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Bipolar Disorder and Neurodegeneration: Implications for Cognitive Decline and Dementia Risk

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INTRODUCTION & AIM

Bipolar disorder (BD) is a chronic psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression. Beyond episodic mood disturbances, increasing evidence suggests that BD may be associated with progressive changes in cognitive functioning and behavior across the lifespan. This poster addresses the research question: How does bipolar disorder affect long-term cognitive functioning, and what evidence links BD to an increased risk of cognitive decline and dementia, particularly **frontotemporal dementia (FTD)** or related syndromes?

METHOD

A **narrative review of scientific literature** was conducted using **PubMed**, **MEDLINE**, **Google Scholar**, and related databases. The review synthesized findings from longitudinal clinical studies, neuropsychological research, and neuroimaging investigations. Particular emphasis was placed on persistent cognitive deficits in executive function, attention, memory, and social cognition, as well as epidemiological studies examining dementia risk in individuals with a history of BD.

RESULTS & DISCUSSION

The classical notion that **Bipolar Disorder (BD)** follows a benign course has increasingly been challenged, raising the **hypothesis that it may represent a progressive condition leading to cognitive impairment and, in some cases, dementia.** Indeed, it has been demonstrated that individuals with **BD have a 2.66-fold higher risk of developing dementia compared to the reference population.**

Several studies indicate that individuals with BD, **both younger and older adults**, frequently exhibit **persistent cognitive deficits that remain even during euthymic periods**, particularly in executive functioning, processing speed, sustained attention, verbal learning, and working memory.

Within the spectrum of dementias, **Frontotemporal Dementia (FTD)** appears to be the condition **most strongly associated with BD**. This hypothesis is supported by epidemiological studies showing that approximately **20% of patients with FTD have a history of mood disorders, many of whom have BD. Compared to other major types of dementia, patients with FTD are more than twice as likely to have a diagnosis of BD.**

FTD is a progressive neurodegenerative disorder affecting the frontal and anterior temporal lobes, typically presenting in midlife and representing the second most common cause of dementia in individuals under 65 years of age. It is characterized by progressive decline in executive and other cognitive functions, as well as behavioral changes. In its **behavioral variant (bvFTD)**, early manifestations often include apathy or abulia, loss of empathy, disinhibition, impulsiveness, and personality changes, with **some patients also exhibiting symptoms resembling mania.**

Epidemiological evidence suggests an **increased risk of later-life cognitive decline and dementia among individuals with BD**, with the diagnosis associated with more than a **doubling of dementia risk over a 13-year period**. There is also a significant phenotypic overlap between cognitive changes in BD and early features of bvFTD, raising the **possibility that BD may, in some cases, represent an early manifestation of dementia.**

Additionally, **studies examining first-degree relatives of BD patients** have reported **deficits in similar neurocognitive domains**. Recent meta-analyses have identified impairments in cognitive flexibility (set-shifting), processing speed, verbal learning, declarative memory, and response inhibition, **suggesting the presence of neurocognitive endophenotypes associated with BD.**

The underlying pathophysiological mechanisms remain unclear. Proposed mechanisms include chronic neuroinflammation, cardiovascular risk factors, medical comorbidities, unhealthy lifestyle behaviors, substance abuse, oxidative stress, mitochondrial dysfunction, and impaired synaptic plasticity.

Greater vulnerability has been reported among individuals with late-onset BD or a high number of affective episodes. Fluctuations in mood and energy levels may contribute to dysregulation of neurotransmitters such as dopamine and serotonin, which play critical roles in cognitive processes. **Notably, the estimated risk of dementia in BD is higher than that reported in meta-analyses of unipolar major depression, raising the question of whether distinct mediating mechanisms underline dementia risk in bipolar versus unipolar disorders.**

There is also evidence that **individuals with BD experience greater loss of gray matter over time, which correlates with the number of affective episodes**, with recurrent mood episodes contributing to cortical thinning and altered functional connectivity within frontotemporal networks. Accordingly, long-standing and recurrent BD may be associated with an increased risk of cognitive decline. **However, the strong association between recent BD diagnosis (≤5 years) and dementia suggest that late-life mood dysregulation may, in some cases, represent an early clinical manifestation of underlying neurodegenerative processes.** It has also been proposed that individuals with BD may experience accelerated aging, contributing to increased risk of dementia and premature mortality, although studies on telomere length have not found significant differences between patients and controls.

In a study by Mendez et al. (2020), among 137 patients with bvFTD, 8% had a prior diagnosis of BD type I or II, with the onset of manic or hypomanic episodes occurring approximately 9 years before the diagnosis of bvFTD. Among these, some patients did not show clinical progression or neuroimaging changes during follow-up and were classified as non-progressive “bvFTD phenocopies.”

In summary, these findings suggest that manic or hypomanic episodes may represent a prodrome of bvFTD, possibly reflecting early involvement of the temporal lobes. Conversely, late-onset BD may also present as a mimic of bvFTD, in the form of a non-progressive phenocopy. Although preliminary, these findings highlight the need for further research into shared mechanisms and the role of BD within the neurodegenerative continuum.

CONCLUSION

These findings suggest that **Bipolar Disorder may involve progressive cognitive trajectories in a subset of individuals, with partial overlap with neurodegenerative processes**. Early intervention, sustained mood stabilization, and longitudinal cognitive monitoring may be critical for mitigating long-term cognitive decline and informing dementia prevention strategies in bipolar disorder.

REFERENCES