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Cognitive Impairment in Bipolar Disorder

Simge Uzman Özbek[1], **Emre Bora**[2,3,4]

[1]*Department of Psychiatry, Kastamonu Education and Research Hospital, Kastamonu, Türkiye*
[2]*Department of Neurosciences, Dokuz Eylül University Health Sciences Institute, İzmir, Türkiye*
[3]*Department of Psychiatry, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye*
[4]*Department of Psychiatry, Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health Melbourne Neuropsychiatry Centre, Victoria, Australia*

ABSTRACT

Cognitive impairment is recognized as a common aspect of bipolar disorder (BD), persisting beyond acute episodes and extending into euthymic periods. Verbal learning, memory, and executive functions exhibit the most pronounced impairments among the affected cognitive domains. Patients with BD also demonstrate social cognitive deficits. However, all patients with BD do not exhibit similar cognitive features. Recent data-driven studies emphasize the heterogeneity of cognitive impairment in BD, identifying 3 distinct subgroups: preserved cognition, selective impairment in specific domains, and global cognitive deficits. This classification highlights the variability in cognitive functioning among individuals with the disorder. The presence of cognitive deficits in healthy relatives of bipolar disorder patients, in individuals at high risk for BD, and in the firstepisode of BD patients suggest a potential neurodevelopmental component. Conversely, studies associating cognitive decline with factors such as illness duration, the number of manic episodes, and age of onset underscore a possible neuroprogressive aspect. There is no consensus on whether BD is a neurodevelopmental or a neuroprogressive disease. Longitudinal studies are needed to clarify the trajectory of cognitive impairment. Although cognitive deficits in BD resemble those observed in schizophrenia, they tend to be less severe, pointing to a transdiagnostic dimension of impairment. Cognitive deficits negatively impact the clinical course, functional outcomes, and quality of life. Future research should focus on the cognitive subgroups, the trajectory of cognitive impairment, personalized treatment strategies, and cognitive rehabilitation.

Keywords: Bipolar disorder, cognition, cognitive function, neurocognition, social cognition

Corresponding author:
Simge Uzman Özbek

E-mail:
simgeuzman@gmail.com

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INTRODUCTION

Bipolar disorder (BD) is a lifelong episodic illness characterized by mood and energy swings that often lead to functional impairment and reduced quality of life. In recent years, cognitive impairment has been increasingly recognized as a well-documented feature of BD, and research in this area has accelerated over the past 2 decades, contributing to a growing body of evidence.[1]

Cognitive impairment is a well-recognized and persistent feature of schizophrenia. Until recent years, it was considered a core symptom of schizophrenia and thought to be specific to this disorder among

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severe psychiatric illnesses. However, accumulating evidence has demonstrated that cognitive impairment follows a transdiagnostic pattern. Meta-analytic evidence has confirmed that BD is also associated with significant cognitive deficits. These impairments persist during mood episodes and in euthymic states.[2] Various factors can negatively impact cognitive functioning in BD, including clinical variables such as subthreshold symptoms, sleep disturbances, and pharmacological treatments.[3]

Neurocognitive functions significantly predict psychosocial functioning.[4] However, BD is heterogeneous in terms of cognitive functions. Unlike schizophrenia, BD includes a subgroup of individuals who exhibit good cognitive functioning, tremendous academic success, and enhanced creativity.[5] Moreover, the presence of similar cognitive deficits in unaffected first-degree relatives suggests a potential genetic predisposition.[6]

In this review, the authors discuss the characteristics of cognitive deficits in BD, the heterogeneity of cognitive functions, the nature and trajectory of cognition in BD, the effects of medication, and the impact of cognition on functional outcomes.

CHARACTERISTICS OF COGNITIVE DEFICITS IN BIPOLAR DISORDER

Traditionally, neurocognitive functions are investigated as different domains. The most dominant approach in recent schizophrenia studies is using 6 MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) neurocognitive domains (processing speed, working memory, verbal learning, visual learning, attention, executive functions), and social cognition.[7] A similar approach is also used in studies investigating cognitive functions in BD.[8]

It is widely recognized that patients with BD experience significant cognitive impairments during acute manic or depressive episodes. Besides, over time, accumulating evidence has shown that cognitive impairment is not limited to acute episodes but persists during euthymic periods as well.[2,9] Meta-analytic findings indicate that BD is associated with significant cognitive deficits across multiple domains, including executive functions, verbal memory, sustained attention, processing speed, and working memory. Among these domains, verbal learning and memory, as well as executive functions, exhibit the most pronounced impairments, with large effect sizes.[4,10-14] Additionally, a meta-analysis by Mann-Wrobel et al[15] (2011) suggested that rather than deficits being confined to specific domains, cognitive impairment in BD may be more widespread, with verbal ability emerging as the only relatively preserved domain.

In addition to neurocognitive deficits, impairments in social cognition have also been observed in BD. Meta-analytic evidence highlights deficits in emotion recognition, emotion processing, theory of mind, social judgment, and social decision-making among bipolar patients in remission.[16,17] When comparing the severity of cognitive impairments, both neurocognitive and social cognitive deficits are found to be less severe in BD than in schizophrenia.[18]

A meta-analysis examining the effects of clinical states on cognitive impairment found that euthymic bipolar patients exhibited significant neurocognitive deficits across all cognitive domains with moderate to large effect sizes. It was observed that patients tested during a manic/mixed or depressive episode showed more pronounced verbal learning impairments compared to those assessed during remission. Additionally, during depressive episodes, patients demonstrated more significant phonemic fluency deficits compared to euthymic patients.[14] Trait-related deficits have been highlighted primarily in verbal memory and sustained attention.[19]

Heterogeneity in Cognitive Functions

Not all patients diagnosed with BD exhibit similar cognitive characteristics, nor do they all face challenges due to cognitive impairment. Early studies on cognition classified patients into 2 groups based on cognitive cut-off scores: those with preserved cognitive function and those with impaired cognitive function. However, findings have been inconsistent due to differences in cognitive assessments and methodological variations across studies.[3,20] Recent data-driven studies and cluster analysis findings have highlighted neurocognitive heterogeneity within BD, drawing attention to distinct cognitive subgroups. These subgroups are often categorized into 3 main groups: 1. Preserved cognition, where individuals demonstrate cognitive performance comparable to healthy controls across various domains. 2. Selective cognitive impairment, characterized by deficits limited to specific areas, such as memory or executive functioning. 3. Global cognitive impairment, marked by widespread and severe deficits across multiple cognitive domains.[21] A recent meta-analysis that included 14 cross-sectional studies investigating cognitive subgroups of BD using data-driven clustering methods supported the 3-cluster solution. These clusters included severe impairment, moderate impairment, and good functioning groups.[5] In the good-functioning subgroup, evidence suggests that executive functions may exceed the average, as highlighted in the same study. Some positive traits of BD, such as creativity, openness to new experiences, and originality, might contribute to the academic and artistic accomplishments observed in some individuals.

Cluster analyses have also identified subgroups related to social cognition in BD. A study identified 2 separate social cognitive (SC) profiles among individuals with BD. Nearly two-thirds of the participants displayed preserved social cognitive abilities, whereas reduced SC performance was correlated with factors such as longer illness duration, male gender, and lower estimated IQ.[22]

One study noted that the evidence does not strongly support the idea that cognitive subgroups of schizophrenia spectrum disorders(SSD) or BD correspond to distinct patterns of brain morphology.[23] Further research in this area is needed. A detailed and precise definition of cognitive subgroups may facilitate the development of personalized cognitive interventions.

Cognition in the Early Stages of Bipolar Disorder

The high-risk approach to BD has gained increasing attention in recent years. Based on some clinical interviews and family history, high-risk status and familial risk for BD were defined. Mild cognitive impairments have been observed in healthy relatives of individuals with BD and those considered at risk but not yet diagnosed. A systematic review indicated that both individuals with BD and, to a lesser extent, their unaffected relatives exhibit cognitive impairments.[1] Like patients with BD, individuals at high risk for BD exhibited significant deficits in processing speed, executive functions, sustained attention, and social cognition.[24] These findings suggest that cognitive impairments may emerge during the prodromal phase of the disorder or indicate an underlying genetic predisposition. The presence of such impairments before illness onset, independent of mood episodes, clinical course, or medication effects, is

important as it may reflect the cognitive status of individuals at risk before the potentially disruptive effects of the illness emerge. On the other hand, it is important to note that, unlike schizophrenia, some patients with BD exhibit supranormal premorbid cognitive performance, which can serve as a predictor for the onset of BD.[25]

Cognitive impairment in BD may reflect its neurodevelopmental nature or function as an endophenotype, potentially serving as a marker of vulnerability.[4,26,27] Among first-degree relatives, deficits in attention, verbal memory, and executive function have been associated with an increased likelihood of illness onset.[6] If evidence of a link between cognitive impairment and illness prediction increases, a comprehensive prediction model that includes additional risk factors could be developed, contributing to planning preventive interventions at early stages.

A study conducted in the pediatric age group found that although the initially observed cognitive deficits improved to some extent over time, the developmental progress in executive functions and verbal memory remained significantly lower in patients with pediatric bipolar disorder (PBD) compared to healthy controls over a 3-year follow-up period.[28] The developmental delay observed in certain neurocognitive functions in PBD may also be attributed to the disruptive impact of BD on maturational processes during early life.

A meta-analysis examining cognitive impairment in both the acute and remission phases of first-episode mania investigated executive functions during the acute phase, identifying impairments in cognitive flexibility. The most consistent finding in the remission phase was a deficit in working memory.[29] Although no significant relationship was found between cognition and clinical variables such as illness duration, age at onset, previous depressive or hypomanic episodes, mood symptoms, or psychotic symptoms, premorbid intelligence was identified as a potential confounding factor in executive dysfunction during mania. Similarly, meta-analytic findings have shown that individuals experiencing their first episode of BD (FEBD) demonstrate significant cognitive impairments across all domains.[11,13] Although most studies in the meta-analysis by Bora and Pantelis included symptomatic patients, similar deficits observed in euthymic samples indicate that cognitive impairment in first-episode BD persists even during remission. This suggests that, as seen in chronic samples, a significant portion of cognitive dysfunction in FEBD cannot be solely attributed to the influence of mood symptoms.[11]

In summary, cognitive impairment seems to be present to some extent in the premorbid phase of BD, with the most pronounced decline occurring during the first episode of the illness.

The Nature and the Trajectory of the Cognitive Deficits in Bipolar Disorder

The longstanding debate regarding cognitive impairment in BD centers on whether these deficits are present from the onset of the illness or if they emerge as a consequence of mood episodes.[30] This discussion is also crucial in determining whether BD follows a neurodevelopmental or neurodegenerative trajectory.

The longitudinal course of cognitive impairment remains controversial, and no clear consensus has been reached. Some studies suggest that variables such as the number of manic episodes and illness duration are associated with cognitive impairment, supporting the hypothesis of illness-related cognitive decline.[31,32] However, these findings are primarily derived from cross-sectional studies, making them susceptible to bias. Causality can only be established through longitudinal research. A recent longitudinal study found that 16.4% of patients experienced cognitive decline, which became more pronounced after the age of 42 and was associated with the number of psychotic episodes.[33] The presence of cognitive decline in some patients but not in others suggests the existence of distinct cognitive subgroups with varying trajectories in BD. Some brain imaging findings support the neuroprogression hypothesis. A recent longitudinal study from the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium revealed that a higher number of manic episodes was linked to a faster rate of cortical thinning in the prefrontal cortex.[34] Similarly, a 6-year longitudinal follow-up study found a decrease in frontal brain regions in those who experienced a manic episode during the study, in contrast to those who did not have manic episodes.[35]

On the other hand, cognitive decline in BD may reflect illness severity rather than simply being a consequence of cumulative mood episodes. More significant cognitive impairment at illness onset may be associated with a more severe disease trajectory. However, in cross-sectional assessments, this impairment could be misattributed to the effects of mood episodes rather than recognized as a marker of an inherently more severe course.

Some meta-analyses examining cognitive function in BD over time have failed to provide strong evidence for progressive cognitive decline.[30,36] Given the limitations of cross-sectional research, understanding the relationship between disease course and neurocognitive function requires further longitudinal studies.

Early cognitive impairments in BD resemble those observed in first-episode schizophrenia, albeit to a lesser degree.[11] While the severity of verbal memory deficits differed between schizophrenia and BD, 1 study indicated that both disorders follow a comparable and stable cognitive trajectory over 5 years of psychiatric treatment.[37]

The relationship between age of onset and cognitive impairment is complex, as BD may exhibit a trimodal distribution of age at onset.[38] Early onset is associated with a worse prognosis, but its relation to cognitive function remains unclear. While some studies have not found a significant association between age of onset and cognitive deficits in younger patients,[13,29] another study has reported relations between age of onset and verbal memory impairment and psychomotor slowing.[26] Identifying a relationship between early illness onset and cognitive impairment may be hindered by the limited age variance at onset in adult studies. Conversely, late-onset BD has been associated with more pronounced cognitive deficits and may be more closely linked to neurodegenerative processes.[39] Data from genetic studies have also shown that the genes CACNA1C, GABBR2, SCN2A, CTSH, MSRA, and SH3PXD2A overlap in BD and dementia.[40] These genes may be associated with neuroprogression of BD to dementia and cognitive decline. These findings may indicate the existence of separate subgroups based on age of onset, with different cognitive trajectories among patients with BD.

Cognitive reserve refers to the brain's ability to tolerate neuropathological damage by using premorbid capacity or developing alternative strategies. Individuals with BD with higher cognitive reserve exhibit better cognitive performance.[41] A recent meta-analysis examining cognitive reserve and cognition in mood disorders suggested a positive association between cognitive reserve and cognitive

functioning and suggested that disease duration may play an essential role in shaping the relationship between cognitive reserve and cognitive function, particularly in the areas of executive function and visual memory.[42]

Although there is evidence supporting both neurodevelopmental and neurodegenerative models, considering the heterogeneity in terms of age of onset, course, cognition, and functioning in BD, the existence of different subgroups may be possible.

Effects of Medication on Cognition

Pharmacological treatments during acute episodes are typically linked to cognitive improvements, primarily due to the alleviation of symptoms. However, in the euthymic phase, the impact of medication on cognitive function becomes more complex, and separating it from the natural course of the disorder is challenging. A study comparing cognitive features in euthymic BD patients treated with lithium, valproate, or antipsychotics found that working memory was more impaired in those receiving antipsychotics compared to those on lithium.[43] While lithium-treated patients have shown better performance in working memory tasks during manic episodes than those on valproate,[44] both lithium and valproate have been linked to cognitive deficits in bipolar depression.[45] In general, valproate is reported to have a more detrimental impact on cognitive function compared to lithium and other anticonvulsants. However, it remains unclear whether the cognitive effects of lithium and valproate are primarily due to symptom management or their direct influence on cognitive processes. Antipsychotics have been shown to negatively affect verbal memory in euthymic bipolar patients, though this may be confounded by illness severity.[9]

It is known that the risk of dementia increases in BD.[40] A Korean database study exploring the dementia risk in elderly BD patients demonstrated that valproate use was associated with a higher risk of developing dementia.[46] On the other hand, the impact of lithium on dementia risk remained inconclusive, indicating that lithium could potentially be a safer mood stabilizer for this group.

Many studies examining the cognitive impact of pharmacological treatments are cross-sectional, limiting their ability to assess long-term effects. Polypharmacy is common among patients with BD, yet its combined impact on cognitive function remains poorly understood. Research on this topic has yielded conflicting results, with some studies reporting cognitive benefits while others suggest potential adverse effects. These discrepancies highlight the need for further longitudinal studies to clarify the role of pharmacological treatments in cognitive outcomes among individuals with BD.

Effects of Cognition on Clinical Course, Functionality, and Quality of Life

Cognitive functions in BD significantly influence various aspects of functional outcomes, including occupational performance, social relationships, and overall quality of life. The persistence of cognitive impairment during the euthymic phase may play a role in its association with functional outcomes.[4]

Among cognitive domains, processing speed, verbal memory, and executive functions have been identified as key predictors of poor functional outcomes.[47] Burdick et al[48] (2010) reported that deficits in verbal learning were specifically linked to occupational functioning, while impairments in processing speed were also significant contributors.

Cognitive impairment is assessed through objective neuropsychological tests and subjective evaluations, which provide valuable insights into patients' perceived cognitive difficulties. A study incorporating objective and subjective cognitive function assessments found that even subtle or self-reported cognitive impairment was associated with poorer psychosocial functioning and lower quality of life estimates.[49]

A systematic review examining the relationship between functional outcomes and 5 domains of social cognition—theory of mind (ToM), emotion processing, attributional bias, empathy, and social perception—revealed significant correlations across all domains.[50] Emotion processing, particularly facial expression recognition, plays a crucial role in the social functioning of individuals with BD. However, findings regarding the association between ToM and functional outcomes were less consistent. The differences between the affective and cognitive components of ToM may account for these inconsistencies. Affective ToM, assessed through tasks such as the Reading the Mind in the Eyes Test, has been found to be significantly impaired in BD patients and strongly associated with reduced functional outcomes. However, the relationship between social cognition and functional outcomes should be interpreted with caution, as many studies included patients with subthreshold or depressive symptoms. Analyses also demonstrated an association between depressive symptoms, emotion processing, and social functioning. Even subsyndromal depression may have a significant impact on social outcomes.

Interventions for Cognitive Deficits in Bipolar Disorder

Cognitive impairment exerts a considerable effect on the day-to-day functioning and quality of life of individuals diagnosed with BD. Consequently, developing effective prevention and intervention strategies is a critical clinical priority. However, there are currently no approved treatments specifically designed to enhance cognitive function in BD. In recent years, cognitive rehabilitation has gained increasing attention, with cognitive remediation aiming to improve functional outcomes by targeting cognitive deficits through structured training. CR typically combines direct training of specific cognitive domains with the development of compensatory strategies and places a strong emphasis on transferring these skills to real-life situations.[51] Facilitating this transfer is crucial, as it enables individuals to apply what they have learned to real-world cognitive challenges. A systematic review of 16 randomized controlled trials was conducted, encompassing 6 on CR, 3 on neuromodulatory techniques such as direct current or repetitive magnetic stimulation, and 7 on pharmacological interventions. This comprehensive review identified CR as the intervention with the most consistent cognitive benefits.[52] However, it is noteworthy that only 1 CR study demonstrated improvements in psychosocial functioning, while other studies that reported any benefits showed improvements limited to self-reported cognitive and psychological measures. Neuromodulatory approaches demonstrated inconsistent efficacy across trials. Concerning pharmacological strategies, preliminary evidence suggests that agents such as modafinil and lurasidone may hold promise for improving cognitive outcomes; however, their clinical utility remains unclear.[53,54] This inconclusive and equivocal evidence prompts significant questions regarding the overall clinical utility of these interventions in enhancing real-life functioning in individuals with BD. Preventive efforts should also focus on modifiable risk factors, such as the minimization of polypharmacy, ensuring adequate sleep hygiene, and addressing subthreshold mood symptoms that may exacerbate cognitive dysfunction. Ultimately,

individualized treatment approaches integrating cognitive, pharmacological, and psychosocial components are warranted to improve long-term outcomes in BD.

CONCLUSION

This review highlights that cognitive impairment in BD is evident in both neurocognitive and social cognition domains. These findings suggest that cognitive deficits persist across both acute and euthymic phases, directly impacting patients' functional outcomes. While some individuals maintain preserved or enhanced cognitive abilities, a significant proportion experiences notable impairments that negatively impact psychosocial and occupational functioning.

Among cognitive domains, executive functions, verbal learning, and memory consistently show the most pronounced deficits. However, whether these impairments stem from a neurodevelopmental or neurodegenerative process remains unclear. Cross-sectional studies cannot establish causality, and longitudinal research is needed to clarify the trajectory of cognitive dysfunction in BD. Given the heterogeneity of cognitive profiles, identifying distinct subgroups and better characterizing cognitive trajectories is crucial.

Future research should focus on early intervention, personalized treatments, and cognitive rehabilitation strategies. Additionally, integrating neuroimaging and genetic studies will contribute to a deeper understanding of the biological underpinnings of cognitive dysfunction. These advancements may facilitate the development of more targeted and effective treatment approaches, ultimately improving the quality of life for individuals with BD.

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