

Is bipolar disorder associated with premature aging?

O transtorno bipolar é associado a envelhecimento prematuro?

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Bipolar disorder (BD) is a chronic and recurrent mental illness, recognized by the presence of manic/hypomanic and depressive episodes. It is associated with significant functional impairment in different domains, including work, finance, social activities, and autonomy.¹ Replicated results on longitudinal observation data of the course of illness also suggest that, at least for a large proportion of patients, BD is also clinically progressive, and a higher number of episodes is associated with more pronounced cognitive deterioration, treatment resistance and functional decline.²

Neuroprogression is a concept recently introduced in the literature to designate the pathological rewiring of the brain in response to the toxicity associated with mood episodes.³ A large body of evidence supports the notion that patients with typical presentations of BD exhibit illness trajectories characterized by the presence of widespread structural brain abnormalities, including changes in cortical thickness⁴ and connectivity.⁵

While the progressive changes occurring in the brain of patients with BD are becoming better characterized, growing evidence also supports the notion that the pathophysiology of BD goes beyond the brain. It is well-known that individuals with BD have high rates of general medical conditions, especially those related to obesity, glucose/insulin dysfunction and inflammation.⁶⁻¹⁰ These diseases are especially present in patients with a long time of illness and multi-episodic presentations,

suggesting that neuroprogression could be linked to a process of multisystemic progression in BD.¹¹

The prototype of the multisystemic wear and tear process of the organism is aging. Interestingly, in the last decade, there has been a renewed interest in the study of different markers of premature aging in BD.¹² For example, there is replicated evidence that individuals with BD have shorter telomeres compared to age- and sex-matched healthy controls.^{13,14} In addition, telomere shortening is more pronounced in individuals with BD in late stages than in those in early stages.^{15,16} Still, genes are not the only cellular structure that seems to be susceptible to premature aging in BD. Recently, Fries et al.¹⁷ demonstrated that it is possible to identify an acceleration of the epigenetic clock in individuals with BD compared to healthy controls. This epigenetic aging can be estimated by studying the methylation of different regions of DNA, which are known to change with age (DNA methylation age), and by the mitochondrial DNA copy number. In that study, older patients with BD presented premature epigenetic aging compared to healthy controls, suggesting that epigenetic changes could be mechanistically linked to psychopathology in BD.¹⁷

Another biological dimension of aging that seems to be altered in BD is the immune system aging. Several reports are available on the association between manic and depressive episodes and proinflammatory states,^{18,19}

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as well as evidence that multiple episodes are able to reprogram the immune system towards a longstanding proinflammatory status.²⁰ Moreover, recent findings suggest that aging-related immune abnormalities in BD go beyond increased levels of proinflammatory cytokines and include dysfunction in different lymphocyte subpopulations such as T-suppressor cells and increased proportions of senescent T cells.^{21,22}

Molecular correlates of aging in mood disorders also include reduced levels of brain-derived neurotrophic factor (BDNF) and oxidative stress imbalances,^{23,24} which are also critical mediators of neuroprogression.²⁵⁻²⁷ These phenomena have been consistently associated with critical neuropsychiatric domains in BD, such as cognitive impairment.^{28,29} BDNF levels in BD decline with age,³⁰ suggesting that this mediator could be implicated in neural accelerated aging in this condition.

The treatment of BD may have a putative effect, reversing and/or retarding imbalances in the pathways related to accelerated aging on the one hand, and activating neurotrophic pathways on the other. BDNF levels, for example, have been well-documented to increase following treatment of acute mania^{31,32} – although BDNF levels may not return to normal levels in chronic scenarios despite clinical improvement with a therapeutic intervention, indicating progression of the disease.³¹ In the last two decades, lithium – one of the main therapeutic agents for BD – has shown to have impacts on multisystemic pathways. For example, proinflammatory states seen in mood episodes seem to be reduced and normalized after lithium therapy.³³ Recent studies also suggest that lithium has a positive effect on leukocyte telomere length.^{34,35} Some studies have reported decreased oxidative stress parameters in plasma levels in early stages in previously unmedicated individuals with BD after 6 weeks,³⁶ and also in individuals with BD during euthymia.³⁷ A neuroprotective effect of lithium could be associated with its potential to increase antioxidant agents and counterbalance the neurotoxicity associated with neuroprogression.

In conclusion, there are emerging data suggesting that BD follows a progressive trajectory in patients with typical presentations, especially when not properly treated.² A large part of central and peripheral changes in BD related to both neuroprogression and multisystemic progression could be understood using the concept of premature aging. The conception of BD as a disease of accelerated aging opens new insights for research into its pathophysiology, prevention and treatment, and reinforces the need for early recognition and intervention. In addition, it opens the possibility of exploring pharmacological and non-pharmacological anti-aging interventions in BD.

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