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Exploring the Mechanism of Amygdala Volume Change in Patients with Bipolar Disorder at Different Stages

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Abstract. Bipolar disorder (BD) is a chronic, relapsing psychiatric condition marked by recurrentepisodes of mania or hypomania and depression. It is primarily divided into Type I, Type II, and cyclothymia disorder. This paper employs a literature review method to explore the mechanisms behind the differences in amygdala volume changes in patients with bipolar disorder (BD) at different stages. By comparing the increased amygdala volume in newly diagnosed BD patients with the decreased volume in long-term BD patients, the study aims to uncover the underlying mechanisms. The article will delve into the changes in amygdala volume from three perspectives: neuroinflammation, dysregulation of the BDNF-TrkB signaling pathway, and the effects of lithium salts. The study concludes that BD patients at different stages exhibit distinct influences on amygdala volume changes in neuroinflammation, dysregulation of the BDNF-TrkB pathway, and the effects of lithium salts.

Keywords: Bipolar disorder, neuroinflammation,BDNF-TrkB, Lithium salt

1. Introduction

Bipolar disorder (BD) is a chronic, relapsing psychiatric condition marked by recurrentepisodes of mania or hypomania and depression [1]. It is primarily divided into Type I, Type II, and cyclothymia disorder. Despite its significant public health burden – affecting 1% to 2% of global population and 0.1% to 0.2% in China – effective treatments remain limited [2]. It is associated with significant functional impairment and elevated risk of suicide [3]. The pathogenesis involves a complex interplay between neural circuitry abnormalities, neurotransmitters imbalance, endocrine dysfunction, and structural brain changes [1]. The amygdala, a key component of the limbic system responsible for emotional regulation and stress processing, has emerged as a focal point in neuroimaging research. For instance, early-stage patients may show significantly increased amygdala volume potentially linked to neuroinflammation or compensatory plasticity, with reduced cognitive function [4]. Whereas long-term or recurrent BD often show significant volume reductions, possibly reflecting chronic neurotoxicity or cumulative stress exposure [5]. However, the underlying mechanisms driving these divergent patterns remain poorly understood. However, the underlying mechanisms driving these divergent patterns remain poorly understood. This review aims to explore the biological basis of amygdala volume changes across disease stages, with the global

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elucidating BD's dynamic neuropathology. Such insights could advance precision psychiatry, refine staging models, and inform early intervention strategies.

2. Amygdala volume trajectories in BD

Recent neuroimaging studies have shown that individuals with first-episode manic or bipolar presentations exhibit significantly larger amygdala volumes compared to healthy controls often accompanied by cognitive dysfunction [4].

In the early stages of the disease (i.e., at the first onset or within two years of the initial diagnosis), imaging studies have observed a significant increase in the overall volume of the amygdala in patients compared to healthy individuals, ranging from 8% to 12% [6, 7].

However, other studies have reported progressive amygdala atrophy in both young and adult patients, indicating a potential neurodegenerative trajectory [8]. Furthermore, elderly BD patients consistently display marked reductions in amygdala volume [9]. This volumetric changes are hypothesized to reflect dynamic pathological processes that evolve across the course of illness. This structural change is associated with memory impairment and emotional instability.

3. Neuroinflammation mechanisms

The dynamic alterations in the volume of the amygdala of patients with BD are a significant indicator of the progression of the illness. This phenomenon is closely associated with the stage-specific characteristics of neuroinflammation: during the acute phase, the inflammation primarily leads to an increase in the volume of the amygdala, while in the chronic phase, neuroinflammation results in neuronal injury and structural atrophy.

3.1. Acute phase

Acute emotional attacks in early-stage BD are associated with microglial activation and elevated release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) [10]. This neuroinflammatory milieu leads to neuronal edema and impaired synaptic plasticity in the amygdala. This acute inflammation may cause short-term amygdala volume enlargement through changes in blood-brain barrier permeability. Interleukin 17A(IL-17A) levels are elevated in the cerebrospinal fluid of patients with acute BD, and this elevation promotes an increase in the volume of the amygdala [11]. In response to acute stress, DNA methyltransferase (DNMT) and histone deacetylase (HDAC) are known to work in tandem to amplify inflammatory responses in the nervous system. The interaction between HDAC and DNMT3A, a DNA methyltransferase, has been observed to inhibit the activity of the inflammatory mediator genes IL-6 and TNF-α. This inhibition leads to the de-methylation of the promoter regions of these genes, thereby releasing the inhibition of their expression [12]. Concurrently, the activity of HDAC is known to cause a disintegration of the nucleosome structure, resulting in the activation of NF-κB genes and the subsequent release of inflammatory mediators. This positive feedback loop involving these two genetic modifications has been implicated in the exacerbation of inflammatory responses [13]. Longitudinal studies have shown that as the disease progresses, chronic inflammation contributes to neuronal loss and progressive atrophy of the amygdala volume [14].

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3.2. Chronic phase

Under a long-term inflammatory state, persistently elevated pro-inflammatory factors (such as TNF-α and IL-1β) breach the blood-brain barrier and enter the central nervous system, triggering abnormal activation of microglia and their transformation into a pro-inflammatory phenotype (M1 type) [15]. This leads to the release of excessive reactive oxygen species (ROS) and the excitatory neurotransmitter glutamate, causing mitochondrial dysfunction and the accumulation of oxidative stress, which directly damages neuronal DNA and initiates apoptotic pathways (such as Caspase-3 activation) [16]. Concurrently, inflammatory factors suppress the neurotrophic support function of astrocytes, exacerbating synaptic loss and neuronal metabolic failure [17]. Ultimately, through neuronal apoptosis, excessive synaptic pruning, and glial scar formation, the volume of the amygdala progressively shrinks, creating a vicious cycle with the emotional regulation disorders and cognitive decline associated with BD.

4. BDNF-TrkB signaling pathway dysregulation

Transient activation of the BDNF-TrkB pathway in patients with recent BD is a compensatory response of the organism to maintain neurohomeostasis, whereas epigenetic silencing, receptor downregulation, and glial cell dysfunction during the long-term course of the disease lead to pathway failure and trigger structural atrophy.

4.1. Acute phase

In response to psychosocial stressors and acute emotional episodes, hypothalamic-pituitary-adrenal (HPA) axis activation induces transient increase in BDNF expression in the amygdala [18]. The HPA is excessively stimulated due to the presence of glucocorticoid hormones (e.g., cortisol), which leads to an increase in glucocorticoid receptor (GR) levels. This, in turn, indirectly promotes the de-methylation of the BDNF gene promoter regions I, II, and III, resulting in increased BDNF transcription [19]. BDNF binds to the TrkB receptor initiates downstream Ras-MAPK/ERK and PI3K-Akt cascades, promoting neuronal growth and dendritic spine formation in amygdala neurons, manifested as a temporary amygdala hypertrophy observed in early BD [20]. Glucocorticoids inhibit the activity of DNA methyltransferase DNMT3A, leading to demethylation of the BDNF gene promoter region IV (stress-sensitive regulatory region), which lifts transcriptional repression and promotes the expression of BDNF mRNA, alleviating excitotoxicity [20]. At the same time, the reduction of histone deacetylase (HDAC) activity loosens the chromatin structure of the promoter region and enhances the binding efficiency of transcription factors, promoting synaptic plasticity and amygdala volume compensatory increase.

4.2. Chronic phase

However, in the long-term course of the disease, sustained oxidative stress and inflammation impair TrkB receptor function via receptor downregulation or phosphorylation deficits, reducing neurotrophic support. This shift leads to reduced synaptic density and volumetric decline over the chronic disease course. BDNF promotes synaptic formation, dendrite branching and neuron survival by activating TrkB receptors. When this pathway is out of order, the synaptic density of amygdala neurons decreases, the synaptic transmission efficiency decreases, and finally the structure shrinks [21]. The persistent high glucocorticoid environment under chronic stress leads to the re-increase of DNA methylation in the promoter IV region of the BDNF gene, which inhibits transcriptional

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activity and reduces the synthesis of BDNF protein [22]. Animal studies have shown that BDNF-TrkB signal defect can reduce the dendritic complexity of neurons and accelerate cell apoptosis [23].

5. Lithium salt-induced neuroplasticity

The dynamic alterations in the volume of the patient's amygdala are closely associated with the progression of the illness and the timing of lithium intervention. Current evidence indicates that lithium exerts a multifaceted molecular mechanism that results in varied effects on the amygdala at different stages of the illness.

5.1. Acute phase

Lithium salts treatment remains a cornerstone of BD management and has been shown to exert neuroprotective effects through modulation of glycogen synthase kinase-3 β (GSK-3 β) inhibitory signaling and enhancement of BDNF-TrkB pathways [24]. Early-phase lithium salts treatment correlates with increased amygdala volumes, as demonstrated by high-resolution MRI studies [5,25]. The application of lithium has been demonstrated to inhibit GSK-3β, thereby activating the Wnt/β-catenin pathway. This, in turn, has been shown to promote the formation of spines in the amygdala and the adjacent neocortex. In the early stages of treatment, the addition of lithium to the patient's regimen has been shown to enhance the proliferation of oligodendrocyte progenitor cells (OPCs), thereby promoting myelin repair. Diffusion tensor imaging (DTI) has revealed a significant increase in the fractional anisotropy (FA) value of the amygdala-insular white matterof the lithium-treated patients, suggesting an improvement in the integrity of the axons. This improvement may be attributable to a structural compensation for the underlying pathophysiological damage [26].

5.2. Chronic phase

In long-term BD patients, lithium salt treatment appears to attenuate but not reverse structural degeneration, suggesting a protective but time-limited benefit [27]. Longitudinal data indicate that while lithium may stabilize volume loss, its efficacy reduces as disease chronicity increases [28]. Recent studies have shown that the dysfunction of the glymphatic system in the brain is related to neurodegenerative diseases [29]. Long-term lithium salt may indirectly affect the function of Aquaporin-4, resulting in the accumulation of metabolic wastes (such as amyloid β-protein) in the amygdala, which will aggravate neuronal damage [30].

The long-term use of lithium has been shown to interfere with the autophagy-lysosome pathway (ALP), thereby inhibiting LC3II expression and increasing p62 accumulation. This results in the deposition of misfolded proteins (such as TREM2 mutations) within the neurons of the amygdala. The toxicity of these misfolded proteins causes cell death, manifesting as a decrease in cell volume [31]. Chronic exposure to lithium has been demonstrated to result in the activation of the mTOR pathway (phosphorylation of p70S6K), leading to the inhibition of proliferation of neural progenitor cells in the hippocampus, thereby indirectly impacting the occurrence of neuronal activity in the amygdala.

6. Critical appraisal and methodological considerations

The converging pattern of early enlargement followed by chronic atrophy across BD stages supports a neuroprogressive model. However, existing studies also reveal certain limitations.

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First most of the current studies treat bipolar disorder (BD) as a homogeneous group, ignoring the heterogeneity of disease stage (acute/chronic phase) and episode type (type I/II). For example, some studies have failed to distinguish amygdala volume differences between patients with BD type I manic episodes and BD type II hypomania, and the effect of illness stage (e.g., first episode vs. multiple relapses) on amygdala structure has not been clarified. In addition, co-morbidities (e.g., anxiety disorders, substance abuse) may confound the specificity of amygdala volume changes, but most studies have not adequately controlled for these confounders.

Second existing studies are mostly based on cross-sectional data and cannot distinguish the temporal dynamics of amygdala volume changes. For example, acute-phase volume increase may be associated with inflammatory responses, whereas chronic-phase atrophy may originate from neuronal loss, but longitudinal follow-up data are lacking to validate the causal relationship. In addition, single time-point measurements are difficult to capture the dynamic modulatory effects of pharmacologic interventions (e.g., lithium) on amygdala structure.

Finally the absence of correlation between function and structure is a recurring theme in research. Most studies examine isolated structural data without incorporating functional connectivity (e.g., brain nuclei-hippocampus) or molecular markers (e.g., BDNF, IL-6) to provide a more comprehensive interpretation. To advance this field, future research should prioritize longitudinal, multimodal imaging studies with consistent staging criteria and refined clinical stratification.

7. Conclusion

This study aims to explore the mechanisms behind the differences in amygdala volume changes in patients with BD at different stages. The findings indicate that the amygdala volume increases in newly diagnosed BD patients, while it decreases in those with a longer duration of the disorder. Analysis suggests that these changes are linked to neuroinflammatory alterations in the brain, dysregulation of the BDNF-TrkB signaling pathway, and the effects of lithium salts. By comparing the changes in amygdala volume across different stages, this study explores the underlying mechanisms, providing evidence that supports previous theories and confirms that there are indeed specific mechanisms influencing the differences in amygdala volume changes among BD patients at various stages. These insights can advance precision psychiatry, refine staging models, and inform early intervention strategies, while also holding significant implications for the field of brain mechanism research in psychiatry. However, the study has limitations that may affect the generalizability of its results. One limitation is the limited review of literature, which restricts a comprehensive comparison of BD patients across different periods; another limitation is the lack of precision in discussing amygdala mechanisms, which means not all aspects of these mechanisms have been covered, a gap that could be addressed in future research. Future studies could focus on collecting more cases of amygdala changes in BD patients at different stages and considering a broader range of amygdala change mechanisms. Overall, this study clarifies the mechanisms behind the differences in amygdala volume changes at various stages, paving the way for the development of related BD treatment drugs through further research in this area.

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