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REVIEW

Cognitive Impairment Mechanism in Patients with Bipolar Disorder

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Abstract: Bipolar disorder (BD) is a common chronic mental disorder usually characterized by manic, hypomanic and depressive episodes. Patients diagnosed with BD have cognitive impairments in both the mood attack and remission stages, that is impairment of attention, memory and executive function. Up till the present moment, the causative mechanisms of cognitive impairment in BD patients remain poorly understood. Several studies have demonstrated that cognitive impairment in patients with bipolar disorder is not associated with a single factor, but with gene polymorphism, brain structural and functional variables, inflammatory and metabolic factors. Herein, we reviewed and summarized the recent reports on cognitive impairment mechanisms in patients with BD. To prevent or alleviate cognitive damage at an early stage, we propose that future research should focus on investigating the pathological mechanism of specific cognitive dimension damage as well as the pathological mechanism network between the damage of each dimension. It is crucial to recognize mechanisms of cognitive impairment for improving the symptoms and prognosis of BD patients, restoring their social function and integration.

Keywords: bipolar disorder, cognitive impairment, mechanism, attention impairment, memory impairment, impairment of executive function

Introduction

Bipolar disorder is one of the most challenging psychiatric diseases, which has an adverse effect on the lives of most patients, with more than 6% dying by suicide within two decades of diagnosis.[1] Patients with bipolar disorder suffer from cognitive impairments not only during the acute phase but also during the remission phase,[2,3] characterized by impairment of attention, memory and executive function.[4] Unfortunately, the mechanisms contributing to cognitive impairment in patients with BD have not been scientifically elucidated. To better understand the pathogenesis of cognitive impairment and to design more effective treatment strategies, it is necessary to explore the mechanism of cognitive impairment. In this article, we reviewed and summarized a significant amount of research on cognitive impairment in patients with BD and the possible associative mechanisms leading to these impairments based on possible factors like gene polymorphism, brain structural and functional variables, inflammatory and metabolic factors, in the hope of providing an outlook for future research.

Major Cognitive Impairment in Patients with Bipolar Disorder and Its Possible Mechanisms

Attention Impairment and Its Possible Mechanisms

The term "attention" describes how the brain concentrates, chooses information, integrates it through perception and understanding, and then uses that knowledge to think, remember, perceive, plan and perform actions.[5] Given that damage to attention will impair cognitive functions, it is essential to elucidate whether the attention of BD patients is impaired.

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A recent study found that compared with healthy controls, BD patients' attention was significantly affected, regardless of the stage of their disease (stable stage, manic stage, depressive stage).[6] Interestingly, a study found that adolescents with BD (14–17 years old) had persistent impairments in attention during remission.[7] Similar studies have found that older patients with euthymic bipolar disorder have poor cognitive function compared to their healthy peers, but their cognitive decline do not worsen over time.[8] However, a 26-week follow-up study on 172 subjects found that the sustained attention score of BD patients was lower than that of healthy controls. Additionally, the attention impairment of BD patients during manic episodes was much more obvious than during depressive episodes.[9] Therefore, attention impairment is present in both adolescents and adults with bipolar disorder and may be present at any time in the development of the disease and is an endophenotype of BD.

In recent years, the mechanism of impaired attention in BD patients has attracted more and more attention from researchers. Previous reports have shown that persistent attention impairment in euthymic BD patients is associated with the CHRNA7 gene, and the CTCT haplotype is correlated with an improvement in attentional task performance in BD patients.[10] Similarly, another study found that different subtypes of cognitive functions improved in BD patients with different ALDH2 genotypes.[11] On the other hand, some scholars believe that the sustained attention impairment of euthymic BD patients is also related to the metabolism of the brain. Continuous attention detection and head MRI scans were conducted on 16 BD patients in the stable phase and 11 healthy controls, revealing that the patients' sustained attention was worse than healthy controls, while the hippocampus, temporal lobe and other brain regions were metabolized slower than normal.[12] Collectively, the above studies illustrate the mechanism of attention impairment in BD patients from the aspects of genetics and metabolism.

Additionally, studies have shown that BD patients' attention, cognitive performance, working memory, executive function, and psychomotor coordination are all affected if the integrity of their white matter fiber bundles is damaged.[13] This suggests that BD patients whose brain structure and brain function have been damaged may have impaired attention and cognitive functions.

Memory Impairment and Its Possible Mechanisms

An individual's memory is a continuous representation of their ideas, experiences, or behavior, and learning is the process by which they acquire that representation.[5] The hippocampus and medial temporal lobe play an important role in memory. A brief assessment of affective cognition in 149 subjects using BAC-A, which includes visual motor, immediate emotional and non-emotional memory, language fluency, delayed emotion, non-emotional memory, and problem-solving, found that BD patients had impaired short-term memory and verbal fluency.[14] A meta-analysis revealed that the cognitive function of BD patients is impaired in any state, which is mainly reflected in the following areas: attention, memory, and psychomotor inhibition.[2] These impairments have a negative effect on the prognosis of patients. In conclusion, the memory of BD patients is impaired to varying degrees during the acute or remission phases.

Several scholars have examined the mechanisms of memory impairment in BD patients and believe that they may be related to genetics and brain function among other factors. BD patients and their first-degree relatives have speech memory impairment, which the impaired speech memory function of BD patients and their relatives may represent the candidate "endophenic" marker of BD.[15] Therefore, some scholars believe that the verbal scene and spatial working memory of BD patients may be related to the genetic matrix.[16] The cognitive scores of BD patients' children with subthreshold symptoms are also lower than those of healthy controls in terms of working memory, verbal memory, and planning.[17] The MCCB (MATRICS Consensus Cognitive Battery) was previously used to assess the cognitive performance of 27 asymptomatic first-degree relatives of BD patients, 47 healthy controls, and 28 BD patients (BD patients not related to first-degree relatives of BD patients); and the results revealed that speech learning, processing speed and working memory performance were candidate endophenotypes with familial risk for BD.[18]

Some studies found that the single nucleotide polymorphisms (SNPs) of BD susceptibility genes were related to dendritic development, neuron survival, synaptic plasticity and memory learning references. A study on the association between BD and several single nucleotide polymorphisms (SNPs) in three strong candidate genes (CACNA1C, CHRNA7 and MAPK1) showed that crs1016388 in CACNA1; rs1514250, rs2337980, rs6494223, rs3826029 and rs4779565 in CHRNA7; rs8136867 alleles in MAPK1 were distributed differently between the case group and the

control group, suggesting that these 3 genes may play a role in BD and subsequently affect the cognitive of BD patients.[19] ANK3 may be a susceptibility gene for BD and BD patients who carry the rs10761482 allele. Another SNP locus has been significantly associated with impaired cognitive functions such as language comprehension, logical memory and processing speed compared with patients carrying the non-risk allele. Meanwhile, in healthy people, those with the risk allele were also impaired in terms of executive function and visual memory.[20] Similarly, some researchers have found that RS9804190, which is a single nucleotide polymorphism in the gene encoding Ankyrin G protein (2014), is associated with BD, and RS9804190 affects the front-temporal lobe structure of BD patients, which is responsible for executive function, memory and other cognitive aspects.[21] In summary, BD patients' memory impairment is related to genes, brain structure and brain function.

Impairment of Executive Function and Its Possible Mechanisms

According to the definition by Alexander Luria (1966), executive function includes subjective intention, goal formation, behavioral sequence planning according to goals, recognition of target consistency with the cognitive route, route switching on time sequence, and evaluation of action results. Guiyun Xu et al previously have shown that BD patients have impaired executive function, and those with bipolar I, bipolar II and unipolar depressive disorder have impairment in executive function, episodic memory, visuospatial memory, verbal fluency, and information processing speed during the acute depressive phase.[22] A long-term follow-up study showed that euthymic BD patients had impaired executive function but did not have worsening cognitive impairment over time.[23] At present, most studies show that the executive function of BD patients is impaired in the acute stage, but there is no unified conclusion on whether there is impairment in the remission stage. There are few international studies with a long-term follow-up (more than 6 years), and a large sample size, consequently, the question remains to be answered, warranting further studies.

Scholars have also studied the mechanism of impaired executive function in BD patients. Cognitive tests were performed on 30 siblings of unaffected BD patients and 30 healthy controls, and it was found that siblings of BD patients performed worse in attention, memory, and executive function than healthy controls. These impairments were consistent with neurobiological models of the frontotemporal lobe and subcortical circuitry in BD patients.[24] In adolescents with BD, there is a negative correlation between serum lipid peroxide (LPH) level and executive function, which may be regulated by the brain-derived neurotrophic factor (BDNF). Therefore, LPH and BDNF might be useful biomarkers for identifying BD patients with poor executive function.[25] Consistently, another study found decreased BDNF levels and worse executive performance in bipolar disorder patients during stable periods or manic episodes compared to healthy subjects, highlighting the importance of BDNF not just across mood phases but also in cognitive functioning.[26] In addition, it has been found that impaired executive function in patients with bipolar I is associated with the MsrA gene, and rs4840463 polymorphism in the MsrA gene may be associated with an increased risk of bipolar I disease in the Chinese population.[27] Similarly, impaired executive function in BD patients was associated with genetic factors, which may be BD endophenotype.[28] Thus, the impaired executive function of BD patients is related to genetics and neural circuits.

Other Aspects: Immune Disorders and Inflammatory Mechanisms

Recent research has indicated that immune system disorders may potentially contribute to the development of BD, and these disorders might affect cognition in a similar manner. A previous study has demonstrated that inflammatory factors are related to cognitive impairment in BD patients.[29] According to the study, elevated serum levels of three inflammatory markers: sTNF-R1, IL-1Ra, and sCD40L, were related with poorer overall cognitive function in BD patients.[30] Another study found that the levels of interleukin-6, interleukin-10 and CCL24 in the blood of patients and their siblings were higher than those of healthy controls, and the activity of glutathione peroxidase and telomere length was decreased, which accelerated aging in patients.[31]

Neuroinflammation plays a role in the pathogenesis of BD, with microglia activation playing a significant role. In addition, pathological changes in brain glial cells, such as astrocytes and oligodendrocytes, have been confirmed in affective disorders, and one of the reasons why lithium is effective in treating BD may be related to its anti-inflammatory effect.[32] BDNF promotes the repair and regeneration of damaged neurons. Several studies have found that BDNF is

significantly lower in BD subjects.[33] Rs6265 polymorphism of BDNF correlates with hippocampal volume,[34] while memory function is related to the hippocampus, suggesting that reduced BDNF may impair the memory function of patients.

Previous reports uncovered that T cells and peripheral monocytes in BD patients were abnormal, and cell dysfunction and brain volume reduction caused by cell apoptosis also resulted in impaired cognitive function in BD patients.[35,36] It correlates with cognitive function and metabolism in patients with bipolar disorder. For instance, Homocysteine (Hcy), a sulfur-containing amino acid that is part of the methionine metabolism can affect cognitive function in several ways, with elevated Hcy levels being associated with cognitive impairment in euthymic BD patients.[37] Insulin resistance is also connected with cognition in people with BD, which is present in more than half of all BD patients and is associated with a chronic course of illness, lack of response to mood stabilizing treatment, cognitive impairment and poor functional outcomes.[38] This manifests that cognitive impairment in patients with bipolar disorder may also be related to metabolism.

Conclusions

According to recent research, BD patients exhibit impaired attention, memory, and executive function during the disease's acute and remission phases. Notably, these studies concluded that cognitive impairments are not caused by a single factor and that the damage mechanism may be associated with gene polymorphism, brain structural and functional variables, inflammatory and metabolic factors, to name a few.

Nevertheless, insufficient research has been performed to confirm the damage to a specific cognitive dimension and the pathological mechanism associated with it, and there is no clear correlation between the damage mechanism and the cognitive dimension.

It is worth mentioning that using task-based fMRI methods, a recent research observed altered activations in the lingual and fusiform gyri between depressed patients and healthy controls,[39] which might be a new idea for researchers to capture changes of cognitive impairment in BD patients.

To prevent or alleviate cognitive damage at an early stage, future research should focus on investigating the pathological mechanism of specific cognitive dimension damage as well as the pathological mechanism network between the damage of each dimension. Thus, identifying cognitive impairment-related mechanisms is crucial to improving the symptoms and prognosis of BD patients, as well as restoring their social function and integration.

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Author Contributions

Yanxiong Huang: Conceptualization, methodology, writing-original draft and review editing. Zhilong Zhang: Methodology, writing-review and editing. Shihao Lin: Methodology, writing-review and editing. Haobin Zhou: Writing-review and editing. Guiyun Xu: Conceptualization, writing-review and editing, funding acquisition, supervision. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; have drafted, revised or critically reviewed the article; have given final approval of the version to be published; have agreed on the journal to which the article will be submitted; and agreed to be accountable for the contents of this article.

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Disclosure

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