Review on Neurophysiological Mechanisms of Depression

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Abstract. Depression is a common and highly disabling mental disorder, whose complex neurophysiological mechanisms have not been fully elucidated. Although the traditional monoaminergic neurotransmitter hypothesis laid the foundation for drug therapy, it fails to explain all its pathological phenomena. In recent years, with the development of neuroimaging and molecular biology techniques, research has gradually delved into multiple levels such as neural circuits, brain structure, and the immune system. This review aims to systematically organize the current mainstream research directions on the neurophysiological mechanisms of depression, focusing on the dysfunction of the prefrontal-limbic system circuit and its associated brain structural changes, as well as the central role of the neuroinflammation mechanism in the development of depression. Through integration and analysis of existing literature, we propose that depression is a syndrome resulting from the interaction of genetic susceptibility and environmental stress factors, leading to neural circuit dysfunction, neurotrophic imbalance, and immune system activation. A deeper understanding of future mechanisms will provide a key theoretical basis for developing novel, fast-acting antidepressant strategies.

Keywords: Depression; Neurophysiological Mechanisms; Prefrontal-Limbic System; Brain Structure; Neuroinflammation; BDNF.

1. Introduction

Major Depressive Disorder (MDD) is a common, recurrent, and highly disabling mental disorder. Its global disease burden is heavy, and according to World Health Organization (WHO) statistics, it is one of the leading causes of disability worldwide [1]. Its characteristic clinical manifestations include persistent low mood, loss of interest, impaired cognitive function (e.g., decreased attention, executive function), and a range of physical symptoms (e.g., sleep, appetite changes). Although various antidepressant drugs (such as selective serotonin reuptake inhibitors, SSRIs) and psychological therapies are widely used in clinical practice, about one-third of patients have treatment-resistant depression (TRD) and respond poorly to existing treatments (Rush et al., 2006). This severe treatment situation reveals the complexity of its pathophysiological mechanisms, far beyond what traditional theories can fully explain, thus motivating researchers to continuously explore new mechanistic dimensions.

The monoaminergic neurotransmitter (5-HT, NE, DA) depletion hypothesis proposed in the 1960s provided the theoretical basis for the development of first-generation antidepressants and remains the cornerstone of clinical medication. However, this hypothesis has significant limitations: firstly, although SSRIs rapidly increase synaptic monoamine levels, their clinical efficacy usually takes 2-4 weeks to manifest, suggesting that their ultimate effect depends on more complex downstream adaptive changes [2]. Secondly, a considerable proportion of patients do not respond to treatments that enhance monoaminergic transmission. These clinical phenomena strongly suggest that the etiology of depression may stem from broader neural circuit dysfunction and system-level physiological dysregulation. Benefiting from the rapid development of neuroimaging (e.g., fMRI, PET) and molecular biology techniques, the research paradigm has successfully shifted from a single neurochemical neurotransmitter imbalance to an integrated understanding of multiple interrelated levels: neural circuits, brain structure, and neuroimmunity. Among them, the prefrontal-limbic system circuit (particularly involving the prefrontal cortex, anterior cingulate cortex, amygdala, and hippocampus) is widely accepted as the core hub for regulating emotion, motivation, and cognitive function, and its dysfunction is widely confirmed to be closely related to the core symptom spectrum

of depression [3-4]. Simultaneously, the neuroinflammation hypothesis has rapidly emerged as another major pillar of new theory, with substantial evidence indicating that the abnormal activation of the innate immune system is a key factor driving the pathological process of depression, providing a new perspective for understanding the heterogeneity and comorbidity (e.g., with cardiovascular disease, diabetes) of depression [5].

Based on this shift in research paradigms, this article aims to systematically organizethe current mainstream international research directions on the neurophysiological mechanisms of depression. We will not reiterate the classic monoamine hypothesis but will focus on two frontier areas with the most substantial evidence and profound interactions: (1) Brain structural abnormalities and neural circuit dysfunction: reviewing morphological changes in key brain regions (e.g., PFC, hippocampus, amygdala) and the underlying neurotrophic factor regulatory mechanisms (e.g., the BDNF hypothesis); (2) Neuroinflammation mechanisms: exploring how peripheral and central immune activation ultimately leads to depressive behavioral phenotypes by affecting neurotransmitter metabolism, the neuroendocrine system, and neuroplasticity.

Through the integration and analysis of existing high-level literature (including systematic reviews and Meta-analyses), we hope to construct a more systematic and comprehensive neurophysiological model of depression and discuss its potential translational value for developing new diagnostic tools and targeted treatment strategies.

2. Neural Structural Abnormalities and Depression

For a long time, depression was considered a functional mental disorder lacking clear biological markers. However, with the popularization of high-resolution magnetic resonance imaging (MRI) technology and the application of large-scale data analysis methods, it has become an indisputable scientific fact that patients with depression exhibit extensive and reproducible brain structural abnormalities. These abnormalities are not confined to a specific brain region but affect large-scale distributed networks involved in emotional processing, cognitive control, and motivational reward, among which the prefrontal-limbic circuitry is the most core [6-7].

Early neuroimaging studies, primarily based on voxel-based morphometry (VBM) comparing brain gray matter volume between patients and healthy controls, found gray matter volume reduction in multiple brain regions in MDD patients. In recent years, large multi-center consortia, such as the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) MDD working group, have greatly enhanced the reliability and generalizability of these findings by conducting meta-analyses of brain imaging data from thousands of subjects worldwide [8]. These studies consistently confirm that compared to healthy controls, MDD patients show significant gray matter volume reductions in the following key brain regions: In the prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex (dlPFC) associated with executive function and emotion regulation, and the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) associated with affective evaluation and decision-making. In the hippocampus, associated with memory consolidation and stress regulation. The anterior insula is associated with interoceptive awareness and emotional experience. The striatum, specifically the nucleus accumbens (NAcc), is associated with reward processing and motivation. These structural changes provide an intuitive neuroanatomical explanation for the clinical symptoms of depression: atrophy of prefrontal regions is associated with decreased cognitive flexibility and impaired emotion regulation; reduced hippocampal volume is associated with memory problems and persistent HPA axis hyperactivity; and changes in reward-related regions directly lead to the core symptom of anhedonia.

Recent research has made significant progress in the following aspects, advancing the depth and breadth of the field:

From Cross-Sectional to Longitudinal Design. Early studies were mostly cross-sectional comparisons, unable to determine whether structural abnormalities were causes or consequences. Current longitudinal tracking studies show that volume reduction in brain regions like the

hippocampus may be a state marker, which can be partially normalized with successful antidepressant treatment (especially electroconvulsive therapy ECT and ketamine) [9]. This proves that these structural changes have a certain degree of plasticity, offering hope for treatment.

Focus on Heterogeneity and Subtypes. Recognizing the high heterogeneity of depression, the latest research is dedicated to finding specific brain structural patterns associated with specific clinical symptom profiles (e.g., anxiety, anhedonia, cognitive impairment). For example, patients with anhedonia as a core symptom may exhibit more pronounced striatal volume reduction [10].

Multimodal Fusion and Machine Learning. Relying solely on structural data has limited accuracy in predicting whether an individual has the disease. The current trend is to combine structural data with functional connectivity, diffusion tensor imaging (DTI, for measuring white matter fiber integrity), and genetic data to build multimodal predictive models. Machine learning algorithms can use these multidimensional data to more accurately distinguish patients from controls and predict treatment response [11].

Insights into Microstructure. Emerging magnetic resonance spectroscopy (MRS) studies allow in vivo measurement of brain chemical concentrations. Studies have found abnormalities in glutamate (Glu) and γ-aminobutyric acid (GABA) levels in brain regions such as the PFC and hippocampus in MDD patients, suggesting that excitatory/inhibitory imbalance may be the underlying chemical basis leading to neuronal atrophy and network dysfunction.

In summary, brain structural abnormalities are a core neurophysiological basis of depression. The research paradigm has evolved from macroscopic volume measurement to exploring specific subregions, microstructure, and dynamic circuits. In the future, through large samples, longitudinal designs, and multimodal data fusion, we will more precisely map the neuroanatomical atlas of depression, laying the foundation for biomarker-based precise diagnosis and treatment.

3. Neuroinflammatory Mechanisms and Depression

A large number of clinical studies have confirmed a strong association between inflammation and depression. A meta-analysis incorporating multiple studies showed that approximately 27%-35% of MDD patients have significantly elevated levels of pro-inflammatory cytokines (such as IL-6, TNF-α, IL-1β) and CRP in peripheral blood [12-13]. The association is bidirectional. Inflammation can induce depression; hepatitis or cancer patients receiving interferon-alpha (IFN-α) therapy have a significantly higher incidence of depression than control groups, providing the most direct human evidence that "inflammation can cause depression"[14]. Depression is also accompanied by inflammation; MDD patients, especially those with symptoms such as anorexia, fatigue, and anhedonia—collectively known as "sickness behavior"—have higher levels of inflammatory markers. Inflammatory cytokines trigger depressive symptoms by affecting several key physiological processes:

Affecting Monoaminergic Neurotransmitter Metabolism.Inflammation activates the enzyme indoleamine 2,3-dioxygenase (IDO), which shifts the metabolic pathway of tryptophan (the precursor of 5-HT) from producing 5-HT to generating kynurenine. Kynurenine can be further metabolized into neurotoxic quinolinic acid (which acts as an NMDA receptor agonist, causing excitotoxicity) and 3-hydroxykynurenine (3-HK) (producing reactive oxygen species), while reducing the production of neuroprotective kynurenic acid. This leads to monoamine depletion, oxidative stress, and neuronal damage [15].

Disrupting HPA Axis Function. Cytokines can stimulate the hypothalamus to release corticotropin-releasing hormone (CRH), leading to persistent HPA axis hyperactivity and glucocorticoid (cortisol) resistance, causing its negative feedback regulation to fail, further exacerbating inflammation and neurotoxicity.

Inhibiting Neurotrophic Support. Inflammatory signals (especially TNF-α) can significantly downregulate the expression and function of brain-derived neurotrophic factor (BDNF). BDNF is a key molecule for maintaining neuronal health, synaptic plasticity, and neurogenesis. Its reduction

directly leads to impaired neurogenesis and synaptic loss in the hippocampus and prefrontal cortex, directly linking to the brain structural abnormalities discussed in the previous chapter.

Altering Reward Circuit Function. Inflammatory cytokines can reduce the activity of dopamine neurons in the ventral tegmental area (VTA)and dopamine release in the nucleus accumbens (NAcc) , which is the direct cause of the core symptom of anhedonia.

Research in this field is moving from proving association to deeply analyzing mechanistic heterogeneity and developing translational applications.

Microglial Activation Imaging.A recent breakthrough involves using positron emission tomography (PET)with specific tracers (such as PBR28, targeting the TSPO protein) to image the activation of microglia in the living brain. Several studies have reported increased TSPO signal in brain regions such as the prefrontal cortex, anterior cingulate cortex, and insula in MDD patients, providing the most direct in vivo evidence for the presence of central neuroinflammation [16-17]. However, results are heterogeneous and may be related to specific clinical symptoms or subtypes.

Identification of Inflammatory Subtypes. Not all depressed patients have inflammation. Research is dedicated to defining an "inflammatory subtype " or "high-inflammatory biotype" of depression. These patients typically have a more specific symptom profile (e.g., significant fatigue, psychomotor retardation, anhedonia), poorer treatment response, and resistance to conventional SSRIs. Identifying such biomarkers (e.g., high CRP) can guide personalized treatment.

Exploration of Anti-Inflammatory Therapies. Numerous clinical trials are evaluating the efficacy of anti-inflammatory drugs (such as the anti-TNF-α monoclonal antibody infliximab, and the COX-2 inhibitor celecoxib) as adjunctive treatments for MDD. Meta-analyses show that celecoxib, in particular, demonstrates clear antidepressant efficacy, especially in patients with high baseline inflammatory marker levels.

Gut Microbiota-Immune-Brain Axis. Recent research has revealed the key role of the gut microbiome as an immune regulator. Gut microbiota dysbiosis can lead to increased intestinal permeability ("leaky gut"), allowing bacterial lipopolysaccharide (LPS) to enter the circulation, triggering systemic low-grade inflammation, which in turn affects the brain. Probiotic and prebiotic interventions are regarded as potential new strategies for modulating immunity and improving mood [18].

4. Conclusion and Perspectives

This review has systematically organized the two core pillars of research on the neurophysiological mechanisms of depression: brain structural abnormalities and neural circuit dysfunction, and neuroinflammatory mechanisms. Evidence indicates that depression is far from single neurochemical neurotransmitter imbalance disease, but rather a complex syndrome arising from the interaction of genetic susceptibility and environmental stress factors, leading to widespread disorders in three major systems: neural circuits, endocrine, and immune. Long-term stress activates the immune system; the induced neuroinflammation impairs neuroplasticity through various molecular pathways, leading to brain structural abnormalities and neural network dysfunction, ultimately manifesting as depression. This provides a more comprehensive and scientific explanation for understanding the chronicity, recurrence, and symptom diversity of depression.

Despite significant progress, the field still faces many challenges. Many current findings remain correlational; there is a need to utilize more advanced animal models (e.g., optogenetics, chemogenetics) and longitudinal clinical studies to clarify the causal (temporal) relationship between these biological changes and depressive symptoms. On the other hand, we can fully leverage multimodal data fusion (imaging, blood, genetics, behavior) and artificial intelligence/machine learning algorithms to discover new, more predictive disease subtypes in a data-driven manner. Future research should also focus on bridging the micro (e.g., specific cytokine signaling like JAK-STAT, NF-κB) and macro levels, and developing rapid-acting anti-inflammatory strategies.

In conclusion, the exploration of the neurophysiological mechanisms of depression has entered a new stage full of vitality and hope. The paradigm shift from monoamines to neuroplasticity and neuroinflammation has not only profoundly renewed our understanding of the disease's essence but also opened up broad space for therapeutic innovation. Through continuous basic and clinical translational research, we are expected to eventually decipher the code of this complex disease and bring more effective and personalized diagnostic and treatment options to millions of patients.

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