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Distinct Neurobiological Mechanisms of Chronic and Acute Stress in Major Depressive Disorder: A Review

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Abstract. Chronic and acute stress are well-known risk factors for major depressive disorder (MDD), yet their distinct neurobiological mechanisms remain incompletely understood. Acute stress disorder (ASD) is most prevalent in adolescents and young adults (ages 15-25), while chronic stress is most common in middle-aged individuals (30-50), with higher rates among women. This review synthesizes current evidence to contrast the effects of acute stress, which is the transient prefrontal-amygdala decoupling and executive dysfunction, with chronic stress, which promotes sustained neuroinflammation, HPA axis dysregulation, and structural brain changes. Key findings demonstrate that acute stress impairs "cool" executive functions (working memory, cognitive flexibility) via amygdala-prefrontal circuit disruption, while chronic stress induces hippocampal atrophy and peripheral immune activation through glucocorticoid resistance and BBB (blood-brain barrier) permeability. Despite these advances, limitations exist, such as the insufficient direct evidence linking specific neural pathways to cognitive deficits.

Keywords: Acute stress, chronic stress, major depressive disorder, executive function, neural pathway

1. Introduction

Chronic and acute stress are significant risk factors for depression, but their distinct neurobiological and psychological mechanisms are poorly understood.

Stress is a pervasive aspect of modern life, with involvement (overcompetence) in both adolescents and adults, and its dysregulation has been continuously linked to mental health disorders, particularly major depressive disorder (MDD). The symptoms of MDD, such as loss of interest in activities, can severely impact people's quality of life, increasing the risk of unemployment, poor academic performance, and failure to deal with interpersonal relationships. According to statistical analysis [1], global depression affects 3.8% of people (about 5% in adults, higher in women and seniors). Besides, depression contributes to more than 700 thousand suicide cases, which is the fourth leading cause of death among people aged 15 to 29 years old.

Stress has been considered a severe risk factor of MDD, as it triggers the body's immune system and leads to neuroinflammation [2]. However, the distinct roles of chronic stress and acute stress in the pathogenesis of MDD still need to be investigated. A systematic review reveals that acute stress impacts executive functions (EFs) like working memory (WM), inhibition, and cognitive flexibility

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in MDD [3]. Another overview concluded that chronic stress is a risk factor for neuroinflammation and depression, pointing out the link between chronic stress and dysregulation of the HPA axis and immune cell glucocorticoid resistance, contributing to hyperactivation of the peripheral immune system and, therefore, the reduction of hippocampus volume [4].

However, few studies have systematically integrated these findings to explain how acute stress-induced connectivity changes (e.g., PFC-amygdala decoupling) mechanistically lead to PFC hypofunctionality and cognitive deficits observed in MDD. Thus, this synthesis aims to clarify existing inconsistencies in the literature and highlight potential biomarkers and therapeutic targets for stress-related cognitive deficits in MDD.

2. Literature review

MDD is a complex disorder caused by dysfunction of multiple pathways and brain regions. The structural alterations (reduced in volume) in the prefrontal cortex, anterior cingulate, cortical grey matter, and hippocampus has been proven to be associated with MDD. Besides, neuropathways like the HPA axis, gut-brain axis, and inflammation result in abnormal axonal growth and abnormal dendritic growth, and pruning [5].

2.1. Acute stress and MDD

In real-life situations, acute stress comes from immediate threats or crises, social stressors, task-related stressors, etc. Unlike chronic stress, acute stress only lasts for a short time and is often triggered by a specific event. Its body response is commonly known as fight-or-flight. It has been proven to alter executive function, including impairment of working memory, cognitive flexibility, and cognitive inhibition. Acute stress triggers a functional trade-off: diminished higher-order cognition in exchange for optimized motor performance. Like the fight-or-flight state, this adaptation could weaken one's cognitive function and cognitive flexibility [3].

During the state of high tension, the amygdala restrains the hot EFs (such as reward processing, risky decisions, and delay discounting) activity, while cool EFs (WM, inhibition, and cognitive flexibility) are associated with PFC activity [3]. According to a meta-analysis done by [6], acute stress is significantly linked with cool EFs - WM, inhibition, and cognitive flexibility.

One recent review confirmed that individuals with major depressive disorder (MDD) and those with subclinical depressive symptoms showed heightened susceptibility to stress-induced WM impairment. This impairment was also predictive of increased depressive symptoms during subsequent stressful periods (e.g., exams). Poorer response inhibition was observed following inflammatory stress (e.g., vaccine administration), but not psychosocial stress. Results were inconclusive for cognitive flexibility due to limited studies [3].

Acute stress impairs WM and cognitive flexibility, likely through its disruptive effects on prefrontal cortex (PFC) functionality. Under stress, the amygdala becomes hyperactive while top-down control from the PFC is diminished [6], leading to a functional decoupling between these regions. This aligns with the corticolimbic dysregulation model of depression, where impaired PFC-amygdala connectivity exacerbates cognitive deficits [3].

2.2. Chronic stress and MDD

By viewing the risk factors of MDD, most of them are closely related to continuous (long-term) events such as low socioeconomic status, poverty, lack of social support, and ambient noise, linking

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to the production of chronic stress.

Chronic unpredictable stress suppresses the activity of specific neurons, such as AgRP neurons, in the arcuate nucleus of the hypothalamus. This suppression leads to altered neuronal firing, enhanced inhibitory synaptic transmission, and reduced neuronal excitability, contributing to depression-related behaviors like anhedonia and despair [7].

According to an overview of chronic stress, neuroinflammation, and depression, the dysregulation of the HPA axis is the primary source to explain the link between the mentioned symptoms. During chronic stress, the HPA axis is overstimulated, leading to dysfunction in the secretion of large amounts of corticotropin-releasing factor (CRF) and cortisol. The imbalance of hormones can lead to reduced hippocampal volume and function, further impairing stress regulation and sensitizing the individual to stress, which promotes depressive symptoms [4].

Chronic stress would induce cells to release Damage-Associated Molecular Patterns (DMAPs), such as high mobility group box-1 (HMGB-1), extracellular ATP, purine bases, metabolites, heat shock proteins (HSPs), S100 proteins, and galectin-3 (Gal-3). S100 proteins, HSPs, and Gal-3 are specially focused due to their pathogenic immunoregulatory roles in comorbid inflammatory disease [4].

Through blood-brain barrier (BBB) disruption, immune cellular trafficking, and glial cell activation, the peripheral immune system would intensify the expression of neuroinflammation [4]. In a study of CUMS mice, researchers have found that TNF-α gains access to the hippocampus due to chronic stress-induced BBB leakage, contributing to depression-like phenotypes [8].

Neuroinflammation, defined as activation of the central innate immune system, results in a depressive phenotype manifested with severe symptomatology and greater morbidity and mortality. Chronic stress exposure-evoked release of cytokines can promote the differentiation of peripheral CD4+ cells into various phenotypes. Among them, Th17 cells have attracted much attention due to their high pathogenic potential in central nervous system (CNS) diseases [9].

3. Case study

3.1. A study of cytokines effect on rats

This study investigated the role of peripheral Th17 cells in chronic stress-induced depression using a rat model subjected to 28 days of chronic restraint stress (CRS).

The researchers found that CRS led to significant depressive-like behaviors, including reduced sucrose preference, increased immobility, and delayed feeding, alongside suppressed weight gain. CRS disrupted the blood-brain barrier (BBB) by increasing permeability and reducing claudin-5 expression, while also leading to neuroinflammation through elevated proinflammatory cytokines (IL-1β, IL-6, TNF-α) and glial activation. Notably, CRS induced a time-dependent increase in naïve CD4+ T cells in the spleen and thymus, followed by Th17 cell accumulation in the dorsal striatum, and is driven by the CCR2/CCL2 chemokine axis. Treatment with SR1001, a Th17 differentiation inhibitor, effectively mitigated depressive behaviors and reduced neuroinflammation, highlighting Th17 cells as key mediators in stress-induced depression.

These findings suggest that targeting Th17 cell recruitment and function could offer a promising therapeutic strategy for early intervention in depression linked to chronic stress.

This study provides robust mechanistic insights into Th17-mediated neuroinflammation in depression, using a well-validated CRS model and multimodal analyses (behaviour, BBB integrity, and immune profiling). The therapeutic potential of SR1001 highlights translational relevance. However, limitations include the exclusive use of male rats, neglecting sex-specific responses, the

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lack of causal evidence (e.g., Th17 depletion) to confirm their necessity, and focus on acute CRS effects, while human depression often involves variable stressors. Generalizability is also constrained by the artificial restraint paradigm. Despite these gaps, the study advances understanding of immune-CNS interactions in depression.

3.2. A study of functional connectivity affected by acute stress

This study introduced the association between the corticolimbic system, which functions to return the body to homeostasis after acute stress, and the amygdala in the development of MDD. The key theories used by this study are the corticolimbic dysregulation model of depression and the stress-induced network reconfiguration hypothesis. The central tenet of the first theory is that MDD involves impaired top-down control of the prefrontal cortex (PFC) over limbic regions (amygdala, hippocampus), leading to emotional dysregulation. For the second one, the central tenet is that acute stress triggers adaptive reconfiguration of brain networks to prioritize survival-related processing (e.g., threat detection over complex cognition).

The study used a multi-modal neuroimaging approach combined with behavioral and physiological measures to investigate acute stress effects on the level of resting state functional connectivity (rsFC) within an a priori corticolimbic connectivity in MDD.

The study recruited 80 participants in total and divided into 3 groups: healthy controls (no stress, n=27), healthy controls (stress, n=26) and MDD parients (stress, n=27).

The study found that MDD patients exhibit attenuated amygdala-dorsal prefrontal cortex (dPFC) connectivity at rest, resembling the post-stress state of healthy controls. This proves that chronic stress. Healthy controls show stress-induced reduction in amygdala connectivity (adaptive decoupling), while MDD patients fail to reconfigure networks (Figure 1). And higher perceived stress (PSS scores) predicts weaker baseline amygdala-dPFC connectivity across all participants.

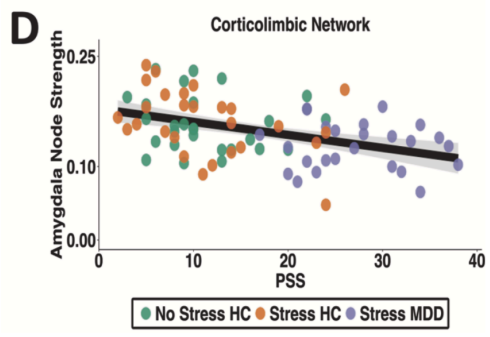


Figure 1. Corticolimbic network [10]

Note: Study design, effects of stress on mood and salivary cortisol and associations with the Perceived Stress Scale (PSS). Association between Pre-MAST amygdala centrality and the PSS *p < .001.

3.3. Summary of cases

These findings collectively support a model where MDD involves both trait-like corticolimbic dysregulation (from chronic stress) and state-specific inflexibility (failed adaptation to new stressors). The researchers propose that the interplay between accumulated stress burden and moment-to-moment neural dynamics plays a pivotal role in depression. The study bridges psychological (subjective stress), neural (connectivity), and behavioral (reinforcement learning)

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levels of analysis, proposing that therapeutic interventions targeting dPFC-amygdala plasticity (e.g., neuromodulation, cognitive training) could restore adaptive stress responses in MDD.

Hossein et al.'s [10] study offers important insights but has limitations. Its key strength lies in the multimodal approach combining acute stress induction, resting-state fMRI, and reinforcement learning tasks, enabling multilevel neurophysiological-behavioral analysis. By differentiating amygdala subnuclei (BLA/CMA) and prefrontal subregions (dorsal/ventral), the study reveals MDD-specific circuit abnormalities, with unmedicated participants enhancing clinical relevance. However, limitations include a modest sample size (n=80), a cross-sectional design precluding causal inferences, and delayed fMRI scanning (40-60 min post-stress), potentially missing immediate neural responses. High collinearity between perceived stress (PSS) and depression severity (BDI-II) complicates interpretation, while 8 mm smoothing may obscure fine-grained connectivity patterns. These methodological constraints provide clear directions for future research.

4. Discussion

The present review emphasizes distinct neurobiological pathways through which acute and chronic stress contribute to Major Depressive Disorder (MDD). Acute stress primarily disrupts prefrontal-amygdala functional connectivity, impairing top-down emotional regulation and executive functions [3]. This aligns with the corticolimbic dysregulation model, where amygdala-dPFC connectivity in MDD patients reflects the post-stress state of healthy controls, hence suggests a failure in adaptive network reconfiguration. In contrast, chronic stress induces sustained neuroinflammation and HPA axis dysfunction. By looking at the BBB disruption, hippocampal volume reduction, and peripheral immune activation [4, 8]. These divergent mechanisms reinforce the necessity for targeted interventions, which are cognitive remediation for acute stress-induced deficits versus anti-inflammatory strategies for chronic stress.

The study by Scott & Dickson [3] provides critical insights into acute stress effects, but its cross-sectional design limits causal inferences. Similarly, while animal models (e.g., CUMS mice) link chronic stress to neuroinflammation [9], their relevance to humans requires further validation.

In terms of methodology issues, such as stress induction protocols (psychosocial vs. immunological) and sample heterogeneity (unmedicated MDD vs. comorbid populations), may explain inconsistent findings across studies, particularly in cognitive flexibility [6].

In clinical situations, these findings can be applied in personalized treatments. For instance, real-time fMRI neurofeedback could strengthen amygdala-PFC connectivity in acute stress susceptibility, while therapies targeting glucocorticoid resistance (e.g., minocycline) might mitigate chronic stress-related neuroinflammation. Future research should prioritize longitudinal designs to see the dynamics of stress effects and investigate the effect of amygdala-PFC connectivity on PFC functionality.

5. Conclusion

This review synthesizes evidence about the interconnected roles of chronic and acute stress in the pathophysiology of MDD. While acute stress primarily disrupts prefrontal-amygdala connectivity, impairing executive functions and emotional regulation, chronic stress drives neuroinflammation and HPA axis dysregulation, leading to structural brain changes and persistent depressive like behaviours. These differences emphasized the need for targeted therapeutic strategies, such as cognitive training for acute stress susceptibility and anti-inflammatory interventions for chronic stress.

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However, limitations in existing research—including heterogeneous stress paradigms, cross-sectional designs, and reliance on animal models—warrant cautious interpretation. Future studies should prioritize longitudinal human cohorts and multi-omics approaches to unravel stress-depression interactions across biological systems (e.g., gut-brain-immune axes). Clinically, integrating these insights into personalized medicine could transform outcomes for stress-related MDD, emphasizing early intervention and mechanism-specific treatments.

The limitation of the review is that the hypothesized relationship between amygdala-prefrontal connectivity disruption and cognitive deficiency in MDD lacks direct evidence in current literature. While acute stress is shown to impair both PFC-dependent executive functions (e.g., WM) and amygdala-PFC connectivity, few studies explicitly bridge these phenomena. This gap should be investigated in future studies.

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