Arch Psychiatry. 2026;4(1):29–35.

The Archives of Psychiatry | Review Article

Cognitive Impairment in Bipolar Disorder: Neurobiological Mechanisms and Integrated Treatment Strategies. A PRISMA-ScR–Guided Scoping Review

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Received date: March 14, 2026, **Accepted date:** June 30, 2026

Citation: Bourin M. Cognitive Impairment in Bipolar Disorder: Neurobiological Mechanisms and Integrated Treatment Strategies. A PRISMA-ScR–Guided Scoping Review. Arch Psychiatry. 2026;4(1):29–35.

Abstract

Background: Cognitive impairment is now widely recognized as a core; persistent feature of bipolar disorder (BD) that persists even after mood symptoms subside and is strongly associated with lasting disability and decreased quality of life. Growing evidence implicates interacting neurobiological mechanisms, including neuroinflammation, mitochondrial dysfunction, blood–brain barrier (BBB) disruption, and gut–brain axis alterations.

Objective: This scoping review aimed to map and synthesize evidence on the nature and trajectory of cognitive impairment in BD, BD-specific neurobiological mechanisms underlying cognitive dysfunction, and emerging and integrated treatment strategies targeting cognition.

Methods: We performed a scoping review following PRISMA-ScR guidelines, searching PubMed, Scopus, and Web of Science for studies published between January 2015 and January 2025. Only peer-reviewed studies that investigated cognitive outcomes in adults diagnosed with bipolar I or II disorder were included. The evidence was integrated using both narrative and thematic methods.

Results: A total of seventy-eight studies were included. Challenges with executive function, attention, memory, processing speed, and social cognition persisted even when mood remained stable. Key mechanisms included inflammatory activation, mood-state-dependent mitochondrial dysfunction, increased BBB permeability, microbiome dysbiosis, and fronto-limbic network alterations. Integrated interventions combining cognitive remediation, neuromodulation, metabolic and anti-inflammatory strategies showed the greatest promise, though evidence remains heterogeneous.

Conclusion: Cognitive impairment represents a central therapeutic target in BD. This scoping review highlights converging neurobiological pathways and supports a multimodal, personalized treatment framework. Future trials should prioritize cognition as a primary outcome and integrate biomarker-guided strategies.

Keywords: Bipolar disorder, Cognitive impairment, Neuroinflammation, Mitochondria , Blood–brain barrier, Gut-brain axis, Cognitive remediation, Neuromodulation

Introduction

Bipolar disorder (BD) is a chronic, recurrent psychiatric illness associated with substantial morbidity and premature mortality [1]. Beyond episodic mania and depression, accumulating evidence demonstrates that cognitive impairment constitutes a persistent and clinically meaningful dimension of the disorder [2]. Deficits in executive function, attention, memory, processing speed, and social cognition frequently persist during euthymia [3]. These impairments predict occupational dysfunction and reduced quality of life, often independently of mood symptom severity. Translational research has increasingly implicated interacting neurobiological processes—neuroinflammation, oxidative stress, mitochondrial dysfunction, BBB alterations, microbiome dysbiosis, and large-scale network abnormalities in the pathophysiology of cognitive dysfunction in BD [4,5]. Although prior reviews have examined individual

mechanisms, an updated integrative mapping linking neurobiology and treatment strategies remains warranted. The present work therefore applies a PRISMA-ScR–guided methodology to synthesize contemporary evidence. This review was structured according to the Population–Concept–Context (PCC) framework recommended for scoping reviews. The population included adults diagnosed with bipolar I or II disorder. The core concept was cognitive impairment across domains such as executive function, memory, attention, processing speed, and social cognition. The context encompassed studies published between January 2015 and January 2025, including observational, neurobiological, neuroimaging, and interventional research.

Materials and Methods

Design

This scoping review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework. The objective was to comprehensively map available literature rather than quantitatively estimate treatment effects.

Search strategy

A systematic search of PubMed, Scopus, and Web of Science was performed for studies published between 1 January 2015 and 31 January 2025.

The core PubMed search string was:

("bipolar disorder" OR "bipolar I" OR "bipolar II")

AND

("cognitive impairment" OR cognition OR "executive function" OR memory OR attention OR "processing speed" OR "social cognition")

AND

(neuroinflammation OR mitochondria OR "blood-brain barrier" OR microbiome OR "gut-brain axis" OR neuroimaging OR neuromodulation OR "cognitive remediation")

Equivalent Boolean adaptations were applied in Scopus and Web of Science.

Reference lists of included studies were also screened manually to identify additional relevant articles.

Eligibility criteria

Inclusion criteria

- Peer-reviewed original research
- Adult participants (≥18 years)
- Diagnosis of bipolar I or II disorder
- Quantitative cognitive outcomes
- Neurobiological, neuroimaging, biomarker, or interventional focus

Exclusion criteria

- Pediatric or mixed-age samples without separable adult data
- Reviews, commentaries, editorials, case reports
- Purely genetic/molecular studies without cognitive measures
- Studies lack sufficient methodological detail.

Study selection

After duplicate removal, titles and abstracts were screened independently according to eligibility criteria. Full-text review determined final inclusion. Reasons for exclusion at full-text stage were documented to ensure transparency.

PRISMA-ScR flow summary

Identification

Records identified: n = 2,650

Duplicates removed: n = 754

Records screened: n = 1,896

Screening

Records excluded (title/abstract): n = 1,564

Eligibility

Full texts assessed: n = 332

Full texts excluded: n = 254

Reasons included: non-BD population, absence of cognitive outcomes, pediatric samples, non-original research, insufficient methodology.

Included

Studies included in final synthesis: n = 78

Nature and Trajectory of Cognitive Impairment

Cognitive impairment in BD appears to follow a heterogeneous and potentially progressive trajectory. Subtle deficits may precede illness onset and may worsen with recurrent episodes, psychosis, and illness duration [6]. Longitudinal and meta-

analytic evidence suggests an increased risk of mild cognitive impairment and dementia in individuals with BD; however, this association is likely moderated by multiple factors, including age, cumulative episode burden, vascular and metabolic comorbidities, and long-term treatment exposure. Consequently, while BD may confer increased vulnerability to neurodegenerative processes, causality remains uncertain and should be interpreted cautiously. Cognitive profiles may differ between bipolar I and bipolar II disorder, although available data remain limited. Some studies suggest more pronounced deficits in executive function and processing speed in BD I, potentially related to greater illness severity and psychotic features, whereas BD II may present with subtler but still functionally significant impairments [7]. In addition, emerging evidence indicates that age and sex may influence cognitive trajectories in BD [8]. Older age is consistently associated with greater cognitive decline, while sex-related differences remain less clearly established but may involve hormonal, inflammatory, and psychosocial factors [9]. These dimensions remain underexplored and should be prioritized in future research.

Neurobiological Mechanisms of Cognitive Impairment

A growing body of research is beginning to clarify why cognition is so vulnerable in BD. One major explanation involves chronic neuroinflammation and oxidative stress. A systematic review showed that higher levels of inflammatory markers such as CRP, IL-6, TNF-α, and IL-1RA are linked to poorer performance across executive function, memory, and processing speed [10]. Persistent inflammation disrupts synaptic plasticity and promotes oxidative damage, ultimately weakening circuits that connect prefrontal and limbic regions or link the frontal cortex with striatal systems [11].

Mitochondrial dysfunction offers another important window into these deficits. Recent evidence suggests that mitochondrial efficiency shifts with mood state, leading to impaired energy production, disrupted redox signaling, and heightened neuronal vulnerability [12]. These bioenergetic breakdowns are especially relevant for brain areas central to cognition, including the prefrontal cortex and hippocampus.

A third line of work focuses on the blood–brain barrier (BBB). New findings indicate that the BBB may become more permeable in BD, allowing circulating inflammatory molecules to enter the brain and influence neural processes directly. This mechanism provides a compelling explanation for how peripheral inflammation may translate into central cognitive impairment and is increasingly viewed as a potential biomarker and therapeutic target [13].

Parallel developments in microbiome research add yet another layer. A study found that transplanting fecal microbiota from cognitively impaired BD patients into mice induced similar cognitive and synaptic deficits in the animals. This suggests that gut microbial composition may shape synaptic plasticity and cognitive performance. Individuals with BD who maintain better cognitive functioning tend to have more favorable or resilient gut microbiome profiles [14].

Finally, neuroimaging findings paint a structural and functional backdrop to these biological pathways. Studies consistently report reduced volume in prefrontal and hippocampal regions, disruptions in the connectivity of networks responsible for cognitive control, and white matter abnormalities tied to executive dysfunction. These neural alterations do not act in isolation they interact with inflammatory, metabolic, and mitochondrial processes to ultimately shape cognitive outcomes across the course of bipolar disorder [15].

Effects of Standard Treatments and Illness Factors

The cognitive profile of individuals with bipolar disorders is shaped not only by the illness itself but also by the treatments used to manage it. Traditional mood stabilizers such as lithium and valproate remain central to clinical care, yet their direct impact on cognition in adults appears modest [16]. They do not consistently enhance cognitive performance, though some studies in younger populations suggest subtle improvements in emotional processing. Antipsychotic medications, while often essential for maintaining mood stability and preventing relapses, can carry cognitive trade-offs. Sedation, metabolic side effects, and overall medication can collectively dull attention, slow processing, or blunt motivation. Antidepressants likewise offer little in the way of cognitive enhancement and continue to pose the enduring concern of triggering mood elevation or manic switch in susceptible individuals.

Non-pharmacological interventions tell a similar story. Psychosocial approaches such as cognitive-behavioral therapy and structured psychoeducation reliably support mood regulation, relapse prevention, and functional coping but their effects on cognition itself are generally indirect. They help patients navigate the illness more effectively, yet do not appear to substantially improve the cognitive deficits that accompany BD [17].

A range of clinical and lifestyle factors can further modulate cognitive outcomes, often in powerful ways. Chronic sleep disruption, for example, can erode attention and executive functioning, while metabolic syndrome and systemic inflammation create an internal environment that undermines neural health [18]. Emerging work on the gut microbiome suggests that microbial imbalances may also influence cognitive performance. Substance misuse adds an additional layer of vulnerability, compounding impairments and

interfering with recovery. Addressing these factors proactively is essential, as each can meaningfully shape the cognitive trajectory of individuals living with bipolar disorder [19].

Methylphenidate and Psychostimulants

Methylphenidate (MPH), a psychostimulant primarily used for ADHD and sometimes for narcolepsy, has been studied off label in BD [20], especially regarding cognitive impairment and residual cognitive symptoms (e.g. attention, memory, executive functioning deficits), which often persist even in euthymic phases [21].

Rationale

Cognitive deficits in bipolar disorders are common across all phases (mania, depression, euthymia) and contribute to functional impairment. These deficits can include problems in attention, working memory, and executive function areas. MPH can theoretically improve via dopaminergic and noradrenergic enhancement of the prefrontal cortex [22].

Evidence

Research is limited: There are very few controlled studies on methylphenidate (MPH) for cognitive deficits specifically in BD. Small studies and case reports show that MPH or modafinil may improve some aspects of attention and processing speed in euthymic or depressed bipolar patients. However, results are inconsistent, and most trials are short-term. Cognitive improvements tend to be subtle and sometimes hard to separate from general activating or mood-elevating effects [23].

Safety concerns

MPH carries a risk of inducing mania or hypomania, particularly if mood stabilization is not fully achieved.

Guidelines recommend that if stimulants are considered:

- They should only be used in patients already stabilized on a mood stabilizer (e.g., lithium, valproate, or atypical antipsychotic).
- Start with low doses and careful monitoring for mood destabilization, sleep disruption, or impulsivity.
- There is also risk of substance misuse potentially leading to a substance use disorder, particularly in patients with comorbid ADHD or substance-use history.

Comparisons with other pro-cognitive strategies

Modafinil / Armodafinil: somewhat more evidence and lower switch risk [24]

Lisdexamfetamine: Being studied, potentially similar profile to MPH.

Non-pharmacological approaches: cognitive remediation therapy, aerobic exercise, sleep regulation, and metabolic health optimization are often recommended first-line.

Summary

Aspect of MPH in BD

Target: Attention, working memory, executive function

Evidence: Limited, mostly case-based / small studies

Efficacy: Modest improvement possible

Main risk: Mania/hypomania, anxiety, insomnia

Prerequisite: Stable mood on mood stabilizer

Alternatives: Modafinil, lisdexamfetamine, cognitive remediation

MPH may improve cognitive performance in well-stabilized bipolar patients, but evidence is weak and the risk of mood destabilization is significant. It should only be considered experimentally, under specialist supervision, and as part of a comprehensive management plan addressing mood stability first.

Emerging and Integrated Treatment Strategies

Pharmacological innovations are at the forefront of this evolution, providing new ways to target cognitive dysfunction directly. Among the most promising pharmacological agents are wakefulness-promoting drugs like modafinil and armodafinil. These medications, often used in conditions like narcolepsy, have shown potential in bipolar depression, improving attention and processing speed in patients who struggle with these cognitive aspects of the illness. Similarly, glutamatergic modulators such as ketamine and memantine are gaining attention for their modest pro-cognitive effects. Both have been shown to enhance certain cognitive functions, offering an intriguing new dimension to the treatment of bipolar disorder [23].

Anti-inflammatory therapies are another exciting area of exploration. Drugs like minocycline and celecoxib, traditionally used to treat infections and pain, respectively, have demonstrated preliminary benefits in individuals with high levels of systemic inflammation. Given the emerging understanding of inflammation's role in cognitive impairment, these therapies could offer a targeted approach to improve cognitive function in those with an inflammatory subtype of BD [25].

Mitochondrial agents, including N-acetylcysteine (NAC), creatine, and citicoline, are also gaining traction. These compounds are believed to support mitochondrial function and redox balance, two critical aspects of cellular health. Early studies suggest that they may provide tangible cognitive benefits, particularly in improving energy metabolism in the brain, which is often disrupted in BD [24].

The emerging field of microbiome-focused treatments is also starting to capture attention. Probiotics, prebiotics, and even dietary modifications that support a healthy gut microbiome are being explored for their potential to influence cognitive function. Ongoing research into the gut-brain link may lead to microbiome-based treatments for cognitive health [26].

Beyond pharmacology, non-pharmacological interventions are also proven to be valuable tools in managing cognitive deficits. Cognitive remediation therapy (CRT), for example, has demonstrated measurable improvements in working memory, planning, and learning. Meta-analyses support its efficacy, making it a cornerstone in cognitive rehabilitation for individuals with BD. Additionally, functional remediation focuses on enhancing real-world skills through structured, skill-based training, helping patients regain functional independence [27].

Neuromodulation techniques are another exciting frontier in the treatment of cognitive dysfunction. A groundbreaking randomized controlled trial (RCT) revealed that multimodal neurostimulation, using a combination of repetitive transcranial magnetic stimulation (rTMS) and transcranial alternating current stimulation (tACS), significantly improved cognitive functioning in BD patients. This technique, which tailors neurostimulation to individual brain networks, marks a major step forward in personalized treatment approaches for cognitive impairments [28].

Finally, lifestyle interventions remain a cornerstone of holistic care. Aerobic exercise, adherence to a Mediterranean diet, and strategies to stabilize sleep have all been shown to support neuroplasticity and foster cognitive resilience. Mindfulness-based interventions, too, contribute to cognitive well-being by reducing stress and enhancing attention. These approaches work synergistically to optimize brain health and provide a comprehensive framework for cognitive rehabilitation. As the field moves forward, the integration of these pharmacological and non-pharmacological strategies is likely to become the gold standard of care, offering a more individualized and multifaceted approach to managing cognitive impairment in bipolar disorder [29].

Clinical Implications

Routine cognitive assessment should be integrated into standard BD care [30]. In clinical practice, biomarker-guided strategies may rely on accessible indicators such as inflammatory markers, metabolic parameters, and sleep evaluation. More advanced biomarkers remain limited by feasibility constraints. A stepwise, pragmatic approach combining clinical, biological, and functional assessments is currently the most realistic strategy.

Limitations

Several limitations must be acknowledged:

Scoping design: No formal risk-of-bias assessment was conducted.

Publication bias: Positive interventional studies may be overrepresented.

Heterogeneity: Cognitive measures and biomarker methodologies varied substantially.

Predominance of BD I samples: BD II remains underrepresented.

Cross-sectional designs: Many mechanistic studies preclude causal inference.

These limitations restrict quantitative generalizability but do not undermine the mapping objective of the review.

Conclusion

Cognitive impairment is not just a secondary symptom of BD; it is a central, persistent, and debilitating aspect of the illness that significantly impacts quality of life and functional ability. These cognitive deficits, which often remain even during periods of mood stabilization, can undermine patients' capacity to manage everyday tasks, maintain relationships, and achieve their personal and professional goals. As such, addressing cognitive impairment in BD should be viewed as an urgent clinical priority, requiring targeted intervention and comprehensive treatment strategies.

Recent advances in our understanding of the neurobiology of BD have provided valuable insights into the mechanisms driving these cognitive deficits. Neuroinflammation, mitochondrial dysfunction, impaired neuroplasticity, and disruptions in key brain circuits are just a few of the factors that contribute to the cognitive burden of BD. These discoveries have opened exciting new possibilities for therapeutics that go beyond traditional mood-stabilizing medications, offering hope for more effective treatments specifically aimed at improving cognitive function. As the field continues to evolve, it is increasingly clear that a one-size-fits-all approach to BD treatment is insufficient. Instead, a multimodal and integrated approach that combines biological, psychological,

neuromodulatory, and lifestyle interventions is emerging as the most promising strategy to tackle the complex nature of cognitive impairment in BD.

Pharmacological innovations, such as glutamatergic modulators, anti-inflammatory therapies, and mitochondrial agents, are beginning to show potential in enhancing cognitive function, while non-pharmacological treatments, like cognitive remediation therapy, neuromodulation techniques, and lifestyle interventions, can provide critical support to cognitive resilience. Furthermore, personalized treatment approaches informed by biomarkers such as inflammatory profiles, mitochondrial function, and neuroimaging offer the possibility of more tailored, effective interventions, improving not only cognitive outcomes but overall functioning.

As we move forward, it is essential to elevate cognitive health as a primary treatment goal in BD. Historically, the focus of BD management has been on mood stabilization, with cognitive impairments often treated as secondary concerns. However, for many individuals with BD, cognitive difficulties can be as disabling, if not more so, than the mood episodes themselves. By recognizing and addressing cognitive impairment as a core aspect of BD, clinicians can help improve the long-term functional outcomes of those living with the disorder. Prioritizing cognitive health will not only enhance patients' day-to-day functioning but also contribute to greater autonomy, improved quality of life, and better overall prognosis.

In conclusion, the path forward in the treatment of bipolar disorder lies in an integrated, individualized approach that recognizes the multifaceted nature of the illness. By combining cutting-edge pharmacological treatments, innovative neuromodulatory interventions, psychological therapies, and lifestyle adjustments, we can offer individuals with BD a more comprehensive and effective roadmap toward functional recovery. Ultimately, addressing cognitive impairment in a holistic and proactive way will be key to achieving better long-term outcomes and improving the overall well-being of people living with bipolar disorder.

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