

# Biomarkers for bipolar disorder: current insights

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**Abstract:** Currently, there exists a lack of definitive diagnostic tools for neuropsychiatric disorders, particularly molecular markers that could help assess the illness and develop more personalized treatments for different disorders. Understanding of the neurobiology and potential novel treatments for bipolar disorder (BD), one of the most complex psychiatric illnesses, remains poor. This review aims to compile the most reproducible findings regarding the molecular, genetic, and structural changes that occur in BD. Neuroimaging studies have indicated alterations in neural circuits, disrupted white matter integrity, alterations in reward activation, and decreased gray matter (GM) volume. Genetic studies have identified variations in a number of genes that confer risk for BD development. Studies involving peripheral biomarkers include alterations in the levels of oxidative stress, inflammation, and neurotrophins. These potential molecular markers could be used as tools for diagnosis, to assess illness progression, and to help with the improvement of more specific and personalized treatments for patients with BD. Identification of biologically relevant markers could improve the quality of life of patients with BD and revolutionize public health.

**Keywords:** biomarkers, neuroimaging, neural activation, gene regulation, microRNAs, oxidative stress, inflammation

## Introduction

Bipolar disorder (BD) is a chronic psychiatric illness with partially unknown pathophysiology and symptoms alternating between mania and depression.<sup>1</sup> As consistently found in postmortem studies, in BD, morphological alterations are associated with disruption of cerebral functions, leading to impairment in the cellular plasticity and resilience of the brain.<sup>2</sup> Currently, many studies have reported alterations in the morphology of brain tissues, brain cells, and in the periphery. These alterations could be directly correlated to dysregulation of the molecular pathways of inflammation and neurotrophins.<sup>3,4</sup>

The factors that regulate neurological cells are expressed in a region-specific manner in the brain and the peripheral tissues. This suggests the possibility of using peripheral markers to address alterations in the brain that occur during the development of BD and other psychiatric disorders. Biomarkers are essential tools necessary to provide insights into the molecular alterations in BD.<sup>2,3</sup> Due to the heterogeneity of this disorder, the possibility of developing specific biomarker is still being explored; however, a set of biomarkers might be available to identify subgroups of patients and also develop new treatments. Our goal is to incorporate and critically review the published literature with regard to the morphological, genetic, and molecular alterations found in BD. The hypothetical use of these findings as potential biomarkers is also examined. Moreover, these markers could be used as tools for diagnosis, to assess illness progression, and to help with the improvement of more specific and personalized treatments for patients

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with BD. This review is separated into distinct sections that comprise structural, genetic, and peripheral alterations in BD. In addition, all the potential biomarkers discussed in this report are illustrated in Table 1.

## Structural abnormalities and neurochemical alterations

### Neuroimaging in BD

BD may present with early episodes of depression, often leading to its misdiagnosis as unipolar depression, which in turn can lead to misdirected treatment.<sup>5</sup> Strategies aimed at improving diagnostic accuracy and treatment approaches for BD are therefore crucial. One such approach is using neuroimaging technologies to identify biomarkers. Neuroimaging technologies include structural neuroimaging, functional imaging, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS).<sup>6</sup> Such technologies have allowed a better understanding of the pathophysiology of BD through observations of structural and functional alterations. These alterations may serve as potential biomarkers for BD and have application in diagnostic or prognostic evaluation.

The ventral prefrontal cortex and the amygdala form a corticolimbic network that is involved in emotional regulation.<sup>7</sup> Functional deficits such as impaired emotional regulation and attention have been implicated in BD.<sup>8</sup> One of the most commonly used tools to characterize such alterations is neuroimaging, which can be divided into either functional or structural studies. Structural neuroimaging showed an increased in volume of the amygdala in patients with BD compared to those with schizophrenia;<sup>9</sup> decreased gray matter (GM) volume in dorsal and ventral prefrontal cortices in BD;<sup>10</sup> and little or no alteration in hippocampal volume in BD compared to healthy subjects.<sup>11</sup> Functional neuroimaging uses functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to determine alterations in parts of the brain in subjects during the performance of tasks that require emotion processing and executive control.<sup>8,12</sup> Several studies have used functional neuroimaging to determine whether a significant difference in emotional processing exists in different states of BD, which can be used as a potential biomarker for diagnostic purposes. Increased amygdala and ventral striatal activity in response to negative stimuli were common in all the three states of BD: euthymia, depression, and mania.<sup>12</sup> This increase in the amygdala and ventral striatal activity was also seen in response to positive stimuli in the euthymic and depressive states, but not in mania.<sup>12</sup> Decreased subcortical and prefrontal neural

activity was seen in the euthymic state, whereas increased subcortical limbic activity was common to the depressive and manic states, and this feature can be used to distinguish BD from unipolar depression.<sup>12</sup> As cognitive abilities are also compromised in BD, functional neuroimaging is used to identify changes in brain areas during cognitive functions in BD. Decreased dorsal cingulate activity was common to both depressive and euthymic states, whereas decreased activity in the ventral prefrontal cortex was common to euthymic and manic states.<sup>12</sup>

It is well established that neural circuit alterations are responsible for the altered emotion and cognition observed in BD. Further discussion of neuroimaging findings that demonstrates altered neural circuits involved in emotion processing and regulation in BD is presented in a review by Phillips and Swartz.<sup>13</sup> Although neuroimaging studies have provided the pathophysiological basis for BD, their use in diagnosis, early detection, and treatment of patients with BD still lacks significant impact. It is important to consider that one of the challenges in using neuroimaging to identify biomarkers is the cost involved. Neuroimaging techniques such as fMRI, to analyze response to different attentional or emotional paradigms, and DTI are expensive and are done only in research settings, which limits their feasibility of application in psychiatric assessment. Another challenge is that neuroimaging measures, at present, do not offer adequate specificity and sensitivity to accurately characterize alterations in BD. However, if more specific neural alterations are found in BD and can be differentiated among other psychiatric conditions, then their applications do hold promise in identifying reliable valid biomarkers. This warrants more established findings to generate a strong consensus on alterations in activation patterns in different brain regions in BD.

In the following sections, we review some studies on neuroimaging to address functional, morphometric, and neurochemical alterations in BD. We aim to largely evaluate differences between patients with BD and nonpsychiatric controls. Although this may provide insights into potential biomarkers that may not be conclusive, they will guide the initial step toward biomarker development that could reflect pathophysiological processes in BD.

### Disruption of white matter integrity in BD

White matter integrity in BD can be assessed by neuroimaging. White matter mainly consists of myelinated axons and is made up of glial cells and oligodendrocytes.<sup>14,15</sup> Abnormalities in

**Table 1** Potential biomarkers for bipolar disorder

Potential markers	Findings comparing patients with BD to non-psychiatric controls					Methods/instruments	Reference
	State not specified						
	Mania	Euthymia	Depression				
Neuroimaging	Amygdala activity	↑	↑	↑		Functional MRI, positron emission tomography	For more information, please see Keener et al <sup>12</sup>
	Ventral striatal activity	↑	↑	↑			
	Subcortical activity		↓				
	Prefrontal activity		↓				
	Subcortical limbic activity	↑		↑			
	Dorsal cingulate activity		↓	↓			
White matter integrity	Ventral prefrontal cortex activity	↓	↓				
	Fraction anisotropy in forceps minor, anterior cingulate cortex, corpus callosum, hippocampal gyrus, thalamus and prefrontal cortex				↓	Diffusion tensor imaging	Versace et al; <sup>15</sup> Brambilla et al; <sup>14</sup> Vederine et al; <sup>23</sup> McIntosh et al <sup>26</sup>
	Radial diffusivity in forceps minor				↑		Versace et al <sup>15</sup>
	Apparent diffusion coefficient in frontal, temporal, parietal, occipital lobes, subgenual regions				↑		Brambilla et al; <sup>14</sup> Hong et al; <sup>24</sup> Kafantaris et al <sup>25</sup>
Reward-related neural activation	Left lateral orbital frontal cortical activity (OFC; BA11/47)	↑	↑			Functional MRI Electroencephalography Event-related potential	Nusslock et al; <sup>42</sup> Birmpohl et al; <sup>43</sup> Harmon-Jones et al; <sup>44</sup> Mason et al <sup>45</sup>
Brain morphometry	Grey matter volume in frontal and subcortical regions				↓	Structural MRI	Savitz et al <sup>53</sup>
	Neuronal and glial cell density and number in prefrontal cortex and subgenual anterior cingulate circuits				↓	3D morphometric method Stereological rotate method	Ongur et al; <sup>61</sup> Rajkowska et al <sup>62</sup>
Neurochemicals	Dopamine transporter levels				↓	Western blot qRT-PCR PET imaging	Rao et al; <sup>74</sup> Anand et al <sup>75</sup>
	Glutamate/glutamine ratio	↑	↑	↑		Proton MR spectroscopy	Yildiz-Yesiloglu and Ankerst; <sup>77</sup> Frye et al; <sup>78</sup> Ongur et al; <sup>79</sup> Dager et al <sup>80</sup>
	VGLUT1 (vesicular glutamate transporter 1) nectrin-G1 and -G2 levels				↑ ↑	qRT-PCR	Eastwood et al <sup>82</sup> Eastwood et al <sup>82</sup>
Genes	CACNA1C, DTNA, FOXP1, GNG2, ITPR2, LSAMP, NPAS3, NCOA2, NTRK3, ODZ4, ANK3, NCAN				↑↓	Large-scale genome-wide association study (GWAS)	Psychiatric GWAS Consortium Bipolar Disorder Working Group; <sup>66</sup> Nurnberger et al; <sup>87</sup> Bhat et al; <sup>88</sup> Soeiro-de-Souza et al; <sup>90</sup> Ruberto et al; <sup>91</sup> Cichon et al <sup>92</sup>
	NRG1, DISC1, BDNF, COMT, 5HTT, TPH2				↑↓	Direct candidate gene approach	Tiway; <sup>93</sup> Rotondo et al <sup>98</sup>

(Continued)

(Continued)

Table 1 (Continued)

Potential markers	Findings comparing patients with BD to non-psychiatric controls			Methods/instruments	Reference
	Mania	Euthymia	Depression		
MicroRNAs	miR-504, miR-145, miR-145, miR-22, miR-133b, miR-154, and miR-889 miR-454, miR-29a, miR-520c-3p, miR-140-3p, miR-767-5p, miR-874, miR-32, and miR-573			↑ qRT-PCR	Kim et al; <sup>105</sup> Geaghan and Cairns <sup>01</sup>
Oxidative stress	Lipid peroxidation			↓	
	↑			Meta-analysis Correlation of serum measures with diffusion tensor imaging findings Immunohistochemistry Western blot Meta-analysis ELISA Immunohistochemistry	Brown et al; <sup>127</sup> Versace et al; <sup>15</sup> Wang et al <sup>121</sup>
	Protein oxidation and nitration			↑↓	Andreazza et al; <sup>122</sup> Brown et al <sup>127</sup>
	DNA and RNA oxidation			↑↓	Machado-Vieira et al <sup>168</sup> Che et al <sup>123</sup>
Inflammation	IL-6, IL-1β, and TNF-α			↑	For more information please see Scola and Andreazza <sup>4</sup>
Neurotrophic factors	Brain-derived neurotrophic factor			↓	For more information please see Scola and Andreazza <sup>4</sup>

**Notes:** (↑) increased, (↓) decreased, (↑↓) altered.

**Abbreviations:** qRT-PCR, quantitative real-time polymerase chain reaction; 3D, three-dimensional; IL, interleukin; TNF, tumor necrosis factor; ELISA, enzyme-linked immunosorbent assay; BD, bipolar disorder; MRI, magnetic resonance imaging.

white matter integrity are most commonly measured using DTI or diffusion-weighted imaging (DWI) that measure fraction anisotropy (FA), radial diffusivity (RD), and apparent diffusion coefficient (ADC).<sup>14,15</sup> FA and ADC measurements indicate white matter consistency and its ability to prevent diffusion of water into the tissues, whereas RD value indicates myelin abnormalities and axonal damage.<sup>14,15</sup> Abnormal values of these measures indicate demyelination and abnormalities in white matter integrity.<sup>14,15</sup>

Since white matter hyperintensities, detected by structural magnetic resonance imaging (MRI), were first reported in patients with BD,<sup>16</sup> they have become one of the most consistent findings replicated in neuroimaging studies of BD.<sup>17,18</sup> White matter hyperintensities were most frequently observed in patients with at least one manic episode (BD-I) with poor treatment response. In addition, patients with at least one hypomanic episode and one depressive episode, also known as BD-II, were characterized by elevated number of white matter hyperintensities in comparison to nonpsychiatric controls.<sup>19</sup> These white matter hyperintensities are thought to impair connectivity involved in control of mood, and thus may lead to underlying mood dysregulation associated with BD.<sup>20</sup> However, these findings are relatively nonspecific to BD, since they are involved in the pathophysiology of other diseases and healthy aging.<sup>21</sup>

Although structural MRI offers an incomplete understanding of the brain's white matter integrity, one neuroimaging approach that is sensitive in detecting white matter microstructure and integrity is DTI.<sup>22</sup> Several studies have examined the FA and ADC from different areas of the brain in patients with BD. Reduced FA and higher RD values were observed in patients with BD, compared to healthy controls, in the forceps minor, indicating myelin abnormalities.<sup>15</sup> In patients with BD, reduced FA was also seen in the anterior cingulate cortex and corpus callosum, while significantly increased ADC was found in the frontal, temporal, parietal, and occipital lobes, indicating demyelination, axonal loss, and disruption of microstructure organization of the white matter.<sup>14</sup> A meta-analysis conducted has reported decreased FA near the hippocampal gyrus and the right anterior and subgenual cingulate cortices.<sup>23</sup> The right anterior and subgenual cingulate cortices are involved in emotion processing; a decrease in ADC in the subgenual regions was also observed.<sup>24,25</sup> Decreased FA in tracts between the thalamus and prefrontal cortex was also observed.<sup>26</sup> White matter abnormalities in these regions, especially in the anterior cingulate cortex, may explain the characteristic alterations in emotional processes seen in BD.<sup>27</sup> Lower FA and increased

ADC may indicate a loss of organization and connectivity in the white matter, which could explain the compromise of white matter integrity seen in patients with BD.

Although interest in reduced white matter connectivity is emerging, majority of DTI results across studies have been controversial and inconsistent when compared to those in other disorders, such as schizophrenia. Some studies have reported decreased,<sup>15,28</sup> increased,<sup>29–33</sup> as well as both increased and decreased integrity in distinct white matter tracts in the same patients with BD.<sup>34</sup> Such differences in DTI findings may suggest the complexity of pathology in different cohorts of BD, differences on how the DTI data were acquired, and the effects of medications, which were not accounted for in the majority of the studies analyses.

DTI could be a useful candidate to assess white matter integrity and facilitate diagnosis and assessment of illness progression in the early stages of BD.<sup>14,23,24,27</sup> Indeed, low FA was found to correlate with genetic vulnerability to BD as well as with lipid peroxidation markers, suggesting the potential role of oxidative stress in altering white matter microstructure.<sup>15,35</sup> However, white matter findings remain inconsistent, suggesting that further studies are needed to validate its potential use as a biomarker for BD.

## Reward-related neural activation as biological marker in BD

Imaging studies also provide meaningful insights into how the brain's reward circuitry regulates reward experiences and affections that guide complex behavior in BD.<sup>36,37</sup> The reward hypersensitivity theory proposes that a factor that confers a risk to bipolar spectrum disorders involves increased motivation to expend effort toward attaining rewards and goals following reward-related events.<sup>37,38</sup> This hypersensitivity is thought to precipitate the hypomanic/manic phase of BD.<sup>38,39</sup> In contrast, reward hypersensitivity can also trigger the depressive phase when goals and rewards are not achieved.<sup>38</sup> This model suggests differential alterations in neural activation during reward processing in BD and depression. Due to frequent misdiagnosis between BD and unipolar depression,<sup>40</sup> it is important to consider the degree to which reward-related neural activation reflects a valuable biomarker that is specific for assessing the traits of BD.

The frontal-striatal neural circuit forms a complex system involved in regulating various aspects of reward processing.<sup>41</sup> Excessive activation of this neural circuit has been implicated in BD.<sup>42</sup> Using fMRI, one study reported elevated activation of the left lateral orbital frontal cortex (OFC; BA11/47) in patients with BD assessed during the manic

phase while anticipating for increasing gains, and decreased left OFC activation during anticipation of increasing loss.<sup>43</sup> Increased OFC and ventral striatal responses during reward anticipation were also found in a subset of euthymic patients compared with non-psychiatric controls, suggesting that reward activation is not state-dependent.<sup>42</sup> Increased left frontal cortical activity is supported by electroencephalographic (EEG) assessment – a neurophysiological index of reward sensitivity – in individuals susceptible to bipolar spectrum diagnosis.<sup>44</sup> Another neurophysiological index is event-related potential (ERP), which is used to examine neuronal responses to feedback (feedback-related negativity [FRN]).<sup>45</sup> Indeed, individuals at risk for hypomania displayed lower FRN during a monetary reward task, suggesting greater reward sensitivity and decreased response to negative feedback.<sup>45</sup> This suggests that patients with BD may display extremely high motivational drives during reward striving, leading to decreased propensity to negatively regulate their elevated reward response. Thus, it is likely that hypersensitivity of the frontal striatal network is a risk factor that predisposes to altered episodes in patients with BD during reward processing.

It is important, however, to have a measureable reward-related biomarker that is consistent throughout all phases of BD, including depression. As depressive patients with BD usually seek treatments and may present this episode initially, measureable biomarkers are needed to facilitate assessment in order to ensure that BD is not misdiagnosed as unipolar depression.<sup>5</sup> Although dysfunction of the reward system is thought to play an important role in both unipolar depression and BD, it can be used for differential diagnosis and assessment.<sup>42,46</sup> EEG and ERP studies have identified diminished left frontal cortical activity<sup>47</sup> and decreased FRN in patients with unipolar depression,<sup>48</sup> suggesting deficits in reward processing and responses. Similarly, diminished activity of the frontostriatal neural circuitry was also seen in other psychiatric illnesses, such as schizophrenia.<sup>49</sup> Depressive patients with BD, on the other hand, maintained increased activity of the left frontal cortex,<sup>42</sup> suggesting that reward processing in this brain region is not dependent on mood state. As an elevated frontal-striatal neural circuit is maintained throughout all phases of BD, it may be a potential biomarker for differential diagnosis and assessment of disease progression in patients with BD versus those with unipolar depression.

Further investigations are needed to unravel different reward-related mechanisms and targets of depression. This would improve our ability to differentiate between bipolar

depression and unipolar depression, without relying on the main feature underlying BD – mania.

## Brain morphometric and neurotransmitter biomarkers in BD

Brain morphometric studies have become increasingly significant since the introduction of noninvasive MRI and other neuroimaging technologies. These advancements allow for the quantification of brain abnormalities based on shape and size over time, providing a whole paradigm of novel diagnostic approaches. In BD, morphometric alterations of certain brain regions might offer insights into potential biological markers and pathologies that are not fully understood at present. These morphometric changes in the brain may dysregulate neuronal circuitry by modifying neurotransmitter release, and thus could impair synaptic plasticity, connectivity, and cellular resilience.<sup>50</sup> Thus, considering neurotransmitter systems as potential biomarkers is important as they are widely distributed throughout the neuronal circuit and are believed to reflect motivational, cognitive, and behavioral manifestations of BD.<sup>51,52</sup>

Structural MRI in patients with BD have indicated decreased GM volume of both frontal and subcortical regions of the brain.<sup>53</sup> Volumetric reduction of GM in these brain areas is considered to be attributable to the ventricular enlargement in BD.<sup>54–57</sup> Interestingly, mood stabilizers such as lithium were able to significantly increase GM volume in previously non-medicated patients with BD compared to healthy controls.<sup>58,59</sup> Following lithium treatment, elevated GM density was demonstrated in diffuse cortical areas independent of mood states, particularly with greatest significance in regions involved in motivational and emotional drives.<sup>60</sup> These findings suggest that patients with BD may have distinct and region-specific morphological profiles of the brain that might be involved in regulating mood and visceral manifestations. Thus, structural MRI could be a potential biomarker for assessing the degree of GM reduction in patients with BD.<sup>29</sup> However, further studies are needed to verify which specific regions are altered in BD and whether GM volume is a marker that reflects clinical outcome.

There is also growing evidence that the reduction of GM volume may reflect morphometric abnormalities of the neurons and glial cells. Several postmortem studies reported a significant reduction of neuronal cell density in the prefrontal cortex and subgenual anterior cingulate circuits (ACC) in individuals with BD.<sup>61–63</sup> The reduction in neuronal density and number appear to be region-, layer-, and cell type-specific.<sup>63–66</sup> Furthermore, reduction in glial cell size might also be implicated in



the pathophysiology of BD.<sup>62</sup> Subjects with BD who were not medicated with lithium or valproate had significantly reduced glial density in the amygdala, suggesting that mood stabilizers might be involved in protecting the integrity of glial cyto-architecture.<sup>67</sup> Additionally, elevated levels of the glial marker protein, S100B, was found in the serum of patients with BD, reflecting potential glial cell injury and malfunction.<sup>68</sup> Thus, S100B levels could be regarded as a potential indicator of glial alteration and status.<sup>69–71</sup> As glial cells provide many important functions to the neurons, loss of glial cells in BD can directly affect the number of neurons. Thus, neuronal and glial cell loss may provide important indications of alterations in neuronal circuits involved in normal mood functioning.

Furthermore, it is important to consider how the observed morphological alterations in the brain could translate into abnormal neurotransmission in BD. First, dysregulation of the dopaminergic system is postulated to underlie extreme moods associated with BD.<sup>72</sup> It was proposed that increased dopaminergic activity during the manic phase results in reduced sensitivity of dopaminergic receptors over time, which in turn may initiate a conversion into the depressive phase.<sup>72</sup> Increased dopaminergic activity is thought to result from alterations in dopamine reuptake mechanisms.<sup>73</sup> Significantly reduced mRNA and protein expression levels of dopamine transporter (DAT) in frontal cortex in subjects with BD compared to healthy controls supports this hypothesis.<sup>74</sup> PET imaging also revealed reduced DAT availability in the bilateral dorsal caudate areas of patients with BD.<sup>75</sup> Thus, altered DAT expression may lead to excessive dopamine transmission underlying the mania of BD. It is important to consider that the dopamine dysregulation in BD is not completely understood and is presently speculative. Further studies are necessary to better understand the mechanisms that underlie dopamine dysregulation in BD. This would help identify important targets related to dopamine neurotransmission that could be used as potential biomarkers to guide diagnosis and assessment of illness progression for patients with BD.

In contrast, glutamatergic dysregulation was also proposed to be involved in the pathophysiology of BD. Proton MR spectroscopy (H-MRS) is a noninvasive brain imaging technology that can quantify metabolites such as glutamate and glutamine in the brain.<sup>76</sup> H-MRS revealed increased levels of combined glutamate/glutamine (Glx) in various cortical regions of patients with BD, independent of mood state.<sup>77</sup> Some studies have shown that levels of glutamate differ between patients with BD and those with unipolar depression. Elevated glutamate levels were consistently observed in ACC of depressive patients with BD,<sup>78–80</sup> whereas

decreased glutamate levels were found in the same brain region in patients with unipolar depression.<sup>81</sup> Furthermore, gene expression of VGLUT1 and nectrin-G1 and -G2 were found to be increased in ACC of patients with BD.<sup>82</sup> As VGLUT1 and nectrin-G proteins are known to be involved in glutamate transmission and formation of synaptic connectivity of excitatory pathways,<sup>82</sup> this suggests that their elevated expression may result in increased glutamate transmission and potential excitotoxic processes in the brains of patients with BD. Furthermore, H-MRS represents a promising biomarker because of its ability to reflect changes in Glx levels in response to treatment. For instance, lithium was able to reduce Glx levels,<sup>83</sup> suggesting its neuroprotective effects during states of increased glutamatergic signaling. As Glx levels in BD were increased independent of mood state, differed from unipolar depression, and decreased in response to lithium, H-MRS findings of glutamate are a potential biomarker for the diagnosis and assessment of BD.

## Genetic alterations and gene regulation

### Genetic alterations in BD

Biomarkers for BD are not only limited to specific structural and neurochemical alterations. Compelling genetic findings in patients with BD have well replicated a number of significant susceptibility genes that may hold clinical promises and allow for the identification of specific biological pathways of interest that underlie the pathophysiology of BD. Currently, no single causative risk gene has been identified as being central to predicting the risk of BD development. However, evidence from molecular genetics strongly suggests polygenic effects where many genetic polymorphisms of small additive effect sizes contribute to the risk of BD.<sup>84</sup>

A large-scale genome-wide association study (GWAS) has examined multitudes of candidate genes with intriguing variable findings, reflective of high heterogeneity in BD.<sup>85,86</sup> Recently, a study that compiled multiple GWAS found altered expression of genes that regulate biological pathways such as hormones, calcium channels, second messenger systems, and glutamate receptor signaling in BD.<sup>87</sup> Particularly, *CACNA1C*, *DTNA*, *FOXP1*, *GNG2*, *ITPR2*, *LSAMP*, *NPAS3*, *NCOA2*, and *NTRK3* were found to be differentially expressed in the dorso-lateral prefrontal cortex in patients with BD, and are hypothesized to be involved in the predisposition to BD.<sup>87</sup> Among these genes, *CACNA1C* has been one of the most consistent replicable findings in BD.<sup>88</sup> *CACNA1C* is a gene that encodes for the alpha 1C subunit of the L-type voltage-gated calcium channel and plays an important role in regulating calcium

processes involved in neuronal signaling.<sup>89</sup> A polymorphism in the *CACNA1C* gene is thought to influence executive and cognitive functioning, both of which are strongly implicated in BD.<sup>90</sup> Such endophenotypes have been associated with dysfunction in various neural circuits such as the hippocampus, amygdala, and the mesolimbic reward system.<sup>88</sup> Other genetic risk variants for BD identified by GWAS that are involved in brain-specific functions include: odd Oz/ten-m (*ODZ4*), which encodes for cell surface proteins important for neuronal signaling;<sup>66</sup> ankyrin 3 (*ANK3*), a gene involved in the regulation of action potentials via sodium channels assembly is thought to influence cognitive processes in BD;<sup>91</sup> and neurocan (*NCAN*), a gene that codes for extracellular matrix glycoproteins is theorized to be involved in cognitive and emotional regulation in BD.<sup>92</sup>

In contrast, direct candidate gene approach has also identified various risk genes for BD. Such genes include *NRG1*, *DISC1*, *BDNF*, and *COMT*.<sup>93</sup> These risk genes are known to interact and appear to confer risks to not only BD but also depression and schizophrenia.<sup>93</sup> Interestingly, a nonconservative polymorphism in the *BDNF* gene that swaps valine for methionine at codon 66 was found to increase mature-BDNF/pro-BDNF levels in the serum of patients with BD, suggesting aberrations in the conversion process and trafficking of BDNF.<sup>94</sup> The variant *BDNF* was associated with vulnerability toward rapid cycling, impairment in CNS function, and risk of suicidal behavior in BD.<sup>95–97</sup> Moreover, other gene variants involved in neurotransmission include *5HTT* and *TPH2*, which have been linked to BD.<sup>98</sup> Particularly, a polymorphism in the *5HTT* promoter region was found to affect lithium response and increase susceptibility to manic episodes associated with antidepressant use in patients with BD.<sup>99,100</sup>

Therefore, it is plausible that genetic alterations may underpin endophenotypes of BD characterized by specific structural and peripheral alterations, drug responses, and CNS functions. Further studies will need to investigate the link between these genetic polymorphisms and structural and biological pathways observed in BD.

## Posttranscriptional dysregulation and microRNAs in BD

Despite the identification of a number of susceptibility genes of relevance to BD, only a few studies have explored how these genes are regulated and why such gene expressions are differentially altered in BD. Exploring regulation of expression patterns of potential susceptibility genes at the posttranscriptional level could provide clues on genetic markers for BD. One level of posttranscriptional gene regu-

latory mechanism associated with BD involves microRNAs (miRNAs).<sup>101</sup> miRNAs are small noncoding RNA molecules that play an important role in regulating gene expression via complementary binding to the 3'-untranslated region of a specific mRNA molecule.<sup>102</sup> Genetic variations in miRNA binding sites could alter gene expression, which could modulate neuronal development and plasticity.<sup>103</sup> This could explain the heterogeneity of BD risk among individuals.<sup>104</sup>

There is emerging evidence from expression studies, suggesting a link between dysregulation of miRNA and BD. A recent review that assessed a wide variety of differentially regulated miRNA reported, on postmortem examination, an upregulation of seven miRNAs and a downregulation of eight miRNAs in the dorsolateral prefrontal cortex of patients with BD in comparison to controls (Table 1).<sup>101,105</sup> Another study also validated gene expression using quantitative real-time polymerase chain reaction (qRT-PCR) and reported that patients with BD presented a trend toward decreased miRNA expression levels, specifically in 19% of miRNAs that were analyzed in the prefrontal cortex (Table 1).<sup>106</sup> More recently, a negative correlation was found between miRNA expression and their gene targets,<sup>105</sup> suggesting that miRNA may act to negatively regulate gene expression.<sup>107</sup> Notably, microarray studies emphasized that individual miRNAs can target multiple genes regulating diverse biological processes, indicating that miRNA can have pleiotropic effects on gene regulation.<sup>108</sup> This supports a key regulatory role of these miRNAs on modulating gene expression of susceptibility genes associated with BD, and suggests that posttranscriptional dysregulation may be involved in BD.

Posttranscriptional dysregulation in BD is also supported by genetic and molecular studies on a number of miRNAs and their target genes. A recent study has shown that polymorphisms in the miRNA-206 gene (rs16882131) and *BDNF* gene (rs6255) interact to modulate the expression of *BDNF*, affect treatment response to lithium and valproate, and influence genetic susceptibility to BD-I.<sup>109</sup> Some miRNAs have been described as important regulators of neurogenesis and formation of synaptic plasticity,<sup>110–112</sup> where a majority of their targeted genes are involved in regulation of ion channels and neuronal processes – both of which have been previously implicated in BD.<sup>113</sup> This supports the potential role of miRNAs in the regulation of brain function and thus, may be involved in the pathophysiology of BD.<sup>113</sup>

Another important fact that must be discussed in this section is the effect of treating patients with BD with mood stabilizers. A number of miRNAs have been found to be upregulated



after treatment with both lithium and valproate.<sup>114</sup> However, this finding is being questioned due to a recent study which reports that valproate causes degradation of an important protein involved in the production of miRNA, leading to a global downregulation of miRNA levels.<sup>115</sup> For example, plasma levels of miR-134 were found reduced in non-medicated and medicated patients at the manic stage compared to controls, increased on following treatment with mood stabilizers, and also correlated with illness severity. These findings suggest that plasma miR-134 levels may be considered a potential peripheral biomarker reflecting the manic symptoms of BD and effective treatment response to mood stabilizers.

Therefore, a group of differentially expressed miRNA has been detected in patients with BD, suggesting its potential as a promising novel biomarker. However, these results should be interpreted in the light of the study's limitations and should be confirmed to check the potential of these molecules as possible biomarkers.

## Peripheral alterations

### Mitochondrial dysfunction and oxidative stress in BD

While structural and genetic biomarkers appear to hold clinical utility in diagnosis, a majority of studies to date focus on biochemical markers that are measureable in the peripheral blood of patients with BD. Particularly, mitochondrial alterations and oxidative stress are important contributors to the pathophysiology of BD.<sup>2</sup> Mitochondria are known to play a critical role in many fundamental processes such as energy production, apoptosis, and reactive oxygen species (ROS) formation under physiological conditions.<sup>117</sup> Dysfunction of the mitochondrial electron transport chain is a consistent reporting in many diseases, including BD.<sup>118</sup> Alterations in mitochondrial functionality are associated with increased production of ROS that can induce oxidative stress and lead to redox modulations of macromolecules.<sup>119,120</sup> Alterations to proteins, lipids, and DNA induced by mitochondrial dysfunction were found in postmortem brain samples,<sup>121–124</sup> as well as in peripheral blood cells,<sup>68,122,125,126</sup> from patients with BD.

Changes in mitochondrial function and redox modulation patterns were strongly associated with lipid peroxidation and DNA aberrations, which include changes in methylated and oxidized DNA.<sup>3</sup> Changes in protein conformation due to carbonylation and nitrosylation were also found; however, these alterations do not represent a strong correlation with the pathophysiology of BD.<sup>127</sup> Importantly, our group and others are already investigating studies with regard to how the lipid peroxidation process and DNA aberrations caused by mito-

chondrial dysfunction occur in BD. These findings will be very important in guiding us to develop new tools for the measurement of illness progression and might also be helpful in the development of more specific treatments for this disorder.

## Inflammation and neurotrophic factors

Mitochondrial dysfunction was also suggested to trigger activation of the inflammatory pathway.<sup>128</sup> Inflammation plays an important role in the pathophysiology of BD. A recent review emphasized the potential role of nod-like receptor pyrin domain containing 3 (NLRP3) as being closely linked to inflammation and mitochondrial dysfunction in BD.<sup>128</sup> In this review, the authors explored a very interesting mechanism of action with regard to the assembly of the NLRP3 inflammasome and initiation of the inflammatory cascade upon mitochondrial dysfunction-induced ROS release.<sup>128</sup> There has been a lack of agreement across a number of studies regarding alterations in expression levels of various inflammatory cytokines.<sup>129</sup> So far, it is well described that interleukin-6 (IL-6), IL-1 $\beta$ , and tumor necrosis factor alpha (TNF- $\alpha$ ) are inflammatory markers consistently increased in BD, supporting their potential use as a biomarker.<sup>130–132</sup> More information regarding inflammatory biomarkers can be found in Scola and Andreazza.<sup>3</sup>

Neurotrophic factors, such as BDNF, are strongly implicated in BD. BDNF plays an important role in supporting the growth, survival, and differentiation of neurons.<sup>133</sup> More information on their general description, mechanisms of action, and their effects on BD is presented in Scola and Andreazza.<sup>4</sup> Currently, decreased peripheral levels of BDNF represent the most consistent finding replicated in studies of BD and is also considered as a potential peripheral biomarker for assessing disease progression.<sup>2</sup> In addition, more studies are needed to better understand how these interleukins and trophic factors exhibit their activities in a multifaceted environment such as BD.

## Future directions

This review focuses mainly on comparing BD with nonpsychiatric controls by evaluating the differences in their pathophysiology. Simply, this is the first step towards biomarker development as it only provides insights into potential biomarkers for diagnosis, but does not provide definitive biomarkers. In order to identify biomarkers that can assess the progression of BD, longitudinal studies are needed. Moreover, it is important to consider whether the biomarker is specific to BD. By assessing whether biomarkers of unipolar depression will uncover the depressive episode in BD

or can help differentiate BD from other psychiatric illnesses such as schizophrenia would be clinically relevant. As studies on biomarker development are still very preliminary, some of the findings described in this review are not specific for BD. This suggests that these outcomes must be replicated in larger cohorts to assess the reliability and validity of these potential biomarkers.

Although there is a clear need for specific and clinically relevant biomarkers for BD, these biomarkers will likely be limited to a particular group of patients or the type of treatment these patients are taking. Therefore, identification of a subset of biomarkers to stratify specific patients within a population is needed in order to tailor treatments to the specific diagnosis of a patient. This would give information on how patients respond to a particular treatment. Moreover, although great improvement has been made in relating alterations to BD, further studies are needed to characterize how these markers addressed are altered in response to treatment with mood stabilizers and severity of the illness. Determining how genetic markers are associated with structural and peripheral alterations in BD would be meaningful as well. Finally, in order for biomarkers for BD to become a practicable goal, the field must progress beyond its current dependence on diagnosis. This involves integrating biomarkers into large-scale prospective cohorts and randomized controlled trials to validate the clinical utility of these biomarkers in determining the risk of BD for it to aid in the development of novel therapies.<sup>2</sup>

## Conclusion

Recent advances in BD have improved our understanding of its pathophysiology, leading to the search of relevant biomarkers. Indeed, the most promising biomarker for BD would be a marker that shows altered levels with disease development, varies according to the severity of disease, and normalizes following treatment with mood stabilizers. Such a marker would be a valuable tool that can be used for diagnosis, prognosis, and monitoring of treatment responses in BD. However, the field of biomarker development in BD is still in an early stage of research. Neuroimaging studies suggest a number of structural changes that could be regarded as potential biomarkers, such as alterations in neural circuits, disrupted white matter integrity, activation of reward-related frontal-striatal neural circuitry, and decreased GM volume. These structural alterations could affect neurotransmission that can drive oscillation between mood states. Studies evaluating the genetic basis of BD highlighted polymorphisms in a number of susceptibility genes, such as those involved in calcium processes and second messenger systems. These genetic insights paved the way for understanding

the role of miRNA-mediated posttranscriptional dysregulation in BD. Finally, studies involving peripheral biomarkers include increased oxidative stress, increased proinflammatory markers, and decreased BDNF levels. Taken together, BD is a very complex illness that encompasses structural, peripheral, and genetic alterations. These alterations are potential biomarkers that could provide insights into treatment approaches and development of novel therapies.

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