




## SPECIAL ARTICLE

# Neurobiology of bipolar disorders: a review of genetic components, signaling pathways, biochemical changes, and neuroimaging findings

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Bipolar disorder (BD) is a chronic mental illness characterized by changes in mood that alternate between mania and hypomania or between depression and mixed states, often associated with functional impairment. Although effective pharmacological and non-pharmacological treatments are available, several patients with BD remain symptomatic. The advance in the understanding of the neurobiology underlying BD could help in the identification of new therapeutic targets as well as biomarkers for early detection, prognosis, and response to treatment in BD. In this review, we discuss genetic, epigenetic, molecular, physiological and neuroimaging findings associated with the neurobiology of BD. Despite the advances in the pathophysiological knowledge of BD, the diagnosis and management of the disease are still essentially clinical. Given the complexity of the brain and the close relationship between environmental exposure and brain function, initiatives that incorporate genetic, epigenetic, molecular, physiological, clinical, environmental data, and brain imaging are necessary to produce information that can be translated into prevention and better outcomes for patients with BD.

**Keywords:** Bipolar disorder; mania; depression; genetics; epigenetics; neurotrophins; mitochondrial dysfunction; oxidative stress; inflammation; hypothalamic-pituitary-adrenal axis; circadian rhythm; neuroimaging

## Introduction

Bipolar disorder (BD) is a severe and chronic psychiatric illness that affects approximately 1-4% of the world population.<sup>1</sup> It is characterized by changes in mood that alternate between mania and hypomania or between depression and mixed states, often associated with functional impairment.<sup>1-3</sup> Although depressive symptoms typically predominate in individuals with BD, the clinical diagnostic hallmark is the presence of manic or hypomanic episodes.<sup>4</sup> During episodes of mania or hypomania, the patient may present symptoms related to elevated mood, including euphoria, feelings of greatness, hyperactivity, increased sexual activity, decreased need for sleep, risky behaviors, irritability, and aggression. Conversely, episodes of depression are characterized by anhedonia, sadness, vegetative symptoms, and psychomotor

retardation. Mixed episodes manifest as simultaneous states of mania and depression.<sup>4</sup> About 14-59% of the individuals with BD report suicidal ideation<sup>5</sup>; 25 to 50% attempt suicide, and almost 20% die due to suicide.<sup>6</sup> Moreover, BD is also associated with increased risk of mortality by other medical conditions, such as cardiovascular disease, diabetes mellitus, external causes of injuries, and respiratory diseases. Life expectancy is decreased by 9 years on average in individuals with BD as compared with the general population.<sup>7</sup>

Despite the demonstrated efficacy of several drugs to treat BD, lithium (Li) is the only drug considered as a mood stabilizer by the Food and Drug Administration (FDA). More than 70 years have passed since this salt was first proposed as a mood stabilizer. Li is effectively used in BD for maintenance and treatment of acute mania episodes; however, it has a modest antidepressant action.<sup>8</sup>

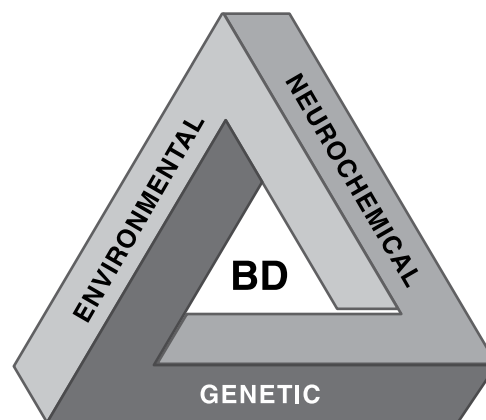
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Anticonvulsants such as valproate (VPA) and carbamazepine are also used to treat BD. Additionally, some typical (e.g., haloperidol and chlorpromazine) and atypical antipsychotics (e.g., aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and asenapine) have also shown efficacy.<sup>9-11</sup> Of note, the treatment of depression in BD is particularly challenging, as several drugs used for treating depressive symptoms, such as selective serotonin reuptake inhibitors (SSRI), can induce a switch to hypomania or mania. Thus, these drugs are usually combined with Li for acute treatment and maintenance of bipolar depression.<sup>12</sup> It is noteworthy that patients with BD commonly face residual mood symptoms, cognitive and functional impairment, psychosocial disability, and decreased quality of life even with the best treatment available.<sup>13,14</sup>

BD has been suggested as a progressive condition, and the delay in diagnosis as well as inappropriate treatment can result in repeated mood episodes, persistent subthreshold symptoms, development of co-morbidities, and progression of the disease with cognitive impairment and functional decline.<sup>15-17</sup> The term “neuroprogression” has thus been conceptualized as the pathological rewiring of the brain that takes place in parallel with the functional and clinical deterioration that may occur in the course of BD; according to this concept, different stages of BD are associated with distinct neurobiological underpinnings.<sup>18-23</sup> Indeed, studies have shown that structural brain changes and cognitive deficits are not consistently found at illness onset, and appear to become more evident with chronicity and recurring episodes.<sup>24-27</sup> Moreover, neuroprogression seems to be related to the cumulative effects of immune dysfunction, enhanced oxidative stress, neurotrophic support breakdown, mitochondrial dysfunction, and impairment of cellular resilience.<sup>20,21,28,29</sup> Neuroprogression has been also associated with lower responsiveness to treatment, especially with Li and cognitive behavioral therapy.<sup>30-32</sup> In this sense, Post et al.<sup>33</sup> have suggested that multiple episodes may lead to permanent alterations in neuronal activity, which may translate into greater liability to relapse and poorer treatment response. Of note, such a progressive feature does not seem to be present across all patients, with some not experiencing as much cognitive or functional impairment as others.<sup>34</sup> This poses the particular challenge of identifying specific subgroups of susceptible patients, which may require a deeper understanding of the biological basis of BD.

Although numerous factors and mechanisms have been proposed to explain the pathophysiology of BD, its definitive etiopathology remains unknown. Nonetheless, it is believed that the etiology of BD involves an interaction between multiple genetic, neurochemical, and environmental factors (Figure 1).<sup>35</sup> Not only would a deep understanding of the neurobiology of BD support the discovery of new targets for effective pharmacological and non-pharmacological therapies, it would also facilitate the identification of biomarkers for diagnosis, prognosis, and response to specific treatments. The last years have witnessed great progress in the understanding of BD pathophysiology. For instance, several lines of thought have led us to believe that BD is associated with



**Figure 1** Etiology of bipolar disorders. The cause of bipolar disorder (BD) is still unknown. However, it has been established that the dynamic interplay between genetic, neurochemical, and environmental factors plays a role in the onset and progression of BD.

neuroprogression, and that over time recurrence may exacerbate subsequent episodes, which are accompanied by functional and cognitive impairment.<sup>20,36-38</sup> An underlying hypothesis is that changes in neuroplasticity, with a decrease in neurotrophic factors combined with mitochondrial dysfunction, oxidative stress, inflammation, circadian rhythm abnormalities, and biological aging acceleration, could be associated with the worsening of mood episodes, refractoriness to treatment, cognitive impairment, and functional disability.<sup>20</sup> This article seeks to discuss studies addressing the neurobiological mechanisms of BD, providing an overview of genetic components, major signaling pathways, biochemical changes, and neuroimaging findings associated with this disorder.

### Genetics and epigenetics of bipolar disorder

Evidence suggests that BD presents a very strong genetic component, with twin studies showing heritability rates (i.e., the extent to which the disorder can be explained by genetic factors) as high as 70-80%.<sup>39,40</sup> The strength of this genetic component is also supported by the increased risk of BD noted in first-degree relatives of patients, including offspring.<sup>41</sup> The risk of BD is significantly higher in children of parents diagnosed with BD vs. offspring of control parents<sup>42,43</sup>; indeed, a plethora of signs and symptoms may accompany such familial risk even in the absence of a full-blown diagnosis of BD.<sup>44-48</sup> This familial aggregation suggests a potential relevance of both inherited genes, which can be tested by molecular genetic analyses, and the “inherited” familial environment, which is also known to be potentially impaired in the face of parental psychopathology.<sup>49,50</sup>

In the search for relevant BD-related genes, several genome-wide association studies (GWASs) conducted in the past years have identified multiple *loci* with a small effect that may account for heritability,<sup>51-62</sup> including 30 recently discovered *loci* encoding ion channels, neurotransmitter transporters, and synaptic components.<sup>63</sup> None of these single nucleotide polymorphisms (SNPs),

however, has been shown to present high penetrance or a large effect size, a finding that is consistent with the complex multifactorial model that is believed to underlie the genetics of BD and other psychiatric disorders. Moreover, the difference in heritability rate calculated through twin studies (70-80%) and that calculated based on molecular genetics findings (approximately 30%) is quite large, suggesting a role of other markers or mechanisms.<sup>64</sup> These may include gene-by-gene interactions, rare genetic markers (current GWASs only assess “common” alterations), gene-by-environment interactions, and epigenetic markers.

Epigenetic mechanisms encompass several pathways that can mediate gene-by-environment interactions and modulate gene expression and activity without altering the DNA sequence. These include, among others, DNA methylation, histone modifications, chromatin remodeling, and the actions of noncoding RNAs. Several of these have been suggested to play significant roles in BD pathophysiology, especially DNA methylation.<sup>65-67</sup> In addition, several epigenetic alterations that may underlie risk/resilience mechanisms have been described in youth at high risk of BD, such as offspring of BD parents.<sup>68,69</sup> Specifically, DNA methylation is a fairly stable epigenetic alteration that has been implicated in BD pathogenesis and progression,<sup>69-71</sup> as well as in the mechanisms of action of several drugs used to treat patients.<sup>65,72-74</sup> DNA methylation in promoters is typically associated with the repression of gene expression and may underlie at least some of the transcriptomic changes reported for BD in multiple tissues.<sup>75-79</sup> Moreover, several preclinical and clinical studies have shown that early-life traumatic experiences can induce stable methylation alterations that persist into adulthood, suggesting epigenetic-based alterations as mediators of the clinical effects of early adversity.<sup>80-82</sup>

Interestingly, one of the mechanisms by which methylomes have been shown to interfere with BD phenotype is the modulation of biological aging processes. Patients with BD have been shown to present several clinical markers that are suggestive of premature aging, including a higher rate of age-related conditions and faster cognitive decline, with previous reports suggesting shortened telomere length compared to controls.<sup>83-85</sup> More recently, a marker of biological aging based solely on DNA methylation levels (“epigenetic age” or “DNA methylation age”)<sup>86</sup> has been used to explore the aging processes in BD, and the results suggest accelerated epigenetic aging in the blood and brain of BD patients compared to controls.<sup>71,87</sup> Recent evidence that the epigenetic clock can be pharmacologically reversed in humans<sup>88</sup> offers an interesting treatment possibility for the modulation of premature aging in BD.

In addition to DNA methylation, noncoding RNAs have also deserved much attention, including gene expression modulators such as microRNAs, long noncoding RNAs, and others.<sup>89</sup> Several alterations in the levels of microRNAs and long noncoding RNAs have been detected in BD samples, some of which have been validated by independent studies.<sup>90,91</sup> Recent studies have also suggested that noncoding RNAs may function as clinically relevant

peripheral biomarkers when assessed from neuron-derived extracellular vesicles, which are currently being investigated in BD patients.<sup>92,93</sup> Altogether, these studies suggest an important role for noncoding RNAs in BD pathophysiology, and also their potential as an important diagnostic and prognostic tool.

### Changes in neuroplasticity and neurotrophic signaling

Neurotrophic factors comprise a group of proteins responsible for regulating neuronal survival processes, neuronal growth, synaptic formation, and cellular plasticity at the central and peripheral nervous systems. Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) are the most common neurotrophic factors studied in psychiatric disorders. However, BDNF is undoubtedly the most studied neurotrophin in BD. Neurotrophins are a specific type of neurotrophic factor, and members of this family include BDNF, NGF, NT-3, and NT-4. Neurotrophins bind and activate a specific family of tyrosine kinase (Trk) receptors, thus promoting modulation of the central nervous system (CNS). There are three specific Trk receptors: NGF binds to TrkA; BDNF and NT-4 bind to TrkB; and NT-3 binds to the TrkC receptor.<sup>94</sup>

The strong interest in BDNF and other neurotrophins in BD was triggered by the discovery that antidepressants and mood stabilizers could act on these molecules, modulating their signaling pathways. Preclinical studies have shown that the chronic use of antidepressants and mood stabilizers, such as Li and VPA, can increase NGF, BDNF, and GDNF levels in the rat brain.<sup>95-98</sup> Currently, a range of studies show decreased levels of BDNF and its receptor TrkB in both blood and brain of patients with BD.<sup>99-103</sup> Additionally, a BDNF gene polymorphism that replaces a valine for a methionine (i.e., valine replacing methionine) at codon 66 (Val66Met) has been repeatedly associated with BD.<sup>104</sup> A previous study also demonstrated decreased plasma NGF levels in patients with BD.<sup>105</sup> Another clinical study showed that NT-3 and NT-4 are elevated in the depressive phase of BD,<sup>106</sup> possibly indicating an attempt by the organism to defend itself against cellular stress. In turn, Barbosa et al.<sup>107</sup> demonstrated decreased NT-3 and NT-4 levels in the manic phase of BD. Given that neurotrophins are essential for neuronal function and survival, it is assumed that the viability of nerve cells can be affected by a persistent reduction of these molecules in the nervous system.

As in clinical studies, preclinical research has demonstrated that amphetamine (AMPH) or ouabain-induced manic behaviors in rats decrease BDNF, NGF, and GDNF levels in the brain of animals.<sup>95,98</sup> Additionally, decreased levels of BDNF, NGF, and GDNF followed depressive-like behaviors in an animal model of depression induced by maternal deprivation or chronic mild stress.<sup>108</sup> A previous preclinical study suggested that neuroadaptations induced by chronic administration of dextroamphetamine (d-AMPH) might mimic neuroprogression in BD, because the brain is

primed for both the manic and depressive episodes which are characteristic of BD. In that study, the authors showed that d-AMPH withdrawal induces depressive- and anxious-like behaviors in rats, as well as a sensitization to manic-like behaviors. In line with this, d-AMPH sensitization decreased the levels of BDNF, NGF, and GDNF and increased the levels of NT-3 and NT-4/5 in the brain of rats.<sup>109</sup>

Together, these clinical and preclinical studies suggest changes in neurotrophic factors as an attractive molecular mechanism to explain the decreased cellular plasticity observed in BD, along with other mechanisms described in detail in the next sections. The hypothesis is that changes in neuroplasticity, including alterations in neurotrophic signaling, could be associated with brain damage, which in turn worsens mood episodes and ultimately induces cognitive and functioning deficits in patients with BD.

### Mitochondrial dysfunction and oxidative stress

Mitochondria are organelles that are responsible, both directly and indirectly, for cellular functions such as energy production; they also function as sources of cellular growth substrates and play crucial roles in oxidative/nitrosative stress, cell resilience and cell death.<sup>110-112</sup> In the brain, mitochondria are critical for the modulation of neuronal activity, short- and long-term neuronal plasticity, cellular resilience, and behavioral adaptations, mainly through actions on long-term potentiation, the hallmark process of learning and memory.<sup>112-115</sup> For more than 50 years, multiple studies have highlighted mitochondrial dysfunction as a common pathway in BD pathophysiology, triggered by mechanisms such as impaired oxidative phosphorylation, shift to glycolytic production of energy, general decrease in energy, and abnormalities in the morphology and intracellular distribution of mitochondria.<sup>116</sup> The “mitochondrial hypothesis” suggests that BD is triggered, at least in part, by mitochondrial dysfunction, which can be intimately linked to a wide range of processes associated with treatment outcomes and disease progression or severity, including inflammation, oxidative stress, stress response systems, and accelerated aging.

A considerable number of studies in the literature has shown an increase in lactate levels and a reduction in intracellular pH (ipH) in the brain of patients with BD, possibly indicating altered mitochondrial function and a glycolytic shift consistent with impaired mitochondrial metabolism in BD.<sup>116-120</sup> Glycolysis-only adenosine triphosphate (ATP) production has been shown to be powerless to maintain normal levels of Na<sup>+</sup>/K<sup>+</sup>-ATPase activity in neurons, inducing a large calcium influx into neurons, followed by glutamate excitotoxicity and neuronal apoptosis, both of which play a central role in neurodegeneration.<sup>121</sup> Mallakh et al.<sup>122</sup> propose that both manic and depressed states in BD could be caused by Na<sup>+</sup>/K<sup>+</sup>-ATPase dysfunction – a small reduction in Na<sup>+</sup>/K<sup>+</sup>-ATPase activity in the brain would lead to a hyperexcitable state (mania) by bringing the resting potential of neurons closer to the threshold for activation and increasing the duration of neurotransmitter release; in turn,

a further reduction in Na<sup>+</sup>/K<sup>+</sup>-ATPase function would bring the resting potential even closer to the threshold for activation, decreasing the amplitude of the action potential and resulting in inhibition of neurotransmitter release (depression).<sup>122</sup>

An additional link between mitochondrial dysfunction and BD is supported by data demonstrating that patients with BD present significantly lower levels of phosphocreatine (PCr) (a high-energy compound) and adenosine diphosphate (ADP) and decreased PCr peak area percentage, suggesting regional hypometabolism in all three mood states.<sup>123</sup> Additionally, the PCr peak area percentage was observed to be decreased in the left frontal lobe of patients during the depressive state, as well as in the right frontal lobe during manic/euthymic states.<sup>124,125</sup> Moreover, previous studies have shown that patients with BD present lower levels of N-acetyl-aspartate (NAA), which is thought to represent a surrogate marker for impaired mitochondria, along with a negative correlation between NAA/creatinine + PCr or NAA levels and illness duration.<sup>126-129</sup> Taken together, these studies provide indirect evidence that mitochondrial dysfunction may play a role in illness progression.<sup>20</sup>

Several clinical and animal studies have reported alterations in various energetic metabolism components, including downregulation of nuclear mRNA molecules and proteins involved in the Krebs cycle, electron transport chain (ETC) I-IV complexes, and creatine kinase, as well as a marked decrease in the activity of ETC complexes and Krebs cycle enzymes.<sup>130-143</sup> Together, these studies suggest a reduced ability to oxidize NADH and FADH and transfer electrons to ubiquinone in BD, resulting in reactive oxygen species (ROS) production through an increase in the rate of electron leakage by ETC complexes.

More recent attention has focused on the maintenance of a healthy mitochondrial pool, which is critically regulated by the dynamics and turnover of the mitochondrial population. A damaged mitochondrion may segregate its damaged components into subcompartments and divide, whereas a healthy mitochondrion with a potential healthier membrane will continue to participate in fusion and fission cycles. Depolarized damaged mitochondria are often degraded through mitophagy via the PTEN-induced kinase 1 (PINK1)-Parkin pathway.<sup>144</sup> Thus, these dynamic processes of mitochondrial fusion, fission, transport, and turnover enable recruitment of healthy mitochondria to subcellular compartments with high demands for ATP; disruptions in any of these processes will lead to mitochondrial pathology, cellular dysfunction, and neurological defects.<sup>145</sup> Previous research findings into mitochondrial morphology have shown that prefrontal cortex neurons of the postmortem brain from patients with BD and peripheral cells from living BD patients display morphological abnormalities (more mitochondria of smaller size) and an abnormal pattern of clumping and marginalization in the intracellular distribution of mitochondria.<sup>146</sup> By drawing on the concept of mitochondrial quality control, recent studies have demonstrated that patients with BD present an imbalance in mitochondrial fission and fusion toward fission, followed by a decrease in the levels of mitophagy proteins and increase in caspase-3 protein

levels in peripheral blood mononuclear cells, suggesting that, in patients with BD, the number of damaged mitochondria exceeds the capacity of mitophagy, and apoptosis becomes the dominant pathway to minimize tissue damage.<sup>147,148</sup>

Moreover, numerous studies have provided evidence of increased ROS production and oxidative stress in patients with BD. Replicated evidence has documented alterations in multiple aspects of oxidative stress regulation, including the production of ROS and reduced antioxidant capacity. Meta-analyses have shown significantly greater levels of lipid peroxidation markers, DNA/RNA damage, and nitric oxide in BD.<sup>149,150</sup> However, mixed results regarding two of the primary antioxidant enzymes, glutathione peroxidase (GPx) and superoxide dismutase (SOD), have been reported in BD, followed by a meta-analysis that did not reach statistical significance for the comparison of GPx and SOD activity levels in individuals with BD vs. controls.<sup>149</sup> Conversely, a recent study by Das et al.<sup>151</sup> showed that, although glutathione levels did not differ in BD and controls, there was a positive, BD-specific correlation between lactate and glutathione levels, indicating a physiological association between the antioxidant system and mitochondrial dysfunction.

Several investigators have reported that excessive oxidative stress in pathological conditions induces point mutations and may result in large deletions of mitochondrial DNA (mtDNA) due to restricted DNA repair ability and the absence of histones in mitochondria. Regarding BD, there is an inconsistency in mtDNA copy number (mtDNAcn) studies that could be attributed to the diversity in clinical features, tissue types, and ethnicity.<sup>71,152-155</sup> A recent meta-analysis identified no significant differences in mtDNAcn exhibited by BD patients or controls, while an Asian-specific meta-analysis for BD-mtDNAcn studies revealed significantly lower mtDNAcn in patients with BD, with a low level of heterogeneity.<sup>155</sup> Moreover, mtDNAcn was inversely correlated with the number of relapses of manic episodes.<sup>154</sup> A possible mechanism for the lower levels of mtDNAcn could be related to DNA polymerase gamma (POLG) dysfunction due to oxidative stress. In fact, recent studies have demonstrated that individuals with BD present downregulation of POLG, the replicative polymerase responsible for maintaining mtDNA, as well as downregulation of the DNA repair enzyme, 8-oxoguanine-DNA glycosylase 1 (OGG1).<sup>156,157</sup>

The accumulating evidence reviewed above delineates multifaceted mitochondrial dysfunction as a pathological factor in BD. Moreover, mitochondrial dysfunction, apoptosis, and non-methylated mtDNA can activate Toll-like receptors and lead to spontaneous inflammasome activation, stimulating cytokine production and inducing rapid activation of the immune system.

### **Immune-inflammatory imbalance and kynurenine pathway**

Immune dysfunction in BD is supported by pre-clinical and clinical evidence showing elevated levels of pro-inflammatory cytokines, including interleukin-4 (IL-4),

interleukin-1beta (IL-1 $\beta$ ), interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha, soluble interleukin-2 receptor (sIL-2R), and soluble receptor of TNF-type 1 (STNFR1), among others, in patients compared to controls.<sup>158-164</sup> A recent systematic review has suggested an important role for acute inflammatory response during mania and depression, with the elevation in proinflammatory cytokines seemingly restored after remission of symptoms.<sup>118</sup> In addition, further findings in BD have also described significant negative associations between inflammatory markers and general cognitive abilities, as well as neuro-anatomical alterations.<sup>165-169</sup> However, another systematic review claims that an absolute conclusion cannot be reached regarding the presence of neuroinflammation in BD, since the findings are not consistent.<sup>170</sup>

Several different mechanisms have been proposed to explain the role of immune dysfunction in BD,<sup>171</sup> including changes in blood-brain barrier, cell death-induced release of damage-associated molecular patterns with consequent immune activation, genetic mechanisms, dysfunction of the gut-brain axis, and a role of the kynurenine pathway. Activation of the kynurenine pathway by cytokines such as interferon-gamma (IFN- $\gamma$ ) and TNF- $\alpha$  is described as one of several contributors to psychiatric pathogenesis. Kynurenine metabolites mediate immune-inflammation and neurodegeneration and can lead to neurotoxicity and impaired neurotransmission. The enzyme indoleamine 2,3-dioxygenase (IDO-1) converts tryptophan into kynurenine and is activated by inflammatory cytokines. Kynurenine is then metabolized into hydroxykynurenine and quinolinic acid in microglia, and into kynurenic acid (KYNA) in astrocytes. Hydroxykynurenine and quinolinic acid are N-methyl-D-aspartic acid (NDMA) agonists and increase the production of free radicals, while KYNA, an N-methyl-D-aspartate (NMDA) receptor antagonist, has neuroprotective effects but also leads to cognitive deficits and psychosis when in higher levels.<sup>172-174</sup>

A previous study showed an imbalance toward the neurotoxicity path derived from kynurenine metabolism, as evidenced by decreased levels of KYNA, in addition to increased hydroxykynurenine/kynurenine ratio in BD compared with healthy controls.<sup>175</sup> The higher hydroxykynurenine levels may correlate to cognitive dysfunction not only in the acute phases of BD, but also in euthymic periods.<sup>27</sup> Recent evidence shows that KYNA levels in cerebrospinal fluid represent a biomarker for psychotic episodes in BD. This higher risk of developing psychosis may be explained by enhanced dopaminergic transmission due to increased brain KYNA concentrations.<sup>176</sup> Conversely, decreased peripheral KYNA and unchanged KYNA levels were observed in the CNS in BD patients during the depressive phase.<sup>177</sup>

Abnormalities in kynurenine metabolism resulting from the inflammatory response displayed in mood disorders may also contribute to the structural (volume reduction) and functional alterations observed in the hippocampus and amygdala.<sup>175,178</sup> One possible explanation for this process is dendritic atrophy in the context of the neurotoxicity occurring in unmedicated patients with BD.<sup>178</sup>

### Hypothalamic-pituitary-adrenal axis

In addition to the genetic component involved in the pathogenesis and pathophysiology of BD, it is known that nongenetic factors, such as psychosocial stress, can trigger the development of mood disorders.<sup>179</sup> The hypothalamic-pituitary-adrenal (HPA) axis is the primary mediator of the biological response to stress. Abnormalities in this system have been associated with the clinical course of BD<sup>180</sup> and may contribute to increased risk of clinical relapse following an intense psychosocially stressful event,<sup>181</sup> although the underlying mechanisms involved in these associations remain essentially unknown.<sup>180</sup>

A meta-analysis has demonstrated that BD is related to a more prominent activity level of the HPA axis, as evidenced by increased basal cortisol, postdexamethasone (PDEX) cortisol, and adrenocorticotrophic hormone (ACTH) levels, along with a higher response to the dexamethasone (DEX)/corticotropin releasing hormone (CRH) test.<sup>182</sup> The alterations described in HPA axis activity vary according to the clinical phase of BD. Although the hyperactive HPA axis seems more prominent during the manic phase, it may persist during clinical remission because euthymic BD patients also display higher levels of cortisol.<sup>182</sup> The clinical heterogeneity of the depressive phase may explain the conflicting findings related to HPA axis activity, with high cortisol levels found in melancholic depression and normal or low cortisol levels associated with atypical depression.<sup>183,184</sup>

Particularly interesting is the study by Fries et al.<sup>70</sup> showing that patients with BD, particularly at a late stage of illness, presented increased salivary PDEX cortisol levels followed by reduced *ex vivo* glucocorticoid receptor (GR) responsiveness and increased basal protein levels of FK506-binding protein 51, a cochaperone known to desensitize GR, in peripheral blood mononuclear cells. Moreover, individuals with BD presented increased methylation at the FK506-binding protein 5 (*FKBP5*) gene, suggesting a dysfunctional negative feedback of the HPA axis and impaired GR responsiveness due to increased *FKBP5* levels and increased *FKBP5* intronic methylation. In this same study, the authors suggest that, as BD progresses, there is decreased resilience to stress and a higher risk of new mood episodes, since stress resilience and coping mechanisms are primarily mediated by the HPA axis. High levels of PDEX cortisol may also be involved in the mechanism of increased late-stage BD recurrence. Therefore, DEX suppression test results and HPA axis hyperactivity may have prognostic value in BD.<sup>70</sup>

Furthermore, the hyperactive HPA axis correlates with an increased risk of cognitive dysfunction<sup>185</sup> and is known to have neurotoxic effects on the hippocampus that can later predispose to dementia.<sup>186</sup> Lee et al.<sup>187</sup> described that patients with BD with poorer cognitive performance had higher levels of serum cortisol, as well as a significant correlation between cognitive function after 24 weeks of standard treatment and longitudinal changes in cortisol levels, reinforcing the hypothesis that serum cortisol may be involved in the psychopathological mechanisms of cognitive decline in BD. Moreover, some evidence suggests that an abnormal HPA axis may explain the

increased number and size of corticotrophs, leading to the larger pituitary volume found in neuroimaging studies of patients with BD vs. healthy controls.<sup>188</sup> Interestingly, some HPA alterations seem to be a trait predisposing to mood disorders – it was demonstrated that first-degree relatives of subjects with BD had elevated baseline cortisol levels and alterations in the response to the DEX/CRH test.<sup>189-191</sup> Accordingly, a previous study with offspring of parents with BD showed that these at-risk children have epigenetic alterations that can modulate GR responsiveness and the HPA axis,<sup>69</sup> ultimately suggesting a biological mechanism by which the stress axis may be compromised in BD and in at-risk subjects.

### Circadian rhythm abnormalities

Sleep disturbances commonly occur in BD and are part of the diagnostic criteria for BD. Normally, there is reduced sleep during manic episodes, and insomnia or hypersomnia during depressive episodes.<sup>4,192</sup> Dampened and shifted circadian rhythms may explain some of the sleep disturbances frequently reported by patients with BD.<sup>193-195</sup> Indeed, circadian dysregulation is associated with BD both during acute episodes and during inter-episode periods, indicating that these disruptions in circadian rhythms may represent biological markers of the BD.<sup>196</sup> Actigraphy studies have demonstrated that individuals at risk for BD exhibit a lower relative amplitude of the rest-activity cycle, and more sleep irregularity than controls.<sup>197</sup> Notably, variability in the sleep-wake cycle has been shown to predict the onset of depressive episodes among people with inter-episode BD.<sup>198</sup> Similarly, patients with BD have been shown to present lower activity levels, also in addition to sleeping longer, taking longer to fall asleep, spending more time in bed and awake in the middle of the night, and showing a more variable pattern of sleep-wake cycles. Data from several studies have suggested that patients also exhibit more considerable intra-daily variability and lower inter-daily stability, as well as relative amplitude of the rest-activity cycle relative to controls.<sup>199</sup>

Additionally, one of the most commonly reported rhythm-related findings in BD is a significantly higher prevalence of evening chronotypes.<sup>200-204</sup> In individuals with BD, eveningness has also been associated with earlier age of onset, rapid-cycling course, and other factors such as reduction in the peak of the melatonin secretion at night.<sup>202</sup> Mondin et al.<sup>205</sup> showed that patients with BD with evening preference had lower levels of IL-6, TNF- $\alpha$  and thiobarbituric acid reactive substance (TBARS), suggesting that chronotype may affect interleukin and oxidative stress levels in BD. Furthermore, population-based studies have demonstrated that the eveningness chronotype is more common in cyclothymic individuals, especially those with at least one prior episode of depression, and some, but not all, temperament studies that are putatively linked to risk of BD (hyperthymic temperament) show a higher prevalence of this chronotype in at-risk populations.<sup>206</sup>

Moreover, the secretion of melatonin and cortisol also follows a circadian pattern. Evidence has indicated that

people with BD exhibit melatonin secretion abnormalities, suggesting that differences in the amount and timing of melatonin secretion may reflect different mood states. During the manic episode, high levels of melatonin were observed during the day, with an advanced nighttime peak,<sup>207</sup> whereas reduced levels and a later onset of melatonin secretion have been reported in bipolar depression compared with unipolar depression, and in euthymic phases of BD compared with matched controls.<sup>208,209</sup> Similarly, 24-h cortisol secretion is significantly higher in patients with BD than in controls, independent of the clinical phase (manic, depressive, or euthymic).<sup>210</sup> These findings are consistent with the observation of increased GR mRNA in the hippocampus and amygdala in patients with BD compared with those in controls.<sup>211</sup>

In the past few decades, several genetic association studies have demonstrated a link between multiple circadian genes and BD, such as *CLOCK*, *ARTNL1*, *CSNK1ε*, *PER3*, *NPAS2*, *NR1D1*, *TIMELESS*, *RORA*, *RORB*, and *GSK3β*. All had modest associations with BD, supporting a polygenic heritability through which multiple genes additively contribute to the risk of BD.<sup>212-220</sup> Although *GSK3β* is considered a likely candidate gene, no association has been reported between BD and the *GSK3β* gene polymorphism. However, the frequency of a copy number variant (CNV) at the *GSK3β* locus was higher in individuals with BD than in controls.<sup>221,222</sup>

In BD, the circadian genes *PER3*, *REV-ERBα*, and *GSK3β* were associated with an early age of disease onset, and the *CRY2*, *CLOCK*, *ARNTL2*, *TIMELESS*, and *CSNK1ε* were related to rapid BD cycling and/or high disease recurrence.<sup>223-226</sup> These findings are consistent with the observation that an early age of onset is associated with more severe circadian disruptions, such as eveningness and sleep quality. Thus, specific circadian genes may be significant in a particular BD subgroup (early onset). Furthermore, these findings suggest that variations in some circadian genes may explain the high sensitivity to rhythm changes observed in BD and may be associated with disease onset or relapse.<sup>196</sup> Additionally, chronotype and genotype association studies in BD showed that the 3111T/C *CLOCK* variant is associated with an extreme night chronotype, and one nonsynonymous *PER3* coding SNP and two *CSNK1ε* intronic SNPs were associated with the night chronotype in BD patients.<sup>212,220</sup>

Circadian genes have also been implicated in bipolar-like behaviors in animal models. The most notable example is the behavior of mice with an exon 19 exclusion in the *CLOCK* gene, which represents a valuable model of mania.<sup>227</sup> These *ClockΔ19* mice display hyperactivity, increased exploratory drive, lowered depression-like behavior, higher impulsivity, abnormal sleep/wake cycles, and increased reward response. *ClockΔ19* mutant mice show a craving for rewarding stimuli similar to patients with BD in the manic state.<sup>228,229</sup> The manic behavior of *CLOCK* mutant mice can be reversed by treatment with Li or by restoring a functional *CLOCK* gene in the ventral tegmental area.<sup>230</sup> Another mouse model involving circadian genes includes transgenic mice that overexpress *GSK3β* and show a manic-like phenotype.<sup>231</sup>

## Neuroimaging findings in bipolar disorder

The first studies using computed tomography (CT) have shown structural abnormalities as significantly larger ventricular-to-brain ratios in groups of individuals with BD compared with controls.<sup>232</sup> Following the pioneering study (among others) of Pearlson & Veroff,<sup>232</sup> cumulative evidence produced by CT and magnetic resonance imaging (MRI) have shown changes in neuroanatomic structures associated with BD. In one of the first reviews concerning volumetric structural neuroimaging in BD, Soares and Mann described a larger third ventricle and a smaller cerebellum, as well as periventricular hyperintensities in BD patients, the latter also found in the elderly with unipolar depression.<sup>233</sup> More recently, the ENIGMA Working Group, which includes 28 international groups, showed reduced bilateral cortical thickness in the frontal, temporal, and parietal regions of patients with BD, especially the left rostral middle frontal cortex, left fusiform gyrus, and left *pars opercularis*. The authors also found an association between the duration of illness with cortical thickness, and increased cortical thickness with the use of Li. A history of psychosis in patients with BD was associated with reduced surface area in the right caudal anterior cingulate cortex and left inferior temporal gyrus compared with patients without psychosis.<sup>234</sup> Regarding the volume of brain regions associated with mood regulation and reward, some studies showed smaller amygdala and hippocampus and a larger striatum, although contrasting findings have also been found.<sup>235-238</sup> The integration of MRI with machine learning methods to distinguish between patients with BD and healthy controls, as well as for clinical stratification, was investigated by Mwangi et al., showing that the algorithm had up to 70% of accuracy and higher probability scores for those in the late-stage category (more than 10 total lifetime manic episodes including hospitalizations).<sup>239</sup> This potential impact of machine learning techniques in the evaluation of individuals with BD was extensively explored in a systematic review by Librenza-Garcia et al.<sup>240</sup> Of 51 studies included, 38 applied machine learning to discriminate between BD and healthy controls or other psychiatric disorders, especially with neuroimaging data.<sup>240</sup> For instance, Fung et al.<sup>241</sup> investigated psychiatric diagnosis accuracy using a support vector machine (SVM) algorithm with brain cortical thickness and surface area data. The authors found that structural brain differences between individuals with BD and major depressive disorder were able to discriminate these psychiatric disorders with 74.3% (adequate) accuracy (sensitivity: 62.5%; specificity: 84.2%).<sup>241</sup> More recently, a Big Data Task Force from the International Society for Bipolar Disorders has expanded this literature review and discussed issues to be addressed in machine learning-based studies, including the main barriers for applying these techniques and strategies to approach them.<sup>242</sup>

Since human behavior, including cognition, emotion, and social interaction, reflects complex neural circuit communication,<sup>243</sup> the signs and symptoms we observe in individuals with psychiatric disorders could be understood as the manifestation of different brain circuitry

dysfunction.<sup>244</sup> Diffusion tensor imaging (DTI) is a neuroimaging technique used to evaluate white matter fiber tract connectivity between different regions, both proximal and distal.<sup>245</sup> A review<sup>246</sup> of DTI studies in subjects with BD showed a consistent decrease in fractional anisotropy (FA) values in patients, especially in the fronto-limbic tracts and *corpus callosum*. As part of the ENIGMA network, Favre et al.<sup>247</sup> investigated white matter abnormalities in patients with BD compared to healthy controls. The authors found white matter microstructure alterations principally within the cingulum, the main pathway in the limbic system, and in interhemispheric connectivity by the *corpus callosum*.<sup>247</sup> Thus, DTI studies have shown consistent abnormalities in regions associated with emotional regulation as well as in structures that integrate these regions interhemispherically.

Foley et al.,<sup>248</sup> based on previous studies from the literature, have investigated whether fractional anisotropy in the uncinate fasciculus distinguished participants with BD-I from those with BD-II and healthy controls. The results showed significantly decreased FA in the uncinate fasciculus in patients with BD-I compared with both healthy controls and BD-II patients, suggesting a distinction in the pathophysiology of BD subtypes. Mahon et al.<sup>249</sup> used DTI to identify white matter biomarkers of genetic risk. To achieve their aim, the authors evaluated participants with BD, unaffected siblings of individuals with BD, and healthy controls. The results showed that FA within the right temporal lobe of unaffected siblings was significantly different, and intermediate in relation to participants with BD and healthy controls, suggesting a biomarker for genetic risk of BD.<sup>249</sup>

Using specific cognitive and emotional tasks, functional MRI (fMRI) methods allow the investigation of neural circuitry associated with distinct behaviors. Using a cognitive control task, Smucny et al.<sup>250</sup> evaluated whether a *continuum* exists in the underlying neural circuitry across participants with a diagnosis of schizophrenia and BD and healthy controls. The authors found a linear trend in the task-associated dorsolateral prefrontal cortex (DLPFC) and superior parietal cortex (SPC) response among the three groups, with participants with schizophrenia showing more severe dysfunction and those with BD an intermediate pattern. These findings show that, despite the different categorical diagnoses, individuals with schizophrenia and BDs may share some neurobiological characteristics.<sup>250</sup>

Functional neuroimaging studies with BD patients have found connectivity dysfunctions in neural circuits associated with emotion processing, emotion regulation and reward processing.<sup>251</sup> Patterns of amygdala activation and connectivity during emotion processing tasks were compared between individuals with BD and unipolar depression by Korgaonkar et al., with both groups in remission.<sup>252</sup> The findings demonstrated lower connectivity of the amygdala with the insula and hippocampus and of the amygdala with the medial orbitofrontal cortex in patients with BD.<sup>252</sup> Individuals with BD also presented a lower modulatory effect of the DLPFC on the amygdala during emotion regulation tasks compared with healthy controls.<sup>253</sup> In a review, Nusslock & Alloy suggest that

hypersensitivity to reward-relevant cues is related to hypo/ manic symptoms, especially excessive approach motivation and psychomotor hyperactivation, representing a risk trait for BD.<sup>254</sup> Acuff et al.<sup>255</sup> compared reward processing circuitry among offspring of bipolar parents, offspring of parents with non-BD disorder, and offspring of healthy parents during a reward processing task using fMRI. The results showed that offspring of parents with BD had lower functional connectivity between the right ventral striatum-left caudal anterior cingulate in response to loss; and higher functional connectivity between the right *pars orbitalis*-left and right orbitofrontal cortex in response to reward, indicating potential neural markers for the risk of BD.<sup>255</sup>

Despite the impressive advances in technology and interesting neuroimaging findings associated with a psychiatric diagnosis,<sup>247</sup> as well as the response to treatment and risk identification,<sup>255,256</sup> there is still no direct clinical application of brain imaging at this moment in psychiatry.

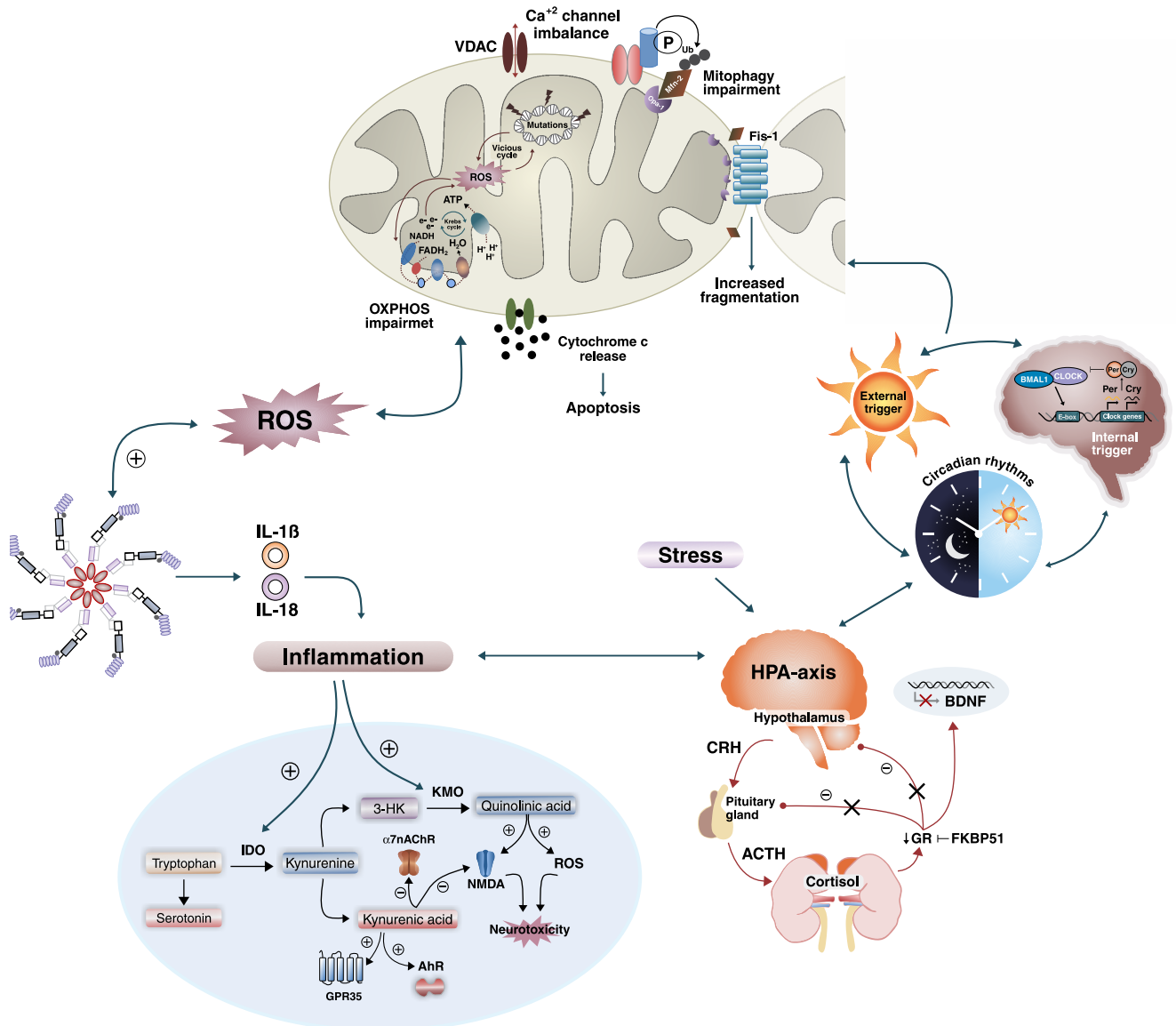
### Conclusion, challenges, and perspectives

The use of tools and technologies that can positively affect mental health parameters using translational approaches still faces several challenges, particularly in the case of BD. First, there is no biomarker with significant biological and clinical validation in BD, which complicates diagnosis and hinders the development of new drugs. Second, the current literature highlights an important limitation of the existing evidence – most studies are still cross-sectional, and thus capable of identifying associations but not causal relationships or longitudinal patterns of development. Third, BD involves heterogeneous symptomatology, various comorbidities, and cognitive impairment, as well as a wide range of genetic and environmental factors. Similarly to other psychiatric disorders, BD is diagnosed based on purely clinical criteria and history taking, interviewing, and behavioral observation; and overlaps pathophysiologically with numerous other disorders.<sup>64,257-260</sup> In this context, the translation of biological findings in BD to the clinical setting is still highly complex, and there is still a long way between translating these initial findings into approved therapies for patients.<sup>261</sup>

As discussed in the present article, brain-imaging studies have shown evidence of change in regional activity, functional connectivity, neuronal activity, and bioenergetics associated with BD, while past research on animals and human models have added mechanistic evidence on bioenergetic dysfunction, inflammation, oxidative stress, as well as abnormalities in signaling networks, HPA axis, and circadian rhythm (Figure 2). In addition to its complexity, brain function is constantly influenced by environmental exposure, which can be associated not only with the risk of mental illness but also resilience and protection.<sup>262</sup> It is not surprising that all of these changes are involved in the neurobiology of BD, a disease with a complicated clinical course involving manic, depressive, mixed, and euthymic episodes.

In addition, studies providing insights into how particular brain abnormalities lead to one, not another specific clinical presentation, and the interaction between immune and neurochemical alterations and cognition are needed





**Figure 2** Summary of recent research on neurobiological mechanisms of BD. Multiple biochemical pathways, not all of which are shown here, interact simultaneously to cause cellular damage. Mitochondrial dysfunction in BD pathophysiology is based on changes affecting oxidative phosphorylation, energy production, increased formation of ROS, mitochondrial DNA damage, membrane permeability,  $Ca^{+2}$  imbalance, and impairment in mitochondrial dynamics and mitophagy. These alterations can lead to increased apoptosis and NLRP3-inflammasome activation. However, this relationship may be bidirectional, wherein mitochondrial dysfunction can increase inflammatory factors, and inflammation can induce ROS production and mitochondrial dysfunction. Inflammation, also reported in BD, is responsible for the activation of enzymes indoleamine 2,3-dioxygenase and kynurenine 3-monooxygenase (KMO), leading to the skewing of the kynurenine metabolic balance toward increased neurotoxicity. Moreover, inflammatory mediators and stress mechanisms activate the HPA axis resulting in secretion of corticosteroids from the adrenal cortex. In BD, the negative feedback of cortisol to the hypothalamus and pituitary components is thought to be impaired, leading to continual activation of the HPA axis and excess cortisol release. Cortisol receptors become desensitized, leading to increased activity of pro-inflammatory immune mediators and downregulation of neurotrophic factors such as the brain-derived neurotrophic factor. Besides, corticosteroids are secreted rhythmically, displaying ultradian and circadian patterns, and *CLOCK*-related genes directly regulate glucocorticoid receptor expression. Circadian rhythms also play a role in mitochondrial functioning by regulating biogenesis, fission/fusion, and mitophagy. These alterations could initiate a vicious cycle where multiple systems and mechanisms exacerbate and accelerate cellular damage, synaptic dysfunction, and impaired neurogenesis, resulting in progressive structural brain changes and cognitive decline thought to contribute to the neuroprogression of BD. 3-HK = 3-hydroxykynurenine; ACTH = adrenocorticotropin hormone; BD = bipolar disorder; BDNF = brain-derived neurotrophic factor;  $Ca$  = calcium; CRH = corticotropin releasing hormone; Fis-1 = mitochondrial fission 1 protein; FKBP51 = FK506-binding protein 51; GR = glucocorticoid receptor; HPA = hypothalamic-pituitary-adrenal; IDO = indoleamine 2,3-dioxygenase; IL = interleukin; KMO = kynurenine 3-monooxygenase; NMDA = N-methyl-D-aspartate; OXPHOS = mitochondrial oxidative phosphorylation; P = phosphorus; ROS = reactive oxygen species.

for a better understanding of the neurobiology of BD. The step towards accurate biomarker identification in psychiatry, including those for BD, will probably require the integration of different sources of evidence. Multidisciplinary research on a single cohort of patients will have more power to increase understanding of BD biology than independent genomic, cell biology, brain imaging, and clinical studies. Moreover, the improvement of technologies related to neuroimaging is undoubtedly a promising measure for advancing the study of neural circuits involved in BD. Finally, longitudinal cohort studies using multimodal and standardized techniques are essential to increase the understanding of BD.

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## Disclosure

The authors report no conflicts of interest.

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