFFECT THE BRAIN

The neuroinflammation hypothesis of depression suggests that stress-associated changes in the immune system induce an elevated inflammatory response in the CNS (e.g., neuroinflammation), which contributes to the development of depression via the neurotoxic effects of proinflammatory cytokines and several metabolites from inflammatory processes.<sup>40</sup> Chronic stress is a prominent etiological factor of depression, and involves the main pathway through which systemic inflammation can lead to increased neuroinflammation. Chronic stress increases the permeability of the blood-brain barrier (BBB) and the production of proinflammatory cytokines, which can be transported across the BBB via circumventricular organs and cytokine-specific BBB transporters.37 The systemic inflammation resulting from chronic stress can disrupt the BBB via mechanisms such as modification of tight junctions, endothelial damage, degradation of glycocalyx, breakdown of glia limitans, and functional changes in astrocytes through pathways involving prostanoids, nitric oxide, reactive oxygen species (ROS), and matrix metalloproteinases.<sup>41</sup> Another involved pathway is via chronic stress increasing the tone of the sympathetic nervous system, which increases the level of peripheral monocytes that can infiltrate the brain and stimulate microglial activity.42 The activated microglial cells will led to the release of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, which exert direct neurotoxic effects on the brain.43 Proinflammatory cytokines stimulate the HPA axis to release cortisol that further exacerbates the systemic stress response, and prolonged exposure to cortisol can impair inflammatory regulation by reducing the sensitivity of the peripheral immune systems to anti-inflammatory feedback, thus constituting a vicious cycle.42 This has led to suggestions that increased levels of proinflammatory cytokines are a biomarker for depression. A recent meta-analysis of peripheral inflammatory markers using the data of 5,166 patients with depression and 5,083 healthy controls found that the serum levels of IL-3, IL-6, IL-12, IL-18, sIL-2R, TNF-a, and CRP were significantly higher in patients with depression than in healthy controls.33

The kynurenine pathway also links the neuroinflammation state (i.e., increased proinflammatory cytokines in the CNS) and neurotoxic effects on the brain. Serotonin is synthesized from the essential amino acid L-tryptophan by tryptophan hydroxylase, whereas proinflammatory cytokines promote another tryptophan metabolism pathway, namely the kynurenine pathway, by increasing the activity of indoleamine 2,3-dioxygenase (IDO), which metabolizes tryptophan to kynurenine.40 Kynurenine is subsequently catabolized by kynurenine 3-monooxygenase into 3-hydroxy-kynurenine (3-HK), 3-hydroxy-anthralinic acid (3-HA), and quinolinic acid (QUIN), which exert neurotoxic effects. Kynurenine is also catabolized by kynurenine aminotransferase into kynurenic acid (KYNA), which exerts a neuroprotective effect.<sup>40</sup> An increase in kynurenine-pathway metabolites due to a shift away from the synthesis of serotonin may deplete serotonin in the CNS, which is closely involved in the pathophysiology of depression.44

Regarding the neurotoxic effects of tryptophan metabolites, 3-HK promotes oxidative stress and neuronal apoptosis as a potent free-radical donor, and 3-HA generates reactive hydrogen peroxide and hydroxyl radicals.<sup>37</sup> In particular, QUIN exerts a neurotoxic effect by modulating glutamatergic neurotransmission. QUIN, which exerts agonistic effects at Nmethyl-d-aspartate (NMDA) receptors, induces glutamate release and simultaneously inhibits glutamate reuptake and the action of glutamine synthetase.37 This leads to increased extracellular glutamate and excitatory neuron activation that cause excitotoxicity and the apoptosis of neurons.<sup>45</sup> In addition, QUIN metabolized into nicotinamide adenine dinucleotide induces oxidative stress and exerts a synergistic detrimental effect via glutamate-mediated excitotoxicity.40 Meanwhile, KYNA counteracts the neurotoxic effects of tryptophan metabolites through antioxidant activity and a nonselective antagonistic effect at NMDA receptors, but such neuroprotective effects of KYNA are weakened in neuroinflammation.<sup>46</sup> The production of KYNA from kynurenine is inhibited by proinflammatory cytokines such as IL-1β, TNF-α, and IFN-y.46 A chronic imbalance in the kynurenine pathway-increases in neurotoxic metabolites (i.e., QUIN, 3-HK, and 3-HA) and decreases in the neuroprotective metabolite (i.e., KYNA)exerts detrimental effects on the brain by disrupting the homeostasis of glutamatergic neurotransmission.47 This results in greater activation of the NMDA receptors, which leads to increases in calcium and sodium influx and potentially causes increased excitotoxicity and apoptosis, decreased synaptic plasticity, and eventually neuron death.<sup>47</sup> This neurotoxic process may increase the vulnerability of an individual to depression. The ratios between KYNA and other neurotoxic metabolites, particularly QUIN, closely reflect the presence of chronic imbalance of kynurenine-pathway metabolites. A recent meta-analysis of these metabolites found that the KYNA/ QUIN, KYNA/3-HK, and KYNA/kynurenine ratios are significantly lower in patients with major depressive disorder (MDD) than in healthy controls.<sup>48</sup>

Furthermore, microglial cells affect glutamatergic neurotransmission via pathways mediated by proinflammatory cytokines and  $\gamma$ -aminobutyric acid (GABA)ergic neurons. Activated microglial cells release IL-6, which increases the expression of nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and NOX2-derived ROS production in GABAergic neurons.<sup>49</sup> The subsequent alteration of GABAergic neurotransmission leads to the loss of inhibition of glutamatergic neurons, which causes an excessive increase in glutamate release and results in glutamate-mediated excitotoxicity in neurons.<sup>50</sup>

## NEUROINFLAMMATION AND DYSFUNCTION OF NEURAL CIRCUITS INVOLVED IN DEPRESSION

As stated in the previous section, the neuroinflammation state can be characterized by increased levels of proinflammatory cytokines in the CNS in response to changes in the peripheral and/or central immune systems.42 Chronic stress activates microglial cells to release proinflammatory cytokines by promoting the infiltration of peripheral monocytes into the brain, resulting in the stimulation of microglial activity.<sup>40</sup> Thereafter, increased levels of proinflammatory cytokines may exert a direct neurotoxic effect or induce glutamate-mediated excitotoxicity by stimulating IDO enzyme activity in microglial cells.<sup>46</sup> This implies that microglial cells play a pivotal role in the link between neuroinflammation and brain damage, and furthermore that microglial cells may provide a clue to how neuroinflammation affects the neural circuits involved in depression.<sup>15</sup> Several studies have suggested that neuroinflammatory processes affect specific brain regions, particularly the anterior cingulate cortex (ACC), prefrontal cortex (PFC), hippocampus, and insula, which are closely involved in the pathophysiology of depression. The density of microglial cells may vary between different parts of the human brain. Previous postmortem studies of patients with depression or suicidal attempters have revealed microglial overactivation mainly in the ACC and PFC, which play critical roles in emotion regulation.<sup>51-53</sup> For example, a postmortem study of 24 patients with MDD and 17 healthy controls found that the ratio of primed ("activated") to ramified ("resting") microglial cells in the dorsal ACC white matter was significantly higher in suicidal attempters with MDD than in healthy controls.<sup>51</sup> In addition, Steiner et al.54 found that the densities of QUINimmunopositive microglial cells in the subgenual ACC and anterior midcingulate cortex were significantly higher in 12 patients with acute depression and suicidal behaviors than in 10 normal controls.

Recent advances in radiotracer techniques have made it possible to measure microglial activation in vivo by quantifying the expression of translocator protein (TSPO) in addition to the microglial cell density.55 TSPO, a widely used marker for neuroinflammation, is a 18-kDa mitochondrial protein located in the outer membrane of microglial cells that is involved in several physiological processes such as cholesterol transport and steroid synthesis.56 However, in several inflammatory conditions, TSPO expression is increased in association with alterations of the functional state and phenotype of microglial cells.<sup>57</sup> Positron-emission tomography (PET) using a radiotracer with a high protein binding affinity for TSPO can be used to measure in vivo microglial activation.55 Recent studies using TSPO PET with radiotracers such as [11C]PK11195, [18F]FEPPA, and [11C]PBR28 found that TSPO expression is significantly higher in patients with MDD than in healthy controls, especially in the PFC, ACC, hippocampal formation, and insula.58-63 TSPO PET studies have also revealed that the TSPO expression level is significantly correlated with various clinical characteristics, including the severity of depressive symptoms,<sup>58</sup> duration of untreated illness,<sup>63</sup> suicidal thoughts,<sup>60</sup> cognitive impairment,<sup>61</sup> and degree of amelioration of depressive symptoms after 16 weeks of cognitive behavioral therapy.64 There is evidence from TSPO PET studies that the contribution of microglial activity-which plays a pivotal role in neuroinflammatory processes-to the pathogenesis of depression is region specific, with a greater involvement of brain regions in charge of emotion regulation and cognitive processing.

Increased microglial activity leads to abnormal glutamatergic neurotransmission and glutamate-mediated excitotoxicity in specific brain regions (those that are more vulnerable to neuroinflammation-mediated damage) via the increased production of QUIN in neuroinflammatory processes.<sup>15</sup> Several magnetic resonance spectroscopy (MRS) studies have found peripheral inflammation to be significantly associated with alterations of glutamate metabolism in the ACC and basal ganglia, which is involved in emotion regulation and reward processing, and that the changes in glutamate metabolism are associated with depressive symptoms.65-67 For example, Haroon et al.65 found that administering IFN-α, which increases peripheral cytokines such as TNF-α and its soluble receptors, was associated with an increase in the normalized concentration of glutamate (i.e., glutamate/creatinine ratio) in the dorsal ACC and left basal ganglia, and that the glutamate concentration was positively correlated with the severity of depressive symptoms. Another study by the same authors found that the plasma level of CRP was positively correlated with the glutamate concentration in the left basal ganglia, which in turn was associated with specific depressive symptoms such as anhedonia and psychomotor speed reduction in medication-free patients with depression.<sup>66</sup> These findings support the hypothesis that the peripheral inflammatory response leads to glutamate metabolism abnormalities through microglial activation in specific brain regions such as the ACC and basal ganglia in patients with depression.<sup>68</sup>

Direct neurotoxic effects of proinflammatory cytokines on adult hippocampal neurogenesis also underlie region-specific neuroinflammation.<sup>40</sup> The subgranular zone of the dentate gyrus in the hippocampus is well known for adult neurogenesis (i.e., the continuous generation of new neurons), and new neurons in the dentate gyrus develop into mature neurons and become functionally integrated into the existing neural circuits.69 There is a neurogenic hypothesis of depression that adult hippocampal neurogenesis is closely involved in the pathophysiology of depression and how this condition responds to antidepressants.<sup>70</sup> Animal studies have found that chronic stress suppresses adult hippocampal neurogenesis,71,72 and experimentally induced increases in this neurogenesis promote resilience to the corticosterone-induced depressivelike behavior.73 In addition, preclinical studies have suggested that stress- and glucocorticoid-induced suppression of adult hippocampal neurogenesis can be prevented or reversed by administering antidepressants,<sup>70</sup> and that reversing hippocampal neurogenesis can block responses to antidepressants.<sup>40</sup> A reduction of the hippocampus volume is the most consistent structural MRI finding in patients with MDD.74,75 Moreover, neuroinflammation can suppress adult hippocampal neurogenesis.40 Preclinical studies have found that inducing an inflammatory response by administering lipopolysaccharide (LPS) or IFN-α leads to depressive-like behavior and attenuation of adult hippocampal neurogenesis in rodents.76-79 The main pathway involved in the association between neuroinflammation and inhibition of adult neurogenesis is microglial activation-induced release of proinflammatory cytokines such as TNF- $\alpha$ , IFN- $\alpha$ , IL-1 $\beta$  and IL-6.<sup>40</sup> IL-1 $\beta$  could be a key proinflammatory cytokine involved in the direct neurotoxic effects acting on adult hippocampal neurogenesis.40 Administering IL-1 $\beta$  or its inducers such as LPS and IFN- $\alpha$ reportedly suppresses hippocampal neurogenesis and increases depressive-like behaviors in animal models.79,80 Strong expression of the IL-1 type-1 receptor in the hippocampus may explain the direct neurotoxic effect of IL-1ß on hippocampal neurogenesis.<sup>81,82</sup> These detrimental effects of proinflammatory cytokines induced by microglial activation may explain the region-specific influence of neuroinflammatory processes in the hippocampus.

## PERIPHERAL INFLAMMATORY MARKERS AND DEPRESSION: FUNCTIONAL NEUROIMAGING FINDINGS

Advances in neuroimaging methods over the past 3 decades have revealed that depression can be characterized by dysfunction of the neural circuits involved in emotion regulation, selfreflection, reward processing, and cognitive control.<sup>13,83</sup> A neural circuit refers to a large-scale neural network consisting of the functionally and structurally interconnected neurons that make up the connectome of the brain.<sup>84</sup> Dysfunction of specific neural circuits has been suggested to be associated with specific psychopathologies of depression, such as persistent low mood, anhedonia, negative bias, rumination of negative thoughts, attention and memory difficulties, and poor cognitive control of negative emotions.85 Based on recent improvements in the understanding of neural-circuit dysfunction in depression, the frontolimbic circuit model of depression suggests that the ventral part of the ACC, the ventromedial prefrontal cortex (vmPFC), and the medial orbitofrontal cortex (OFC) perform recognition and implicit/automatic regulation of emotional salience generated by the amygdala in response to external emotional stimuli. Meanwhile, the lateral part of the PFC, including the dorsolateral prefrontal cortex (dlPFC), the ventrolateral prefrontal cortex (vlPFC), and the dorsal part of the ACC, perform cognitive, voluntary, and effortful emotion regulation; namely, the top-down control of emotion.13 In this neural-circuit model, different types of neural-circuit dysfunction such as abnormally elevated activity of the amygdala and vmPFC, decreased activity of the dlPFC, and reduced functional connectivity between the vmPFC and amygdala-which reflect the failure of top-down control of emotion-are associated with overwhelming negative emotion and persistent low mood.<sup>86</sup> Regarding reward processing, the ventral striatum, vmPFC, OFC, and dorsal ACC are reportedly involved in the sensitivity to and anticipation of salient reward stimuli, while different types of reward-processing neural-circuit dysfunction such as decreased ventral striatal activity, increased habituation of the ventral striatum, and greater activation of the OFC and vmPFC in response to reward stimuli are associated with anhedonia.<sup>84</sup> Furthermore, aberrant functional patterns in the cognitive control network consisting of the dlPFC, ACC, dorsal parietal cortex, and precentral gyrus are associated with impairments in cognitive processes such as working memory and selective attention in depression.87 The default mode network (DMN) consisting of the posterior cingulate cortex (PCC), vmPFC, and angular gyrus is closely involved in self-referential thinking at rest.84 Dysfunction of the DMN, and especially hyperconnectivity of the anterior medial part of the PFC, has been reported to be associated with the rumination of negative thoughts, which is a characteristic symptomatology of depression.<sup>88-90</sup>

Several neuroimaging studies have investigated the causal relationship between systemic inflammation and functional alterations in the neural circuits involved in the pathophysiology of depression. In addition to neuroimaging studies conducted in patients with depression, several studies have investigated the nonpsychiatric population, such as whether experimentally induced systemic inflammation (e.g., by typhoid vaccination, IFN-α treatment, or low-dose endotoxin) may alter the activity pattern of neural circuits involved in emotion, motivation, and cognition.91-94 For example, a functional MRI (fMRI) study by Harrison et al.92 using a probabilistic instrumental learning task, in which participants had to learn to seek a high-probability reward and avoid a high-probability punishment, investigated whether acute inflammatory challenges (i.e., typhoid vaccination at 2.5-3.5 h before the fMRI scan) affected the activity patterns of the ventral striatum and anterior insula, which are involved in reward and punishment prediction, respectively. That study found that typhoid vaccination was associated with a lower reward prediction error in the ventral striatum and higher punishment prediction error in the anterior insula, indicating that acute inflammation may enhance the sensitivity to punishments versus rewards.92 In the same vein as that study, an fMRI study by Eisenberger et al.93 found that administering low-dose endotoxin was associated with decreased ventral striatal activity in response to monetary reward cues, which was related to self-rated depressive mood in healthy participants. These findings indicate that acute systemic inflammation may induce disturbances in neural processes of motivational behavior, which can lead to anhedonia in depression. Moreover, other fMRI studies with similar designs have found experimentally induced inflammatory challenges to be associated with increased subgenual ACC activity and decreased functional connectivity of the subgenual ACC with the amygdala, medial PFC, or ventral striatum in an emotion-processing task,<sup>91</sup> or reductions in graphic-theory-based global network connectivity and efficiency, both of which are associated with mood deterioration.94 A particularly interesting observation has been that acute laboratory-based social stressors in the absence of experimentally induced inflammatory challenges are associated with increased levels of peripheral inflammatory markers (e.g., IL-6, TNF- $\alpha$ , and soluble receptor for TNF- $\alpha$ ), which in turn are associated with increased amygdala activity and functional connectivity of the amygdala with the dorsomedial prefrontal cortex (dmPFC)95 or increased dorsal ACC and anterior insula activity96 during social-stress tasks in healthy young adults.

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Given the aforementioned neuroimaging findings in the nonpsychiatric population and the hypothesis that the peripheral inflammatory state is associated with the neuroinflammatory state,53 MRI has been used increasingly to investigate the association between blood levels of peripheral inflammatory markers and functional neuroimaging markers in patients with depression.38,97-102 Regarding reward-processing neural-circuit dysfunction, striatal activity was found to be negatively correlated with serum CRP levels in patients with depression. Burrows et al.<sup>102</sup> found that patients with MDD and a high CRP level (>3 mg/L) showed lower activation of the dorsal caudate, thalamus, left insula, and left precuneus compared with patients with MDD and a low CRP level ( $\leq 3 \text{ mg/L}$ ) when anticipating a win in the monetary incentive delay task. A resting-state fMRI study found that the CRP level was negatively correlated with functional connectivity between the ventral striatum and vmPFC, which in turn was correlated with the severity of anhedonia in patients with MDD.38 An fMRI study by Conejero et al.97 used a social exclusion task to reveal that the activation pattern of the emotion-regulation neural circuit in response to social-rejectioninduced psychological distress was associated with peripheral inflammation in currently euthymic patients with MDD. Those authors found that the serum IL-1ß level was negatively correlated with the activation level of the right OFC, whereas the IL-2 level was positively correlated with the activation levels of the right ACC, insula, and OFC during explicit social exclusion versus a social-inclusion task.97 Another fMRI study found that the blood level of arachidonic acid, which is the main precursor of proinflammatory eicosanoids, was negatively correlated with the activity of the left amygdala during an emotional-face task.98 The functional network between the amygdala and vmPFC is the critical part of the emotion-regulation neural circuit because the vmPFC is involved in the automatic and implicit regulation of negative emotions generated by the amygdala.86 Similarly, a resting-state fMRI study found that the serum CRP level was negatively correlated with functional connectivity between the right vmPFC and left amygdala, which in turn was associated with anxiety symptoms in patients with depression.<sup>101</sup> Yin et al.<sup>100</sup> found that the plasma CRP level was negatively correlated with global brain connectivity in the vmPFC cluster and with functional connectivity of the vmPFC with other brain regions. This finding implies that the vmPFC is a pivotal part of the brain network influenced by systemic inflammation. Regarding cognitive impairment in depression, autobiographical memory (AM) deficit-the difficulty of recalling specific personal past events with a tendency to recall more-general events without their details-is a well-known predictor of the onset and course of depression.103 An fMRI study using an emotionally valenced

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AM recall task found that patients with MDD recalled fewer specific AMs and showed increased activity in the left hippocampus during AM recall, which was negatively correlated with the KYNA/3-HK ratio.<sup>99</sup> This indicated that a shift toward neurotoxic metabolites in the kynurenine pathway may lead to AM deficits via changes in the activity of the hippocampus.

## PERIPHERAL INFLAMMATORY MARKERS AND DEPRESSION: STRUCTURAL NEUROIMAGING FINDINGS

The concordance of structural and functional brain abnormalities is well documented in depression, and co-localization of structural and functional disease effects is anticipated in depression.<sup>104,105</sup> A recent meta-analysis found a correspondence between abnormalities of gray-matter volumes and resting-state brain activation in the subgenual ACC, hippocampus, amygdala, and putamen in patients with MDD.<sup>106</sup> Structural and functional brain alterations might have a bidirectional property with regard to their association with neuroinflammation. Functional brain abnormalities observed in depression may be mediated by the underlying structural abnormalities influenced by neuroinflammation, and chronic functional alterations of the brain induced by neuroinflammation may lead to morphological changes in the brain.<sup>107</sup> From the perspective of brain network dysfunction, changes in the gray-matter volume and cortical thickness may represent the structural basis of dysfunction in nodes of the brain network, while microstructural abnormalities of white-matter tracts may represent the disruption of pathways between the nodes of the brain network.<sup>87</sup> Based on the assumption that neuroinflammation-induced functional and structural abnormalities could be strongly intercorrelated, several structural MRI studies have explored the relationships between peripheral inflammatory markers (which may be surrogate markers for neuroinflammation) and structural neuroimaging markers such as the cortical gray matter and subcortical volumes, cortical thickness, and white-matter-tract integrity in patients with depression.

Regarding subcortical volume alterations, structural MRI studies of peripheral inflammatory markers have identified an association between the striatal volume and kynurenine-pathway metabolites in patients with depression. Savitz et al.<sup>108</sup> found that the serum kynurenine-to-tryptophan ratio, which represents IDO enzyme activity in the kynurenine pathway, was negatively correlated with the striatal volume (sum of the volumes of nucleus accumbens, caudate, and putamen). Those authors additionally found that the KYNA/QUIN ratio, which was decreased in patients with MDD, was non-significantly

correlated with the severity of anhedonia. Neurogenesis in the hippocampus, which plays a critical role in emotion regulation and cognitive processing, can be enhanced by the actions of antidepressants and inhibited by neuroinflammatory processes in depression.40,70 Two recent studies investigated changes in the hippocampus volume induced by antidepressants and electroconvulsive therapy (ECT), and their correlation with changes in the levels of peripheral inflammatory markers after treating patients with depression. Belge et al.<sup>109</sup> found that an increase in the combined volume of both hippocampi was negatively correlated with the reduction of the plasma IL-6 and TNF-a levels after ECT sessions in patients with MDD. However, another structural MRI study found that the right hippocampus volume was significantly increased after six intravenous infusions of ketamine over 12 days in patients with MDD; however, that volume change was not associated with changes in the levels of peripheral inflammatory markers such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and KYNA after the treatment.<sup>110</sup>

Smagula et al.111 found that the plasma level of the chemokine eotaxin was significantly negatively correlated with the cortical gray-matter volume of the whole brain in patients with late-life depression (at an age of  $\geq 60$  years). Those authors additionally observed that the level of eotaxin was negatively correlated with executive function (set-shifting performance) as measured by the Trail-Making Test.111 Another structural MRI study (by Chen et al.<sup>112</sup>) investigated 44 patients with mood disorders (22 with MDD and 22 with bipolar disorder) and 22 healthy controls, and found that the serum level of TNF-a receptor-1 was positively correlated with the gray-matter volume of the left middle frontal cortex, which was positively correlated with executive function as measured by the Wisconsin Card Sorting Test in the entire sample. Similar to the aforementioned two studies, a study involving a larger sample of the nonpsychiatric population found significant correlations between several peripheral markers and the gray-matter volume. A prospective cohort study by Gu et al.<sup>113</sup> investigating a non-demented elderly population found that the serum IL-6 and CRP levels were negatively correlated with the gray-matter volume of the whole brain in a cross-sectional analysis. Those authors additionally found that the volumes of widespread brain regions such as the pallidum, thalamus, and frontal, occipital, parietal, and temporal regions were negatively correlated with the serum IL-6 level.113

Regarding the associations between peripheral inflammatory markers and changes in the cortical thickness, Meier et al.<sup>39</sup> investigated the association between the serum level of kynurenine-pathway metabolites and the thickness of cortical regions of the frontolimbic neural circuits of emotion regulation (dlPFC, frontopolar PFC, OFC, and ACC), and found that the KYNA/3-HK and log(KYNA)/QUIN ratios mediated the association between a diagnosis of MDD and cortical thinning in the dorsal ACC. Those authors additionally observed that the log(KYNA)/QUIN ratio was negatively correlated with the severity of anhedonia and that the KYNA/3-HK ratio mediated the negative correlation between the CRP level and the thickness of the dorsal ACC.<sup>39</sup> Han et al.<sup>114</sup> measured the serum level of protein FAM19A5, a novel chemokine-like peptide that reflects the degree of reactive astrogliosis (i.e., chronic activation of astrocytes in response to CNS injury), and investigated its correlation with the cortical thickness in patients with MDD. In addition to microglial cells, astrocytes are involved in the production of proinflammatory cytokines and dysregulation of glutamatergic neurotransmission in neuroinflammatory processes.<sup>68</sup> Han et al.<sup>114</sup> found that the serum FAM19A5 level was significantly higher in patients with MDD than in healthy controls, and negatively correlated with the thicknesses of the left vlPFC, right dmPFC, left PCC, right cuneus, and both precunei, which showed significant cortical thinning in patients with MDD compared with healthy controls. These findings are in accordance with those of a meta-analysis by the ENIGMA MDD Working Group that investigated the data of 2,148 patients with MDD and 7,957 healthy controls, which found cortical thinning in the OFC, ACC, PCC, and prefrontal regions (which overlap emotion-regulation neural circuits) in adult patients with MDD.115

Neuroimaging studies combining fMRI and structural MRI data have suggested that diffusion-tensor-image parameters, which measure the microstructural connectivity that reflects the mobility of water molecules within the white-matter tracts, are strongly correlated with resting-state functional connectivity in brain networks.<sup>116-119</sup> Thus, alterations in white-matter-tract integrity may provide the structural basis of neuralcircuit dysfunction in the brain.87 Regarding the associations between the integrity of white-matter tracts and peripheral inflammatory markers, a study using a tract-based spatial statistics method found that the serum IL-1ß level was significantly negatively correlated with fractional anisotropy (FA) values of the left uncinate fasciculus, genu of the corpus callosum, and bilateral inferior fronto-occipital fasciculus (IFOF) in patients with MDD.120 Those authors additionally observed that the FA values of the bilateral IFOF and genu of the corpus callosum were significantly decreased in patients with MDD.<sup>120</sup> Similarly, another meta-analysis by the ENIGMA MDD Working Group found that the FA values of the genu and body of the corpus callosum and IFOF were significantly reduced in adult patients with MDD.121

## CONCLUSION

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This narrative review has discussed the neurobiological mechanisms underlying the interplay between peripheral and central inflammatory processes, alterations in kynurenine-pathway metabolism and glutamatergic neurotransmission, neuralcircuit dysfunction, and the pathophysiology of depression (Fig. 1). Summarizing the mechanism of inflammation-induced neural-circuit dysfunction in depression, chronic stress stimulates microglial activity through increased BBB permeability and infiltration of peripheral monocytes into the brain.<sup>42</sup> Microglial cells subsequently increase the production of proinflammatory cytokines, which exert a direct neurotoxic effect (e.g., adult hippocampal neurogenesis) and promote a shift from the synthesis of serotonin to the synthesis of kynurenine-pathway metabolites by stimulating IDO activity.40 Finally, the increase in the neurotoxic kynurenine-pathway metabolites induces glutamate-mediated excitotoxicity in neurons. From the perspective of neuroinflammation and neural-circuit dysfunction, the hypothesized region specificity of microglial activation during neuroinflammatory processes contributes to the vulnerability of the specific brain regions of neural circuits that are involved in emotion regulation, reward processing, and cognitive control to inflammation-mediated brain injury.<sup>15,86</sup> This hypothesis is supported by the findings of the aforementioned postmortem studies of microglial activity, TSPO PET imaging, and MRS studies. Furthermore, the detrimental effect of neuroinflammation on adult hippocampal neurogenesis may support this hypothesis.40

Based on the assumption that peripheral and central inflammation processes are strongly intercorrelated, several MRI studies have investigated the associations of the blood levels of inflammatory markers such as CRP, IL-1β, IL-6, and TNF-a with functional and structural neuroimaging markers in patients with depression. Functional neuroimaging studies have found increased levels of peripheral inflammatory markers to be associated with aberrant activation patterns in several brain regions such as the ACC, PFC, OFC, amygdala, and striatum, and with alterations in functional connectivity between these regions, which in turn are associated with specific depression symptomatologies such as persistent low mood, anhedonia, anxiety, and cognitive impairment. Moreover, structural neuroimaging has revealed that increased levels of peripheral inflammatory markers are associated with a reductions in the cortical gray matter and subcortical volumes, cortical thinning, and damaged white-matter-tract integrity in patients with depression. These neuroimaging findings may improve our understanding of the relationships between neuroinflammatory processes at the molecular level (mainly derived from preclinical studies) and macroscale in vivo neural-circuit dysfunction in depression.

This review has revealed several possible directions for future neuroimaging studies in this field. First, substantial inconsistencies have been observed in previous studies regarding the types of inflammatory and neuroimaging markers used. Only some previous studies have found inflammatory markers (e.g., CRP, IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) to be significantly associated with neuroimaging markers, and these discrepancies may be due to insufficient sample sizes (only a few dozen participants) in previous inflammation-related MRI studies.<sup>38,39,100,114</sup> However, these inconsistencies may also be attributable to other factors such as the use of specific inflammatory markers that are more closely related to brain injury, and specific types of functional or structural neuroimaging modalities being more vulnerable to the detrimental effects of neuroinflammation. Furthermore, the brains of patients with longer illness durations may have greater exposure to the neurotoxic effects of neuroinflammation. Given the significant correlations between the duration of depression and brain structural and functional alterations in previous studies,122,123 illness duration is a potential moderator of the relationship between inflammation and neuroimaging markers in depression. However, to the best of our knowledge, no study has investigated the moderating effect of illness duration on the associations between inflammatory markers and brain structural and functional changes in depression, and so future studies should investigate these issues.

Second, most neuroimaging studies in this field have had cross-sectional designs, with only a few longitudinal studies having been performed.<sup>113</sup> This situation means that the causal relationship between the neuroinflammation state and neural-circuit dysfunction in depression remains unclear. Future neuroimaging studies with a longitudinal design are required to determine whether an increase in peripheral or central inflammation leads to structural and functional alterations of the brain in depression.

Third, there are potential factors such as a genetic predisposition or the gut microbiome mediating or moderating the relationship between inflammation and neural-circuit dysfunction in depression.<sup>124,125</sup> For example, a recent study by Green et al.<sup>126</sup> found that the DNA methylation score of the CRP gene was associated with a reduction in global gray matter/cortical volumes and damaged integrity of the white matter in widespread tracts in patients with MDD, whereas no significant association was found between the serum CRP level and structural changes in the brain. Future studies should take these factors into consideration.

Fourth, there is accumulating evidence that neuroinflammation leads to specific types of neural-circuit dysfunction, which may be associated with specific depression symptom-

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atology. Future studies should investigate the putative biotype based on the inflammation state, which might be useful for providing treatment guidance when selecting anti-inflammatory agents for depression based on an individual's inflammatory state, as a concept of precision psychiatry.127,128

Finally, given the relative lack of research in this field, further neuroimaging studies using comparable methodologies and meta-analyses thereof may yield conclusive evidence on



**Fig. 1.** Schematic representation of the mechanism of inflammation-induced neural-circuit dysfunction (B) and the related brain regions (A) in depression. Chronic stress leads to the elevation of SNS tone and dysregulation of the HPA axis. This will increase the production of peripheral proinflammatory cytokines, BBB permeability, and infiltration of peripheral monocytes into the brain. The infiltrating monocytes stimulate microglial activity, which promotes a shift from serotonin synthesis to the synthesis of kynurenine-pathway metabolites by stimulating the IDO activity. The increase in neurotoxic kynurenine-pathway metabolites and decrease in KYNA lead to glutamate-mediated excitotoxicity, and the increased proinflammatory cytokines in the CNS exert a direct neurotoxic effect. These processes affect neural-circuit dysfunction in an interactive manner with region-specific neuroinflammatory processes. Dysfunction of the neural circuits involved in emotion regulation, reward processing, cognitive control, and self-referential thinking lead to depression-related psychopathologies. ACC, anterior cingulate cortex; BBB, blood-brain barrier; CNS, central nervous system; dACC, dorsal anterior cingulate cortex; dIPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; HPA, hypothalamus-pituitary-adrenal; IDO, indoleamine 2,3-dioxygenase; KYNA, kynurenic acid; OFC, orbitofrontal cortex; VC, posterior cingulate cortex; wmPFC, ventrolateral prefrontal cortex; vmPFC, ventrolateral prefrontal cortex; vmPFC, ventrolateral prefrontal cortex; vmPFC, ventrolateral prefrontal cortex; VS, ventral striatum.

the association between neuroinflammation and neural-circuit dysfunction with regard to the pathophysiology of depression.

#### Availability of Data and Material \_

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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