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REVIEW

The emerging neuroimmune hypothesis of bipolar disorder: An updated overview of neuroimmune and microglial findings

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Abstract

Bipolar disorder (BD) is a severe and multifactorial disease, with onset usually in young adulthood, which follows a progressive course throughout life. Replicated epidemiological studies have suggested inflammatory mechanisms and neuroimmune risk factors as primary contributors to the onset and development of BD. While not all patients display overt markers of inflammation, significant evidence suggests that aberrant immune signaling contributes to all stages of the disease and seems to be mood phase dependent, likely explaining the heterogeneity of findings observed in this population. As the brain's immune cells, microglia orchestrate the brain's immune response and play a critical role in maintaining the brain's health across the lifespan. Microglia are also highly sensitive to environmental changes and respond to physiological and pathological events by adapting their functions, structure, and molecular expression. Recently, it has been highlighted that instead of a single population of cells, microglia comprise a heterogeneous community with specialized states adjusted according to the local molecular cues and intercellular interactions. Early evidence has highlighted the contribution of microglia to BD neuropathology, notably for severe outcomes, such as suicidality. However, the roles and diversity of microglial states in

Abbreviations: 5-HT, Serotonin; ACAA2, Acetyl-CoA Acyltransferase 2; ACC, Anterior cingulate cortex; ACh, Acetylcholine; ADAMTSS, A-disintegrin and metalloproteinase with thrombospondin motifs; aMCC, anterior mid cingulate cortex; AMPH, Amphetamine; Arg1, Arginase 1; ATPA, Adenosine triphosphatase; BD, Bipolar disorder; BDNF, Brain-derived neurotrophic factor; BG, Basal ganglia; BH4, Tetrahydrobiopterin; CCL11, C-C motif chemokine 11; CCR5, C-C chemokine receptor type 5; cf, Cell-free; CHI3L1, Chitinase 3-like1; CINC-1, Cytokine-induced neutrophil chemoattractant 1; CNS, Central nervous system; CNTNAP5, Contactin-associated protein-like 5; CRP, C-reactive protein; CSF, Cerebrospinal fluid; CURD, Chronic unpredictable rhythm disturbances; CXCL10, C-X-C motif chemokine 10; DA, Dopaminergic; D-AMPH, Dextroamphetamine; DLPFC, Dorsolateral prefrontal cortex; DMN, Default mode network; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ECP, eosinophilic cationic protein; EYS, Eyes shut homolog; FA, Fractional anisotropy; FACS, Fluorescence-activated cell scanning; FC, Functional connectivity; GABA, Gamma-aminobutyric acid; GAD65A, Anti-glutamic acid decarboxylase-65; GAD67A, anti-glutamic acid decarboxylase-67; GM, Gray matter; GWAS, Genome-wide association studies; HAT, Histone acetyltransferases; HLA-DR, Major Histocompatibility Complex Class II DR; HSV1, herpes simplex virus type 1; IBA1, Ionized calcium binding adaptor molecule 1; IGF-2, Insulin-like growth factor-2; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IL, Interleukin; IL-1RA, One cytokine receptor antagonist; iMG, inducible microglia; iNOS, inducible nitric oxide synthase; IP-10, Interferon-γ-Induced protein 10; KD, Knockdown; KI, Knockin; KO, Knockout; LAG3, Lymphocyte activation gene 3; Li, Lithium; LPS, lipopolysaccharide; MCL, Mannosylated clodronate liposome; MCP-1, Monocyte chemoattractant protein-1; MDD, Major depressive disorder; MFG, medial frontal gyrus; MHC, Major histocompatibility complex; MHI, Mitochondrial health index; MIMS, Microglia inflamed in multiple sclerosis; MRI, Magnetic resonance imaging; MS, Multiple sclerosis; mtDNA, Mitochondrial DNA; MyD88, Myeloid differentiation factor 88; NAA, N-acetylaspartate; NAc, Nucleus accumbens; NE, Norepinephrine; NFIB, nuclear factor I B; NF-kappa-B p65, nuclear factor-kappa B p65; NNAG, N-acetyl-aspartyl-glutamate; NPC, Neural progenitor cells; ODZ4, Teneurin transmembrane protein 4; OFC, Orbitofrontal cortex; OPC, Oligodendrocyte progenitor cells; OUA, Ouabain; p75NTR, p75 neurotrophin receptor; PDGF-a, Platelet-derived growth factors; PFC, prefrontal cortex; PLP, Proteolipid protein; PSD, Prolonged sleep deprivation; RA, Rheumatoid arthritis; RD, Radial diffusivity; RDoC, Research Domain Criteria; SGZ, Subgranular zone; sIL-2R, Soluble cytokine receptor; sIL-2R, Soluble IL-2 receptor; SMN, Sensorimotor network; SN, Salience network; SNP, Single nucleotide polymorphism; STAT, signal transducer and activator of transcription; SVZ, Subventricular zone; TLR, Toll-like receptor; TNF1R, TNF receptor 1, in their respective alphabetic positions; TNF-α, Tumor necrosis factor α; TPOA, Thyroperoxidase antibodies; TRANCE/TNFSF11, TNF-related activation-induced cytokine/TNF superfamily member 11; TSPO, Translocator protein; UK, United Kingdom; VDAC, voltage-dependent anion channel; VTA, Ventral tegmental area; WM, White matter.

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this disease are still largely undermined. This review brings an updated overview of current literature on the contribution of neuroimmune risk factors for the onset and progression of BD, the most prominent neuroimmune abnormalities (including biomarker, neuroimaging, ex vivo studies) and the most recent findings of microglial involvement in BD neuropathology. Combining these different shreds of evidence, we aim to propose a unifying hypothesis for BD pathophysiology centered on neuroimmune abnormalities and microglia. Also, we highlight the urgent need to apply novel multi-system biology approaches to characterize the diversity of microglial states and functions involved in this enigmatic disorder, which can open bright perspectives for novel biomarkers and therapeutic discoveries.

KEYWORDS
bipolar disorder, cytokines, inflammation, microglia, neuroimmune risk factors

1 | INTRODUCTION

Bipolar disorder (BD) is a severe neuropsychiatric condition affecting an estimated 1%–3% of the global population and representing a leading cause of disability (Harrison et al., 2018; Merikangas et al., 2011). It is associated with high rates of mortality, premature death by suicide (Hayes et al., 2015), and clinical comorbidities such as anxiety disorders, substance abuse disorders, diabetes, thyroid disease, and cardiovascular conditions (Yan et al., 2023). BD is characterized by severe and persistent mood changes, cycling between manic,depressive and mixed episodes, with intermittent periods of stable mood referred to as euthymia (Carvalho et al., 2020; Grande et al., 2016; Miklowitz & Johnson, 2006). Emil Kraepelin was a pioneer in the conceptualization of BD as a disease entity using a nosological psychiatric approach (Zivanovic & Nedic, 2012), and at the time, he named the disorder manic-depressive insanity (Goes, 2023; Kraepelin, 1921). The modern diagnostic criteria of BD were summarized in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), which established specific major and minor criteria for the clinical diagnosis of BD (Goes, 2023; Harrison et al., 2018; McIntyre et al., 2020). Indeed, the current diagnostic criteria for BD include core symptoms of depression and mania/hypomania (Chakrabarti, 2022; Marangoni et al., 2016). However, despite the huge societal burden associated with this condition, the understanding of BD pathophysiology still represents a major challenge in contemporary psychiatry (Ferrari et al., 2016; Kato et al., 2021).

In the last decades, a growing number of biological alterations have been detected in the blood/serum and across multiple brain regions of patients with BD (through neuroimaging and post-mortem studies) (Harrison et al., 2018). These alterations include abnormalities in brain activity and structure, both in gray and white matter (Harrison et al., 2018). In addition, more recent immune-inflammatory mediators, including cytokines, chemokines and immune cell activity markers, were identified across several populations with BD (Benedetti et al., 2020; Goldsmith et al., 2016; Poletti et al., 2021). However, the association between these changes and the core clinical and psychopathological features of the disease, as well as how they relate to or influence the increasingly accepted progressive course of this disorder, remain largely elusive.

In this context, microglia, the brain's resident immune cells, are key players in maintaining the brain's health across the lifespan and upon life challenges, such as environmental stress, sleep abnormalities, substance use, and others (Tremblay, 2021). All these challenges are common triggers of mood swings in patients with BD (Rodrigues Cordeiro et al., 2023). Also, microglia participate in several critical physiological functions ranging from glio-, vasculo-, and neurogenesis to synaptic homeostasis and myelination, production and release of soluble factors, and phagocytosis of cell debris, apoptotic bodies and synapses (Šimončičová et al., 2022; Tremblay, 2021). These functions have been demonstrated not only as fundamental for central nervous system (CNS) health, but their disruption might be central to the genesis of many neuropsychiatric disorders such as BD (Gonçalves de Andrade et al., 2022; Tay et al., 2017, 2018). In this review, we comprehensively summarize the current clinical and preclinical literature in the field. We also aim to propose a unifying and coherent conceptual framework for BD pathophysiology which is centered on neuroimmune abnormalities and microglia. By integrating different shreds of evidence of clinical, immune-inflammatory and brain neuroimaging disturbances in BD, and very initial data directly involving microglia (from post-mortem, neuroimaging and ex vivo studies), we developed a hypothesis which may guide future understanding of the neuro- and microglial biology of this disorder.

2 | CLASSICAL AND CURRENT HYPOTHESES FOR BD NEUROBIOLOGY

2.1 | Neurotransmitter abnormalities

Classically, BD neurobiology has been associated with an imbalance of neurotransmitters, including glutamate, gamma-aminobutyric acid (GABA), dopamine (DA), serotonin (5-HT), acetylcholine (ACh), and norepinephrine (NE) (Manji et al., 2003; Salvadore et al., 2010; Tang et al., 2022). Neurotransmitter interactions are dynamic, while changes in receptor sensitivity and neurotransmitter reuptake over time may contribute to mood instability and the cyclic nature of BD (Tang et al., 2022). In this context, a shift toward increased neuronal

firing rates of glutamatergic and DA neurons in limbic brain regions, such as nucleus accumbens (NAc) and ventral tegmental area (VTA), was reported to be involved in manic episodes (de Bartolomeis et al., 2014; Lee et al., 2018). Since glutamate is converted to glutamine predominantly by astrocytes (Aldana et al., 2020), the ratio of glutamine to glutamate has been proposed as a discriminatory factor between depressive and manic episodes (Yüksel & Öngür, 2010). Studies have shown that patients experiencing manic symptoms have an increased glutamate and glutamate/glutamine ratio in some limbic regions, notably the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), parieto-occipital cortex and insula, which is compatible with higher excitatory neurotransmission during this mood phase, whereas a decreased ratio in some limbic regions was found in depressed patients with BD (Shen & Tomar, 2021; Yüksel & Öngür, 2010).

The most classical theory for BD is dopaminergic, suggesting that DA transmission is dynamically altered in all BD mood phases (Ashok et al., 2017; Berk et al., 2007). Indeed, DA plays a vital role in key brain processes such as pleasure anticipation, motivation, impulsivity, and cognitive functions, greatly impaired in BD (Bressan & Crippa, 2005; Seamans & Yang, 2004). According to this theory, during manic/hypomanic episodes, abnormally elevated DA transmission, named hyperdopaminergia, characterized by the increased firing of DA neurons in limbic areas, such as the NAc and VTA, and increased DA bioavailability, contribute to the emergence of manic symptoms. Also, following this increased dopaminergic state, adaptative mechanisms lead to a down-regulation of dopaminergic receptor sensitivity and increased DA reuptake, leading to an overall decrease in DA transmission (hypodopaminergia) that induces depressive symptoms. This theory poses the DA neurotransmission system as the core biological factor explaining the cyclic nature and mood instability observed in BD (Ashok et al., 2017; Berk et al., 2007). Despite the promising and explaining potential of this theory for at least part of BD clinical and neurochemical manifestations, this theory is limited as it cannot fully explain BD heterogeneity of presentations, as well as more recent biological findings in this disorder.

The DA hypothesis was modified to include abnormalities in the cholinergic system, resulting in the catecholaminergic-cholinergic hypothesis of BD, which proposes that a shift in these neurotransmitters toward increased cholinergic activity is involved in bipolar depression while increased catecholamine (dopamine, NE) activity is associated with manic episodes (Salvadore et al., 2010; van Enkhuizen et al., 2015). Regarding the dopaminergic component of this theory, it was supported by the extensive evidence showing the cyclic nature of DA availability, dopaminergic D2 receptor density and DA reuptake in the limbic brain (especially the striatum) across different BD mood phases (Altinay et al., 2016; Anand et al., 2011; Dubol et al., 2020). Regarding cholinergic transmission, previous studies have shown decreased M2 and M3 muscarinic receptor binding within the ACC of individuals with bipolar depression compared to patients with MDD and healthy controls (Cannon et al., 2006; Gibbons et al., 2015). In these studies, radioligand binding was reduced by direct competition with the endogenous acetylcholine, indicating increased cholinergic bioavailability (Gibbons et al., 2015). This reduced binding was confirmed in post-mortem studies examining the prefrontal cortex of patients with BD, and was suppressed by acetylcholine washout from the brain specimens, confirming this association (Gibbons et al., 2015; Zavitsanou et al., 2005). Also, increased choline levels were reported in the brain of depressed patients with BD measured in vivo, further supporting this hypothesis (Shi et al., 2014; Steingard et al., 2000).

2.2 | Neurotrophins and BDNF

In the last decades, studies have also suggested that changes in the expression and signaling of some neurotrophins, notably brain-derived neurotrophic factor (BDNF), may additionally contribute to the mood states involved in BD (Tsai, 2004). It has been proposed that lower levels of peripheral BDNF in both depressive and manic phases compared to healthy controls can be a key player underlying the cognitive deficits and depressive symptoms in these patients (Fernandes et al., 2015; Petersen et al., 2021; Rowland et al., 2018; Wang et al., 2020). However, conflicting findings instead posit increased BDNF levels in adolescent patients with BD (Petersen et al., 2021) or early-onset patients (Tsai, 2004). This may be because of fluctuations of BDNF levels during the time course of BD, where early episodes are associated with higher levels of BDNF, which can represent a compensatory adaptation to the progressive decline observed in patients with late-stage BD, in which functional impairment is also more severe (Kauer-Sant'Anna et al., 2009). Furthermore, BNDF levels in patients with BD may additionally be predictive of symptom severity, since lower BDNF levels were associated with more severe depressive episodes (Fernandes et al., 2015; Karthikeyan et al., 2022).

BDNF is a neuropeptide that plays numerous important roles in synaptic development and plasticity. It can regulate synapse formation in multiple ways, such as increasing the arborization of axons and dendrites, inducing axonal and dendritic bouton formation, and stabilizing existing synapses, being fundamental for normal cognitive and behavioral functions (Wang et al., 2022). BDNF is synthesized as a precursor form, named pro-BDNF, which can be processed into its mature isoform, mature BDNF (mBDNF) (Je et al., 2013). These two forms of BDNF bind to two different cell surface receptors: pro-BDNF binds to the pan-neurotrophin receptor p75 ($p75^{NTR}$), whereas mBDNF preferentially binds to the tyrosine receptor kinase B (TrkB). By binding to distinct receptors, pro-BDNF and mBDNF elicit seemingly opposite biological effects at synapses: the first acting as a synapse atrophy signal and the second as a synapse maturation/stabilization signal (Je et al., 2013). Previous studies have highlighted marked changes in the levels of pro- and mBDNF in biological specimens of BD, with some possible diagnostic applications (Lin et al., 2021; Zhao et al., 2017). Comparing the serum levels of pro-BDNF and mBDNF in patients with BD (with acute depressive symptoms), major depressive disorder (MDD), and healthy controls, Zhao et al. (2017) found decreased levels of mBDNF, as well as a decreased ratio of mBDNF to pro-BDNF in patients with BD compared to MDD (Zhao et al., 2017). These findings were confirmed by subsequent work showing reduced mBDNF levels in peripheral lymphocytes of patients with BD compared to MDD (Lin et al., 2021). Another study demonstrated that the serum

levels of mBDNF and the ratio mBDNF/pro-BDNF were significantly higher in euthymic patients with BD treated with mood stabilizers than in healthy controls. However, the serum levels of pro-BDNF were significantly lower in the patients versus controls. These effects can be attributed to the chronic mood stabilizer treatment or changes that characterize the euthymic phase of BD (Södersten et al., 2014).

Regarding brain post-mortem findings, there is a paucity of evidence. Yang, Ren, et al. (2017) reported reduced mBDNF levels in the post-mortem parietal cortex of patients with MDD, schizophrenia and BD compared to control participants. In contrast, the levels of pro-BDNF and BDNF pro-peptide (a precursor of proBNDF) in the cerebellum were significantly lower in BD than in controls (Yang, Ren, et al., 2017). Therefore, despite being a promising diagnostic biomarker of BD with potential translational implications for assisting the differential diagnosis of BD, more investigation is still necessary to understand the involvement of the distinct BDNF isoforms in the neurobiology of BD and their possible translational applications.

2.3 | Abnormal mitochondrial bioenergetics

Abnormalities in energy metabolism have been observed in BD. Studies have shown a 16%–21% increase in BD occurrence in individuals with primary mitochondrial diseases (Quiroz et al., 2008), making mitochondrial deficits a significant biological risk factor for BD (Kato, 2017). Furthermore, an increased prevalence of aberrant mutations and polymorphisms of mitochondrial DNA (mtDNA) was found in patients with BD (Clay et al., 2011). Among the mtDNA variants, two rare variants, m.114C.T and m.16300A.G, were highly expressed in these patients, leading to mitochondrial dysfunction (Kasahara & Kato, 2018). Recently, Cordeiro et al. (2023) found a marked association between reduced mitochondrial health index (MHI), an index created by integrating the activity of three mitochondrial enzymes (complexes I, II, and IV) and the content of mtDNA copy numbers, and poor clinical outcomes in BD (Cordeiro et al., 2023). Indeed, a noteworthy inverse correlation between illness severity and MHI was identified, with lower MHI and higher cell-free mtDNA levels being detected in patients with longer illness duration, worse functional status, and higher depressive symptoms (Cordeiro et al., 2023). Therefore, despite compelling evidence for the role of mitochondrial dysfunction as a biological determining factor for BD, the specific mechanisms ruling these energic deficits (genetic, environmental influences) and the brain circuits affected by these disturbances have not yet been fully identified, and further research is necessary (Allen et al., 2018; Caruso et al., 2019; Kato, 2017).

2.4 | Inflammation and neurotransmitter catabolites

In the last decade, abnormal CNS inflammation and increased levels of peripheral proinflammatory cytokines have also been proposed as key underlying factors for BD pathophysiology (Benedetti et al., 2020; Berk et al., 2013; Kageyama et al., 2018). This CNS inflammation can contribute to abnormal reactivity of glial cells and, thus, lead to reduced protective functions and progressive neurodegeneration (Tang et al., 2022; Watkins et al., 2014). Abnormalities in several proinflammatory cytokines, for example, interleukin (IL)-6, IL-2, and IL-8, and an imbalance between pro/anti-inflammatory mediators have been reported in patients with BD across all mood phases with particularities dependent on each disease state, which will be further discussed in this review (Goldsmith et al., 2016; Kim et al., 2007; Munkholm et al., 2015; Tang et al., 2022). Furthermore, proinflammatory cytokines disrupt the synthesis and metabolism of neurotransmitters, including 5-HT and DA, increasing their metabolism or depleting their substrate contents (e.g., tryptophan) and enzymatic cofactors (e.g., tetrahydrobiopterin [BH_4]), besides generating toxic byproducts (e.g., kynurenine derivatives) (Zhang et al., 2021). Notably, reduced serum levels of tryptophan have been consistently reported in patients with BD, especially in acute manic episodes, concomitantly with reduced levels of kynurenine, kynurenic acid, and kynurenic acid/quinolinic acid ratio, indicating a shift toward the production of neurotoxic tryptophan catabolites, such as quinolinic acid (Bartoli et al., 2021; Hebbrecht et al., 2021). However, more studies are necessary to determine the full profile of tryptophan metabolites and altered enzymatic routes involved in different mood phases of BD and its progressive course. Therefore, here we briefly outline some of the major theories to explain the underlying neurobiology of BD. Deeply dissecting their contribution to BD neurobiology is not the main scope of this review; for further details, other comprehensive reviews in the field are suggested (Scaini et al., 2020; Young & Juruena, 2021).

3 | ANIMAL MODELS OF BIPOLAR DISORDER: AN ONGOING EFFORT FOR VALIDITY OPTIMIZATION

The development of valid animal models is critical for comprehending the underlying biological mechanisms and screening potential new therapies for this disorder (Hodes et al., 2016; Kumar et al., 2016; McCarty et al., 2021). However, notably for BD, the validity of animal models remains highly debated, with no current animal model accurately able to fully resemble its complexity (Beyer & Freund, 2017; Tang et al., 2022). Each modeling approach has certain advantages and caveats which will be further discussed below (for a detailed and schematic view, also see Table 1). The criteria for evaluating the validity of animal models for psychiatric disorders are based on three main aspects that each model must aim to maximize to be translationally valid: face (phenotypic) validity, predictive (pharmacological) validity, and construct (etiology) validity (Beyer & Freund, 2017; Einat, 2014). For BD, face validity refers to the ability of the model to replicate the symptoms associated with mania and bipolar depression, exhibiting a phenotypic resemblance to the disorder in humans (Logan & McClung, 2016).

Predictive validity evaluates whether the symptoms induced in the model can be reversed by the same treatment modalities shown to be effective in humans, mainly standard mood stabilizers, such as lithium (Li) or valproate (Logan & McClung, 2016). Construct validity is the most difficult to achieve as it involves establishing a connection between the animal model and the human condition by mimicking the underlying causes and mechanisms of the disorder (Logan & McClung, 2016; Valvassori, Dal-Pont, Tonin, et al., 2019). Considering that BD is not fully understood, most animal models are able to recapitulate only one or a few features related to BD pathophysiology, and this aspect usually represents the most significant limitation of current animal models of this disease (Cosgrove et al., 2016).

The cyclic nature of mood episodes in BD is an additional challenge for the development of translationally valid animal models for this condition, especially in rodents (Valvassori et al., 2013). The majority of current BD animal models induce manic-like, depressive-like, or mixed symptoms, but none fully captures the cyclic (and progressive) course of the disorder, including euthymic states (Kato et al., 2016; Machado-Vieira et al., 2004; Valvassori et al., 2013). Recent advances have allowed the development of models representing both mania and depression-like symptoms in the same animal, although switching between mood episodes remains a challenge (Sidor et al., 2015; Valvassori et al., 2021; Young et al., 2018). Also, previous animal models of BD have relied on the assumption that unipolar (or MDD) and bipolar depression share similar pathophysiology and phenotypic presentations because of inconsistent or limited studies investigating possible differences between these conditions and their behavioral correlates in rodents (if they exist) (Cosgrove et al., 2016; Kato et al., 2016). Therefore, the development of animal models able to properly recapitulate the phenotypical distinction and specific biological correlates of bipolar depression and unipolar depression remains an open question in the field that should be addressed to allow for the development of better translational models (Beyer & Freund, 2017; Kato et al., 2016).

The emotional and neurocognitive aspects of BD symptomatology are challenging to replicate in animals, especially given the amalgamation of symptoms and emotional liability characteristic of this disorder, often mixed with personality traits or personality-related disorders (Freund & Juckel, 2019; Ghaemi & Dalley, 2014). Recently, a new framework for psychiatric research, the Research Domain Criteria (RDoC) initiative, proposed to assess psychiatric diseases by breaking them down into five multi-level domains: arousal, positive valence, negative valence, social interactions, and cognition (Insel et al., 2010). This conceptual framework has been proposed as an assessment of validity for animal models of psychiatric disorders, including BD (Cosgrove et al., 2016). This assumption relies on the fact that some of these neurobehavioral (emotional, cognitive) domains are evolutionarily preserved in rodents, and can be assessed behaviorally (Bigot et al., 2022). However, despite being promising, some researchers have argued that the criteria proposed by RDoC do not completely account for the natural history of the disorder, including the contribution of multiple etiological risk factors, heterogeneity of clinical presentations, or differential response to medications and, therefore, has a limited ability to be applied to such a heterogenous disorder as BD (Casey et al., 2013; Ross & Margolis, 2019; Weinberger et al., 2015).

These criteria, both the three-concept validation and RDoC, remain challenging to fully satisfy; however, they have yielded valuable insights into the mechanisms associated with BD and have enabled the design of promising models with some level of translational validity (Li et al., 2023; Lima et al., 2019; Young et al., 2018). In this review, we compiled the current literature on the categories of animal models for BD, including genetic, pharmacological, and environmental models, and how they partially or successfully fulfill each translational validity aspect, as well as their main caveats and limitations. Briefly, genetic models utilize the modification of a gene that plays a relevant role in BD pathophysiology, including knockout (KO), knockin (KI), knockdown (KD), and other mutation strategies. These include *Clock*Δ19 and *Ntrk1* mutant mice, *FADS1/2*, *HINT1*, *SH2*, *ANK3*, *ErbB4*, and *Plcg1* KO mice, *SH3* KI mice, and *DAT* KD mice (Cao et al., 2018; Garzón-Niño et al., 2017; Yamamoto et al., 2023; Young et al., 2018). Environmental models rely on physical manipulation of the rodent's surroundings, usually by exposing them to environmental stressors or disrupting their sleep cycle and circadian rhythms. These include the recently developed chronic unpredictable rhythm disturbances (CURD) and prolonged sleep deprivation (PSD) models (Arora et al., 2021; Li et al., 2023). Pharmacological models employ drug administration to mimic BD neurochemical abnormalities, including amphetamine sensitization/withdrawal, inhibition of gamma-aminobutyric acid (GABA)ergic neurons, administration of other DA stimulants, such as fenproporex and GBR12909, and metabolic-energetic disruptors, such as the inhibitor of the Na+/K+–ATPase sodium-potassium ion pump ouabain (Bigot et al., 2022; Chaves Filho et al., 2021; de Queiroz et al., 2018; Valvassori, Dal-Pont, Resende, et al., 2019). For specific details about these models, please see Table 1.

4 | INTERACTION BETWEEN GENETIC AND ENVIRONMENTAL NEUROIMMUNE RISK FACTORS IN THE ONSET AND DISEASE PROGRESSION OF BD

In general, genetics and environmental factors interact for the emergence of the full-blown disease commonly early in adult life and can also set the vulnerability for mood switches in these patients (Craddock & Sklar, 2013). Regarding genetic factors, a heritability of up to 85% was estimated for BD on the basis of family and twin studies (Bienvenu et al., 2011; Craddock & Sklar, 2013; Song et al., 2015). In this context, genome-wide association studies (GWAS) have identified main candidate genes and single nucleotide polymorphisms (SNPs) associated with BD (Cichon et al., 2011; Psychiatric

GWAS Consortium Bipolar Disorder Working Group, 2011; Uemura et al., 2016). Despite the fact that these genetic variants confer a higher risk for BD, it remains unclear how they translate into biological mechanisms that explain the pathobiological processes leading to the disease (Gordovez & McMahon, 2020).

A recent study utilized a combined approach of linking SNPs highly enriched in a cohort of patients with BD (a GWAS approach) with neuroimmune markers detected in the cerebrospinal fluid (CSF) of these patients (Zhang et al., 2020). Of note, increased levels of the monocytic inflammatory markers monocyte chemoattractant protein-1 (MCP-1) and chitinase 3-like 1 (CHI3L) in the CSF of patients were linked with SNPs of selected genes. The strongest association for CSF MCP-1 was located within rs10438979 in the *ACAA2* (Acetyl-CoA Acyltransferase 2) gene, while for CSF YKL-40, the strongest association was for the SNPs rs150248456 in *CNTNAP5* (contactin-associated protein-like 5) gene and rs11753319 in *EYS* (eyes shut homolog) gene (Zhang et al., 2020). These genes are involved with metabolic-energetic processes, such as mitochondrial fatty acid beta-oxidation spiral, and extracellular matrix composition and intercellular communication, and are highly expressed in the brain (Rose et al., 2020; Zou et al., 2017). Therefore, although these genes were not the most frequently enriched in some previous GWAS studies in BD, these findings indicate that they are strongly associated with a subcohort of patients presenting increased monocytic markers and active proinflammatory status in the CNS (Zhang et al., 2020).

Furthermore, it has been demonstrated that immunogenetic susceptibility may amplify the effects of environmental risk factors and increase susceptibility to BD (Oliveira et al., 2016, 2017). Of note, a strong gene–environment interaction was found between the SNP rs3804099 Toll-like receptor (TLR)2 and pre- and perinatal *Toxoplasma gondii* IgG seropositivity for conferring risk for BD (Oliveira et al., 2017). Another study by Oliveira et al. (2015) explored the interaction between immunogenetic variants and early-life adversities in a sample of patients with BD (Oliveira et al., 2015). A cumulative effect of a genetic variant of TLR2 (rs3804099) and self-reported childhood sexual abuse was detected at the age of BD onset (Oliveira et al., 2015). The genetic susceptibility represented by TLR2 gene variants likely contributes to abnormal neuroimmune responses to early-life stressors, and potentially forms a pathological substrate for subsequent emergence of the disease later in life (Oliveira et al., 2015, 2016, 2017). Nevertheless, genetic findings are highly related to specific populations and results from correlation models may not be generalized to all BD populations.

However, some environmental risk factors without a clear heritable association or gene interaction have also been identified as disease triggers for BD, attesting to the relevance of the environment to this disease development. As a multiple hit disease model, neuroimmune events in early life, especially childhood abuse (e.g., emotional, physical, sexual, or combined abuse) were demonstrated to be independent predictive factors for BD type I incidence, particularly in males and they increased risk of comorbidities, such as post-traumatic stress disorders and alcoholism (Brown et al., 2005; Hyun et al., 2000). Also, viral infections at any time during pregnancy were associated with an increased incidence of BD in exposed offspring (nearly 4-fold increased risk compared to the non-exposed population) (Parboosing et al., 2013). A similar risk association was identified for BD with psychotic features (almost 5-fold increased risk compared to controls) (Canetta et al., 2014). However, conflicting evidence found no increased risk for BD after general (bacteria, virus, or parasite) infections during any time of pregnancy, contrary to an increased risk of autism spectrum disorder and MDD (Al-Haddad et al., 2019). Additional evidence supporting the role of neuroimmune risk factors early in life in BD came from a large longitudinal birth cohort trial in the United Kingdom (UK), including 14,062 live births (Hayes et al., 2017). In this study, the levels of IL-6 and C-reactive protein (CRP) in blood samples of 3,361 children at age 9 showed a positive association with BD diagnosis with hypomanic symptoms at the age of 22 (Hayes et al., 2017). Altogether, this evidence highlights the complex interaction between pathogens, early-life stressors, the maternal immune system and the fetus in determining the risk of psychopathological outcomes, such as BD, with more studies needed to provide a clear picture of the mechanisms underlying this association.

Adult life infection with *Toxoplasma gondii* was also shown to confer an increased risk for BD or serve as a disease trigger, especially for manic episodes (Dickerson et al., 2014). In a study with over 130 patients with BD and 160 healthy controls, a significant association between BD diagnosis and *Toxoplasma gondii* IgG seropositivity was found (odds ratio of 1.765) compared to healthy controls (Oliveira et al., 2016). Other studies have confirmed this positive association between BD diagnosis and seropositive status of immunoglobulin G (IgG), but also immunoglobulin M (IgM) for *T. gondii* (Hamdani et al., 2013; Oliveira et al., 2016, 2017; Tedla et al., 2011). Regarding mood episodes, an increased IgM antibody level of *T. gondii*, indicating a recent infection or re-infection, was significantly associated with manic symptoms (Dickerson et al., 2014).

Autoimmune diseases, especially virus-triggered autoimmune diseases, were also linked to the emergence of BD in some cohorts, suggesting that a subsequent maladaptive autoimmune response to previous infection can act as a risk factor for BD (Oliveira et al., 2017; Rosenblat & McIntyre, 2017). In a Danish population-based study including approximately 10,000 patients with BD, a heightened risk for developing BD was found in individuals with a history of postviral autoimmune syndromes, such as Guillain-Barré and autoimmune hepatitis. In these patients, BD disease onset was at least 5 years earlier compared to respective control subjects (Eaton et al., 2010). In a subsequent study including herpes simplex virus type 1 (HSV-1) seropositive European individuals with BD, IgG antibody levels for HSV-1 positively correlated with higher cognitive impairment during euthymic phases (Gerber et al., 2012). Additionally, patients with chronic inflammatory conditions, such as Crohn's disease, showed an increased risk of BD compared to healthy controls (Eaton et al., 2010).

TABLE 1 Animal models of bipolar disorder and translational validity aspects.

Model		Authors	Modeled mood phase	Phenotypic validity
Genetic	*Clock*Δ19 mutant mice	Sidor et al. (2015)	Switching between mania (daytime) and euthymia (nighttime)	Daytime (7:00 am–7:00 pm): ↓ anxiety, ↓ immobility, ↑ preference for sucrose, ↑ exploratory behavior, ↑ risk-taking behavior Nighttime (7:00 pm–7:00 am): Manic behavior returned to same level as the naïve controls
	*Clock*Δ19 mutant mice	Parekh et al. (2018)	Mania	↑ exploratory behavior, ↑ sensitivity to rewarding substances (cocaine)
	*Clock*Δ19 mutant mice	Kristensen et al. (2018)	Mania	Hyperactivity, ↓ anxiety, ↓ depression-like behavior, ↑ preference for rewarding stimuli
	*Clock*Δ19 mutant mice	Liu et al. (2021)	Mania	Hyperactivity, ↓ anxiety, ↓ depression-like behavior
	Fads1/2 KO mice	Yamamoto et al. (2023)	Mixed mania and depression	↓ need for sleep, ↑ goal-directed behavior, ↓ immobility Spontaneous hypoactivity, abnormal circadian rhythm
	HINT1 KO mice	Garzón-Niño et al. (2017)	Mixed mania and depression	Mania: Hyperactivity, ↑ preference for rewarding stimuli (sucrose), ↓ immobility, ↑ sensitivity to AMPH
		Sánchez-Blázquez et al. (2018)		Increased vulnerability to depression-like behavior (following acute stress)
	SH3 KI mice (OX)	Han et al. (2013)	Mania	↑ locomotion, ↓ pre-pulse inhibition (PPI), ↓ immobility, ↑ acoustic startle response, ↓ social interaction, hyperactivity, altered circadian rhythms
	SH2 KO mice	Pappas et al. (2017)	Mixed mania and depression	Mania: ↑ locomotion, ↑ reward-seeking behavior, disrupted sleep patterns, social and cognitive deficits Depression: anhedonia
	Ank3 conditional KO mice	Zhu et al. (2017)	Mixed mania and depression (switching between states with repeated stress)	Mania: Hyperactivity, ↑ exploratory behavior, ↓ anxiety, ↓ immobility Depression (seen with social defeat stress): ↓ exploratory behavior, ↓ locomotion, ↑ anxiety, ↑ immobility
	DAT KD mice	Young et al. (2018)	Switching mania and depression	In short-active photoperiod: ↑ sensitivity to punishment/aversive stimuli, ↑ immobility In long-active photoperiod: ↑ risk-taking behavior, ↑ preference for rewarding stimuli
	DAT KD mice	Kwiatkowski et al. (2019)	Mania	Hyperactivity, ↑ exploratory behavior, ↓ spatial discrimination
	Ntrk1 mutant mice	Nakajima et al. (2020)	Depression	Depression-like behavior in response to physostigmine (↑ immobility)
	ErbB4 KO mice	Cao et al. (2018)	Mania	Hyperactivity, ↓ anxiety, ↑ preference for sucrose, ↓ immobility
	Plcg1 KO mice	Yang, Ren, et al. (2017); Yang, Jung, et al. (2017)	Mania	Hyperactivity, ↓ anxiety, ↓ immobility, hedonic-like behavior, ↑ startle response, ↑ preference for sucrose, ↓ freeze response, impaired cognitive ability

Predictive validity	Construct validity	Limitations
Daytime tyrosine hydroxylase (TH) inhibition reverses mania-like behaviors; ↓ VTA neuron activity reverses mania-like behaviors (but not depressive-like behaviors); Mood stabilizers not tested	Daytime: ↑ dopaminergic (DA) tone (VTA) and TH activity Nighttime: ↑ DA tone (VTA) and TH activity	Chronic stimulation of DA neurons (7 days) in VTA only induced anxiety but not depressive-like behaviors (contradicts previous literature); Cholinergic neurotransmission was not evaluated; Only evaluated male mice
Overexpression of GluA1 in the nucleus accumbens (NAc) attenuates mania-like behavior; Mood stabilizers not tested	↓ GLUA1 expression (NAc); ↑ DA tone (VTA + extracellular levels)	Did not evaluate specifically dopaminergic medium spiny neurons (MSNs) and their afferents in *ClockΔ19* mutant mouse slices
Chronic Lithium (Li) treatment reverses mania-like behaviors and changes in neurobiology	Not investigated in this study	Did not specify which neurobiological abnormalities were found in these mice
Mania-like behavior reversed by chronic valproate (10 days of administration)	↑ DA and 5-HT release (right hemisphere hippocampus)	Some discrepancy in brain regions where DA levels were elevated; Did not look at function of *Clock* gene in medial prefrontal cortex (mPFC); Only evaluated male mice
Docosahexaenoic acid (DHA) or DHA + Eicosapentaenoic acid (EPA) supplementation ↓ frequency of depression-like episodes; Treatment with Li had prophylactic effect	↓ fatty acid desaturase 1/2 (FADS1/2) activity; FADS1/2 is a risk gene for BD	Female mice had less frequent hyperactivity bouts (HABs) than males; Male mice did not exhibit a depression phenotype
Protein kinase C (PKC) inhibitors, lamotrigine, risperidone promoted depressive-like behaviors (counteracted mania-like behaviors); GSK3β inhibitors and valproate reversed mania-like behaviors	↑ PKC, protein kinase A (PKA) and GSK3β activity; ↑ NMDAR/AMPA receptor ratio; HINT1 is a risk gene for BD	Possible differences in GSK3β gene splicing; No chronic administration of mood stabilizers; Only evaluated male mice
Administration of σ1R antagonists (S1RA, BD1047, BD1063, PD144418), GSK3β inhibitors and valproate attenuated mania-like behavior	Increased Akt/GSK3β signaling	
Valproate but not Li reversed mania-like behavior	Changes in excitatory/inhibitory synaptic balance (↑ excitation)	Spontaneous seizures; Need to evaluate *shank3*-independent pathways; Only male mice were evaluated
Li reversed circadian abnormalities; Li and valproate ↓ hyperactivity	Slight reduction of post-synaptic density (PSD) thickness in hippocampus; ↓ NMDA activity; ↑ AMPA activity	Varied phenotypes depending on *shank2* mutation
Li and valproate ↓ mania-like behaviors	↑ c-fos; ↓ inhibitory synapses; ankyrin 3 (ANK3) is a genome-wide association study (GWAS) identified risk gene for BD	Behavioral testing done only during the day; Possible alternate gene splicing in humans; Did not evaluate sex differences
Not investigated in this paper	↓ TH- positive neurons and ↑ somatostatin-positive neurons (both in PVN of hypothalamus) ↑ TH- positive neurons and ↓ somatostatin-positive neurons (both in PVN of hypothalamus)	C57BL/6J mice cannot synthesize melatonin; Mice only allowed 2 weeks of acclimation to photoperiods; No translational photoperiods; Did not test any mood stabilizers; Only evaluated male mice
Chronic valproate (28 days of administration) reverses locomotion	Not investigated in this review; Suggested dopamine transporters (DAT) polymorphisms/ ↓ DAT expression in BD	Li not tested and some discrepancies in effects of valproate
Not shown in this study	Neurotrophic tyrosine kinase receptor 1 (*NTRK1*) is a risk gene for BD; ↑ basal pERK levels in hippocampus (link to cholinergic transmission)	No known predictive/ pharmacological validity; Only used tail suspension as a test for depression-like behavior
Li reversed spontaneous neuronal firing and mania-like behavior; noradrenergic (NE) receptor antagonist (prazosin) and DA receptor antagonist (SCH23390) reversed mania-like behavior	↑ NE neuronal activity in locus coeruleus (LC); ↑ TH-Ser40; ↑ NE and DA concentration (CSF and LC); ↑ NMDAR function (in LC-NE neurons)	No specificity for BD (ErbB4 involved in schizophrenia pathogenesis); Only evaluated male mice
Not shown in this study	Phospholipase C Gamma 1 (PLCG1) is a locus for BD susceptibility; Changes in inhibitory neurons and brain-derived neurotrophic factor (BDNF) expression	No difference in NMDAR/AMPAR ratio; No testing of mood stabilizers; Only evaluated male mice

(Continues)

TABLE 1 (Continued)

Model		Authors	Modeled mood phase	Phenotypic validity
Environmental	CURD	Li et al. (2023)	Mania	Hyperactivity, sleep disturbances, ↓ immobility, ↑ social interactions, ↑ exploration
	CUMR	Li et al. (2023)	Depression	Hypoactivity, sleep disturbances, ↑ immobility, ↓ social interactions, ↓ exploration
	Paradoxical sleep deprivation (PrxSD)	Valvassori et al. (2017)	Mania	↑ locomotion
Pharmacological	AMPH sensitization (abuse and withdrawal)	Pathak et al. (2015)	Mixed state, mania, euthymia and depression	Mania: hyperlocomotion Euthymia: basal locomotion Depression: anhedonia, ↓ preference for sucrose, ↓ procedural memory
	AMPH	Hodes et al. (2018)	Mania	↑ locomotion
	AMPH	Menegas et al. (2020)	Mania	↑ risk-taking behavior, ↑ locomotion, ↑ exploratory behaviors
	m-AMPH	Valvassori et al. (2020)	Mania	↑ hyperlocomotion, ↑ risk-taking behavior, ↑ grooming
	Fenproporex	Rezin et al. (2014)	Mania	↑ locomotion, ↑ risk-taking behavior, ↑ exploratory behaviors
	VTA GABAergic neuron inhibition	Yu et al. (2019)	Mania	Changes in sleep patterns
	GBR12909	Bastos et al. (2018)	Mania	↑ locomotion
	GBR 12909	Bigot et al. (2022)	Mania Mixed state	Hyperlocomotion, ↑ anxiety, ↓ preference for rewarding stimuli, ↑ combativeness, ↑ aversion to unpleasant stimuli
	Ouabain (OUA)	Varela et al. (2015)	Mania	↑ locomotion
	OUA	Amodeo et al. (2017)	Mania	Hyperactivity, impaired reversal learning, ↑ regressive errors

Predictive validity	Construct validity	Limitations
Li and valproic acid treatment reversed behavioral changes and reversed expression of molecular indicators	↑ c-fos, ↓serotonin transporter (SERT) expression, ↑5-HT, ↑ GSK3β activation	Model not able to cycle through mood phases; Used major depression disorder (MDD) endophenotypes to compare with this model which can differ from bipolar depression; Only evaluated male mice
Li and valproic acid treatment was not tested in this model	↓ c-fos, ↑ SERT expression, ↓ 5-HT, ↑ GSK3β activation	Model not able to cycle through mood phases; Used major depression disorder (MDD) endophenotypes to compare with this model which can differ from bipolar depression; Only evaluated male mice
Treatment with Li ↓ locomotion; Treatment with Li prevented ↑ in ACTH, corticosterone, oxidative damage to lipids and DNA, and ↑ in glutathione peroxidase (GPx) and glucocorticoid receptor levels; Li treatment and pretreatment ↓ some but not all changes in cytokines	↑adrenocorticotropic hormone (ACTH) and corticosterone levels; ↑ oxidative damage to lipids [4-HNE and 8-isoprostane (8-ISO)] and DNA [8-hydroxy-2′-deoxyguanosine (8-OHdG)]; ↑ GPx activity (hippocampus and frontal lobe); ↑ IL-1β (frontal cortex and hippocampus), IL-4 (frontal cortex), and IL-10 levels (frontal cortex and hippocampus)	Some discrepancies with previous literature regarding Li effect on hypothalamic–pituitary–adrenal (HPA) axis; Only hyperlocomotion was evaluated as a behavioral index of manic-like behavior; Only evaluated male mice
Li and quetiapine reversed hyperactivity	↑ H3K9me1 and H3K9me3; Altered functional connectivity (↓ between frontal cortex and striatum, ↑ between amygdala and hippocampus)	Arc expression (used as a marker of functional connectivity) measured at a single time point; Differences in sensitization based on mouse strain used; Only evaluated male mice
Treatment with anti-ouabain antibodies protected against hyperactivity and attenuated antioxidant activity and oxidative damage	Changes in antioxidant enzymes [superoxide dismutase (SOD), catalase (CAT), GPx] and non-protein sulfhydryl groups (NPSH), free-radical scavenger, in hippocampus and frontal cortex; ↑ oxidative damage to lipids (lipid peroxidation)	AMPH ↑ DA transmission (BD is not only a disease of DA dysfunction); Did not test long term amphetamine affects; No testing of standard mood stabilizers; Only evaluated male mice
Folic acid + Li was more effective in preventing and reversing mania behaviors than either alone	↑ GPx activity, TNF-α and IL-1β levels (frontal cortex, hippocampus, striatum); ↓ glutathione reductase (GR) activity (striatum)	Measured homocysteine (Hcy) levels, a possible marker of BD, but not specific; Only evaluated male rats
Li and some PKC inhibitors reversed some mania-like behaviors	↑ markers of oxidative damage	Only one dose of each inhibitor used; May be more PKC isoforms implicated; Only evaluated male rats
Reversal and prevention of mania-like behaviors with Li and valproate	↓ Krebs cycle enzyme activity	Energy metabolism only observed in the hippocampus; Only evaluated male rats
Not tested in this study	VTA GABAergic neurons active during wakefulness and rapid-eye-movements (REM) sleep	The inhibition of VTA GABAergic neurons is not specific to bipolar disorder; No testing of mood stabilizers; Only evaluated male mice
Li but not valproate reversed hyperactivity; Aripiprazole prevented hyperlocomotion	Changes in brain cytokine levels (↑ in IL-2, IL-6, IFN-γ, IL-4, IL-10) and neurotrophic factors [↑ BDNF in PFC, ↓ neural growth factor (NGF) in hippocampus]	Chronic treatment with Li, valproate or aripiprazole (3 days of twice a day administration) did not prevent hyperlocomotion; Changes in cytokines/neurotrophic factors are not specific to BD; Only evaluated male mice
Hyperlocomotion is reversed by Li, valproate or aripiprazole	Not specifically tested in this paper	Mice displayed ↑ anxiety which is not consistent with mania phenotype; No neurobiological evaluation of DA neurotransmission; Only evaluated male mice
Treatment with Li, sodium butyrate (inhibitor of histone deacetylases) and valproate reversed mania-like behavior and most of the ↓ BDNF, NGF and glial cell line-derived neurotrophic factor (GDNF) in PFC and hippocampus	↓ BDNF, NGF and GDNF (PFC and hippocampus)	Possible neurotoxic effects of histone deacetylases (HDACs) inhibitors (sodium butyrate); Only evaluated male rats
Li, valproate, or direct BDNF injection shown to reverse mania behavior and restore BDNF levels in frontal cortex	Ion dysregulation; ↓ expression of BDNF (frontal cortex)	Only evaluated male rats; No assessment of brain regions other than the frontal cortex

(Continues)

TABLE 1 (Continued)

Model	Authors	Modeled mood phase	Phenotypic validity
OUA	Valvassori, Dal-Pont, Resende, et al. (2019); Valvassori, Dal-Pont, Tonin, et al. (2019)	Mixed mania and depression	Manic-like behaviors 7 days after administration (↑ locomotion, exploration and risk-taking behavior) but not seen 9 days after Depression-like behaviors 14 days after administration (↓ sweet food consumption, ↑ immobility) but not 9 days after
OUA	Varela et al. (2015)	Mania	↑ locomotion, ↑ exploratory behavior
OUA	Valvassori et al. (2021)	Mixed mania and depression	Immediately: ↑ locomotion, ↑ exploration, ↑ grooming, ↑ immobility, After 14 days: No ↑ in locomotion, ↓ grooming, impaired aversive and recognition memory
OUA	Valvassori et al. (2021)	Mixed mania and depression	Manic-like behaviors (↑ locomotion, exploration and risk-taking behavior) but not seen 14 days after administration Depression-like behaviors 14 days after administration (↑ immobility, ↓ swim time)
OUA	Possamai-Della et al. (2022)	Mixed mania and depression	Manic-like behaviors (↑ locomotion, exploration and risk-taking behavior) 7 days after administration Depression-like behaviors 14 days after administration (↑ immobility, ↓ swim time, ↓ sweet food consumption)

Abbreviations: ↑, significant increase; ↓, significant decrease; ↔, no significant effect; 4-HNE, 4-hydroxy-2-nonenal; 5-HT, serotonin; 8-ISO, 8-isoprostane; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; ACTH, adrenocorticotropic hormone; Akt, protein kinase B; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor; ANK3, Ankyrin 3; Arc, activity-regulated cytoskeleton-associated protein; ATP, adenosine triphosphate; BD, Bipolar disorder; BDNF, brain-derived neurotrophic factor; CAT, catalase; CINC-1, cytokine-induced neutrophil chemoattractant 1; CREB, cAMP response element-binding protein; CS, citrate synthase; CSF, cerebrospinal fluid; CUMR, chronic unpredictable mild restraint; CURD, chronic unpredictable rhythm disturbances; DA, dopaminergic; DAT, dopamine transporter; DHA, docosahexaenoic acid; DNA, deoxyribonucleic acid; DNMT, DNA methyltransferase enzyme; EPA, eicosapentaenoic acid; ErbB4, erb-b2 receptor tyrosine kinase 4; FADS1/2, fatty acid desaturase 1/2; FST, forced swim test; GABA, gamma-aminobutyric acid; GDNF, glial cell line-derived neurotrophic factor; GluA1, glutamate A1; GPx, glutathione peroxidase; GR, glutathione reductase; GSK3β, glycogen synthase kinase 3β; GWAS, genome-wide association studies; H3K9me1/3, histone 3 mono/tri-methylated at lysine 9; HABs, hyperactivity bouts; HAT, histone acetyltransferase; Hcy, homocysteine; HDAC, histone deacetylase; HINT1, histidine triad nucleotide-binding protein 1; HPA axis, hypothalamic–pituitary adrenal axis; IFN-γ, interferon-γ; IL-1β/4/10/2/6, Interleukin-1β/4/10/2/6; KD, knockdown; KI, knockin; KO, knockout; LC-NE, locus coeruleus-noradrenergic; Li, Lithium; MD, malate dehydrogenase; MDD, major depressive disorder; mPFC, medial prefrontal cortex; MSNs, medium spiny neurons; NAc, nucleus accumbens; NE, noradrenergic; NGF, nerve growth factor; NMDAR, glutamate N-methyl-D-aspartate receptor; NPSH, Non-protein thiol; NT3, neurotrophin-3; Ntrk1, neurotrophic tyrosine kinase receptor 1; OUA, ouabain; OX, overexpression; PC, protein carbonyl; pERK, phosphorylated extracellular signal-regulated kinase; PFC, prefrontal cortex; PKA, protein kinase A; PKC, protein kinase C; Plcg1, phospholipase Cγ1; PPI, pre-pulse inhibition; PrxSD, paradoxical sleep deprivation; PSD, post-synaptic density; PVN, paraventricular nucleus; REM, rapid-eye movement; S1R, sigma 1 receptor; SD, succinate dehydrogenase; SERT, serotonin transporter; SH2/3, shank2/3; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substance; TH, tyrosine hydroxylase; TH-Ser40, tyrosine hydroxylase-serine 40; TMX, tamoxifen; TNF-α, tumor necrosis factor α; TrkB, tropomyosin-related kinase B; VTA, ventral tegmental area; WT, wildtype; σ1R, sigma receptor type 1.

Studies tracking antibody-specific autoimmunity in patients with BD revealed a high prevalence of specific autoantibodies in the serum, such as anti-thyroperoxidase antibodies (TPOA), anti-H/K adenosine triphosphatase (ATPA), anti-glutamic acid decarboxylase-65 (GAD65A), and anti-GAD-67 (GAD67A) (Kupka et al., 2002; Padmos et al., 2004). Additionally, comorbid autoimmune-atopic diseases such as rheumatoid arthritis (RA), Sjögren syndrome and psoriasis, were associated with a higher risk of mania shift after the onset of monoaminergic antidepressant treatment (Perugi et al., 2015). Also, a Taiwan case–control study

Predictive validity	Construct validity	Limitations
Li pretreatment (7 days of administration) prevented OUA-induced manic-like behaviors; Li reversed the ↑ locomotion, exploration and risk-taking behavior Li treatment (9 days of administration) reversed the ↑ immobility; Li treatment (14 days of administration) partially reversed the ↑ immobility; Li treatment ↑ the ↓ sweet food consumption Li treatment reversed inhibition of Na^+/K^+ ATPase, alterations in HPA axis and oxidative stress damage	↓ in Na^+/K^+ ATPase activity (frontal cortex after 7 days, whole brain after 7–9 days); ↑ ACTH, corticosterone (serum) and weight of adrenal gland (14 days after administration); altered oxidative stress parameters (↑ oxidative lipid damage, ↑ GR and GPx activity)	Only evaluated male rats
Treatment with Li, valproate, and sodium butyrate reversed hyperactivity and ↓ HDAC, ↓ DNA methyltransferase (DNMT) and ↓ Histone acetyltransferases (HAT)	↓ Na^+/K^+ ATPase activity (in erythrocytes)	OUA did not induce changes in HDAC, DNMT or HAT; Only evaluated male rats
Not directly tested in this study	↓ pro-BDNF and BDNF levels (frontal cortex); ↓Tropomyosin receptor kinase B (TrkB) and ↓cAMP response binding elements factor (CREB) levels (frontal cortex and hippocampus)	Pro-BDNF and BDNF return to baseline after 18 days but memory deficits remain; Only evaluated male rats; Did not directly test mood stabilizers effect
Li treatment fully reversed mania behaviors Li treatment partially reversed depression-like behaviors	↑ proinflammatory cytokines IL-1β, IL-6, TNF-α and Cytokine-induced neutrophil chemoattractant 1 (CINC-1) in frontal cortex, hippocampus; ↑ anti-inflammatory cytokine IL-10 in frontal cortex, hippocampus	Only evaluated male rats; Inflammatory markers collected from brain tissue (frontal cortex, hippocampus) rather than blood
Li and valproate reversed mania-like behaviors Li and valproate partially reversed depression-like behaviors; impramine reversed depression-like behaviors and ACTH levels; Li and valproate but not impramine reversed BDNF and NGF levels; Li and valproate but not impramine reversed NT3 levels and GDNF (but combination of impramine with Li did)	↓ BDNF and NGF levels (frontal cortex and hippocampus); ↑ ACTH levels and weight of adrenal gland; ↓ neurotrophin 3 (NT3) in the hippocampus 14 days after administration; ↓ GDNF levels 14 days after administration in the frontal cortex	Only evaluated male rats; No control group used; No direct morphological index of neurogenesis was measured in the frontal cortex or hippocampus

including over 5,000 patients found a 2-fold increased risk of developing BD following an RA diagnosis in a period of 8–10 years, compared to healthy controls (Hsu et al., 2014).

Therefore, genetic and environmental neuroimmune risk factors, as well as their complex interactions, are deeply associated with the incidence and disease course of BD. Of note, SNPs in immune-related genes, autoimmune diseases, early-life adversities (infections and stressors), and adult-life infections seem to interact to mediate abnormal immune responses that have the potential to act as triggers for the onset, mood swifts, and progression of this disorder.

Nevertheless, most of these findings are based on correlative and non-causal associations in a variety of clinical studies where different methodologies and populations with particular demographics were included. Therefore, assertive conclusions between these neuroimmune risk factors and BD etiopathogenesis should be cautioned. However, the current pool of evidence shows the potential contribution of neuroimmune abnormalities to the emergence of this complex mental disorder.

5 | A RE-EMERGING NEUROINFLAMMATORY HYPOTHESIS: IS MICROGLIAL DYSFUNCTION A CENTRAL PATHOBIOLOGICAL MECHANISM OF BD?

5.1 | Evidence of abnormal systemic and brain immune responses in BD

5.1.1 | Clinical findings

In the last decades, it has been proposed that a chronic low-grade systemic inflammatory status follows BD's disease course (Benedetti et al., 2020). This has been reinforced by compiled evidence from previous meta-analyses reporting increased levels of proinflammatory cytokines (e.g., IL-6 and TNF-α), one soluble cytokine receptor (sIL-2R), and one cytokine receptor antagonist (IL-1RA) in acutely ill patients with BD compared to healthy controls. Also, in chronically ill patients with BD, certain cytokines (e.g., IL-6) showed a progressive increase following the disease course (Goldsmith et al., 2016; Modabbernia et al., 2013). In addition, a very recent meta-analysis evaluating the network of cytokines across several major psychiatric disorders including approximately 450 trials with BD has identified increased levels of IL-2, TNF-α, IL-6, and CRP in the BD cohort compared to the MDD and control groups. Increased levels of IL-10 were also detected in the BD cohort (Zhang et al., 2023). However, in this study, distinct clinical features (early vs. chronic illness; euthymic vs. acute mood phases; type I vs. type II) were not assessed, making associations between the immune-inflammatory findings and specific disease features not possible.

Additional studies investigating distinct mood phases of BD (e.g., mania, depression and euthymia), severity and stage of disease (early-, late- or chronic illness) have brought insightful considerations regarding the profile of immune-inflammatory changes involved in the mood shift and progression of the disorder (Kim et al., 2007; Misiak et al., 2020; Rowland et al., 2018; Skibinska et al., 2022; Wu et al., 2022). A heightened systemic proinflammatory response in patients with acute mania compared to euthymic patients with BD and healthy controls has been described, with a positive correlation between these markers and maniac symptoms. Among the inflammatory markers, serum levels of TNF-α, IL-1β, IL-2, IL-6, and acute phase high-sensitive (hs)-CRP were reported to be significantly increased during the manic state (Brietzke et al., 2009; Goldsmith et al., 2016; Karthikeyan et al., 2022). Also, in a recent longitudinal comparison of young patients with BD (mean age 18 years), usually the time point of the disease onset, hypomanic/manic episodes were associated with higher IL-8 and TNF-α serum levels compared to early depressed episodes (Skibinska et al., 2022).

Regarding the depressive phase, some studies have shown increased serum levels of IL-8, IL-1β, IL-6, and chemokine eotaxin-1/CCL11 compared to euthymic patients and controls (Brietzke et al., 2009; Goldsmith et al., 2016). A recent meta-analysis including 1,221 BD patients and 663 controls showed elevated levels of IL-8, MCP-1, eotaxin-1, and interferon-γ-induced protein 10 (IP-10) in these patients compared with healthy controls. A subgroup analysis revealed that elevated levels of IL-8 and MCP-1 appeared only in patients during their depressive phase, while increased levels of eotaxin-1 and IP-10 were associated with chronic euthymic patients (Misiak et al., 2020). Additionally, a cytokine evaluation based on the stratification of severity of maniac and depressive episodes in patients with BD showed that the serum levels of IL-6, IL-10, and IL-17, and the IL-6/IL-10 ratio were only significantly lower in mild depressive episodes, while MCP-1 and IL-10, and the IL-17/IL-10 ratio were only significantly lower in patients with severe depression episodes compared to healthy controls. In hypomania/mania, mild and moderate cases showed increased levels of TNF-α, IL-2, and IL-17 and the IL-6/IL-10 ratio, while severe cases showed lower IL-6 and IL-17, and the IL-6/IL-10 ratio, but the neutrophil/lymphocyte ratio was higher compared to controls (Wu et al., 2022). The current evidence points toward state-dependent alterations in the systemic inflammatory status of patients with BD, with a potentially heightened inflammatory response in manic/hypomanic states, while depression episodes appear associated with a suppression of innate pleiotropic cytokines and redirection toward increased chemokine signaling, such as IL-8 and MCP-1.

There is growing evidence that BD is associated with accelerated aging (Lewandowski et al., 2014). Immune-inflammatory markers were proposed as major findings in the progressive course of BD (Mohite et al., 2020; Panizzutti et al., 2015; Réus et al., 2015). Indeed, in a cross-sectional evaluation of cytokines and chemokines in early- and late-stage patients with BD (staged based on functionality levels, number of mood episodes and severity of symptoms), only the serum levels of eotaxin-1 were significantly increased in late-stage patients with BD (Panizzutti et al., 2015). Also, a negative correlation was reported in chronic euthymic BD patients between the eotaxin-1 levels and the volume of the left-hemisphere superior temporal gyrus, involved in emotional processing, and progressively impaired in the late-stage illness (Mohite et al., 2020). Accordingly, in previous studies, increased levels of eotaxin-1 and IP-10/CXCL10 were reported in the serum of chronic euthymic patients (Barbosa et al., 2014; Magalhaes et al., 2014). Comparisons between early and late-stage BD patients also showed that euthymic early-stage patients showed increased IL-10 serum levels compared to late-stage patients, while increased TNF-α levels and total leukocytes, neutrophils, and monocytes counts were significantly increased in euthymic late-stage patients compared to early-stage patients and healthy controls (Tatay-Manteiga et al., 2017).

Marked alterations in the populations of peripheral immune cells were also reported in BD. Indeed, Barbosa et al. (2014) reported that

TABLE 2 Inflammatory and neuroimmune findings in BD: Preclinical and clinical evidence.

Authors	Study design	Main findings	Caveats and limitations
Preclinical findings			
Valvassori et al. (2015)	Male Wistar rats were treated with D-amphetamine (D-AMPH) or saline (Sal) for 14 days; from day 8, Lithium (Li) and Sal were administered. Locomotion was assessed by open-field test; The levels [Interleukin (IL)-1b, IL-4, IL-6, IL-10, and tumor necrosis factor (TNF)-α] were evaluated in cerebrospinal fluid (CSF), serum, frontal cortex, striatum, and hippocampus.	D-AMPH-induced hyperactivity in rats. IL-4 ↑, IL-6 ↑, IL-10 ↑, and TNF-α ↑ in the frontal cortex, striatum, and serum. Li reversed manic-like behavior and cytokine alterations.	Only one mood phase was evaluated (mania); Limited number of neuroimmune markers were included; One time point evaluation, no possibility to understand the temporal course of neuroimmune changes; no sex differences were evaluated.
Gubert et al. (2016)	Analyses of the modulatory effects of P2X7 purinergic receptor (P2X7R) agonist and antagonist. Mice received D-AMPH (2 mg/kg) intraperitoneally once a day for 7 days and behavior was assessed by open-field test; assessment of the levels of proinflammatory cytokine (IL-1β, IL-6, TNF-α), thiobarbituric acid reactive substances (TBARS) and brain-derived neurotrophic factor (BDNF) in the striatum, prefrontal cortex and hippocampus.	D-AMPH-induced hyperactivity in mice. Acute AMPH: IL-1β ↑ Chronic D-AMPH: IL-1β ↑ in striatum, BDNF ↓ in prefrontal cortex, TBARS ↑ in hippocampus Blocked or absent P2X7R: reduced hyperactivity in mice P2X7R antagonist: TBARS ↓ in hippocampus, IL-1β ↓in striatum P2X7R: a potential therapeutic target related in BD.	Only one mood phase was evaluated (mania); Limited number of neuroimmune markers were included; No direct evaluation of the receptor expression (protein and gene expression) and post-translational states, as well, as no evaluation of related intracellular downstream signaling; no sex differences were evaluated.
Valvassori, Dal-Pont, Tonin, et al. (2019)	Evaluation of the effects of the coadministration of Li and celecoxib (Cel). Male Wistar rats received D-AMPH (2 mg/kg) intraperitoneally once a day for 14 days. In the last 7 days, the animals also received Li (24 mg/kg), Cel (20 mg/kg), Li + Cel or water via gavage. The levels of cytokines (IL-1β, IL-4, IL-10, and TNF-α) were evaluated in serum, frontal cortex, and striatum.	D-AMPH-induced hyperactivity in rats. IL-4 ↑, IL-10 ↑, and TNF-α ↑ in the serum, frontal cortex, and striatum compared to controls, Li + Cel: IL-4 ↓, IL-10 ↓, and TNF-α ↓ in the serum, frontal cortex, and striatum compared to controls. Cel: IL-10 ↓ levels in the serum, TNF-α ↓ only in the striatum. Li: TNF-α ↓ in frontal cortex, and striatum. Li or Cel: IL-4 ↓ in the serum and reversed the effects of d-AMPH on this parameter in the frontal cortex. Li + Cel was more effective against the inflammation induced by d-AMPH.	Only one mood phase was evaluated (mania); Limited number of neuroimmune markers were included; Few doses tested for the pharmacological interventions; no sex differences were evaluated.
Bristot et al. (2019)	Male Wistar rats were treated with lisdexamfetamine dimesylate (LDX) (10 mg/kg) or saline for 7 days. The animals also simultaneously received an intraperitoneal administration of Li (47.5 mg/kg) or saline twice a day for 6 more days. Locomotion was assessed by open-field test, followed by a single intraperitoneal lipopolysaccharide (LPS) (5 mg/kg) injection. Serum levels of BDNF protein and TNF, IL-1b, IL-10, and inducible nitric oxide synthase (iNOS) were measured.	LDX: induced hyperactivity in the animals and serum BDNF ↑. TNF-a↔, IL-1b↔, IL-10 ↔, iNOS ↔, but prevent LPS-induced iNOS increases. Li: reduce hyperactivity; BDNF ↔, TNF-a↔, IL-1b↔, IL-10 ↔ in serum; LPS: TNF-a ↑, IL-1b ↑, and IL-10 ↑; iNOS ↑.	Limitation regarding the behavioral evaluation which did not allow detection of multiple behavioral traits, but only hyperactivity; IL-6 could not be evaluated because of kit insufficiencies; No brain tissue evaluated; Control groups did not receive vehicle injection as those that received LPS injection; No conclusion about the protective potential of Li on the cumulative effect of LDX and LPS; no sex differences were evaluated.

(Continues)

TABLE 2 (Continued)

Authors	Study design	Main findings	Caveats and limitations
Menegas et al. (2020)	For 14 days, male Wistar rats were treated with water, Li (25 mg/kg), folic acid (FA) (50 mg/kg) or a combination of Li + FA by gavage. Animals received intraperitoneally methamphetamine (m-AMPH) (1 mg/kg) or saline between days 8 and 15. Behavior was assessed by open-field test. IL-1 β, TNF-α, glutathione peroxidase (GPx), glutathione reductase (GR), 8-Isoporostane (8-ISO), 4-hydroxy-2-nonenal (4-HNE), and carbonyl were assessed in the frontal cortex, striatum, and hippocampus.	m-AMPH: induces hyperactivity maniac like behavior; 8-ISO ↑, 4-HNE ↑, carbonyl ↑, GPx ↑, IL-1 β ↑, TNF-α ↑ in the frontal cortex, striatum, and hippocampus; GR↓ in striatum; Li: no effect on the behavioral alterations induced by m-AMPH; carbonyl ↓ in frontal cortex, 8-ISO ↓ in striatum; FA: prevent maniac behavior; TNF-α ↓ frontal cortex and striatum, 4-HNE ↓ striatum, 8-ISO ↓ hippocampus and striatum, carbonyl ↓ hippocampus Li + FA: prevent maniac behavior; 8-ISO ↓, 4-HNE ↓, carbonyl ↓, IL-1 β ↓, TNF-α ↓ in the frontal cortex, striatum, and hippocampus; GR ↑ in striatum.	Only one mood phase was evaluated (mania); Limited number of neuroimmune markers were included; Limitation of animal model regarding the behavioral evaluation which did not allow detection of multiple behavioral traits; no sex differences were evaluated.
Chaves Filho et al. (2021)	Evaluation of the effects of Doxycycline (DOXY) against behavioral, neuroinflammatory, and pro-oxidative changes induced by a manic model. Male mice received d-AMPH (2.0 mg/kg) or saline for 14 days. Between days 8 and 14, animals received Li, DOXY (25 or 50 mg/kg), Li + DOXY on both doses. Behavior tests were performed. The expression of TNF-α, myeloperoxidase (MPO), lipid peroxidation, Ionized calcium-binding adaptor molecule 1 (IBA1), iNOS, nitrite, and glycogen synthase kinase-3 beta (GSK3β) was evaluated in the prefrontal cortex, hippocampus, and amygdala.	d-AMPH: hyperlocomotion and impaired recognition and working memory. TNF-α ↑, MPO ↑, and lipid peroxidation ↑ Li: reversed hyperlocomotion but no restored cognitive alterations. TNF-α ↓, MPO ↓, and lipid peroxidation ↓ DOXY: reversed hyperlocomotion and restored cognitive alterations. TNF-α ↓, MPO ↓, and lipid peroxidation ↓; hippocampal IBA1 ↓, iNOS ↓, nitrite ↓ DOXY+Li: reversed hyperlocomotion and restored cognitive alterations. phosphorylated form of GSK3β ↓.	Only one mood phase was evaluated (mania); Limited number of neuroimmune markers were included; no sex differences were evaluated.
Valvassori et al. (2022)	Male Wistar rats received a single intracerebroventricular administration of ouabain (OUA) or artificial CFS (aCFS) for 14 days. From day 4, the rats received Sal or Li for 8 days. Behavior was assessed. Open-field test was performed on day 7 after OUA. Open-field test and forced swim test were performed on day 14 after OUA. IL-1β, IL-6, IL-10, TNF-α and cytokine-induced neutrophil chemoattractant 1 (CINC-1) were assessed in the frontal cortex and hippocampus.	OUA: locomotion ↑ after 7 days (mania-like behavior), and immobility ↑ after 14 days (depression-like behavior); IL-1β ↑, IL-6 ↑, IL-10 ↑, TNF-α ↑, and CINC-1 ↑ in the frontal cortex and hippocampus. Li: reversed the mania-like behavior and partially reversed the depression-like behavior; IL-1β ↓, IL-6 ↓, IL-10 ↓, TNF-α ↓, and CINC-1 ↓ in the frontal cortex and hippocampus.	Limited number of neuroimmune markers were included; Limitation of animal model regarding the behavioral evaluation which did not allow detection of multiple behavioral traits, but only hyperactivity for mania and despair-like behavior for depression; no sex differences were evaluated.
Géa et al. (2022)	Male Wistar rats received d-AMPH (2 mg/kg) or Sal for 14 days. Between days 8 and 14, animals were treated with Li (47.5 mg/kg) or Sal twice a day. Locomotor behavior was assessed via open-field test. The levels of TNF-α, claudin-5 and TBARS were quantified in the serum, prefrontal cortex, hippocampus, and striatum.	D-AMPH-induced hyperactivity; TBARS and TNF-α were positively and strongly correlated in the striatum Li: reduced hyperactivity; TBARS ↑ in serum.	Only one mood phase was evaluated (mania); Lack of a dynamic marker of blood–brain-barrier (BBB) integrity and limited number of neuroimmune biomarkers; no sex differences were evaluated.
Clinical findings			
Brietzke et al. (2009)	61 patients with BD were recruited. 14 were in euthymic state, 23 and 24 were in manic and depressive episodes, respectively. A comparison group included 25 healthy volunteers. Serum cytokine levels (TNF-α, IL-2, IL-4, IL-6, IL-10, interferon (IFN)-γ) were assessed.	During mania: IL-2 ↑, IL-4 ↑and IL-6 ↑compared to healthy controls. During depression: IL-6 ↑ compared to healthy controls. Patients in remission: IL-4 ↑ compared to healthy controls Positive correlation of mood symptoms with IL-6 and IL-2. Cytokine changes more pronounced during acute episodes than in euthymia.	Low sample size; low statistical power; Limited number of neuroimmune markers were included; Only serum evaluation.

TABLE 2 (Continued)

Authors	Study design	Main findings	Caveats and limitations
Modabbernia et al. (2013)	Meta-analysis of 30 studies with a total of 1351 BD patients and 1248 healthy controls. Cytokines, chemokines, or soluble serum cytokine receptors concentrations [IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, CCL2, sIL-2R, INF-γ, sIL-6R, TNF-α, sTNFR1, and IL-1 receptor antagonist (RA)] between patients with BD and healthy controls were compared.	BD patients: IL-4 ↑, IL-10 ↑, sIL-2R ↑, sIL-6R ↑, TNF-α ↑, sTNFR1 ↑, and IL-1 RA ↑ in patients compared with healthy controls. Phasic difference was present for TNF-α, sTNFR1, sIL-2R, IL-6, and IL-1RA, whereas it was absent for IL-4 and IL-10.	Cross-sectional study design; No differentiation between distinct mood phases, such as manic and depressive episodes; Different models were used in study design, not allowing longitudinal comparison; Limited number of neuroimmune markers were included; Only serum evaluation.
Jakobsson et al. (2015)	221 euthymic patients with BD and 112 healthy controls were recruited. Serum samples were collected. For CSF sampling, 125 euthymic patients with BD and 87 healthy controls were included Serum and CSF levels of monocyte chemoattractant protein (MCP)-1, YKL-40 (Chitinase 3-like 1), soluble cluster of differentiation (sCD)14, tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 were measured.	MCP-1 ↑ and YKL-40 ↑ in CFS CD14 ↑and YKL-40 ↑ increased in serum in patients compared with controls CSF levels of MCP-1 and YKL-40 correlated with the serum levels Differences between patients and controls in CSF levels of MCP-1 and YKL-40 were independent of serum levels.	Cross-sectional study design; only euthymic patients recruited; Low statistical power due reduced N; Limited number of neuroimmune markers were included, and the markers examined are proxies, not direct measures of microglial reactivity.
Isgren et al. (2015)	121 euthymic BD patients and 71 age and sex matched control subjects. 11 different cytokines in CSF were analyzed.	IL-8 ↑ in BD patients as compared to controls. The other cytokines measured were only detectable in part of the samples. Li- and antipsychotic treatment: IL-8 ↑.	Only euthymic patients were recruited. Unclear if the findings reflect immune aberrations in BD, or if they are because of the effects of medication. Limited number of neuroimmune markers were included, only in the CSF.
Hope et al. (2015)	111 patients with BD and 241 healthy controls were included. General intellectual abilities (Oral Vocabulary, Number Series, Verbal Attention, Letter-Pattern Matching, Phonological Processing, Story Recall, and Visualization) were assessed. Serum concentrations of sTNF-R1, IL-1Ra, osteoprotegerin, von Willebrand factor, C-reactive protein, IL-6 and CD40 were determined.	Significant negative associations with general cognitive function were found for sTNF-R1, IL-1Ra and sCD40 ligand. General cognitive abilities were significantly associated with sCD40L and IL-1Ra in patients with BD.	No differentiation between distinct mood phases, such as manic and depressive episodes; Cross-sectional study design; Limited number of neuroimmune markers; Only serum evaluation.
Poletti et al. (2021)	76 patients with BD in an acute depression episode were recruited. A neuropsychological evaluation was performed. Plasma levels of cytokines, chemokines and growth factors (such as IL-1β, IL-6, CC chemokine ligand (CCL)2, CCL4, CCL5, CXC chemokine ligand (CXCL)10, and basic fibroblast growth factor (bFGF)) were determined.	IL-1β ↑, IL-6 ↑, CCL2 ↑, CCL4 ↑, CCL5 ↑, CXCL10 ↑, and bFGF ↑ associated with apoor cognitive performance.	No healthy control group was included; lack of information regarding previous psychopharmacological treatments; only patients with acute depressive episodes were considered; Limited number of neuroimmune markers; Only serum evaluation.

Abbreviations: ↑, significant increase; ↓, significant decrease; ↔, no significant effect; 4-HNE, 4-hydroxy-2-nonenal; 8-ISO, 8-Isoporostane; aCFS, artificial cerebrospinal fluid; AMPH, amphetamine; BBB, blood brain barrier; bFGF, basic fibroblast growth actor; BP, bipolar disorder; CCL, CC chemokine ligand; Cel, celecoxib; CINC-1, Cytokine-induced neutrophil chemoattractant 1; CSF, cerebrospinal fluid; CXCL, CXC chemokine ligand; DOXY, doxycycline; FA, folic acid; GPx, glutathione peroxidase; GR, glutathione reductase; GSK3 β, glycogen synthase kinase-3 beta; IBA1, ionized calcium-binding adaptor molecule 1; IFN, interferon; IL, interleukin; iNOS, nitric oxide synthase; LDX, lisdexamfetamine dimesylate; Li, lithium; LPS, lipopolysaccharides; MCP, monocyte chemoattractant protein; MPO, myeloperoxidase; OUA, ouabain; P2X7R, P2X7 purinergic receptor; RA, receptor antagonist; Sal, saline; sCD, soluble cluster of differentiation; TBARS, thiobarbituric acid reactive substances; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor.

euthymic chronic patients with BD type I showed an increased proportion of monocytes (CD14+), as well as a reduced proportion of T cells (CD3+) and cytotoxic T cells (CD3+CD8+). These patients exhibited a higher percentage of reactive T CD4+CD25+ cells, and a lower percentage of IL-10-expressing regulatory T cells. Patients with BD further showed increased rates of interferon (IFN)-γ/IL-4 and IFN-γ/IL-10, pointing toward a basally heightened proinflammatory Th1 cytokine and cell-mediated systemic response (Barbosa et al., 2014). Additional analysis using fluorescence-activated cell scanning (FACS) revealed higher numbers of circulating reactive T CD4+ cells (indicated by expression levels of major histocompatibility complex (MHC)-class II, CD25, CD69, and CD71) and elevated sIL-2R levels in the serum of BD type I and II patients compared with healthy controls. Investigating by acute mood state, manic patients displayed a higher profile of proinflammatory reactive T cells and increased levels of sIL-2R versus depressed and euthymic patients with BD (Knijff et al., 2007).

5.1.2 | Preclinical findings

Regarding animal models of BD, most of the studies evaluating neuroimmune disturbances in these models were limited to one mood phase or models with limited translational validity (especially for construct validity). In this context, in mania models induced by DA agents, such as D-AMPH, previous studies showed an up-regulation of several proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, in limbic regions (e.g., hippocampus and striatum), following the emergence of manic-like symptoms, such as hyperlocomotion and risk-taking/impulsivity behavior (Chaves Filho et al., 2021; Gubert et al., 2016; Valvassori et al., 2015; Valvassori, Dal-Pont, Tonin, et al., 2019). In this context, previous evidence revealed that repeated AMPH exposure can induce increases in microglial density and proinflammatory reactivity in limbic structures, such as the striatum, as a mechanism underlying the DA nerve terminals damage (Thomas, Dowgiert, et al., 2004; Thomas, Walker, et al., 2004).

In a cyclic rat model of mania and depression induced by intracerebroventricular injection of the sodium-potassium ion pump inhibitor ouabain, an increase only in the levels of IL-6 across the brain (striatum), serum and CSF was detected in the manic-like phase (Tonin et al., 2014). However, the depression-like phase was accompanied by a marked increase in the levels of the proinflammatory cytokines IL-1β, IL-6, IL-10, TNF-α, and the acute phase reactant cytokine-induced neutrophil chemoattractant 1 (CINC-1), in the frontal cortex and hippocampus. Treatment with Li, as a mood stabilizer, reversed these inflammatory alterations (Géa et al., 2022; Menegas et al., 2020; Valvassori et al., 2015, 2022; Valvassori, Dal-Pont, Tonin, et al., 2019). Notably, increased levels of IL-1β, IL-6 and TNF-α have been frequently reported in clinical trials as key neuroimmune findings in the pathophysiology of BD (Söderlund et al., 2011), suggesting a possible translational validity of these mania models regarding neuroimmune constructs (Brietzke et al., 2009; Modabbernia et al., 2013; Poletti et al., 2021; Valvassori et al., 2015, 2022).

Furthermore, in these BD models (e.g., induced by amphetamines or ouabain), neurotrophic markers, such as BDNF, and oxidative/nitrosative stress markers, such as lipid peroxidation and the activity of the enzyme myeloperoxidase, were enhanced with the brain's increase in proinflammatory cytokines, supporting the role of inflammation in mediating these other pathological alterations in BD pathogenesis (Bristot et al., 2019; Chaves Filho et al., 2021; Géa et al., 2022; Gubert et al., 2016). However, some severe limitations constrain the potential of making assertive interpretations about the findings from these models as most of these studies relied on pharmacological interventions to mimic BD features, raising limitations regarding the ability to model the gene–environment interactions. Also, usually, sex differences and age differences were not assessed, and a limited number of neuroimmune markers were examined (see Table 2). Therefore, the current pool of evidence suggests that an abnormal peripheral and brain immune response may play a role in the pathophysiology of BD. However, more studies are necessary to better understand the full spectrum of neuroimmune changes involved in this disorder. For more details on the inflammatory and neuroimmune findings in BD, please see Table 2.

5.2 | Evidence of structural and functional brain abnormalities in BD and possible interaction with the brain' neuroimmune status

5.2.1 | Gray matter abnormalities in BD

Evidence from structural neuroimaging helps to posit a neuroimmune hypothesis for BD; however, the possible roles of microglia, as the brain's immune cells, in these structural and functional brain abnormalities are largely unknown (Niu et al., 2019; Savitz & Drevets, 2011). While no marked gray matter (GM) abnormalities have been detected in first-mania episode or in the early stages of BD, a progressive loss of GM volume, especially in the frontal-cortical regions occurs as the disease progresses, especially associated with the number of acute mood episodes (mania and depression) (Clark & Sahakian, 2008). A systematic review of longitudinal studies using structural magnetic resonance imaging (MRI) analysis showed marked reductions in the GM of the left rostral ACC and right frontal-insular cortex in chronically ill patients with BD (Förster et al., 2023). By contrast, the duration of illness and number of mood episodes were positively associated in some studies with increased GM volume in the basal ganglia (e.g., ventral striatum) and left amygdala in these patients (Hajek, Gunde, et al., 2009; Hajek, Kopecek, et al., 2009).

Additional longitudinal studies have reinforced this association, showing chronic cortical abnormalities within the frontal networks subserving emotional regulation in BD, such as the ACC and ventrolateral prefrontal cortex of chronic BD patients, with less consistent findings in temporal and subcortical regions (Kebets et al., 2021; Sankar et al., 2021). Abnormalities in the activity pattern of frontal networks measured through functional MRI were also reported for patients in different mood phases. In depressed patients, an up-regulation of sad emotions and the appraisal (or re-evaluation) of sad

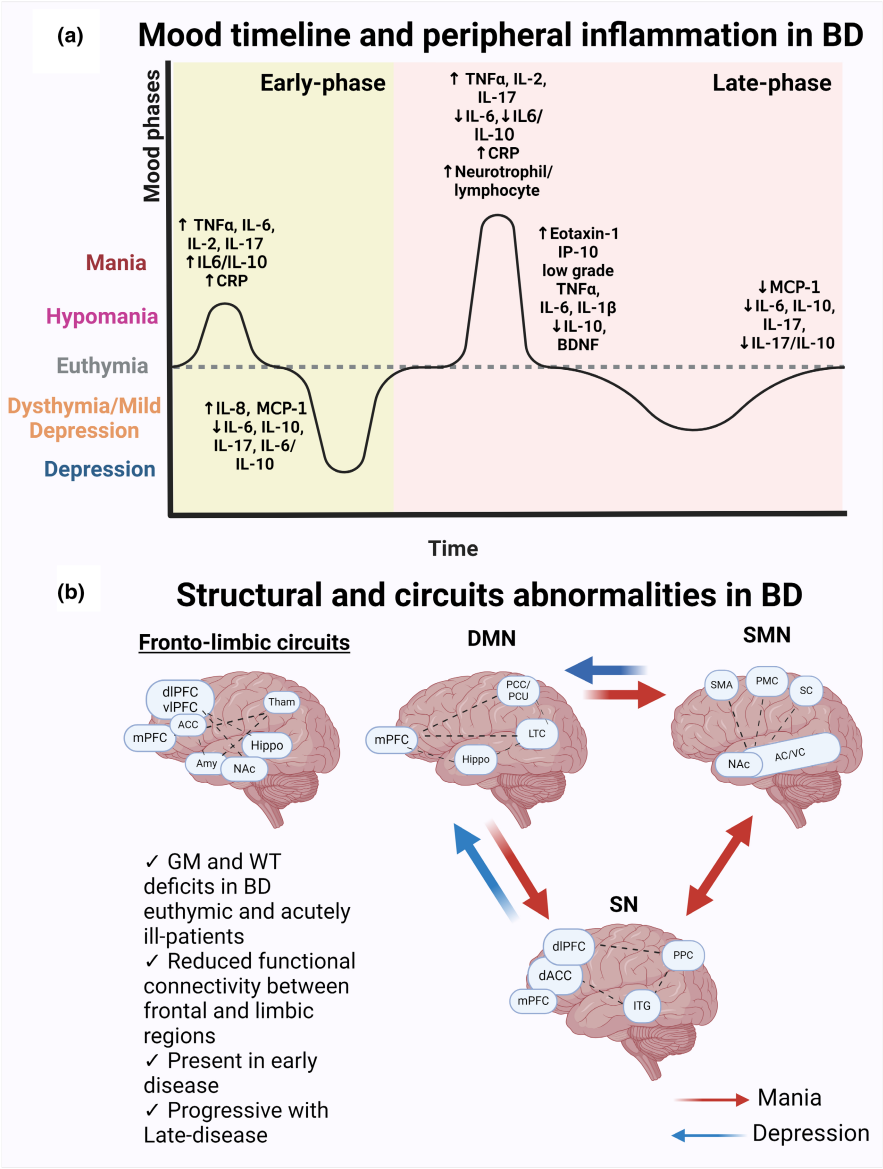

FIGURE 1 Systemic immune/inflammatory status and structural and circuit abnormalities in BD. BD has been associated with marked alterations in the levels of multiple inflammatory-immune mediators, which vary according to the mood phase, chronicity of the disorder, and use of mood stabilizers. In the upper panel (a), we summarized the most consensual findings from the current pool of evidence of inflammatory/immune mediators in BD along a mood timeline considering mood states and chronicity (early and late-stage disease). In the bottom panel (b), we summarized the main structural and circuit abnormalities detected in BD. Starting early on the disease course, deficits in the GM and WM structure and cytoarchitecture in the front-limbic circuits composed by mPFC, dlPFC, vlPFC, ACC, Amy, Hippo, Tham and NAc, and white fibers that connect these regions, exacerbate during acute mood states, notably during manic episodes, and with the disease progression (late-stage). Additionally, the alterations in these circuits impact the functional networks of the brain: hyperactivation of the DMN and hypoactivation of the SMN and SN have been reported in depression, while the opposite pattern has been associated with mania (blue arrows indicate a trend of network shift in depression, while the red ones indicate network shift in mania). ACC, anterior cingulate cortex; Amy, amygdala; BD, bipolar disorder; DMN, default mode network; dlPFC, dorsolateral prefrontal cortex; GM, gray matter; Hippo, hippocampus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; SN, salience network; SMN, sensorimotor network; Tham, thalamus; vlPFC, ventrolateral prefrontal cortex; WM, white matter. Figure created with Biorender.

emotions were associated with decreased activity in the right ACC (Rive et al., 2015). By contrast, in hypomanic patients, the inability to regulate happy and sad emotions was associated with aberrant hyperactivity in the right ventrolateral PFC and right ACC, together with a disrupted functional coherence (or decoupling) with the amygdala (Morris et al., 2012).

5.2.2 | White matter abnormalities in BD

White matter (WM) abnormalities are an important hallmark of BD neuropathology (Hajek et al., 2005). Reduced WM volumes were observed in patients with BD, even during the first maniac episodes (Adler et al., 2006; Ramírez-Bermúdez et al., 2021). WM

microstructural alterations mainly shown in diffusion MRI studies, such as decreased fractional anisotropy and increased radial diffusivity, were robustly detected in patients with BD (Lu et al., 2012). The most consistent WM changes in BD were found in the anterior cingulum and corpus callosum (e.g., genu and body), and in frontal areas (e.g., orbitofrontal cortex, subgenual regions, and parahippocampal areas), which mostly connect to other regions of the limbic system (e.g., hippocampus and amygdala) (Bellani et al., 2012; Lu et al., 2012; Sarrazin et al., 2015). Interestingly, although widespread WM abnormalities were described for all phases of BD (Favre et al., 2019), the most consistent alterations in structural connectivity were detected during acute manic/hypomanic episodes (Favre et al., 2019; Manelis et al., 2021). Accordingly, neuropathological analysis of post-mortem brains of patients with BD revealed abnormalities, usually reductions in the density of oligodendrocytes, along with myelin reduction, in anterior brain regions, correlating with illness duration and symptom severity (Gigante et al., 2011; Valdés-Tovar et al., 2022).

Previous studies have detected important associations between WM abnormalities and immune-inflammatory alterations in BD. Magioncalda et al. (2018) revealed a positive correlation between WM alterations in diffusion MRI and the reduction in circulating terminal effector CD8+ T cells, especially in patients with BD recruited during mania (Magioncalda et al., 2018). Notably, this correlation was found only for terminal effector CD8+ T cells, CD8+ CD28-CD45RA+ cells, and CD8+ IFN-γ+ cells in mania. Since these are effectors cells prone to tissue migration, these authors suggested that their reduction in the circulation can potentially represent an increase in their migration to these anterior brain regions (Magioncalda et al., 2018). More recently, WM alterations in frontal regions, such as the cingulum, superior and inferior longitudinal fasciculi, and inferior fronto-occipital fasciculi, were found to correlate with the serum levels of Th1- and other proinflammatory cytokines, namely IFN-γ and TNF-α, in euthymic patients with BD (Poletti et al., 2021).

These structural changes were accompanied by abnormalities in functional connectivity (FC). For instance, increased FC between the thalamus and sensorimotor cortex along with decreased FC between the thalamus and frontal regions have been consistently described in patients with BD across all mood phases (Guo et al., 2021; Liu et al., 2019). At the network level, functional dysconnectivity within the default mode network (DMN) was repeatedly reported (Zovetti et al., 2020). The DMN is a large brain network primarily composed of frontal regions, such as the dorsal medial PFC, posterior cingulate cortex, and angular gyrus. It is known for being active during internal goal-oriented and conceptual cognitive tasks, which are markedly disrupted in manic BD episodes and late-stage patients (Buckner, 2013; Yoon et al., 2020).

Functional alterations were also reported in other main networks, including the sensorimotor network (SMN) and salience network (SN) in BD (Yoon et al., 2020). Notably, it has been shown that the thalamus-SMN FC increased by switching from mainly negative connectivity in healthy subjects to mainly positive connectivity in manic episodes, reflecting an abnormally increased thalamus and SMN connectivity during this disease state (Martino et al., 2016). By contrast, the thalamus-SMN FC changed from negative to dysconnectivity in depression episodes (Martino et al., 2016). Additional subcortical–cortical FC alterations were found in different BD phases: increased FC between basal ganglia (such as substantia nigra DA-nuclei) and thalamus in mania, and increased FC between amygdala and SMN areas, such as the basal ganglia (dorsal causal putamen) and temporal areas (insula and temporal gyrus) in depression phase (Altinay et al., 2016; Martino et al., 2020).

Current data suggests that FC between 5HT-related raphe nuclei (RNi) and basal ganglia-thalamic regions is reduced in mania, while FC between DA-related SNc and basal ganglia-thalamic regions is reduced in depression (Conio et al., 2020; Magioncalda et al., 2015). These abnormalities are consistent with findings from biochemical and behavioral studies using preclinical models showing that deficits in 5-HT activity are associated with manic-like symptomatology (e.g., behavioral impulsivity), while deficits in DA activity are associated with BD depression (e.g., motor inhibition and anhedonia) (Bigot et al., 2022; de Queiroz et al., 2018; Maddaloni et al., 2018). Therefore, these findings suggest that the manic and depressive phases of BD are characterized by distinct functional reconfigurations of intrinsic brain activity and circuits; however, the dynamic mechanisms and main cellular players that mediate these alterations are largely unknown (for an overview of BD-associated immune-inflammatory abnormalities and circuit changes, see Figure 1).

5.3 | Mood stabilizers' effects in Neuroimmune abnormalities: Relevance for therapeutic actions in BD

Li is a well-known drug for alleviating the symptomatology and progression of BD (Benard et al., 2016; Volkmann et al., 2020). Previous findings demonstrated that Li attenuates inflammation-induced neuropathology through its normalizing actions on the induction of inflammatory/reactive states of microglia (Dong et al., 2014). Notably, Li inhibits lipopolysaccharide (LPS)-induced IL-6 and TNF-α release in mouse primary microglial cells (Dong et al., 2014). The actions of Li were mediated (at least partially) through the inhibition of the enzyme glycogen synthase kinase 3 beta (GSK3β) (Cao et al., 2017; Chatterjee & Beaulieu, 2022) and the signal transducers and activators of transcription-1 and 3 (STAT-1 and 3) pathways (Göttert et al., 2022). These pathways are markedly implicated in the mounting of an abnormal inflammatory response of microglia, in neurodegeneration contexts, such as Alzheimer's disease and aging-related cognitive decline (Duda et al., 2018; Koistinaho et al., 2011).

Besides Li, valproic acid, classically an anticonvulsant agent, has been used as a standard therapeutic for BD (Chen et al., 2007). Valproic acid attenuated LPS-induced microglial reactivity and resulting neuronal death by inhibiting histone deacetylases (HDAC) 1 and 2 (Chen et al., 2007; Durham et al., 2017). These HDACs and other histone deacetylase from the same family were suggested to be key regulators during the initiation, progression, and termination

of inflammatory gene expression through epigenetic modifications involved in neurodegenerative and autoimmune diseases (Dai et al., 2021). Therefore, these findings provide a preliminary rationale for the anti-inflammatory and potentially modulatory actions of valproic acid and other anticonvulsants with mood stabilizer properties in modulating microglial reactivity; however, further evidence is warranted.

Additionally, in vivo studies have provided insights into Li's immunomodulatory actions (Gould et al., 2004; Zhou et al., 2017). In mice subjected to the lisdexamfetamine-induced mania model and subsequently injected with LPS, Li was able to attenuate the serum up-regulation of proinflammatory cytokines (TNF-α, IL-6 and IL-1β) and inducible nitric oxide synthase (iNOS) induced by the endotoxin (Bristot et al., 2019). Similarly, in the AMPH-induced mouse model of mania, Li attenuated the increased levels of pro- (e.g., TNF-α) and anti-inflammatory (IL-10 and IL-4) cytokines in the PFC and hippocampus, and this effect was potentiated by co-treatment with the selective inhibitor of cyclooxygenase-2 (COX-2) celecoxib (Menegas et al., 2020; Valvassori, Dal-Pont, Tonin, et al., 2019).

In the clinical setting, the immunomodulatory actions of Li in patients with BD have been equally demonstrated. In a systematic review, Van den Ameele et al. (2016) screened over 560 clinical studies, and reached the conclusion that Li chronic treatment (≥2 months of continuous treatment) was associated with normalization in the blood levels of several cytokines, including TNF-α, IFN-γ, IL-6, IL-2, IL-4 and IL-10, in patients with BD, while valproic acid and antipsychotics showed no effect (van den Ameele et al., 2016). Also, in an ex vivo study, monocytic cells of euthymic patients with BD (treated and non-treated with Li) were cultured *in vitro* and exposed to LPS and/or graded concentrations of Li chloride. Both the monocytes of control patients and patients non-treated with Li showed an exacerbated up-regulation of IL-6 and the IL-6/IL-1β ratio. Interestingly, only the chronic treatment with Li in patients and not the acute *in vitro* treatment restored abnormalities in these cytokines (Knijff et al., 2007).

A longitudinal clinical trial evaluating 267 chronic patients with BD demonstrated that significantly higher levels of hs-CRP were negatively correlated with the duration of Li treatment (Queissner et al., 2021). Finally, a recent study released as a preprint provided significant evidence of Li effects in BD and the immunogenetics basis of this disorder. This study found a moderate association of several genes involved in immune and intercellular responses, for example, hyaluronan synthase 3 (HAS3), ADAM metallopeptidase thrombospondin type 1 motif 5 (ADAMTS5), IL1B and nuclear factor I B (NFIB), with Li's therapeutic response in 2,374 patients with BD. Network and functional enrichment analyses uncovered an overrepresentation of pathways involved in cell adhesion and matrix remodeling, which converged on the well-known Li-induced inhibition of GSK-3β. Additionally, polygenic score analysis suggested serum cytokine ligands, such as CXCL1, eosinophilic cationic protein (ECP), TNF-related activation-induced cytokine/TNF superfamily member 11 (TRANCE/TNFSF11) and TNF receptor 1 (TNFR1), as potential circulating biomarkers of Li's response in patients with BD, but further validation for each marker is necessary (Herrera-Rivero et al., 2023). Therefore, compelling clinical and preclinical evidence support potent anti-inflammatory and immunomodulatory actions of mood stabilizers, particularly Li, with some preliminary evidence that the activity of these agents can counteract microglial proinflammatory reactive states. However, the mechanisms underlying these agents' actions on microglia in BD-related contexts require further investigation.

6 | MICROGLIA AS A CENTRAL HUB FOR THE INFLUENCES OF ALTERED NEUROIMMUNE STATUS IN BD

6.1 | An overview of microglial homeostatic functions in adult CNS homeostasis

Microglia play a plethora of roles required for CNS development, maturation, activity, plasticity, and integrity across the lifespan. Microglia shape neural circuits by modulating the strength of synaptic transmission, sculpting synapses and maintaining the myelin sheath integrity (Tay et al., 2017; Tremblay, 2021). They promote the survival and differentiation of oligodendrocytes and their precursors as well as astrocytes from development into adulthood (Tay et al., 2017). Also, microglia are critical for phagocytosing dead cells, myelin debris and protein aggregates, besides secreting soluble factors, such as chemoattractants, cytokines, and neurotropic factors that contribute to mediating the brain's immune responses, tissue repair and inflammation-resolving responses (Šimončičová et al., 2022; Tremblay, 2021).

In the adult brain, microglia are integral components of neurogenic niches in the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus, contributing to the survival of neural progenitor cells (NPC) and their differentiation into fully integrated neurons among the olfactory bulb and hippocampus, respectively (McCarty et al., 2021). Microglia phagocytose apoptotic NPCs generated during adult neurogenesis, preventing exacerbated inflammation caused by the release of apoptosis-derived molecules and cell debris (Sierra et al., 2010). Microglia also eliminate excess newborn progenitor cells during development, contributing to maintaining a homeostatic pool of progenitor cells in these neurogenic niches into adulthood (Diaz-Aparicio et al., 2020).

Microglia shape neural circuits through the formation, refinement and elimination of synapses (Tremblay et al., 2010; Wake et al., 2009). During normal physiological conditions, microglia can eliminate presynaptic axon terminals in an activity and sensory experience-dependent way through direct phagocytosis (complement-mediated) (Tremblay et al., 2010; Werneburg et al., 2020). Also, microglia regulate synapse structure and function by intervening their processes in-between the pre- and post-synaptic terminals, physically displacing them, a phenomenon called synaptic stripping (Trapp et al., 2007). This phenomenon was demonstrated to be critical for the neuroprotective mechanisms against ischemic injury and excitotoxicity in cortical neurons of adult mice (Chen

et al., 2014). In their set of interactions with synapses, microglia can also perform a partial phagocytosis, named trogocytosis, where they nibble presynaptic terminals of excitatory and inhibitory synapses (Weinhard et al., 2018). Besides these direct contacts, microglia influence synapse homeostasis by secreting soluble trophic factors, such as BDNF, which act on their respective receptors (e.g., TrkB) on post-synaptic terminals, stimulating synapse maturation and formation during learning and memory processes (Parkhurst et al., 2013).

Microglia additionally play key functions during all stages of myelin formation, remyelination, and myelin repair (Domingues et al., 2016). As mentioned, WM abnormalities are a hallmark of BD neuropathology, which seems to be a relevant underlying factor for the functional dysconnectivity observed between key mood-regulating brain areas, especially frontal and limbic ones (Bellani et al., 2012; Favre et al., 2019). Oligodendrocytes derive from oligodendrocyte progenitor cells (OPC), which hold the capacity to proliferate, migrate, and differentiate into mature myelinating cells (Domingues et al., 2016). Previous reports have shown that in homeostatic conditions, microglia support OPC survival and differentiation into mature oligodendrocytes (Nicholas et al., 2001; Olah et al., 2012). Co-culture studies have revealed that mouse primary microglial cells stimulate the synthesis of myelin-specific galactolipids (e.g., sulfatide) and myelin-specific proteins (e.g., myelin basic protein [MBP] and proteolipid protein [PLP]) in oligodendrocytes and OPCs (Miller et al., 2007; Pang et al., 2012). These effects were mainly attributed to the secretion of soluble factors, such as insulin-like growth factor-2 (IGF-2), hepatocyte growth factor (Lalive et al., 2005; Nicholas et al., 2002), and galectin-3 (Hoyos et al., 2014).

Demyelination is often followed by remyelination, the default process by which new OPCs are recruited to differentiate into myelinating oligodendrocytes and by which myelin sheaths are restored (Domingues et al., 2016). However, the proinflammatory milieu driven by cytokines, notably IL-1β, TNF-α and IL-6, surrounding some demyelinated lesions can compromise and limit the efficacy of the remyelination process (Holloway et al., 2023; Nicholas et al., 2001). Microglia expressing the C-C chemokine receptor type 5 (CCR5) receptor were identified within early remyelinating lesions in patients at early stages of multiple sclerosis (MS), suggesting their function in initiating remyelination through the secretion of anti-inflammatory and trophic factors, such as IGF-1 and IGF-2 (Nicholas et al., 2002; Trebst et al., 2008). Ablation of microglia further impaired the chondroitin sulfate proteoglycan production necessary for myelin repair after demyelination (Kucharova & Stallcup, 2015).

Microglia contribute to the clearance of myelin debris upon myelin injury, which is also a critical step in the remyelination process (Lampron et al., 2015). The inflammatory reactivity of microglia markedly influences their roles in remyelination. Miron et al. (2013) found that the process of remyelination was dependent on microglia changing from a state highly expressing proinflammatory mediators (e.g., IL-1β and TNF-α) toward a subset highly expressing arginase 1 (Arg1) and trophic factors (e.g., IGF-1) (Miron et al., 2013). Predominantly depleting these anti-inflammatory microglial states using mannosylated clodronate liposomes (MCLs) that bind to mannose receptors decreased the expression of myelin differentiation markers, such as myelin-associated glycoprotein (MAG) and MBP, after demyelination (Miron et al., 2013). Other strategies able to modulate microglial reactivity toward anti-inflammatory states, such as omega-3 polyunsaturated fatty acids (Chen et al., 2018), recombinant IL-4 intranasal delivery (Zhang et al., 2019) or experimental vaccines inducing an antibody-mediated reaction against targets involved in the microglial proinflammatory responses (Fan et al., 2018), were able to promote remyelination in the context of CNS injury, such as stroke, traumatic injury and MS. However, despite very promising results, no current evidence has yet demonstrated microglial contribution to the WM and myelin pathology observed in BD.

6.2 | Microglial findings and BD pathophysiology

The research investigating changes in microglial states over the course of BD is mainly limited to in vivo human imaging studies (using largely non-specific radioligands) and post-mortem studies. While the studies conducted to date differ in the conclusions they reached, the involvement of microglia in BD pathophysiology appears influenced by the reported brain regions, methods used to assess microglial features (e.g., morphology, protein or gene expression), patients' clinical features and lateralized distribution of microglia between brain hemispheres (Haarman et al., 2014, 2016; Petrasch-Parwez et al., 2020).

Regarding the neuroimaging studies, the [11C]-(R)-563 PK11195, a translocator protein (TSPO) positron emission tomography (PET) radiotracer, has been used as a generic marker of CNS inflammation and reactive glial (and microglial) states (Guilarte et al., 2022). Haarman et al. (2014) first demonstrated an increased TSPO-binding profile in the right hippocampus of 15 euthymic patients with BD type I compared to healthy controls. Despite significant, this neuroimaging finding did not show any association with other clinical variables, such as illness duration or mood episode number (Haarman et al., 2014). Subsequently, the same group performed an integrated analysis combining structural MRI scan combined with magnetic resonance spectroscopy and [^{11}C]-(*R*)-PK11195 PET scan, revealing a positive association between TSPO-binding signal in the left hippocampus with decreased *N*-acetylaspartate (NAA), *N*-acetyl-aspartyl-glutamate (NAAG), creatine (Cr) and phosphocreatine (PCr) concentrations and the severity of previous depression symptoms in euthymic patients with BD type I, suggesting associations between a possible profile of glial immunoreactivity and metabolic abnormalities in the hippocampus of patients with BD (Haarman et al., 2016).

In isolated peripheral blood mononuclear cells (PBMCs) of chronic euthymic patients with BD type I, increased markers of NRL family pyrin domain containing 3 (NLRP3) inflammasome activation, such as NLRP3, ASC, caspase-1, IL-1β, and IL-18, were additionally shown to be increased following heightened levels of TSPO-related

TABLE 3 Microglial abnormalities in BD: Sum-up of the clinical findings.

Authors	Study design	Markers	Main findings	Caveats or limitation
Hercher et al. (2014)	Microglia density in white matter adjacent to dorsolateral prefrontal cortex (DLPFC) in post-mortem patients with BD and controls	Ionized calcium-binding adaptor molecule 1 (IBA1)	No difference between patients with BD and controls	IBA1 marker not specific to microglia Lateralization of microglia not taken into account Cause of death not taken into account Microglial function/ phenotype not taken into account
Sneeboer et al. (2019)	Density, gene expression, protein expression in medial frontal gyrus, superior temporal gyrus, and hypothalamus post-mortem brains of BD subjects, and controls	IBA1	No difference between BD group and controls	Lateralization of microglia not taken into account Cause of death not taken into account
Petrasch-Parwez et al. (2020)	Distribution of microglia (indicated by IBA1 staining) in anterior midcingulate cortex (aMCC) of BD subjects, and control subjects Distribution of IBA1-stained microglia within BD subjects, and control subjects	IBA1	No difference in IBA1 stained microglial density between BD subjects, and control subjects Right lateralization in terms of microglia density was observed in the BD group, but not in the control group	IBA1 marker not specific to microglia Microglial function/ phenotype not taken into account
Haarman et al. (2014)	Use of radiopharmaceutical Translocator protein (TSPO) tracer [11C]-(R)-PK11195 to investigate the presence of neuroinflammation in the living human brain	[11C]-(R)-PK11195	Increased binding of [11C]-(R)-PK11195 in the right hippocampus in BD patients	[11C]-(R)-PK11195 does not bind specifically to microglia
Naggan et al. (2023)	Comparison of major histocompatibility complex (MHC)-class II, and lymphocyte activation gene 3 (LAG3) levels between BD patients who died of suicide, BD patients who did not die of suicide, and controls	Purinergic P2RY12 receptor (microglia-selective); MHC II; LAG3	No difference between BD patients, and controls BD suicide victims increased levels of microglia expressing P2RY12, MHC II labeled microglia, and reduced levels of LAG3; negative correlations between microglial LAG3 expression levels, and microglia expressing P2RY12, and MHC II	Lateralization of microglia distribution not taken into account Presence of different microglial phenotypes not taken into account
Rao et al. (2010)	Comparison of the expression of proinflammatory markers post-mortem between BD patients and healthy controls	NR-1, NR-2A, NR-2B, NR-3A, IL-1β, IL-1R, MyD88, TNF-α, GFAP, iNOS, nNOS, CD11b, p50, p65, c-fos	Increased mRNA and protein expression of IL-1b, IL-1R, MyD88, NF-kappa-B p65 subunit, markers of microglia reactivity, including Cd11b and HLA-DR	Limitations in the ability to measure microglial structural and functional states Insufficient clinical characterization of the patients investigated

(Continues)

TABLE 3 (Continued)

Authors	Study design	Markers	Main findings	Caveats or limitation
Scaini et al. (2019)	Investigation of inflammasome activity and mitophagic pathway activation in isolated peripheral blood mononuclear cells (PBMCs) of BD patients and healthy controls	TSPO, voltage-dependent anion channel (VDAC), p62/SQSTM1, LC3, NLR family pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), pro-caspase 1, IL-1β and IL-18 levels, caspase 1 activity	Up-regulation of the TSPO-VDAC complex in BD patients, down-regulated release of mitophagic proteins, and NLRP3 inflammasome activity	Small sample size; cross-sectional study design; only markers of mitochondria and NLRP3 pathway investigated

Abbreviations: aMCC, anterior midcingulate cortex; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; BD, bipolar disorder; CD, cell differentiation; DLPFC, dorsolateral prefrontal cortex; GFAP, glial fibrillary acidic protein; IBA1, ionized calcium-binding adaptor molecule 1; IL, interleukin; iNOS, inducible nitric oxide synthase; LAG3, lymphocyte activation gene 3; LC3, microtubule-associated protein light chain 3; MHC, major histocompatibility complex; MyD88, myeloid differentiation factor 88; NF-kappa-B, nuclear trasncriptional factor kappa B; NLRP3, NLR family pyrin domain containing 3; nNOS, neuronal nitric oxides synthase; NR, NMDA receptor; P2RY12, purinergic receptor P2Y12; PBMCs, peripheral blood mononuclear cells; SQSTM1, sequestosome-1; TNF, tumor necrosis factor; TSPO, translocator protein; VDAC, voltage-dependent anion channel.

proteins (TSPO and voltage-dependent anion channel [VDAC]). These researchers identified a positive correlation between TSPO-related markers in PBMCs and the severity of manic and depression episodes, and inverse correlations with functionality scores in these patients (Scaini et al., 2019). Additionally, Ohgidani et al. (2016) isolated PBMCs from the blood of rapid-cycling patients with BD at different mood phases (manic and depression), and induced their transformation into inducible microglia-like (iMG) cells. These cells, despite differing transcriptionally and embryonically from resident microglia, can mimic microglial features, such as ramified morphology, expression of inflammatory cytokines, and phagocytic activity (Ohgidani et al., 2016). These researchers found an up-regulation of anti-inflammatory markers, notably the mannose receptor CD206 and proinflammatory marker TNF-α, in cells isolated from acute manic states compared to acute depressive states. Despite being limited by the cross-sectional design and the short number of patients included, these findings indicate a possible influence of mood states in modifying microglial molecular expression (Ohgidani et al., 2016), which needs to be further demonstrated.

Regarding post-mortem studies in BD patients, Rao et al. (2010) provided initial evidence of an abnormal proinflammatory milieu in the post-mortem prefrontal cortex of patients with BD, indicated by increased mRNA and protein expression of IL-1β, IL-1 receptor (IL-1R), myeloid differentiation factor 88 (MyD88), and nuclear factor-kappa B p65 (NF-kappa-B p65) subunit, besides increased expression of markers usually associated with microglial reactivity yet non-selectively, such as CD11b and MHC II cell surface receptor (HLA-DR). However, in this study, several limitations were identified regarding the ability to assess microglial states, and a lack of in-depth clinical characterization of the patients involved, making assumptions about microglial involvement in BD limited (Rao et al., 2010). Other studies have shown negative or no significant differences in the expression of microglial markers, as well as in microglial density and morphology. One previous study demonstrated a reduced mRNA expression of the microglia and macrophage markers CD68 and CD11b in the post-mortem cingulate cortex of chronic BD type I and II patients (Seredenina et al., 2017). Additionally, two post-mortem studies showed no difference in the number or morphology of cells stained for the microglia and macrophage marker ionized calcium-binding adaptor molecule 1 (IBA1) in the PFC (Hercher et al., 2014) or for HLA-DR in the amygdala (Hamidi et al., 2004) of patients with BD type I. However, most of these studies lacked power of analysis because of the inclusion of a small cohort of patients, the absence of stratification based on clinical features (time of disease, severity of symptoms, suicidality), and the use of only one method to assess microglial changes (e.g., single immunostainings or single marker protein expression).

Also noteworthy is the potential impact of brain lateralization on the microglial findings. The evidence put forth by Petrasch-Parwez et al. (2020) indicates that generic approaches considering both hemispheres equally can blunt potential differences related to microglial findings in patients with BD (Petrasch-Parwez et al., 2020). These researchers showed the existence of a strong lateralization in

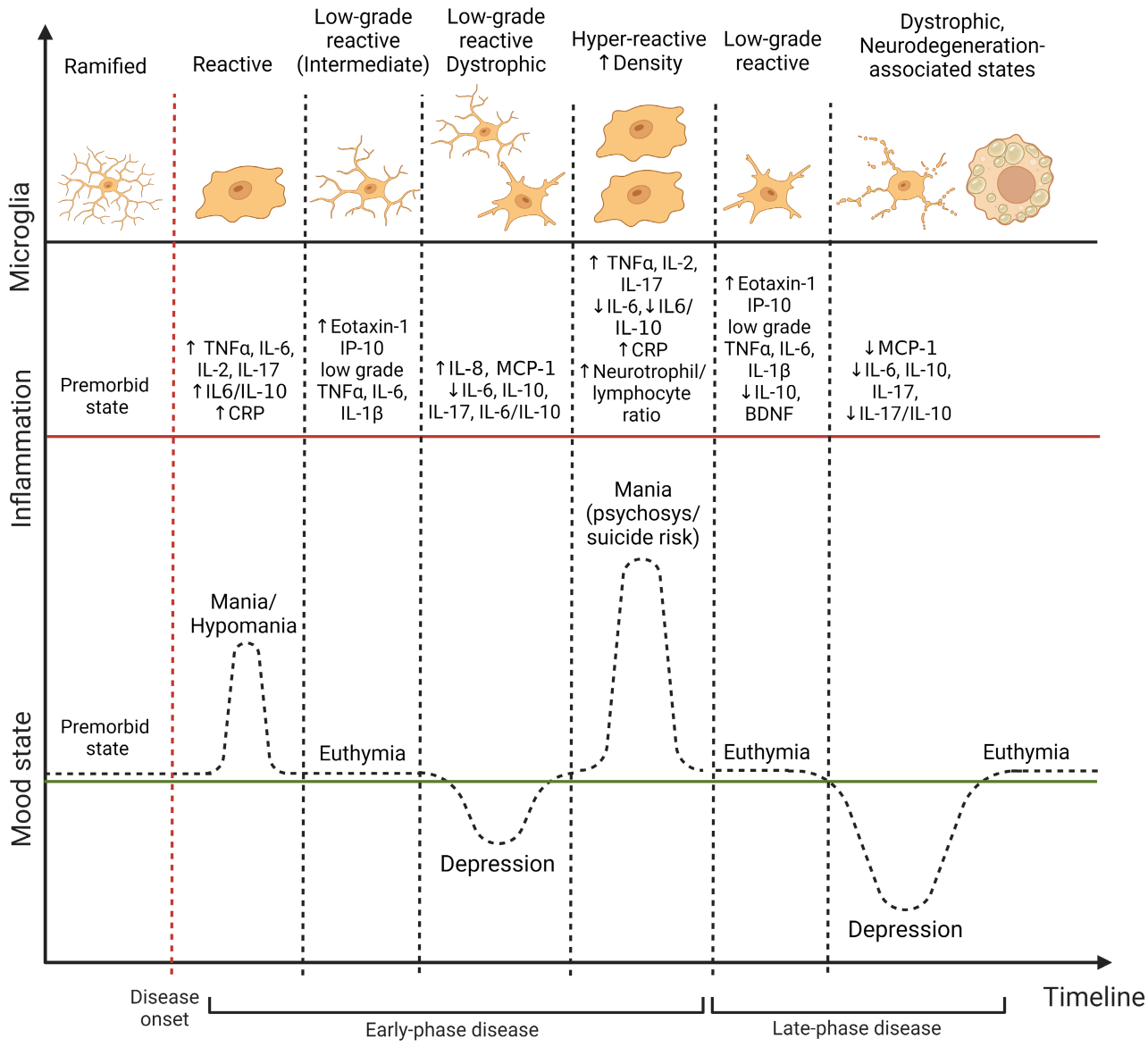

FIGURE 2 Representative timeline of mood phases, disease progression, systemic neuroimmune status, and hypothesized microglial states involved the natural course of BD. The disease onset (red dashed line) occurs approximately at the age 17–21 years, and in half of the patients, it is characterized by the first manic episode. This episode, usually mild to moderate, is associated with an increase in the serum levels of proinflammatory cytokines, such as TNF-α, IL-6, IL-8, IL-2, IL-17, and high levels of acute phase-reactants, such CRP. These symptoms can be succeeded by variable euthymic periods, marked by increased levels of chemokines, such as eotaxin-1, IP-10, and low-grade levels of cytokines (e.g., TNF-α, IL-6). Mild to moderate depression episodes are followed by increased levels of IL-8 and MCP-1, and decreased levels of IL-6, IL-10, and IL-6/IL-10 ratio. Subsequently, severe manic episodes, usually associated with psychotic symptoms and high suicide risk, are followed by increased levels of TNF-α, IL-2, IL-17, CRP, decreased IL-6 and IL6/IL-10 ratio and high neutrophil/lymphocyte ratio. In late disease, euthymic phases are similarly accompanied by increased eotaxin-1, IP-10 and low-grade inflammation, besides depleted levels of IL-10 and BDNF. Late disease depression, usually severe and longer episodes, is marked by reduced MCP-1, IL-6, IL-10, IL-17, and IL-17/IL-10, suggesting an overall immunosuppression/immunosenescence. Regarding microglia, we hypothesize that these cells assume a reactive state since the early-manic episodes, progressive to low-grade reactive states in early-disease euthymia and depression episodes. In severe manic episodes, especially those associated with suicidality, microglia would assume hyper-reactive states with increased density. Finally, in the late disease, predominantly marked by severe cognitive impairment and depressive symptoms, microglia would adopt dystrophic or neurodegeneration-associated states, resembling pathological states that were associated with other neurodegenerative conditions, such as Alzheimer's and Parkinson's disease. BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; IL, interleukin; IP-10, interferon-γ-induced protein 10 kDa; MCP-1, monocyte chemoattractant protein-1; TNF, tumor necrosis factor. Figure created with Biorender.

the distribution of microglia in patients with BD (Petrasch-Parwez et al., 2020). Using IBA1 staining, in the anterior midcingulate cortex (aMCC) of patients with BD and healthy controls, they found that the overall number of microglia did not differ between patients and controls, when both hemispheres were taken into account together (Petrasch-Parwez et al., 2020). However, when microglial density was selectively assessed in each hemisphere, a strong right lateralization in terms of microglial density was observed in the BD group compared to healthy controls (Petrasch-Parwez et al., 2020).

More recent studies have attempted to overcome these limitations (Naggan et al., 2023; Sneeboer et al., 2019). One recent study applied a multi-level approach, including *in situ* post-mortem immunostainings, microglial magnetic cell sorting and gene expression, to determine microglial changes in post-mortem brains of patients with BD. These authors, however, did not find any significant differences in microglial density (identified by IBA1 staining), and mRNA expression of proinflammatory (e.g., CD68, HLA-DRA, IL6, IL1β) and homeostatic microglial markers (TMEM119 and P2RY12) in isolated microglial cells of the medial frontal gyrus (MFG), superior temporal gyrus and thalamus of patients with BD. These authors also kept the isolated microglial cells in ex vivo cultures, and challenged them with LPS; however, no significant difference was detected between patients and healthy controls regarding microglial gene expression (Sneeboer et al., 2019).

Further, a recent study shed light on this possible association between microglia, BD, and suicide risk. Naggan et al. (2023) performed immunostainings on post-mortem hippocampal sections of 15 patients with BD type I and 12 controls using the microglia-specific marker P2RY12. This marker targets resident microglia in the CNS (Mildner et al., 2017; Naggan et al., 2023) and shows consistent expression across the lifespan in humans (Mildner et al., 2017). These researchers performed a co-staining with the marker MHC II, usually associated with microglial reactive states in neurodegeneration, such as Alzheimer's disease (Balança et al., 2021; Chen & Colonna, 2021). They found that only the subgroup of patients with BD who committed suicide ($N=9$ of 15) had increased microglial density (indicated by the P2RY12-staining) and increased co-staining with MHC II (P2RY12-MHC II double-staining). Also, a negative correlation between the expression of a novel microglial checkpoint lymphocyte activation gene 3 (LAG3), previously associated with dystrophic microglial states involved in depression (Rimmerman et al., 2022), and the density of microglia and abundance of MHC II-reactive microglia in suicide patients with BD was detected. These findings of increased microglial density and possibly heightened proinflammatory reactive states only in patients with BD who committed suicide (compared with patients who died for other reasons) are consistent with extensive literature implicating abnormal microglial reactivity in suicide across different psychiatric disorders (Gonçalves de Andrade et al., 2022; Steiner et al., 2011; Torres-Platas et al., 2014). For an overview of the current literature on microglial findings in BD, please see Table 3.

Therefore, through epidemiological, neuroimaging, and biomarker studies, it is becoming clear that there is a strong involvement of abnormal systemic and brain immune responses (and potentially microglia) in BD neuropathology. However, the roles of these cells in BD so far have only started to be demonstrated and a more detailed profiling of microglial functions and states in this complex disease is still lacking. Using single-cell technologies and integrative analyses of gene and protein expression, some diverse and context-dependent microglial states have been observed across many diseases, species and models (Yaqubi et al., 2023). Some examples of these states are the disease-associated microglia (DAMs), originally associated with Alzheimer's pathology models (Deczkowska et al., 2018); microglial neurodegenerative phenotype (MgND) documented across several disease models (Krasemann et al., 2017; Wei & Li, 2022); microglia inflamed in MS (MIMS) (Absinta et al., 2021); and Parkinson's disease microglial signature (Langston et al., 2022; Paolicelli et al., 2022; Tremblay, 2021).

Considering BD complexity and heterogeneity, it is expected that a high microglial diversity might be involved in this enigmatic disorder. Therefore, we hypothesize that during acute mood episodes, particularly manic episodes, microglia influenced by a heightened systemic proinflammatory state assume more intense proinflammatory reactive states, potentially related to the GM and WM structural and functional abnormalities (especially in the frontal-cortical regions) evidenced in patients BD. This can be followed by an inability to reinstate basal homeostatic functions and surveillant states of microglia, in a microenvironment ruled by chemokines and mediators, associated tow accelerated aging and immunosenescence, with an expression of eotaxin-1 and IL-8. Also, a low-grade chronic inflammatory state, represented by sustained levels of IL-6 and TNF-α, predominantly linked to depression and late-stage phases of the disease, can contribute to a progressive impairment of microglial homeostatic functions along the disease course. Together, a complex interaction between systemic and brain immune responses orchestrated by multiple microglial states in BD, here named *BD-associated microglial states*, could represent a key contributor to BD neuropathology, which needs to be further explored (Figure 2).

6.3 | Gut microbiota: A missing link between microglia and BD pathophysiology?

The term microbiota refers to the collection of living microorganisms that are found within a specific environment, such as the gut (Berg et al., 2020). Through dynamic interactions, it has been increasingly accepted that intestinal microbes can influence microglial functions continuously throughout life (Ben-Azu et al., 2023; Cook & Prinz, 2022). Most of the evidence showing direct influences of the gut microbiome on microglial adult functions came from rodent studies, especially in germ-free (GF) conditions, which, despite being an artificial model, provide insights into the influence of the microbiota based on the consequences of its absence (Thomson et al., 2022). It was shown that microglia from adult GF animals display increased density and aberrant morphology (indicated by IBA1 staining), with long processes and more extensively overlapping territories (Erny et al., 2015; Luck et al., 2020). The transcriptomic profile of GF microglia (isolated by FACS based on CD11b high, CD45

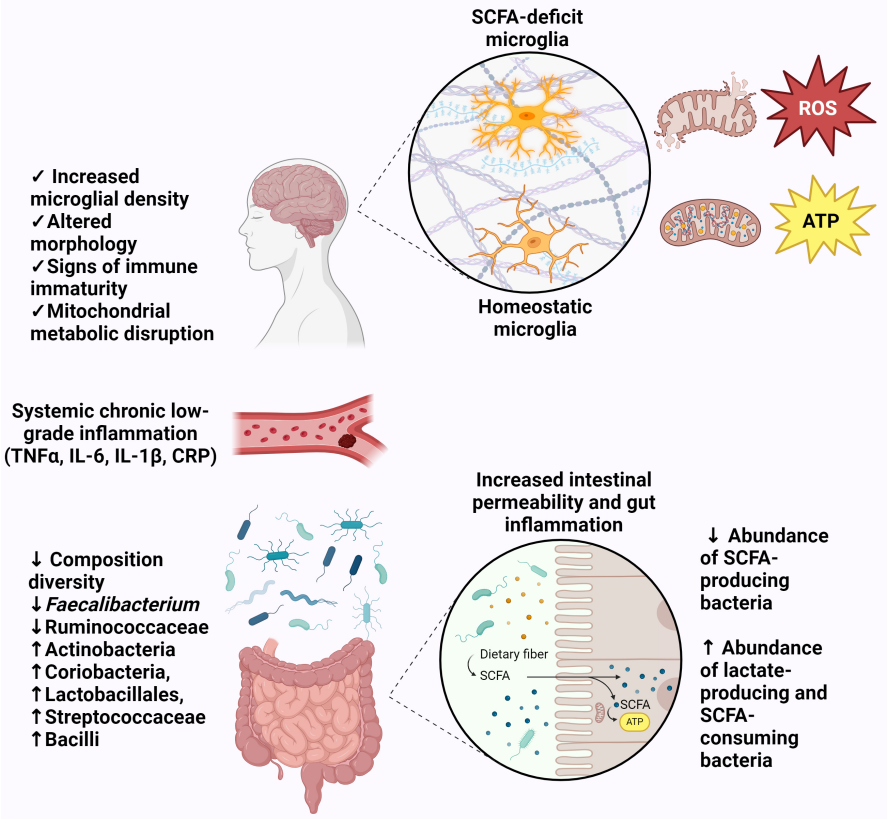

FIGURE 3 Gut microbiota alterations in BD and influences on systemic low-grade inflammation and microglial homeostatic functions. A disturbed composition marked by reduced diversity and reduced representation of SCFA-producing bacteria, notably Faecalibacterium and Ruminococcaceae, have been described in stool samples of patients with BD. Also, an increased abundance of lactate-producing bacteria, such as Lactobacillales and Bacilli, have been reported. We hypothesize that these gut microbiota alterations culminate into a systemic reduction in the SCFA levels, notably acetate and butyrate, that induces an increase in intestinal permeability and inflammation contributing to the systemic low-grade levels of proinflammatory cytokines observed in these patients. The deficit in SCFA and low-grade inflammation could lead to reported deficits in microglial homeostatic functions, notably bioenergetic mitochondrial metabolism. ATP, adenosine triphosphate; CRP, c-reactive protein; IL, interleukin; ROS, reactive oxygen species; SCFA, short-chain fatty acids; TNF, tumor necrosis factor. Figure created with Biorender.

low expression) showed signs of immune immaturity and decreased expression of immune function genes, such as *Cd86*, *Ly86* and *Hif1a*, compared to normal microbiota-mice (Erny et al., 2015). Among the mechanisms by which the microbiota influences microglia, a role for microbiota-derived products, notably short-chain fatty acids (SCFA), e.g., acetate, propionate, and butyrate, which can translocate from the intestinal epithelium into the circulation and cross the blood–brain barrier, is increasingly accepted (Parada Venegas et al., 2019). An SCFA mix, composed of sodium propionate, sodium butyrate, and sodium acetate, reversed the microglial molecular and morphological phenotype induced by the absence of gut microbiota in adult mice (Erny et al., 2015). This immature phenotype was epigenetically imprinted by histone acetylase transferases (HAT) activity on genes associated with microglial metabolism. In this context, acetate supplementation restored these defects in microglial metabolism associated with GF conditions (Erny et al., 2021).

Gut microbiota abnormalities have been reported in several neuropsychiatric conditions (for reviews on this topic, see Ben-Azu et al., 2023; Shoubridge et al., 2022). Evans et al. (2017) provide the first detailed analysis of the gut microbiome composition and associations with clinical variables in BD. Analyzing stool samples of individuals with BD (115) and controls (64), they found decreased representation of the *Faecalibacterium* genus within this population, and a positive relationship between this genus and better self-reported health outcomes and anxiety symptoms (Evans et al., 2017). By analyzing stool samples of BD (32) and controls (10), Painold et al. (2019) reported an overall up-regulation of the phylum Actinobacteria and the class Coriobacteria, and a down-regulation in abundance of the genera *Ruminococcaceae* and *Faecalibacterium*, in patients with BD compared with controls. This study provided insights into the link between peripheral inflammatory cytokines and the abundance of specific types of bacteria in BD (Painold et al., 2019). It reported a positive association between the serum levels of IL-6 and increased levels of Lactobacillales, Streptococcaceae and Bacilli. Also, the abundance of Lactobacillaceae was positively associated with the prevalence of obesity and metabolic syndrome in BD (Painold et al., 2019). Furthermore, a systematic review assessing gut microbiota profiling studies in BD found consistent findings across studies:

a reduced diversity composition relative to controls, and a notable reduction in the abundance of SCFA-producing bacteria, specially acetate and butyrate, for example, family Ruminococcaceae, genus *Faecalibacterium*, and species *Faecalibacterium prausnitzii* (Sublette et al., 2021). Combined, these studies indicate that alterations in the gut microbiome may be linked to BD etiology and implicated in the genesis of systemic inflammation in this disorder (Evans et al., 2017; Painold et al., 2019; Sublette et al., 2021). Notably, the reduction in the abundance of SCFA-producing bacteria can underlie the genesis of neuroimmune abnormalities associated with this condition, but further research is necessary to clarify the mechanisms linking gut microbiota with altered microglial functions in BD-relevant contexts. For an overview of these findings, please see Figure 3. For a specific review of the topic, please see (Ortega et al., 2023).

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

BD is a debilitating and complex disorder compromising multiple clinical and behavioral endophenotypes. Intricate gene–environment interaction appear to be involved in the genesis, development, and progression of this disorder. It has been increasingly accepted that neuroimmune factors, both genetic or environmental, such as early or late-life infections, psychological stress and autoimmune or chronic inflammatory conditions, can strongly impact the risk of emergence of this disease across the lifespan. Also, the robust literature showing altered neuroimmune markers in the serum of patients with BD indicates a heightened proinflammatory systemic response, especially during acute manic states, while chronicity of the disorder seems to be characteristically associated with markers of cellular aging and immunosenescence. In this context, microglia, the brain's resident immune cells, perform several critical functions required to maintain brain homeostasis across the lifespan. The current evidence supporting microglial involvement in BD neuropathology is in its beginning; however, recent data advocates for their strong involvement in suicidality during BD, and for an impact of brain lateralization in the assessment of microglial findings in this condition. Considering the recent technological advances in the microglial field, including the use of integrated multi-omics, single-cell technologies, and non-invasive live imaging tools, it is peremptory to employ these combined approaches to better characterize the diversity of microglial states and functions involved in BD at multiple levels of complexity (e.g., genome, transcriptome, proteome, metabolome, phenome), instead of relying on single approaches or markers. An in-depth comprehension of microglial involvement in BD pathophysiology can open promising perspectives for biomarker discovery and novel treatment approaches for this still enigmatic psychiatric condition.

AUTHOR CONTRIBUTIONS

Adriano Chaves-Filho: Conceptualization; methodology; investigation; writing – review and editing; writing – original draft; validation; formal analysis; data curation; supervision; project administration; resources; visualization. **Capri Eyres:** Writing – original draft; data curation; methodology; formal analysis. **Leonie Blöbaum:** Data curation; formal analysis; writing – original draft; methodology. **Antonia Landwehr:** Formal analysis; data curation; methodology; writing – original draft. **Marie-Ève Tremblay:** Conceptualization; visualization; writing – review and editing; supervision; project administration; resources; validation; writing – original draft; investigation.

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The authors have no conflicts of interest to declare that are relevant to the content of this article.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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