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# Research on the Immune Mechanisms of Cognitive Impairment in Depression

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**Abstract:** Major Depressive Disorder (MDD) is a prevalent mental disorder characterized primarily by persistent feelings of sadness. Over the past decade, accumulating evidence has demonstrated that patients with depression exhibit cognitive impairments, such as deficits in attention, learning and memory, and executive function. Cognitive impairment is a significant symptom and prognostic indicator of depression, and can manifest at any stage of MDD onset. Research over the past two decades has indicated a close relationship between the immune system and the onset of depression. This article will elucidate the immunological mechanisms underlying cognitive impairment in depression from the perspectives of brain immune mechanisms, systemic (peripheral) immune mechanisms, and their bidirectional regulation, aiming to provide novel theoretical insights for the treatment of cognitive impairment in depression.
**Keywords:** Depression; Cognitive impairment; Brain immunity; Systemic (peripheral) immunity; Bidirectional regulation

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## 1. Introduction

Depression is a mood disorder characterized by persistent feelings of sadness and anhedonia [1]. According to data from the World Health Organization, depression is the most common cause of disability worldwide today, with an estimated 3.8% of the global population affected [2]. Depression is a recurrent condition: on one hand, remission from depression is difficult to achieve, with 20–40% of patients with severe depression not showing a clinical response to current antidepressant treatments [3]. On the other hand, severe depression also exhibits a high recurrence rate: in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, approximately 74% of individuals experienced a recurrence, and 18% experienced more than 10 recurrences or lifelong episodes [4].

Cognitive impairment is not only a common symptom of severe depressive disorder but also a frequent residual symptom after treatment for depression, serving as one of the risk factors for depression recurrence [5]. During severe depressive episodes, cognitive functions such as alertness, psychomotor speed, attention, memory, and executive function are impaired [6]. According to statistics, cognitive impairment accompanies severe depressive episodes 85–94% of the time, and even during non-severe depressive episodes, it is present 39–44% of the time [7]. Other studies have shown that 73% of patients with Major Depressive Disorder (MDD) regained normal cognitive function after the alleviation of their depressive symptoms; however, some MDD patients continue to experience cognitive deficits [6].

As an accompanying symptom of depression, cognitive dysfunction reduces the susceptibility of MDD patients to pharmacological treatments, increases the risk of relapse, and severely impairs patients' quality of life. Cognitive-oriented non-pharmacological interventions have also shown promising results in improving the condition of MDD patients [8]. Studies over the past two decades have suggested that immune system dysfunction may be one of the pathogenic mechanisms underlying cognitive impairment in depression, and drugs targeting key immune pathways can alleviate both depressive and cognitive symptoms [9]. This study aims to explore the immune mechanisms of cognitive dysfunction in depression, with the hope of providing therapeutic prospects for MDD patients with persistent cognitive impairment.

## 2. Immune mechanisms in the brain

### 2.1. Microglia

Microglia (MG) play a central role in the immune response within the central nervous system and are closely associated with the onset and progression of depression, as well as cognitive memory impairment [10]. An imbalance between the activated M1 and M2 states (M1 > M2) of microglia leads to mood disorders; during chronic episodes of mood disorders, the balance shifts toward the M1 pro-inflammatory state, which is triggered by Toll-like receptor (TLR) activation caused by inflammatory cytokines such as IL-1β, IL-6, and TNF-α [11]. In the Chronic Unpredictable Stress (CUS) model, chronic stress can activate microglia in mice, leading them to phagocytose synapses of nearby pyramidal neurons, resulting in neuronal atrophy and subsequent impairment of learning and memory abilities [12]. Research has found that microglia-mediated inflammatory responses are highly dependent on the activity of glycogen synthase kinase-3β (GSK3β), with increased GSK3β mRNA expression observed in postmortem hippocampal samples from MDD patients [13]. GSK-3β can impair cognitive function by inhibiting neurogenesis in the adult hippocampal region, damaging synaptic plasticity, and causing neuronal cell damage [14]. The use of GSK-3β-targeted inhibitors (such as SB216763) in animal models can reverse microglial hyperactivation and improve cognitive function [16]. Additionally, studies have shown that the activation of microglia in the hippocampal and prefrontal cortex (PFC) regions of mice requires the involvement of nucleotide-binding oligomerization domain-like receptor protein 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) [15]. Following chronic stress, NLRP3 activity increases, and NLRP3 can promote the maturation of IL-1β by activating caspase-1, forming a positive feedback loop that leads to memory impairment [16,17]. Furthermore, microglia in the hippocampal region of patients with major depressive disorder (MDD) are highly activated and secrete excessive inflammatory cytokines [18]. The increase in interleukin IL-1β directly targets proximal neurons, leading to neuronal viability loss and thereby causing working memory impairment [19]. Simultaneously, elevated levels of IL-8 and TNF-α further activate microglia, resulting in β-amyloid protein deposition, enhancing oxidative stress reactions, and exacerbating brain nerve damage [20]. Autopsy findings have revealed increased TLR4 expression in the prefrontal cortex (PFC) of MDD patients, which promotes microglial activation and enhances inflammatory responses [21]. TLR4, in turn, exacerbates cognitive impairment by inducing neuroinflammation [22]. Additionally, studies have shown that microglia in CUS model mice impair neuroplasticity and spatial memory by inhibiting the phosphorylation of glutamate receptor 1 (GluR1). However, the use of minocycline to increase GluR1 phosphorylation can alleviate spatial memory impairment [23]. In summary, studying the cognitive impairment mediated by microglial activation in depression will contribute to the advancement of clinical treatment for depression.

### 2.2. Astrocytes

In the PFC region of rats subjected to the CUS model, a decrease in the number of astrocytes expressing the specific marker glial fibrillary acidic protein (GFAP) has been detected [24]. Meanwhile, astrocytes also exhibit morphological and structural changes, including cell shrinkage, shortening and weakened association of cellular foot processes, downregulation of glucocorticoid receptors, and impaired functions such as glutamate transmission and lactate release, which ultimately lead to cognitive impairment [25]. Another study has demonstrated that astrocytes in the cortex of IL-

10tm1/tm1 mice with reduced IL-10 expression are activated and more prone to adopting the A1 phenotype. After LPS injection, IL-10tm1/tm1 mice exhibit a higher number of A1 astrocytes in brain tissue, which may contribute to their severe depressive-like behavior and learning and memory deficits [26]. These changes in astrocytes result in alterations in various molecules and neurotransmitters in the prefrontal cortex, hippocampus, amygdala, striatum, and hypothalamus, involving imbalances in dopamine, serotonin, glutamate, and GABA neurotransmission, leading to cognitive symptoms in different brain regions [27]. Research has found that in CUMS model mice, the hypothalamic orexin-1 level increases, impairing glycolysis by inhibiting HIF-1α within astrocytes, leading to decreased lactate release, affecting its transport to neurons, and subsequently reducing the expression of brain-derived neurotrophic factor (BDNF) in neurons, thereby impairing hippocampal neuroplasticity and causing decreased learning and memory ability in CUMS model mice [5]. Studies have found that in the Flinders Sensitive Line (FSL) depression model, reactive astrocytes in the rat prefrontal cortex exhibit reduced volume and fewer branches, but an increased number of GABA cells [28]. Additionally, increased GABA uptake by neurons in the hippocampal DG region of APP/PS1 mice impairs synaptic plasticity and learning and memory [29]. Since depression is an independent risk factor for AD, we hypothesize that increased GABA may be one of the molecular mechanisms underlying cognitive impairment in depression. Research indicates that in CUMS mice, the number of astrocytes in the hippocampus decreases, but the secretion of central nervous system-specific protein β (S100β) protein and mRNA increases [30]. Elevated S100β protein in the hippocampal DG region hinders the maturation of neural stem cells, reduces neurogenesis, and impairs learning and memory abilities [31]. Glutamate transporter-1 (GLT-1) is primarily expressed in astrocytes [32]. In patients with major depressive disorder (MDD), the reduction in the number of astrocytes in the hippocampus is accompanied by a decrease in GLT-1 expression. In a rat stress model, the use of the GLT-1 inhibitor dihydrokainic acid (DHK) to block glutamate uptake by central astrocytes induces a depression-like phenotype. The rats exhibit common symptoms of depression, including anhedonia and cognitive dysfunction [33]. Therefore, astrocytes are closely linked to depression and cognitive impairment, influencing their pathology and symptoms. In-depth research may bring new directions for the diagnosis and treatment of depression.

# 3. Body (Peripheral) immune mechanisms

## 3.1. Innate immunity

Due to the continuous impact of social psychological or environmental stress, MDD patients experience repeated and long-term activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis (HPA axis), which significantly affects the development, activation status, and distribution of peripheral immune cells that promote harmful inflammatory responses, leading to immune disorders in the body [34]. With the activation of monocytes/macrophages, there is an increase in the production of inflammatory cytokines IL-6 and IL-1β [35]. Systemic increases in IL-1β may penetrate the compromised blood-brain barrier in MDD patients and enter brain tissue, causing working memory dysfunction [19]. At the same time, another study points out that this chronic stress-mediated increase in IL-6 in peripheral circulation can also lead to a decline in cognitive ability [36]. Observations in CUMS model mice have shown an increase in the number of monocytes and granulocytes in the blood, along with significantly elevated levels of IL-8 and IL-1β in peripheral blood, which further impairs cognitive function, supporting the aforementioned viewpoint [37]. Additionally, the NLRP3 inflammasome in peripheral blood monocytes/macrophages of MDD patients is also activated, exacerbating systemic inflammatory responses through caspase-1-dependent IL-1β maturation, thereby impairing patients' attention [38]. However, the NLRP3 inhibitor MCC950 has been shown in clinical trials to significantly reduce peripheral IL-1β levels and improve attention deficits in patients [39]. However, some studies have demonstrated that in a mouse model of LPS-induced depression, inhibiting the accumulation of peripheral $Ly6C^{high}$ monocytes in brain tissue significantly reduces the activation of astrocytes in brain regions such as the hippocampus, hypothalamus, and cortex, thereby improving neuroinflammation and protecting cognitive function [40]. NK cells are innate lymphocytes with dual functions of cytotoxicity and immunoregulation. In patients with major depressive disorder (MDD), the cytotoxicity of NK cells

in peripheral blood decreases, along with a reduction in cell number and insufficient maturation, indirectly leading to a decline in the ability of NK cells in the dentate gyrus of the brain to clear senescent neuroblasts, affecting neurogenesis and consequently impairing cognitive function [41–43]. In summary, innate immune impairment in MDD patients can also trigger immune inflammation, thereby impairing cognitive function.

### 3.2. Adaptive immunity

A growing body of data indicates a decrease in $CD4^+$ T helper cells in the peripheral blood of MDD patients [44]. Some studies have shown that immature microglia require $CD4^+$ T cells to enter the brain for full maturation to an adult state. Therefore, the deficiency of $CD4^+$ T cells in MDD patients can affect brain development, as well as emotional control and learning ability in adult mice [45]. Numerous reviews and meta-analyses have shown that MDD is associated with abnormal phenotypes of helper T cell (Th) 17 cells in peripheral blood [46]. In MDD patients, the immune inflammatory response system (primarily activating Th-17) may be activated [46]. Interleukin-17A (IL-17A), as a characteristic cytokine of Th17 cells plays a crucial role in inducing the expression of chemokines and cytokines during the process where Th17 cells recognize pro-inflammatory signals and activate neutrophils [47–49]. In clinical studies, adult patients with depression have higher serum levels of IL-17 and a greater number of Th17 cells producing IL-17 compared to healthy controls [50]. Some studies have indicated that plasma IL-17 levels can serve as a plasma biomarker for distinguishing between Alzheimer's disease (AD) patients and cognitively healthy individuals [51]. Since the endothelial cells of the blood-brain barrier can express IL-17A receptors, the increased IL-17A in the plasma can bind to its receptors, leading to the disruption of tight junction (TJ) molecules in the blood-brain barrier and downregulating the expression of TJ molecules [52,53]. As the integrity of the blood-brain barrier is compromised, more neutrophils and Th17 cells will enter the brain parenchyma, resulting in increased production of IL-17A and more severe cognitive dysfunction [54].

Additionally, in a mouse model of cumulative prenatal mild stress (CPMS), researchers have observed an increase in the differentiation and quantity of Th17 cells. The production of IL-17 further stimulates the activation of microglia in the hippocampus, amygdala, and prefrontal cortex of CPMS mice, impairing cognitive function [50]. After Aβ injection, IL-17 levels rise in both the blood and cerebrospinal fluid of rats, and researchers have found that the balance of the Th17 immune system is disrupted at this time, which is closely related to cognitive decline [55]. There are relatively few studies on the involvement of B lymphocytes in cognitive impairment in depression; however, some peripheral blood phenotypic studies in humans with depression indicate that compared to non-depressed controls, patients have a higher number of circulating B cells and a reduced number of regulatory B cells producing interleukin-10 (IL-10), suggesting that depression may be associated with expanded and dysregulated peripheral blood B cells [56]. Furthermore, researchers have discovered an increase in B cells in the frontal cortex and meningeal tissues of 5 × FAD mice: the increased B cells produce more interleukin-35 (IL-35) in the prefrontal cortex, which exacerbates Aβ pathology and leads to memory impairment [57].

## 4. Bidirectional regulation between brain and body (Peripheral) immune mechanisms

In addition to their independent roles, there is also bidirectional communication between the brain and the body's (peripheral) immune system.

### 4.1. Peripheral immune regulation of the brain

Peripheral immune regulation of the brain relies on the disruption of the blood-brain barrier: Although the blood-brain barrier (BBB) hinders communication between the brain and the peripheral immune system [58,59], evidence suggests the existence of bidirectional immune regulation between the two: In a mouse model of chronic social defeat stress (CSDS), research has found that long-term chronic social stress leads to increased blood-brain barrier permeability by downregulating the expression of tight junction protein Claudin5 (Cldn5) in the nucleus accumbens of mouse brains, in conjunction with stress-induced peripheral immune-related signals. This, in turn, allows interleukin-6 (IL-6) in the

bloodstream to cross the blood-brain barrier, ultimately inducing depression-like behaviors and impairing cognitive function [60]. Additionally, a significant reduction in the expression of tight junction protein-5 was observed in the hippocampal gray matter of postmortem samples from patients with major depressive disorder (MDD) [61]. These findings demonstrate that the blood-brain barrier is compromised in depression: in MDD patients, the production of peripheral pro-inflammatory cytokines reduces kynurenine, leading to decreased resistance of the cerebral cortex to the neurotoxicity of quinolinic acid and glutamate in the synaptic cleft. This altered balance results in increased activation of NMDA receptors, increased influx of calcium and sodium, potentially increasing cellular excitotoxicity, reducing synaptic plasticity, and leading to apoptosis [62,63]. Studies have shown that monocytes in the plasma of CSDS mice secrete increased levels of matrix metalloproteinase MMP8, which can enter the brain parenchyma through the compromised blood-brain barrier and increase the extracellular matrix volume fraction in the Nac brain region, thereby reducing neuronal excitability and contributing to depressive cognitive dysfunction [64]. Furthermore, research has found that in the brains of MDD patients, there is not only an increased infiltration of microglia but also an active recruitment of peripheral monocytes, neutrophils, and other cells into the brain, further activating microglia and leading to the secretion of cytokines, chemokines, and secondary messengers, which impair neuronal plasticity and integrity, thereby resulting in cognitive dysfunction [65].

## 4.2. Immune regulation of the brain on the periphery

The brain regulates the peripheral immune system primarily through the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Under physiological conditions, the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) can promote beneficial immune responses. However, in patients with major depressive disorder (MDD), the HPA axis and SNS are repeatedly and chronically activated, which continuously activates peripheral immune cells and produces harmful inflammatory mediators, leading to immune dysfunction in the body [66]. Studies have shown that chronic stress can lead to a sustained increase in cortisol levels in the peripheral blood of humans. Excess cortisol entering the brain can induce hippocampal neuron apoptosis and synaptic plasticity damage through glucocorticoid receptors (GRs), resulting in cognitive impairment [67,68]. Meanwhile, the persistent stress present in MDD patients causes the release of norepinephrine from sympathetic nerve endings, which activates peripheral macrophages through β2 adrenergic receptors, promoting the release of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines further enter the brain through open regions of the blood-brain barrier, damaging neurons in the hippocampus and medial temporal lobe and causing cognitive impairment [69–71].

## 4.3. Glymphatic system

The glymphatic system hypothesis was first proposed by the Iliff research team in 2012. They injected a fluorescent agent into the cisterna magna of anesthetized mice and used a two-photon microscope to observe the path of the cerebrospinal fluid (CSF) fluorescent tracer. They found that CSF enters the brain parenchyma along the perivascular space of arteries, then undergoes material exchange with interstitial fluid (ISF), and finally, both are transported to the perivascular space of veins and flow out of the brain in the form of bulk flow [72]. Some aquaporin-4 (AQP4) water channel proteins are distributed on the plasma membrane of the vascular endfeet of astrocytes, participating in the fluid exchange between CSF and ISF and the clearance of waste [72]. In an experiment, researchers found that mice subjected to chronic unpredictable mild stress (CUMS) exhibited reduced arterial pulsation and compliance in the brain, along with depolarized expression of AQP4. This severely impaired the function of the glymphatic system, leading to neuroinflammation and cerebrovascular dysfunction, and resulting in cognitive deficits. However, dietary supplementation with polyunsaturated fatty acids (PUFAs) in mice could improve these deficits and alleviate depression-related cognitive decline [73]. In addition, researchers such as Borsini found that exposing human hippocampal neurons to inflammatory cytokines INF-α or IL-6 reduced the expression of the AQP4 gene. They inferred that the high levels of INF-α or IL-6 in the brains of patients with major depressive disorder (MDD) might impair cognitive function by reducing AQP4 [74]. Studies have also indicated that impaired clearance function of the glymphatic system in mice subjected to chronic unpredictable mild stress (CUMS)

increased the deposition of amyloid β-protein (Aβ) in the brain and led to neurodegeneration. However, intraperitoneal injection of fluoxetine could reverse the damaging effects of CUMS on the mouse glymphatic system and also enhance Aβ clearance, thereby alleviating cognitive impairment [75].

## 5. Conclusion and prospects

In summary, through multifaceted research, we have discovered that microglia and astrocytes in the brain's immune mechanism, along with innate and adaptive immunity in the body's (peripheral) immune mechanism, collectively form a complex and interconnected immune network that participates in the regulation of depression and cognitive impairment. The disruption of the blood-brain barrier and the glymphatic system serves as a bridge for bidirectional immune regulation, enabling the body to respond to changes brought about by depressive cognitive impairment as a complete immune system.

Despite the significant progress made in the research on depression and cognitive impairment, further exploration is still needed to elucidate the more refined mechanisms of action among various immune cells, molecules, and signaling pathways. Clinically, developing new-generation antidepressants guided by specific immune targets (such as TLR4, NLPR3, etc.) holds promise for improving treatment response rates compared to traditional antidepressants. Additionally, employing immunomodulatory therapy for depressed patients with cognitive impairment and implementing nutritional interventions targeting inflammatory responses may offer new avenues for treating depression.

## Disclosure statement

The author declares no conflict of interest.

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