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Ferroptosis as a potential molecular mechanism of bipolar disorder

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The unclear pathogenesis of bipolar disorder (BD) poses a challenge, especially with the striking rates of comorbid medical and psychiatric disorders, treatment resistance, and premature mortality in the absence of a specific diagnostic marker. We put forward the hypothesis of ferroptosis, a recently identified iron-dependent cell death, as a potential underlying mechanism of BD. We aimed to portray the possibility of ferroptosis involvement in BD pathogenesis as a doorway to encourage both animal and clinical studies on the topic. Ferroptosis is associated with multiple psychiatric disorders, including major depressive disorder, stress-induced anxiety, post-traumatic stress disorder, autism spectrum disorder, and alcohol use disorder. In addition, ferroptosis-related genes have been identified in schizophrenia, which shares genetic liabilities with BD. One of the top five most significant genes in BD in a recent genome-wide association study, FADS 2, is involved in ferroptosis. The three hallmarks of ferroptosis intersect with the pathogenesis of BD, including iron dysregulation, lipid peroxidation, and the failure of antioxidant systems. Other pieces of BD pathogenesis, including inflammation, mitochondrial dysfunction, calcium dysregulation, neurotransmission disturbance, and affection of synaptic plasticity and myelination, are either a preface or an aftermath of iron dysregulation. Additionally, circadian rhythm abnormalities and hypothalamic-pituitary-adrenal axis disturbances in BD could be another point where ferroptosis and BD intersect. Moreover, some BD treatments, such as lithium, haloperidol, olanzapine, clozapine, valproic acid, and electroconvulsive therapy, show anti-ferroptosis action in other contexts. These observations present a strong case for ferroptosis as a potential underlying mechanism of BD. Therefore, we call for studies that address iron accumulation in the brain in BD patients, postmortem tissues, and BD animal models. We call for genetic studies to look for the genetic signature of ferroptosis in BD patients. In addition, we call for studies on different BD models to assess the expression of ferroptosis markers. Our hypothesis has substantial implications if validated, including the use of ferroptosis-related genes and ferroptosis markers as a prognostic marker for BD and a potential therapeutic target based on ferroptosis inhibitors.

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INTRODUCTION

Bipolar disorder (BD) is a complex chronic mood disorder characterized by fluctuations of mania, hypomania, and depressive episodes with two main clinical subtypes: bipolar I and bipolar II disorders. According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [1], bipolar I disorder (BDI) is characterized by at least one manic episode, which could be followed or preceded by hypomanic or depressive episodes. However, depressive episodes are not necessary for the diagnosis of BDI. Bipolar II disorder (BD II) is distinguished by at least one hypomanic episode and at least one major depressive episode, with no manic episodes reported [2].

Despite the 1–2% global prevalence [3], BD is considered one of the leading causes of disability worldwide [4], especially with its early onset in adolescence or early adulthood [5]. BD patients show high rates of concomitant morbidity and mortality, with 10-20 years less life expectancy than the general population [6]. Cardiovascular disorders [7], tobacco smoking [8], metabolic syndrome [9], and suicide [10] are among the leading causes behind the premature mortality among BD patients. About 15–20% of BD patients die by suicide [11–13]. The course of BD is also intensified by other comorbid psychiatric disorders [14] such as anxiety disorders [15], attention deficit hyperactivity disorder (ADHD) [16], alcohol use disorder (AUD), substance use disorder [17], and binge eating disorder [18], as well as cognitive impairment [19], implying a potential intersection of their pathogenesis. Treatment resistance is a common dilemma in the course of BD management, despite the increasingly validated therapeutic options [20]. In a two-year prospective study of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), only 58.4% of 1469 symptomatic patients showed recovery, and 48.5% of patients suffered from recurrences during the two-year follow-up [21]. Nierenberg et al. reported recovery rates of 4.6–23.8% in the STEP-BD study, using lamotrigine, inositol, and risperidone in 66 unresponsive patients to mood stabilizers and at least one antidepressant [22]. Adding to the

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failure of therapeutic options, another BD challenge stems from the partially unclear pathogenesis, which feeds into the other challenge of being solely diagnosed clinically with no specified diagnostic tests or biomarkers [23]. Thus, uncovering BD pathogenesis is imperative, as it would not only provide a clearer understanding of the nature of the disease but would also provide answers for diagnostic markers and novel therapeutic options. In this review, we put forward a hypothesis about ferroptosis as a part of BD pathogenesis, which would encourage both animal and clinical studies on the topic and add richness to the drastically deficient literature on the potential role of ferroptosis in BD pathogenesis. We consider this review to be the first step towards future studies on the role of ferroptosis in BD, which would provide potentially new biomarkers and therapeutic targets.

OVERVIEW OF BIPOLAR DISORDER PATHOGENESIS

Despite the plausible hypothesis of an interplay between genetic, environmental, and neurochemical factors in BD, its pathogenesis is still elusive [24]. Heritability comprises a huge part of BD pathogenesis; over 80% in twin studies [25]. BD shows a non-Mendelian inheritance, with the most recent genome-wide association study by the Psychiatric Genomics Consortium identifying 64 independent genetic loci associated with BD, each of which has a small effect [26]. Genetic correlation analyses have also shown strong positive genetic correlations between BD and schizophrenia, suggesting a shared genetic architecture between the two diseases [26]. Several environmental factors were reported to possibly affect the clinical course of BD, such as maternal smoking, intrauterine infection, childhood trauma, and viral infections in adulthood [27]. Additionally, the pathogenesis of BD was reported to include oxidative stress, mitochondrial dysfunction, and aberrant calcium signalling [24]. BD patients show evidence of low-grade systemic inflammation and potential neuroinflammation [28, 29]. Deficits in neurotransmission [30–32], myelination [33, 34], and neuroplasticity [24] were also reported as pieces of the BD puzzle. Moreover, BD patients show abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis [35] and circadian rhythm, which evidently affect the course of the disease [36]. Lipid peroxidation, a hallmark of ferroptosis [37], and altered lipid-related cascades hold a crucial role in BD pathogenesis [38].

Cell death was repeatedly reported in both animal and clinical studies on BD. In an ouabain-induced rat model of mania, both frontal cortex and hippocampus showed a significantly high content of thiobarbituric acid reactive species (TBARS), a lipid peroxidation marker, and mitochondrial superoxide, indicating oxidative stress. That increase was associated with a higher expression of the proapoptotic protein, Bcl-2-associated X protein (Bax), and a lower expression of the antiapoptotic, B-cell lymphoma 2 (bcl-2) [39]. Using liquid chromatography–mass spectrometry and multi-analyte platforms, Herberth et al. identified about 60 differentially expressed molecules involved in cell death/survival in peripheral blood mononuclear cells (PBMCs) and serum from euthymic BD patients ($n = 16$ BDI and 16 BDII) compared to matched healthy controls [40]. Kim et al. reported higher expression of pro-apoptotic factors (Bax, caspase-9 and caspase-3) and a reduced expression of anti-apoptotic factors (brain-derived neurotrophic factor (BDNF) and Bcl-2) at both mRNA and protein levels in postmortem prefrontal cortex of BD patients ($n = 10$) compared to age-matched controls [41]. In addition, Scaini et al. reported similar findings in the peripheral blood mononuclear cells in BDI ($n = 16$). They found activated apoptotic pathways with higher levels of Bax and lower levels of Bcl-2 [42]. Interestingly, Mishra et al. found increased sensitivity to cell death in neural progenitor cells derived from lithium non-responsive after the administration of methamphetamine, which models the clinical features of mania [43]. Despite the multiple studies on apoptosis, as a type of regulated cell death [44], and the intense research efforts to clarify BD etiopathogenesis, no studies have addressed ferroptosis, another type of regulated cell death [44], as a potential part of BD pathogenesis, leaving an immense research gap that we aim to address.

OVERVIEW OF FERROPTOSIS AND ITS MOLECULAR MACHINERY

Ferroptosis, a term coined almost a decade ago, is a non-apoptotic iron-dependent form of regulated cell death [45] (reviewed in more detail in our previous publication [46]). Undergoing ferroptosis, cells get swollen, mitochondria decrease in size, and the plasma membrane thins out and eventually ruptures [47, 48]. Lipid peroxidation is the main event needed for a cell to die from ferroptosis. Lipid peroxidation can fulfill the ominous fate of ferroptosis in the presence of three prerequisites: accumulated lipid radicals, excessive labile reactive iron, and failed cell antioxidant defense systems [37].

Lipid peroxidation

Lipid peroxidation is the oxidative degradation of lipids as a consequence of oxygen interaction with unsaturated fatty acids, forming lipid radicals, including lipid peroxides ($LOO^{\bullet}$) and lipid hydroperoxides ($LOOH^{\bullet}$) [49], which can trigger a chain reaction of lipid radical formation [50–52] (for more details, refer to Fig. 3 in our previous publication [46]). This chain reaction ends up forming highly toxic lipid peroxidation degradation products such as malonaldehyde (MDA) and 4-Hydroxynonenal (4-HNE) [53]. These byproducts can change the structure and function of DNA and cellular proteins, fostering a state of cytotoxicity [53–55]. As the chain reaction progresses, the cell's membrane lipid bilayer is damaged [56].

Ferroptosis sensitivity heightens when the content of poly-unsaturated fatty acids (PUFA) increases. The abundance of PUFA in cell membrane phospholipids renders cell membranes vulnerable to lipid peroxidation because PUFA are susceptible to radical attacks and forming lipid radicals themselves [57]. Acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) is a crucial enzyme for incorporating PUFA into phospholipids by binding them to coenzyme A to produce PUFA-CoAs [58]. Therefore, ACSL4 can induce ferroptosis by promoting a robust content of PUFA-containing phospholipids [59]. Lipid peroxidation and lipid hydroperoxide ($LOOH^{\bullet}$) formation can also occur enzymatically by cytochrome P450 oxidoreductase, cyclooxygenases (COXs), lipoxygenases (LOXs), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs), which can alter the lipid landscape and promote ferroptosis [60].

Failure of antioxidant defence

Failure of antioxidant defence against lipid peroxidation is a prominent feature of ferroptosis induction [61]. Glutathione peroxidase 4 (GPX4) is one of the most dedicated phospholipid repair systems. The GPX4 enzyme is an oxidoreductase that reduces hydroperoxides ($OOH^{\bullet}$) to their corresponding non-harmful alcohols. Next, the oxidized GPX4 is reduced by glutathione (GSH), allowing GPX4 to repeat its action [62]. GSH is the most plentiful cellular antioxidant and is formed of glutamate, glycine, and cysteine [63]. A crucial component for GSH synthesis is the Cystine/Glutamate antiporter, or system Xc- [64]. System Xc- is formed of a heavy chain subunit and a light chain subunit called xCT, or Solute carrier family 7 member 11 (SLC7A11). SLC7A11 allows glutamate to be exported and cystine to be imported. Cystine, the oxidized form of cysteine, can then be reduced to cysteine, which is needed for GSH formation [65, 66] (see figure 4 in our previous publication [46]). GPX4 inactivation or deletion, GSH depletion, and SLC7A11 blunted expression strongly promote ferroptosis [61, 67, 68]. The decreased expression of nuclear factor erythroid 2-related factor 2 (NrF2) is also another

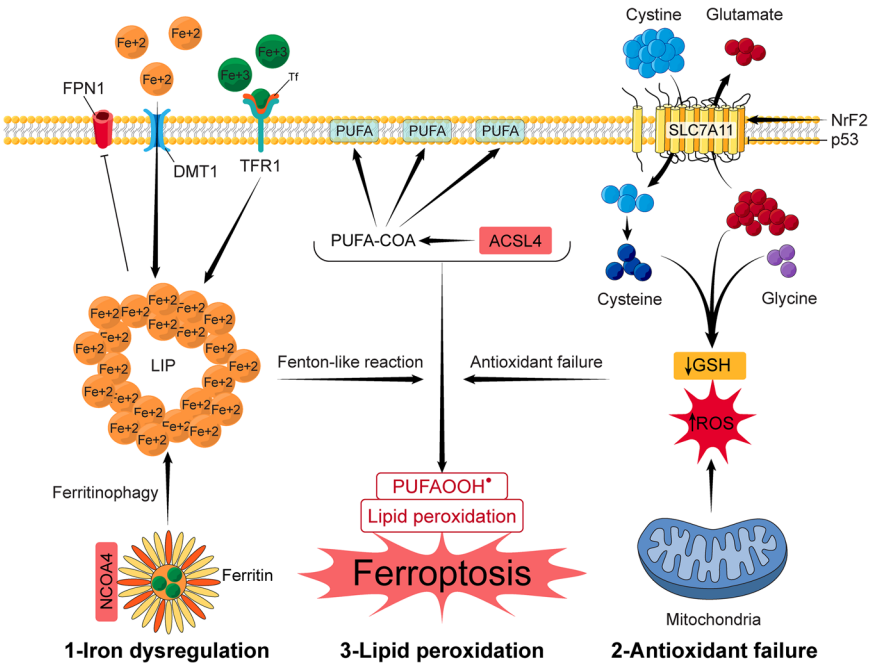

Fig. 1 Ferroptosis machinery. Ferroptosis is an iron-dependent cell death which is executed by lipid peroxidation. Iron dysregulation, antioxidant failure, and lipid peroxidation are the three hallmarks of ferroptosis. 1- Iron dysregulation: the labile iron pool (LIP) or free redox iron increases during ferroptosis through three ways. First, imported iron through the upregulated divalent metal transporter 1 (DMT1) and transferrin receptors-1 (TFR1) adds up to the LIP. Second, iron exportation is limited by degradation of the only iron exporter, ferroportin 1 (FPN1), increasing the LIP. Third, iron is released from its ferritin stores by the nuclear receptor co-activator 4 (NCOA4)-mediated ferritinophagy or ferritin degradation. The highly available Ferrous iron (Fe+2) invokes lipid peroxidation and therefore ferroptosis through a Fenton-like reaction. 2-Failure of antioxidant defence: accumulated reactive oxygen species (ROS) overwhelms antioxidant defence system. During ferroptosis, the Solute carrier family 7 member 11 (SLC7A11) is downregulated by the decrease of nuclear factor erythroid 2-related factor 2 (NrF2) and the increase of P53, which prevents cystine entry into the cell and therefore decrease the formation of glutathione (GSH). 3- Lipid peroxidation: acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) increases during ferroptosis and incorporates more polyunsaturated fatty acids (PUFA) into membrane phospholipid by converting them to PUFA-CoAs. ROS initiates a chain reaction of lipid peroxidation forming lipid hydroperoxides (PUFAOOH$^{\bullet}$), which is amplified by the increased LIP, promoting ferroptosis. Fe^{+3} ferric iron, TF transferrin.

strong promotor of ferroptosis [69]. NrF2 is the major transcriptional factor that controls the expression of GSH, its related transporters, and enzymes and directly activates the SLC7A11 [70, 71]. Tumor protein 53 (P53) is another transcriptional factor that controls the expression of SLC7A11. The higher the activation of P53, the lower the expression of SLC7A11, which enables the induction of ferroptosis [72].

Iron dysregulation

As the name suggests, iron plays an imperative role in ferroptosis. In the cell, iron is either used for various biological processes, exported, stored as ferritin, or resides freely in a redox state, forming the labile iron pool (LIP). LIP is the protein-unbound, exchangeable, and chelatable portion of iron, which has redox features (the ability to go through reduction-oxidation reactions) [73]. Iron can feed the production of lipid radicals through a Fenton-like reaction. The Fenton reaction is a sequence of redox reactions catalyzed by the labile ferrous iron (Fe+2) pool. Fe+2 reacts with LOOH$^{\bullet}$, forming a highly reactive alkoxyl (L-O$^{\bullet}$) radical [74, 75]. Iron helps the action of LOX to form LOOH$^{\bullet}$ radicals, thereby fostering ferroptosis [76]. Under normal conditions, iron can enter the cell as transferrin through transferrin receptor 1 (TFR1) [77]. The non-transferrin-bound iron enters the cell through the divalent metal transporter 1 (DMT1) [78]. Iron can exit cells through ferroportin 1 (FPN1), which is the only iron exporter. FPN1 is under the control of hepcidin, the only hormonal regulator of iron. When iron systemic availability exceeds normal levels, hepcidin degrades FPN1, trapping iron into the cell [79] (see Figure 5 in our previous publication [46]). For iron to be released from its storage form in the cell, ferritin undergoes an autophagic degradation called ferritinophagy. Ferritinophagy is mediated by the nuclear receptor co-activator 4 (NCOA4), increasing the LIP [80, 81]. All iron-related proteins and transporters undergo molecular regulation through the iron regulatory proteins/iron-responsive elements (IRPs/IRE) system. IRP1 and IRP2 are cytosolic proteins that bind to IRE in different target genes mRNA, controlling their translation [82]. When the IRPs are activated, they promote the expression of TFR1 and DMT1 and inhibit that of FPN1 and ferritin, which favors the increment of the LIP [83, 84]. For iron to promote ferroptosis induction, it loses its tight regulation to amplify the LIP. TFR1 upregulation supplies the LIP with more iron uptake; therefore, TFR1 high expression is a prominent feature of ferroptosis [85]. In addition, the upregulation of DMT1 acts as a ferroptosis mediator [86]. The overexpression of IRPs [87], the downregulation of FPN1 [88, 89], and the enhanced hepcidin production [90] all lead to the same outcome. NCOA4-mediated ferritinophagy is aggravated by the decrease of NrF2, which releases more iron to the LIP and promotes ferroptosis [91]. Moreover, the decrease in NrF2 downregulates H (heavy chain) ferritin, leading to increased ferroptosis [92]. Clockophagy is the autophagic degradation of clock gene transcriptional factors, which also mediates ferroptosis. GPX4 inhibitors suppress the expression of BMAL1/ARNTL (brain and muscle ARNT-like 1 or aryl hydrocarbon receptor nuclear translocator-like protein 1), which is the main clock gene transcriptional factor. GPX4 inhibitors also decrease the expression of ARNTL-targeted clock genes (PER1 and CRY1). Both the suppressed expression and the autophagic degradation of BMAL1/ARNTL promote ferroptosis [93]. (Fig. 1)

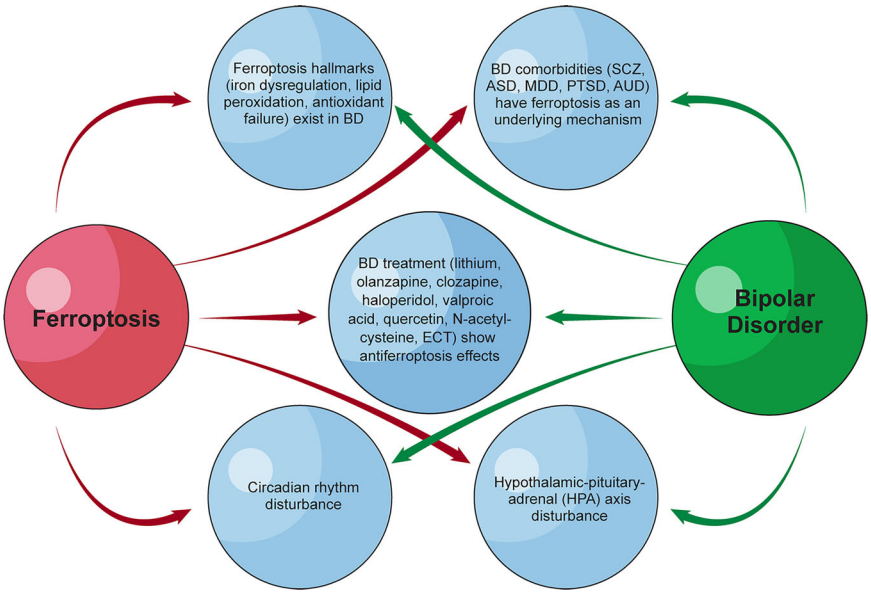

Fig. 2 Overview of intersection points between bipolar disorder and ferroptosis. Our hypothesis of ferroptosis being implicated in the pathogenesis of bipolar disorder (BD) is supported by 1-Ferroptosis being involved in the pathogenesis of some of BD comorbidities, including Schizophrenia (SCZ), autism spectrum disorder (ASD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and alcohol use disorder (AUD). 2-The existence of ferroptosis hallmarks in BD. 3- Hypothalamic-adrenal axis disturbance in BD pathogenesis, which could induce ferroptosis. 4- Circadian rhythm disturbance in BD, which is echoed by the ferroptosis-induced degradation of circadian rhythm transcriptional factors (clockophagy). 5- Drugs used in BD treatment have antiferroptosis effect in other contexts.

INTERSECTION OF BIPOLAR DISORDER PATHOGENESIS AND FERROPTOSIS

We present the hypothesis of ferroptosis as one of the missing pieces of BD pathogenesis. We raise the question of whether ferroptosis is implicated in the pathogenesis of BD with a rationale based on the following five observations. (Fig. 2).

Ferroptosis in other psychiatric disorders

Despite being recently discovered [45], ferroptosis was reported to be involved in the pathogenesis of multiple psychiatric disorders. The role of ferroptosis in the pathological mechanism of major depressive disorder(MDD) was shown, where lower GSH and GPX and higher MDA were reported in the prefrontal cortex of depressed patients. Antidepressant drugs showed higher levels of hippocampal GPX4 and lower levels of ROS in depressed mice, with amelioration of depressive behavior [94]. Chen et al. reported the construction of three ferroptosis-related genes (ALOX15B, RPLP0, and HP) for MDD diagnosis {Chen, 2023 #231}. Interestingly, Shlien et al found a common deleted region including *ALOX15B* in patients with developmental disorder, bipolar disorder, and severe cognitive impairment {Shlien, 2010 #227}. In addition, RPLP0 was found to be downregulated in both MDD and BD {Feng, 2020 #228}. Li et al. showed that ferroptosis inhibition improves depressive behavior in a chronic unpredictable mild stress mouse model [95, 96] Stress induced anxiety after 14 day chronic restrain stress showed ferroptosis, with higher oxidative stress and lipid peroxidation markers [97]. Zhu et al. identified three crucial ferroptosis-related genes (ACSL4, ACO1, and GSS) and used them to establish a predictive model of post-traumatic stress disorder (PTSD) [98]. Intriguingly, ACO1 was found to be approximately 1.3 times higher in BD {Sahay, 2024 #229}. Zhang et al. reported ferroptosis in the BTBR T+ tf/J mouse model of autism spectrum disorder (ASD) [99], *Moreover, ferroptosis was reported behind AUD-depressive and anxiety-like behaviors in mice* [100, 101]. The course of BD is complicated by some of these disorders, including AUD [102], anxiety [103], and ASD [104], which implies a potential intersection of their pathogenesis at ferroptosis. On a more evident note, ferroptosis-related genes have been identified in schizophrenia [105, 106]. Such an observation sparks interest, especially since BD shares familial susceptibility [107], gene expression alterations [108], and some neuropharmacological mechanisms such as dopamine disturbance [109] and glutamatergic dysfunction [110] with schizophrenia. However, evidence of such an intersection is still warranted.

Hallmarks of ferroptosis intersect with bipolar disorder pathogenesis

Iron dysregulation. Iron disturbance is a recurring finding in the context of multiple psychiatric disorders. Both iron deficiency and iron overload actively play a role in the pathophysiology of numerous mental disorders, including depression, schizophrenia, PTSD, ASD, and ADHD, indicating that optimal iron economy is needed for optimal brain functionality [111]. In a nationwide population-based study, 2957 children and adolescents with iron deficiency anemia (IDA) showed a higher risk than their matched controls of developing unipolar depressive disorder, BD, anxiety disorder, ASD, ADHD, tic disorder, and developmental delay, with a higher risk of developing BD and tic disorder in female patients with IDA [112]. Lee et al. in a more recent nationwide population-based study, showed a similar outcome in 19,397 adults with IDA and 38,794 controls, with a higher incidence of anxiety disorders, depression, sleep disorders, and psychotic disorders in those with IDA. However, they further found a lower risk of psychiatric disorders in IDA subjects on iron supplementation compared to those with no iron supplementation [113]. We previously reported lower serum ferritin levels in COVID-19 patients with psychiatric comorbidities ($n = 212$) compared to COVID-19 patients without psychiatric comorbidities ($n = 416$) [114]. At the other end of the spectrum, using a proxy measure of brain iron concentration (1/nT2*) from 5 min resting-state fMRI data of publicly available cohorts of individuals with schizophrenia ($n = 72$) and matched controls ($n = 73$), Sonnenschein et al. reported a significantly higher amount of iron deposition in the ventral lateral thalamus of schizophrenia patients, which increased with age [115]. Lotan et al. detected higher iron accumulation in the prefrontal cortex of

post-mortem brains of schizophrenia patients ($n = 86$) compared to their matched controls ($n = 85$). Interestingly, they further reported a paradoxical lower expression of ferritin, the iron storage protein that keeps iron in an inactive non-redox state, in schizophrenia patients [116]. Huang et al. reported higher serum ferritin levels in chronic hemodialysis patients with major depression ($n = 15$) compared to those with no major depression ($n = 92$) [117]. Zhu et al. also showed that patients with ischemic stroke ($n = 196$) who developed post-stroke depression ($n = 56$) two months post-stroke had higher serum ferritin levels at admission compared to those with no depression, with a significant association between both serum ferritin levels and depression [118]. Similarly, BD patients in a depressed state exhibited higher serum ferritin levels compared to those with euthymia [119], which implies a change in iron homeostasis even in different BD phases. In a study of serum trace elements in schizophrenia ($n = 11$) and BD patients ($n = 7$ lithium treated and $n = 8$ lithium non-treated), serum iron was significantly high in BD patients without lithium treatment compared to the healthy controls ($n = 11$) [120]. In addition, in a paradoxical sleep deprivation mania model, mice that received deferoxamine, an iron chelator, with n-acetylcysteine, an antioxidant, showed an improvement in manic-like behavior and oxidative damage in both the hippocampus and frontal cortex [121]. However, in a study of 137 patients (schizophrenia = 57 and bipolar disorder = 80), ferroportin was higher only in schizophrenia, with no changes in either condition in serum hepcidin or serum ferritin [122]. These findings should be considered with the limitation of measuring serum levels with no brain iron level detection. An interesting case study of treatment-resistant mania showed an underlying case of neurodegeneration with iron brain accumulation (NBIA), proposing a potential association of resistant mania with iron accumulation [123]. Despite that these studies indicate a plausibly important role of iron homeostasis in BD pathogenesis, the literature is extremely poor in clinical studies on brain iron accumulation in BD either in postmortem tissues or assessed by MRI-based quantitative susceptibility mapping (QSM). Nevertheless, our hypothesis is based on the concept that high brain iron contributes to ferroptosis, and the increased prevalence of bipolar disorder in patients with iron deficiency anemia could be attributed to a different mechanism besides ferroptosis, which necessitate both animal and clinical studies.

Neuroinflammation and iron: Low-grade systemic inflammation and neuroinflammation seem to comprise a piece of BD pathogenesis. For example, BD patients exhibit high plasma levels and brain mRNA expression of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) [28], and high acute phase reactants, such as C-reactive protein (CRP) [124]. Similarly, in a meta-analysis of 18 studies, BD patients showed higher serum levels of pro-inflammatory cytokines, including IL-2 receptor, TNF-α, soluble TNF-α receptor type 1, soluble IL-6 receptor, and IL-4 [29]. Jakobsson et al. reported higher CSF levels of monocyte chemoattractant protein-1 (MCP-1) and chitinase-3-like protein 1 (YKL-40) in 125 BD patients and higher serum levels of soluble cluster of differentiation 14 (sCD14) and YKL-40 in 221 BD patients. They showed a correlation between the serum and CSF MCP-1 and YKL-40, which implies a state of systemic inflammation, neuroinflammation, and microglial activation [125]. Since iron dysregulation is heavily intertwined with inflammation and microglial activation in both directions [126], the reported inflammation in BD could be an inducer or a consequence of iron dysregulation. Interestingly, in a study of drug naïve first episode manic patients ($n = 56$), serum ferritin was positively correlated with the BPRS (Brief Psychiatric Rating Scale) and YMRS (Young Mania Rating Scale) scores and patients showed higher inflammatory indices compared to their matched controls [127]. Nevertheless, whether brain iron overload is associated with neuroinflammation in BD patient has not been investigated and needs further studies.

Neurotransmission and iron: Disrupted neurotransmission, especially of dopamine and glutamate, is another piece of the BD pathogenesis puzzle. Dopamine-increased activity is strongly implicated in manic episodes [128]. In addition, products of dopamine metabolism through monoamine oxidase are pro-oxidants, promoting hydrogen peroxide (H2O2) production and oxidative damage [30]. Glutamatergic dysfunction impacts disease severity [31], with higher levels of glutamate mostly in the anterior cingulate cortex and prefrontal cortex, as shown in magnetic resonance spectroscopy (^{1}H-MRS) studies [32]. Iron is crucial for the function of multiple neurotransmitters, including dopamine, norepinephrine, and serotonin [129]. Iron and dopamine share a toxic relationship since dopamine can increase intracellular iron accumulation and, by doing so, promote an oxidative stress response [130]. On the other hand, iron promotes the toxicity of some of the dopamine metabolism neurotoxic products [131]. Dopamine itself can be auto-oxidized by iron, produces free radicals and be converted into 6-hydrodopamine that inhibits mitochondrial electron transport chain [132]. In addition, iron and glutamate interact, as iron is involved in the synthesis of glutamate by activating cytosolic aconitase enzyme [133] and glutamate can increase the total brain iron content by making it easier for iron to enter the cell through the upregulation of DMT1. Glutamate upregulates DMT1 through nuclear factor κB (NF-κB) and protein kinase C (PKC). PKC enhances DMT1 protein expression through inhibition of DMT1 mRNA degradation [134].

Myelination, neuroplasticity, and iron: Brains of BD patients show gray matter thinning with reduced myelin staining [34] and decreased expression of oligodendrocyte-related genes [33], indicating altered myelination. Iron happens to be indispensable for myelin formation [135]. In line with the disrupted myelination in BD and the possible role of iron dysregulation, Heidari et al. reported that neurodegeneration with brain iron accumulation, a rare group of neurogenetic diseases marked by iron buildup in the basal ganglia, shows both psychiatric features and iron-induced myelin disturbance [136]. Besides altered myelination, patients with BD show altered neurotrophic factors, especially BDNF which was reported to be deficient in both serum [137] and brains of BD patients [138]. Iron overload was repeatedly reported to decrease BDNF levels [139, 140]. Intriguingly, BDNF mimetics show anti-ferroptosis action [141]. Indeed, Li et al. found that, in addition to the anti-ferroptotic actions of electroconvulsive therapy (ECT), it also increased BDNF expression in a rat model of chronic, unpredictable mild stress [142]. Ferroptosis can be responsible for demyelination and loss of oligodendrocytes as shown by Li et al. in an autoimmune encephalomyelitis animal model through ferritinophagy [143].

Mitochondrial dysfunction, calcium influx, and iron: Several lines of evidence have shown that mitochondrial dysfunction and oxidative stress are integral to BD pathogenesis. For example, the mitochondria of BD patients showed morphological abnormalities in the prefrontal cortex neurons in postmortem brain tissues [144]. Mitochondria morphological changes are associated with dysfunction and altered energy metabolism, whereby adenosine triphosphate (ATP) production is insufficient to maintain the Na+/K+-ATPase neuronal activity, which leads to massive calcium (Ca^{+2}) influx followed by glutamate toxicity [24]. This observation of higher calcium influx in BD is intriguing in the context of iron overload since calcium and iron have a bidirectional relationship where high Ca^{+2} influx causes increased LIP and iron overload promotes massive Ca^{+2} influx [145, 146]. In addition, high levels of intracellular Ca^{+2} and iron cause mitochondrial dysfunction, ROS generation, and ferroptosis [147]. This cyclic relation could have an

important role in BD pathogenesis, which needs intensified directed research.

Lipid peroxidation and iron: Being a transition metal, iron can effortlessly exchange electrons and switch between ferrous (Fe^{+2}) and ferric (Fe^{+3}) forms [148]. This transition is tightly controlled to avoid piled-up free Fe^{+2} iron, which would let electrons loose and aid free radical production and oxidative stress [135, 149]. Due to this feature, iron accumulation can foster the production of lipid radicals through a Fenton-like reaction and the progression to lipid peroxidation [74].

Lipid peroxidation and failure of antioxidant systems. Lipid peroxidation, the executioner of ferroptosis [37], has been iteratively reported as a crucial part of BD pathophysiology. A meta-analysis of 60 BD studies showed that BD patients exhibit heightened levels of lipid peroxidation biomarkers, including MDA, 4-HNE, and peroxides. In addition, the ratio of all lipid peroxidation biomarkers to all lipid-associated antioxidant defenses was significantly higher in BD patients, than in both healthy controls and patients with major depressive disorder [150]. Moreover, a meta-analysis of 44 BD-focused studies showed higher levels of MDA and lower levels of GSH, a major part of the lipid peroxidation repair system, in BD patients compared to their healthy controls. They also reported lower levels of glutathione peroxidase (GPX), a lipid peroxidation antioxidant enzyme, in medication-free manic patients [151]. Similarly, a meta-analysis of 11 BD studies showed significantly increased levels of MDA in BD patients compared to healthy controls and decreased MDA levels in patients taking psychotropic medications [152]. Andreazza et al. reported higher levels of peripheral lipid hydroperoxides in 24 euthymic BD patients. Interestingly, peripheral lipid hydroperoxides explained more than half of the variance in white matter alterations in BD patients, using diffusion tensor imaging measures [153]. Post-mortem brain tissues of BD patients also revealed higher levels of HNE-4 compared to nonpsychiatric, non-neurologic controls [154].

Oxidative stress, which is tightly intertwined with lipid peroxidation, has also been heavily reported as an integral part of BD pathogenesis. A meta-analysis of 27 studies ($n = 971$ BD patients) showed higher DNA and ribonucleic acid (RNA) damage along with increased lipid peroxidation and nitric oxide levels, a potent free radical, which implies oxidative stress and the potential failure of antioxidant defenses [155]. To further demonstrate the prominent role of lipid peroxidation in the context of BD, a postmortem brain study of 10 BD patients revealed a disrupted pathway of arachidonic acid (AA), which is a major PUFA in brain cell membranes, in the frontal cortex [60]. They found higher expression of AA-selective cytosolic phospholipase A2 (CPLA2), COX-2, and membrane prostaglandin E synthase (mPGES) in the cortex of individuals with BD compared to controls [38]. CPLA2 releases AA from the membrane, and once AA is free, it can act as a precursor for proinflammatory substances. In addition, COX-2, which is encoded by prostaglandin-endoperoxide synthase (PTGS2), converts AA to multiple prostaglandins, including prostaglandin E2 (PGE2), which is also involved in inflammation. Higher expression of PTGS2, COX-2 and PGE2 is associated with ferroptosis induction [156], while mPGES deficiency is associated with ferroptosis inhibition [157]. Higher expression of PTGS2, COX-2, and mPGES in both ferroptosis and BD makes a compelling argument for ferroptosis being a key component of BD pathogenesis. As a further validation of our argument, lithium, valproate, carbamazepine, and lamotrigine, all lowered the AA turnover or metabolic cascade, showing lower expression of COX-2 and PGE2 in rat brains. While valproate decreased the expression of ACSL4, a major ferroptosis-induction marker [59], clozapine and olanzapine decreased AA plasma availability [158]. Together, these findings suggest the intersection of BD pathogenesis and the ferroptosis executioner, lipid peroxidation. This relationship is also evident at a genetic level, as the deletion of fatty acid desaturase 1/2 (FADS1/2) genes in mice showed BD-like behavior with both hypo and hyperactive episodes, which responded to lithium [159]. Further, in the most recent genome-wide association study performed by the Psychiatric Genomics Consortium BD work group, both FADS1 and FADS2 were part of the top five most significant genes ($p = 1.62e{-}12$ and $p = 9.51e{-}13$ for FADS1 and FADS2, respectively) [26]. Interestingly, FADS2 has been shown to be a ferroptosis inhibitor [160]. In addition, the expression of NrF2, the major antioxidant transcriptional factor, which is a strong negative regulator of ferroptosis [69], decreased in a study of 100 BD patients [161].

Hypothalamic-pituitary-adrenal axis (HPA) disturbance

Aberrant activity of the HPA is associated with the clinical course of BD [35]. A meta-analysis of 41 studies showed that BD is associated with a hyperactive HPA axis with increased levels of basal cortisol, post-dexamethasone cortisol, and adrenocorticotropic hormone (ACTH), which were positively associated with mania and increased risk of cognitive impairment [162]. However, Watson et al. showed persistent abnormalities in the HPA axis in euthymic BD patients [163]. In addition, BD patients, especially at a late stage, show decreased responsiveness of glucocorticoid receptors [164]. In a lateral hypothalamic-kindled rat model of acute mania, serum corticosterone levels increased with an altered dynamic in a mathematical model of the HPA axis [165]. Dexamethasone was found to induce ferroptosis through depleting GSH [166] and through the p53/SLC7A11/GPX4 pathway [167]. These findings suggest a potential intersection of BD and ferroptosis, even at the HPA axis.

Circadian rhythm abnormalities

Patients with BD suffer from sleep disturbance, which is intimately associated with circadian rhythm disturbances and an underlying deficiency or epigenetic modulation of BMAL1/ARNTL and CLOCK (circadian locomotor output cycles kaput), the two main transcriptional factors for circadian clock genes. CLOCK and BMAL1/ARNTL disruption is implicated in inflammation, mitochondrial dysfunction, dopamine, and serotonin disturbance in BD patients [36, 168], as well as in iron dysregulation [169]. The autophagic degradation of BMAL1 and CLOCK, termed "Clockophagy", is a recently identified pathway for ferroptosis [93], which could intersect with BD pathogenesis.

Anti-ferroptosis action of bipolar disorder treatment

Lithium, the gold standard treatment for BD, exerts its therapeutic action mainly through inhibition of the glycogen synthase kinase-3β (GSK-3β) [170]. Interestingly, GSK-3β was reported as a positive regulator of ferroptosis. The pharmacological inhibition or genetic knockdown of GSK-3β caused an increase in ferroptosis resistance by preventing the disruption of iron homeostasis caused by GSK-3β [171]. Additionally, GSK-3β disrupts the antioxidant defense system by manipulating the expression of NrF2, thereby facilitating ferroptosis [172]. Interestingly, the pharmacological inhibition of GSK-3β by lithium activates NrF2, providing plausibility for certain aspects of lithium's mechanism of action to occur through ferroptosis inhibition through the GSK-3β/ NrF2 pathway [173]. Lithium is also implicated in antagonizing lipid peroxidation. In a rat sleep deprivation model, lithium decreased the elevated MDA levels in the hippocampus and forebrain, indicating its role against lipid peroxidation [174]. Some of the antipsychotic medications used in treatment-resistant mania, such as olanzapine and clozapine, also show anti-ferroptotic action. Olanzapine and its derivative, which showed even more potent anti-ferroptosis action, inhibited ferroptosis in mice HT22 hippocampal cells through trapping free radicals, exerting an antioxidant action [175]. Interestingly, Liu et al. found an anti-ferroptosis action of olanzapine against pancreatitis in the mouse pancreatic acinar cell

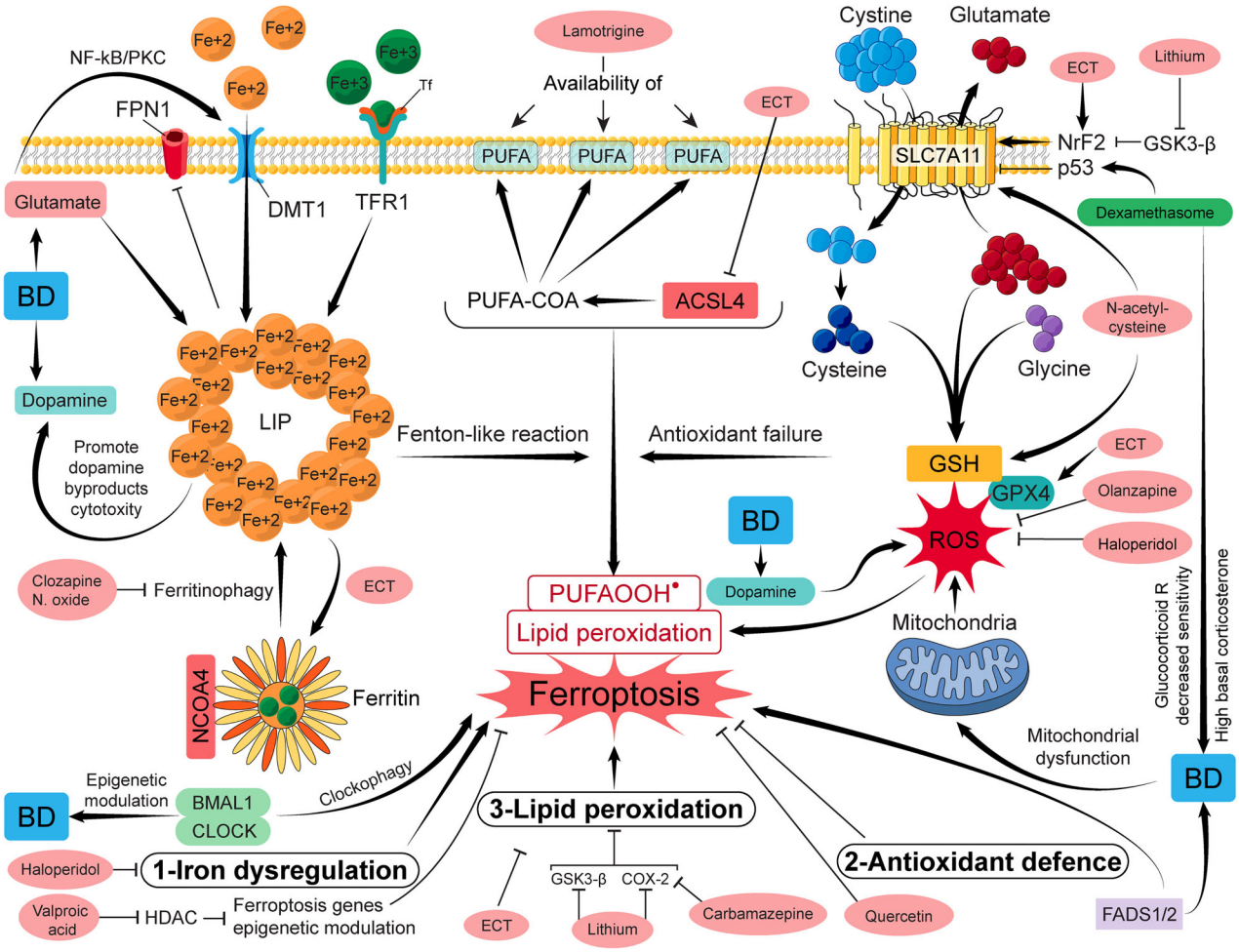

Fig. 3 Hypothetical mechanism of ferroptosis in bipolar disorder pathogenesis. BD shows high glutamate levels, which can increase the LIP by increasing expression of DMT1 through the NF-κB/PKC. The increased LIP, which could happen through higher iron importation by TFR1 and DMT1 or less exportation by FPN1, can promote the cytotoxicity of dopamine byproducts which is already increased in BD. The increased LIP can promote lipid radical formation (PUFAOOH˙) through a Fenton-like reaction, which ends up in lipid peroxidation and ferroptosis. Mitochondrial dysfunction in BD can lead to overwhelming the antioxidant defence system with ROS production. The high dopamine levels in BD can also participate in the increased ROS levels. The antioxidant failure in BD can cause disturbance in GSH, GPX4, and NrF2 which leads eventually to high ROS, lipid peroxidation, and ferroptosis. BD shows decreased sensitivity of glucocorticoid receptors along with high basal levels of corticosterone, while dexamethasone can induce ferroptosis by activation of p53, which decreases the expression of SLC7A11 and, therefore, the entry of cystine and production of GSH. Epigenetic modulation of circadian transcriptional factors (BMAL1 and Clock) is a prominent event in BD and their degradation (clockophagy) induces ferroptosis. FADS2 is strongly implicated in both BD pathogenesis and ferroptosis induction. Multiple BD treatments inhibit ferroptosis. ECT inhibits ferroptosis by activating NrF2, which increases the expression of SLC7A11 and loads Fe^{+2} into ferritin, decreasing the LIP. ECT also activates GPX4 and inhibits ACSL4 and lipid peroxidation. Lithium inhibits ferroptosis by inhibiting the GSK3-β that inhibits NrF2, increasing the expression of SLC7A11. Lithium inhibits lipid peroxidation and ferroptosis by inhibiting both COX-2 and GSK3- β. Carbamazepine inhibits lipid peroxidation and ferroptosis by inhibiting COX-2. Clozapine N oxide, a metabolite of clozapine inhibits ferroptosis through inhibition of NCOA4-mediated ferritinophagy, which decreases ferritin degradation and build-up of the LIP. Haloperidol can inhibit iron dysregulation and thereby ferroptosis. Valproic acid inhibits HDAC, which in turn inhibits the epigenetic modulation of ferroptosis genes and ferroptosis. N -acetylcysteine inhibits ferroptosis by increasing both SLC7A11 and GSH. Both olanzapine and haloperidol inhibit ferroptosis through ROS scavenging action. Lamotrigine decreases the availability of PUFA. BD bipolar disorder, LIP labile iron pool, Fe^{+2} ferrous iron, Fe^{+3} ferric iron, DMT1 divalent metallic transporter 1, TFR1 transferrin receptor 1, TF transferrin, FPN1 ferroportin 1, NF-κB nuclear factor kappa B, PKC protein kinase C, NCOA4 nuclear receptor co-activator 4, ECT electroconvulsive therapy, NrF2 nuclear factor erythroid 2-related factor 2, HDAC histone deacetylase, BMAL1 brain and muscle ARNT-like 1 or aryl hydrocarbon receptor nuclear translocator-like protein 1, CLOCK circadian locomotor output cycles kaput, ROS reactive oxygen species, GSH glutathione, GPX4 glutathione peroxidase 4, SLC7A11 solute carrier family 7 member 11, ACSL4 acyl-coenzyme A synthetase long-chain family member 4, GSK3- β glycogen synthase kinase-3 beta, PUFA polyunsaturated fatty acid, FADS1/2 fatty acid desaturase1/2, COX-2 cyclooxygenase-2.

line 266-6 through its radical scavenging action, which reduced lipid peroxidation [176]. The clozapine metabolite, clozapine-N-Oxide, inhibited ferroptosis-induced dopaminergic cell death through inhibiting NCOA-4 mediated ferritinophagy [177]. Moreover, haloperidol, a first-generation antipsychotic, which can be used in acute mania, showed an anti-ferroptotic effect in hippocampal HT22 cells independent of its antagonistic action on dopamine receptors. Haloperidol decreased ferrous iron accumulation in lysosomes, which decreased ROS production [178]. Further, valproic acid, an anti-convulsant used in BD treatment [179], has been shown to have an anti-ferroptosis action in a cauda equina injury rat model through its known short-chain fatty acid histone deacetylase (HDAC) inhibition [180]. Quercetin is an antioxidant flavonoid that showed improvement

in manic-like behavior in a paradoxical sleep deprivation mouse model through attenuation of lipid peroxidation and enhancement of GSH levels [181]. The same quercetin was repeatedly reported to have an anti-ferroptosis action [182]. N-acetylcysteine, an antioxidant, GSH precursor, and Xc system agonist could act as an adjuvant treatment in BD patients [183]. In a study of 28 treatment-resistant BD patients, ECT showed a decrease in the pre-treatment elevated levels of MDA, a lipid peroxidation biomarker, in responders compared to non-responders [184]. Strikingly, in a rat model of chronic unpredictable mild stress, rats that received ECT showed higher expression of ferroptosis negative regulators, including GPX4, NrF2, and ferritin heavy chain 1, in addition to lower expression of the ferroptosis-inducing ACSL4 [142]. The recently discovered anti-ferroptotic actions of some of the BD treatment is nothing but compelling to elucidate the interplay of ferroptosis molecular machinery and BD pathogenesis (Fig. 3).

CONCLUSION

Ferroptosis can be a missing piece of the unclear pathogenesis of BD. This hypothesis is rooted in multiple observations. First, the association of ferroptosis with multiple psychiatric disorders, which already exist as comorbidities in BD, supports a potential intersection of their mechanisms. The identification of ferroptosis-related genes in schizophrenia, which already shares genetic alterations with BD. Second, the three hallmarks of ferroptosis, iron dysregulation, lipid peroxidation, and antioxidant system failure, are evident in BD patients. Lipid peroxidation, the executioner of ferroptosis, holds an undeniable role in the pathogenesis of BD. Iron disruption, the inducer of ferroptosis, could result in or from inflammation, mitochondrial dysfunction, calcium disturbance, neurotransmission disturbance, and affection of synaptic plasticity and myelination, which are all elements of BD pathogenesis. Third and fourth, HPA axis and circadian rhythm abnormalities are intersection points between ferroptosis and BD. Finally, multiple treatments of BD show anti-ferroptosis action in different contexts. Therefore, we call for studies that address iron accumulation in the brain in BD patients, using QSM and in postmortem tissues of BD patients. We call for genetic studies to look for the genetic signature of ferroptosis in BD patients. In addition, we call for studies on different BD models to assess the expression of ferroptosis markers. Validating our hypothesis would fill an existing gap in the literature and would have tremendous implications for finding both diagnostic and prognostic biomarkers for BD and for expanding the management possibilities.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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