



The Impact of Lithium on Brain Function in Bipolar Disorder: An Updated Review of Functional Magnetic Resonance Imaging Studies

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Abstract

Lithium remains a gold standard treatment for bipolar disorder (BD), and functional magnetic resonance imaging (fMRI) studies have contributed to clarifying its impact on neural circuitries in affected individuals. However, the specific neurobiological mechanisms through which lithium exerts its effects on brain function are not fully understood. In this review, we aimed to summarize the results of recent fMRI studies evaluating the impact of lithium on brain functional activity and connectivity in patients diagnosed with BD. We performed a literature search of available sources found in the PubMed database reported in English since 2016, when the last available review on this topic was published. Five fMRI studies in resting-state condition and six studies performed during the execution of emotional tasks met the inclusion criteria. Overall, the available evidence supports normalizing effects of lithium on brain activity and connectivity. Most of these studies reported a normalization in prefrontal regions and interconnected areas involved in emotion regulation and processing, regardless of the task employed. Importantly, lithium treatment showed distinct patterns of activity/connectivity changes compared with other treatments. Finally, lithium modulation of neural circuitries was found to be associated with clinical improvement in BD. These results are consistent with the hypothesis that selective abnormalities in neural circuitries supporting emotion processing and regulation improve during lithium treatment in BD. However, the heterogeneity of the examined studies regarding study design, sample selection, and analysis methods might limit the generalizability of the findings and lead to difficulties in comparing the results. Therefore, in future studies, larger cohorts and homogeneous experimental tasks are needed to further corroborate these findings.

1 Introduction

Bipolar disorder (BD) is a chronic psychiatric disorder characterized by fluctuations in mood state within recurrent episodes of mania, hypomania, and depression [1]. It occurs in

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Key Points

The precise nature of the changes that lithium exerts on brain function is still uncertain.

Recent functional magnetic resonance imaging studies exploring the effect of lithium on the brain were reviewed.

Lithium appears to regulate prefrontal cortical activity involved in emotion regulation and processing.

Lithium's modulation of neural circuitries is associated with clinical improvement.

approximately 2% of the global population and has a typical onset in adolescence or more rarely in late childhood [1, 2]. BD also appears to be associated with cognitive impairment and low psychosocial functioning, even during periods of remission [3]. Overall, this can lead to a low quality of

life and long-term disability, which significantly impact on direct and indirect public health costs [4].

Over the past decades, a number of consistent neurobiological alterations have been detected in BD. Specifically, several strands of evidence suggest an altered modulation of neurotransmitters, such as dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA), across different mood states [5]. Moreover, at a neural level, several studies found abnormalities in calcium signaling, endoplasmic reticulum stress response, mitochondrial oxidative pathway, membrane ion channel function, as well as circadian system- and apoptosis-related genes [6]. Several neuroimaging studies also found structural brain abnormalities, such as white matter (WM) alterations, especially in structures involved in emotional regulation, such as the anterior frontal lobe, corpus callosum, and cingulate cortex [7]. Also, the increased volume of several brain regions, such as the right lateral ventricular, the left temporal lobe, and the right putamen, seems to be associated with illness duration and time without treatment [8]. Importantly, besides these morphological deficits, the introduction of functional magnetic resonance imaging (fMRI) techniques has contributed to also detecting abnormal brain activity and functional connectivity (FC) in patients with BD [9], which may ultimately help to develop novel interventions [10]. This technique is employed to observe changes in blood oxygen level-dependent (BOLD) signal to identify areas of increased or decreased neuronal activity in resting-state conditions (rs-fMRI) or during the performance of tasks [11]. In particular, task-based fMRI studies analyze and evaluate specific functional domains and brain activation patterns during emotional and cognitive processes, whereas rs-fMRI investigations focus on spontaneous fluctuations in BOLD signal to explore brain functional organization [12]. Many fMRI studies performed during the execution of emotional tasks reported hypo-activation in brain regions that are part of neural circuitries supporting emotion processing, emotion regulation, and reward processing in patients with BD [13–15]. Additionally, many rs-fMRI studies reported FC alterations in cortico-limbic networks in BD [16, 17], which have been also found to be associated with specific patterns of cognitive and affective symptoms in patients with BD [18, 19].

Lithium is one of the most widely used medications for treating BD [20, 21], especially because of its effectiveness across different stages of the disorder [22] and its ability to prevent further mood episodes in maintenance treatment [23, 24]. Indeed, lithium monotherapy remains a first-line option for acute mania and for the maintenance of euthymic state in clinical practice guidelines [25]. Lithium is also recommended in the treatment of bipolar depression, especially in combination with other medications [25]. Moreover,

lithium has been shown to significantly decrease the rate of suicides and overall mortality [26] and reduce cognitive decline in patients with BD [27]. Recent studies suggest that lithium may exert its putative clinical effects by acting on signal transduction and gene expression [28, 29]. Moreover, lithium appears to have complex cellular and intracellular effects, regulating excitatory and inhibitory neurotransmission [29]. Specifically, by acting pre- and post-synaptically, lithium seems to modulate dopamine, glutamate, and GABA neurotransmission. Indeed, lithium appears to inhibit excitatory neurotransmission by decreasing dopamine and glutamate levels [30]. Conversely, inhibitory neurotransmission seems to be promoted by increasing the level of GABA in the plasma [30]. At the same time, lithium seems to also target second messenger systems at the intracellular level, further modulating neurotransmission [31]. Furthermore, several studies found that lithium reduced oxidative stress by modulating the adenylyl-cyclase and phospho-inositide pathways, as well as protein kinase C [31]. Additionally, lithium has been shown to have neuroprotective and neurotrophic properties, promoting cellular longevity and neural plasticity [32, 33].

However, despite these findings, the neural and molecular mechanisms of action of lithium remain unclear. In this regard, several studies have investigated the impact of lithium treatment on structural and functional neuroimaging measures, contributing to the understanding of pathogenetic mechanisms in BD. The most recent reviews on this topic (published between 2008 and 2016) [34–36] summarized the neuroimaging findings of longitudinal and cross-sectional studies that explored the impact of pharmacological treatments on the brain in BD and showed a normalizing effect of mood stabilizers in these patients in terms of brain structure and function. Specifically, Hafeman et al. [35] found that the association between lithium use and increased gray matter volumes (GMV)—particularly in the hippocampus, amygdala, anterior cingulate cortex (ACC), and subgenual cingulate cortex—was the most robust finding observed in the reviewed structural neuroimaging studies. Of note, the authors also reported that GMV increases correlated positively with treatment responses [35]. Additionally, a review of structural MRI studies summarized the effects of lithium treatment on the hippocampus and found that its use was associated with increased volume in patients with BD [37]. More recently, Laidi and Houenou [34] extensively reviewed the functional effects of pharmacological treatments on brain activity in BD and found that mood stabilizers had normalizing effects on prefrontal cortex (PFC) activation during both emotional and cognitive tasks, whereas rs-fMRI studies yielded heterogeneous results [34]. Importantly, only a small number of fMRI studies included in this review specifically assessed the effects of lithium. However, these studies indicated that lithium medication in patients with BD

normalized neural responses to emotional stimuli towards the levels observed in healthy controls (HC) in the globus pallidus/thalamus and the dorsal PFC [38]. Moreover, lithium treatment was associated with inferior frontal gyrus activation when compared with patients with BD not taking lithium [39]. Finally, a longitudinal fMRI study employing a cognitive task examined brain activation differences between pre- and post-lithium treatment in a small sample of patients with BD and showed that, after lithium, the mean brain activation significantly decreased in the precentral gyrus, the supplemental motor area, and Broca's area [40].

Given a growing interest in the functional impact of lithium treatment in recent years [41, 42], we aimed to provide an updated overview of recently published task-dependent and rs-fMRI studies assessing the effect of lithium on brain activity and FC in patients with BD.

We conducted this review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reviews [43]. A comprehensive computer-based search was conducted on PubMed using “bipolar disorder AND lithium AND fMRI” and “bipolar disorder AND lithium AND functional connectivity” until March 2021. We included the articles retrieved directly through the database search combining terms related to the effectiveness of lithium on brain functional activity and connectivity in studies including an fMRI scan in a resting-state condition or during tasks. We included only studies published from 2016 onwards since a previous review was published on this topic before this date [34]. The eligible population included individuals of any sex or age with BD, regardless of the current mood state (euthymic, manic, or depressed). Importantly, we included both longitudinal studies comparing pre- and post-treatment fMRI signals and cross-sectional studies that evaluated patients with BD treated with lithium compared with (1) HC, (2) untreated patients with BD, or (3) patients with BD treated with other medications. Studies using other neuroimaging methods and those that did not specifically explore the effect of lithium treatment were excluded. Finally, we excluded studies that (1) did not include a human sample, (2) were not original research articles, and (3) were written in languages other than English. After title and abstract screening, 66 potentially eligible studies were retrieved for full-text screening. Two members of the team (EB, LDF) independently screened the abstract of the identified records. In case of disagreement, the record was included to allow its evaluation at the next screening phase. The full text of potentially eligible studies was then independently screened by two members of the team (EB, LDF). Any disagreement was resolved by consensus with a third member of the team (ADA). In total, 55 studies were excluded for failure to match the eligibility criteria reported in the previous section. Finally, 11 studies matched our inclusion criteria (five studies in the

resting-state condition and six studies during emotional task investigations) (Fig. 1). A data extraction sheet was created to record the following information: sociodemographic and clinical characteristics of participants, the fMRI methodological approach employed, and the main brain imaging results obtained (Table 1).

2 Resting-State Functional Magnetic Resonance Imaging (fMRI) Studies

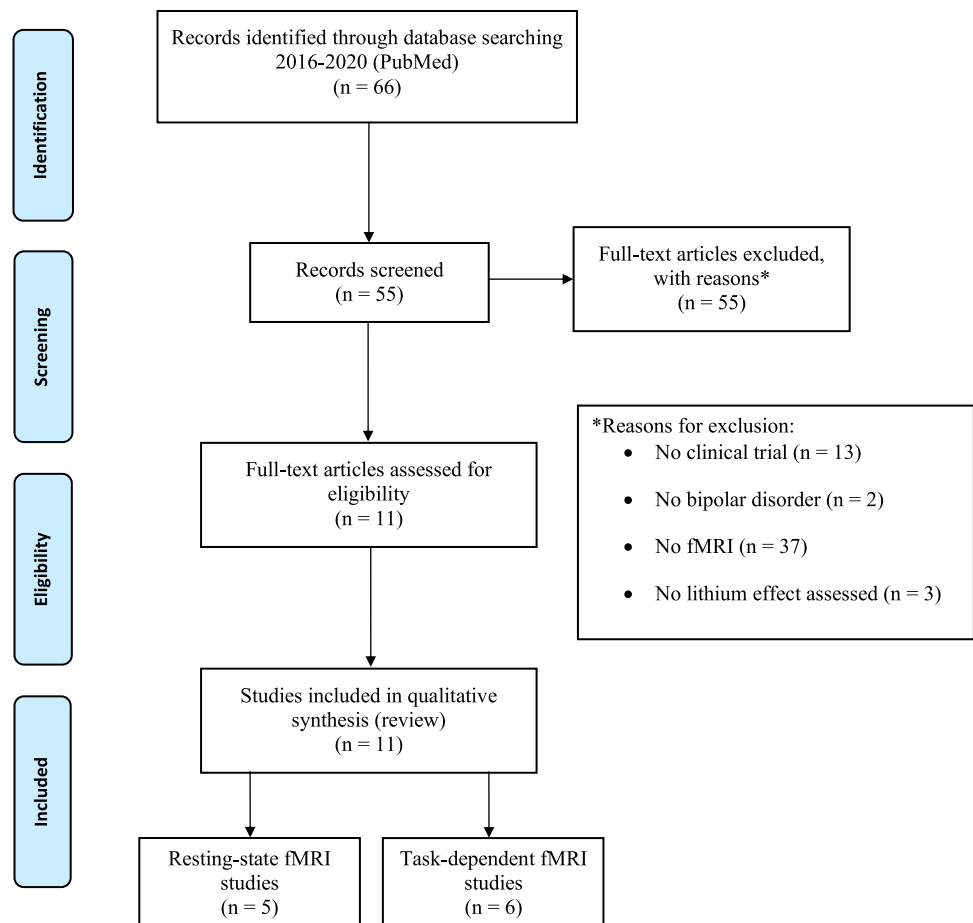
In this review, we included five rs-fMRI studies that assessed the effect of lithium monotherapy on brain FC [44–48].

Altinay et al. [45] evaluated the resting-state FC in 12 hypomanic and 12 depressed patients with BD following treatment with lithium after 2 and 8 weeks. Resting-state FC was also compared with neuroimaging data obtained from 12 HC scanned at the same time points. Lithium monotherapy was associated with increased amygdala–medial orbitofrontal cortex connectivity after 8 weeks of treatment in patients with BD, regardless of their mood state. Moreover, the authors showed that increased amygdala–ventromedial PFC connectivity was correlated with clinical improvement at weeks 2 and 8, as measured with the Clinical Global Impression scale.

Spielberg et al. [44] also showed the effect of lithium monotherapy in a similar sample of 13 hypomanic and 13 depressed patients with BD after 2 and 8 weeks of treatment compared with 13 closely matched HC. In this study, all participants were medication free at baseline for at least 2 weeks prior to study inclusion. Graph theory methods were used to analyze treatment effects on rs-fMRI signal. Lithium treatment was associated with decreased FC between the amygdala and superior frontal gyrus, a brain network previously found to be hyper-connected in patients with BD with (hypo)manic symptoms [49]. Furthermore, the impact of lithium on connectivity differed according to patients' mood at baseline. Specifically, patients who had been hypomanic at baseline showed connectivity decreases over time in the (hypo)mania-related amygdala-centered network, whereas the opposite was observed for those who had been depressed at baseline.

Dandash et al. [46] conducted a single-blinded randomized controlled trial over 12 months in 61 patients with a first episode of mania (FEM) and 30 HC. Notably, patients with aFEM were stabilized for a minimum of 2 weeks on lithium plus quetiapine then randomly assigned to either lithium or quetiapine treatment for 12 months. Of the 61 recruited subjects, 19 in the quetiapine group and 20 in the lithium group underwent rs-fMRI sessions. The effects of treatment on striatal FC were assessed using voxel-wise general linear modelling. At baseline, patients with an FEM showed reduced connectivity in the dorsal and caudal

Fig. 1 Flow chart of study selection. *fMRI* functional magnetic resonance imaging



cortico-striatal systems and increased connectivity in a circuit linking the ventral striatum with the medial orbitofrontal cortex, cerebellum, and thalamus compared with the HC group. Maintenance treatment with lithium reduced abnormally increased FC between the ventral striatum and the cerebellum in patients with a FEM. Interestingly, the authors also found that lithium was faster than quetiapine at normalizing brain hyperconnectivity in patients with BD.

More recently, Zhou et al. [47] examined fractional amplitude of low-frequency fluctuations (fALFF) within the default mode network (DMN) in 29 HC and in a sample of 23 depressed patients with BD at baseline and after 16 weeks of treatment with escitalopram and lithium. After treatment, patients with BD showed increased fALFF in different DMN regions, such as the middle and superior frontal gyrus, ACC, posterior cingulate cortex, precuneus, middle and superior temporal gyrus, and supramarginal gyrus, suggesting that treatment corrected the altered resting-state functionality in BD. Furthermore, the authors found a positive correlation between the change in fALFF within the DMN and the improvement of depression symptoms in Hamilton Depression Rating Scale (HDRS) scores.

Finally, Doucet et al. [48] explored resting-state connectivity in 122 patients with BD and 93 HC using the Person-Based Similarity Index (PBSI) for neuroimaging profiles, a novel method that quantifies the similarity of the neuroimaging profile of each participant to that of the other members of the study sample [50]. Interestingly, the PBSI for connectivity integration of 29 patients treated with lithium compared with those who were not prescribed lithium showed greater similarity with the profiles of HC. Moreover, the degree of similarity between imaging profiles was associated with intelligence quotient (for cortical thickness) and age (for functional integration) rather than clinical variables.

In summary, most of the included rs-fMRI studies [44–47] investigated the longitudinal effects of lithium on resting-state brain networks in the clinical treatment of BD, showing changes in FC after treatment with lithium. The interval between fMRI scans ranged from 8 to 52 weeks. Interestingly, the majority of patients responded or remitted following treatment, regardless of clinical stage and mood phase. However, the substantial methodological differences observed across studies limited the comparability

Table 1 Sociodemographic and clinical characteristics of patients in the included original studies

Study	Participants: N (M/F)	Age, years ^a	Intervention (n treated patients)	Baseline clinical assessment, total score ^a	fMRI method	Study design	Main results
Resting-state fMRI studies							
Altinay et al. [45]	BDD: 12 (7/5) BDM: 12 (4/8) HC: 12 (5/7)	BDD: 35.00 ± 11.00 BDM: 31.00 ± 12.00 HC: 32.00 ± 9.00	LIT monotherapy (24)	BDD HDRS: 21.00 ± 5.00 BDM HDRS: 7.00 ± 4.00 BDD YMRS: 3.00 ± 3.00 BDM YMRS: 16.00 ± 1.00	3 T	Longitudinal study; 8 wk follow-up	Treated pts with BD showed increased AMG-mOFC connectivity after 8 wk of tx. Increased AMG-vMPFC connectivity correlated with clinical improvement at 2 and 8 wk of tx
Dandash et al. [46]	BDM: 39 (30/9) HC: 30 (12/18)	BDM: 21.45 ± 2.31 HC: 21.40 ± 2.46	LIT monotherapy (20) vs. QUE monotherapy (19)	NR	3 T	Longitudinal study; 12 mo follow-up	Pts with BDM receiving LIT showed more rapid normalization of ventral striatum-cerebellum hyperconnectivity than pts receiving QUE at 3 and 12 mo tx
Spielberg et al. [44]	BDD: 13 (8/5) BDM: 13 (4/9) HC: 13 (5/8)	BDD: 36.6 ± 11.8 BDM: 32.5 ± 12.4 HC: 32.8 ± 9.4	LIT monotherapy (26)	BDD HDRS: 20.90 ± 4.50 BDM HDRS: 6.60 ± 3.50 BDD YMRS: 3.20 ± 2.70 BDM YMRS: 15.60 ± 1.40	3 T	Longitudinal study; 8 wk follow-up	Pts with BD receiving LIT showed decreased connectivity in a brain network involving AMG and SFG. Impact of LIT on AMG function differed according to BL mood (AMG clustering coefficient decreased in BDM and increased in BDD)
Doucet et al. [48]	BD: 122 (55/67) HC: 93 (41/52)	BD: 31.81 ± NR HC: 31.29 ± NR	LIT (29), antipsychotics (58), antidepressants (32) or untreated (19)	BPRS 46.3 ± 19.8 BPRS 32.6 ± 8.7	3 T	Transversal study	Pts receiving LIT had greater similarity to HC in network integration than pts not receiving LIT

Table 1 (continued)

Study	Participants: N (M/F)	Age, years ^a	Intervention (n treated patients)	Baseline clinical assessment, total score ^a	fMRI method	Study design	Main results
Zhou et al. [47]	BDD: 23 (12/11) HC: 29 (13/16)	BDD: 19 ± 16–39 HC: 21 ± 15–32	LIT and ESC (23)	HDRS: 23 ± 29–19	3 T	Longitudinal study; 16 wk follow-up	Pts with BDD receiving LIT and ESC had increased activity (fALFF) in FG, bilateral ACC, left angular, left middle temporal gyrus, left superior temporal gyrus, and left supra-marginal gyrus
Task-based fMRI studies							
Strakowski et al. [54] ^a	BDM: 42 (17/25) HC: 41 (20/21)	BDM: 18.00 ± 5.00 HC: 22.00 ± 6.00	LIT monotherapy (19) vs. QUE monotherapy (23)	HDRS: 14.00 ± 8.00 YMRS: 25.00 ± 5.00	EP; 4 T	Longitudinal study; 8 wk follow-up	Pts with BDM receiving LIT or QUE had decreased fMRI activation in AMG and subcortical structures at 8 wk of tx. Activation differences across these regions also associated with clinical remission
Benedetti et al. [53]	BDD AA: 91 (54/37) BDD *G: 108 (70/38)	BDD AA: 48.98 ± 10.94 BDD *G: 46.43 ± 11.94	LIT and chronotherapy (77)	BDD AA HDRS: 11.99 ± 2.43 BDD *G HDRS: 12.67 ± 2.15	FM; 3 T	Transversal study	Treated pts with BDD with the Homer 1 gene AA genotype had increased ACC and pre-central gyrus activation vs. G carriers
Furlan et al. [55]	BDD: 22 (5/17) BDM: 8 (4/4) HC: 36 (12/24)	BDD: 43.32 ± 11.08 BDM: 46.75 ± 11.83 HC: 41.75 ± 8.99	LIT monotherapy (23)	BDD HDRS: 20.16 ± 7.05 BDM YMRS: 25.60 ± 8.76	EP and non-EP; 3 T	Transversal study	Duration of LIT tx associated with increased AMG-parahippocampal gyrus connectivity during emotional processing in pts with BD

Table 1 (continued)

Study	Participants: N (M/F)	Age, years ^a	Intervention (n treated patients)	Baseline clinical assessment, total score ^a	fMRI method	Study design	Main results
Li et al. [52]	BDE LIT: 13 (3/10) BDE VAL: 16(6/10) HC: 16 (7/9)	BDE: 29.6 ± 9.12 HC: 29.4 ± 7.47	LIT monotherapy (13) vs. VAL monotherapy (16)	HDRS: 1.1 ± 1.61 YMRS: 0.8 ± 1.09	EP, FM; 3 T	Transversal study	Pls with BD receiving LIT had increased fMRI activation in the ACC and lingual gyrus in response to the positive pictures relative to neutral pictures than pls receiving VAL and HC
Rootes-Murdy et al. [51]	BDD: 4 (0/4) BDE: 8 (2/6) HC: 21 (6/15)	BDD: 29.75 ± 12.8 BDE: 41.63 ± 14.03 HC: 36.33 ± 12.96	LIT monotherapy (12)	BDD BDI: 14.00 ± 3.37 BDE BDI: 5.29 ± 4.75	EP; 7 T	Transversal study	BD LIT responders had greater fMRI activity in inferior frontal gyrus, middle frontal gyrus, and cingulate gyrus than non-responders. LIT non-responders had increased fMRI activation in superior temporal gyrus, caudate, insula, and inferior frontal gyrus. HC had greater fMRI activation in superior temporal gyrus than LIT responders
Lippard et al. [56] ^a	BDM: 42 (17/25) HC: 41 (20/21)	BDM: 18.00 ± 5.00 HC: 22.00 ± 6.00	LIT monotherapy (19) vs. QUE monotherapy (23)	HDRS: 14.00 ± 8.00 YMRS: 25.00 ± 5.00	EP; 4 T	Longitudinal study; 8 wk follow-up	BDM non-remitters had increased ACC-caudate connectivity and loss of negative connectivity between rACC-AMG than HC. BDM remitters had increased negative connectivity between AMG and ACC

AA Homer 1 gene variant AA homozygote, ACC anterior cingulate cortex, AMG amygdala, BD bipolar disorder, BDD bipolar disorder depressed, BDE bipolar disorder euthymic, BDI Beck Depression Inventory, BDM bipolar disorder manic/hypomanic, BL baseline, BPRS Brief Psychiatric Rating Scale, EP emotional pictures task, ESC escitalopram, F female, fALFF fractional amplitude of low-frequency fluctuations, FG frontal gyrus, FM face-matching task, fMRI functional magnetic resonance imaging, G Homer 1 gene variant G carrier, HC healthy control, HDRS Hamilton Depression Rating Scale, LIT lithium, M male, mo months, mOFC medial orbitofrontal cortex, NR not reported, pls patients, QUE quetiapine, rACC rostral anterior cingulate cortex, SFG superior frontal gyrus, T tesla, tx treatment, VAL valproate, vMPFC ventromedial prefrontal cortex, wk week(s), YMRS Young Mania Rating Scale

^aData are presented as mean ± standard deviation

^bLippard et al. [56] and Strakowski et al. [54] employed the same sample

and generalizability of fMRI findings, which did not yield a specific FC pattern across the samples.

3 Task-Dependent fMRI Studies

Six fMRI studies included in this review explored the effect of lithium in patients with BD on brain activity and connectivity during processing of emotional tasks [51–56].

Li et al. [52] investigated brain activation patterns during emotion processing in euthymic patients with BD treated with either lithium ($N=13$) or valproate ($N=16$) and in HC ($N=16$). All patients were euthymic for at least 3 months before participation in this study. Emotional processing was assessed using an emotional pictures task and a face-matching task. The main findings were that patients with BD treated with lithium showed a higher activation in the ACC and lingual gyrus for “positive versus neutral” contrast than did patients with BD treated with valproate and HC subjects. Of note, no abnormal activity patterns were observed in the amygdala.

In another study that compared lithium and other treatments in BD, Strakowski et al. [54] investigated neural responses to treatment with either lithium or quetiapine for 8 weeks in 42 patients with a FEM and 41 HC during a continuous performance task with emotional distracters. fMRI scans were obtained at baseline and then after 1 and 8 weeks of treatment. The authors found a decreased activation in amygdala and subcortical structures in subjects treated with lithium or quetiapine, ultimately suggesting that medications may modulate abnormal brain hyperactivation in patients with a FEM. Interestingly, patients with BD receiving lithium showed a greater response rate than those receiving quetiapine, although at a non-significant level. Also, observed differences across subcortical structures were associated with clinical improvement on the Young Mania Rating Scale and the HDRS. To extend these findings, the same authors carried out a second study performing a secondary analysis to investigate changes of FC in patients with a FEM who remitted after 8 weeks of treatment compared with those who did not [56]. Specifically, at baseline, non-remitters showed an increase in positive connectivity between the right anterior cingulate and caudate and a loss of negative connectivity between the right anterior cingulate and amygdala, compared with HC. Individuals who remitted following treatment showed an increase in negative connectivity between the amygdala and the left anterior cingulate 8 weeks following treatment, suggesting that differences in FC may represent potential targets of treatment response prediction.

Similarly, Rootes-Murdy et al. [51] examined the relationship between response to lithium treatment and brain function during an emotional face task. A prospective trial in 12 depressed and euthymic patients with BD treated with

lithium monotherapy was conducted for up to 24 months. An additional sample of 21 HC was recruited. Lithium non-responders showed greater activation in the superior temporal gyrus, caudate, insula, and inferior frontal gyrus. Conversely, lithium responders showed increased activation in the inferior and middle frontal gyrus and the cingulate gyrus compared with non-responders. Additionally, lithium responders displayed lower activation in the superior temporal gyrus compared with HC.

Furthermore, in a study that investigated the relationship between disruptions of the immune system and brain connectivity in BD, Furlan et al. [55] measured changes in diffusion tensor imaging and fMRI signal in 30 manic or depressed patients with BD treated with lithium during a face-matching task. Interestingly, they found that lithium treatment was associated with higher circulating immune system natural killer cells and changes in brain connectivity. Additionally, duration of lithium treatment was associated with higher FC between the amygdala and parahippocampal gyrus during emotional processing in patients with BD.

Finally, the same research group [53] also investigated the role of Homer 1 gene variants, which are known to play a crucial role in synaptic plasticity and are a target for antidepressants and mood stabilizers [57], in treatment response in patients with BD. Specifically, 199 patients with BD affected by a major depressive episode were included in this study: 147 patients were studied with structural MRI of grey matter and WM and 50 with fMRI while performing an emotional task. In this study, neural correlates of implicit emotional processing were investigated with a face-matching paradigm task in 50 depressed patients with BD divided according to Homer 1 gene variants. The authors found that, among patients with BD treated with lithium, those with the AA risk genotype showed greater BOLD fMRI neural responses to emotional stimuli in the ACC than did the G carriers.

In summary, most of these fMRI studies employed a task that consisted of the presentation of neutral and emotional pictures to investigate emotional processing in HC and patients with BD [51, 52, 54–56]. These studies indicated that lithium treatment in patients with BD modulated neural activation in regions that have been reported as the key substrates of emotion processing and regulation, such as the PFC, the ACC, and the amygdala [58].

4 Discussion

Taken together, the reviewed studies confirmed that BD is characterized by altered brain connectivity and activation in selective brain regions, not only in the active phases of the illness—either manic [44–46, 48, 54, 55] or depressed [44, 45, 47, 48, 51, 53, 55]—but also in euthymic states [45, 52]. Interestingly, several studies [44–46] reported

altered connectivity between PFC and subcortical structures, especially amygdala and striatum, which is not surprising, especially because the amygdala and PFC are known to play a key role in emotional and cognitive processing and regulation in BD [59, 60]. These abnormalities may play an important role in the pathophysiology of BD and be causally associated with clinical symptoms and manifestations [61, 62]. Specifically, the altered connectivity patterns in brain networks involved in emotional and cognitive processing [63, 64] observed in euthymic patients with BD may result in a poor control of emotions and cognitive impairment, even during periods of remission [65]. This suggests that the euthymic state may not necessarily reflect full recovery [52] and perhaps explains the subthreshold inter-episode symptoms that are commonly observed in BD patients [66, 67].

Importantly, most of the reviewed fMRI studies found an effect of lithium treatment on functional neuroimaging results. Specifically, lithium appears to globally regulate FC [44–48, 55] and brain activation [47, 51–54] in patients with BD across different mood states, although not always in the same direction. Importantly, most of the fMRI studies that compared individuals with BD and HC found that functional abnormalities in patients with BD were reduced after lithium treatment, regardless of the fMRI task employed [44, 48, 51, 52, 54]. These findings suggest that clinical improvement during treatment may reflect a restoration of the physiological FC and activity observed in HC, which seems to be in line with the findings reported by previous fMRI studies in BD [34–36] and in other psychiatric disorders, including schizophrenia [68, 69] and depression [70]. Therefore, overall, these findings support the hypothesis that lithium treatment has ameliorating effects in BD, leading to a more physiological modulation of brain function in brain regions involved in emotion processing and regulation.

In more detail, despite the heterogeneity in study designs and analysis methods, most of the examined studies reported an effect of lithium in similar brain regions that are part of large-scale functional networks in patients with BD [45–47, 49]. Specifically, lithium monotherapy regulated FC between amygdala and PFC [44, 45], suggesting that this treatment may modulate the neurobiological circuitry connected to emotion and cognitive dysregulation in patients with BD [44]. Moreover, the fMRI studies employing emotional tasks to assess the effect of lithium on brain activation reported that this medication increased the activation of different regions known to be involved in emotion processing and regulation in patients with BD, such as the PFC [51], the cingulate cortex [52], and limbic structures, including the amygdala [54]. Therefore, these findings corroborate the hypothesis that treatment with lithium may lead to functional changes in key

prefrontal regions and interconnected cortical and subcortical areas involved in processing of emotional stimuli [34].

Importantly, lithium modulation of brain activity and connectivity of these regions was also associated with clinical improvement in patients with BD [45, 47, 56], as patients with BD who responded to lithium showed increased activation in prefrontal and cingulate cortices [51] and amygdala [54] compared with those who did not respond to treatment. These results support previous findings in the literature [35], suggesting regulatory effects of treatment on cortical and subcortical brain function that relate to improvement in manic or depressive symptoms of patients with BD.

Interestingly, several fMRI studies compared the neural effects of lithium with those of different pharmacologic treatments commonly used in BD. Specifically, lithium was compared with anticonvulsant mood stabilizers and atypical antipsychotics in both resting-state [46, 48, 52] and task-dependent fMRI studies [54, 56]. In this regard, the action of lithium was more rapid than that of quetiapine in normalizing altered brain activation/connectivity in treated manic patients with BD [46, 54]. Additionally, patients with BD receiving lithium compared with those receiving other pharmacological agents showed increased activation in the cingulate and visual cortex during emotional processing [52] and greater similarity in FC with the profiles of HC [48]. Taken together, these findings suggest that distinct types of medications may have different effects on brain activity/connectivity, albeit converging towards similar effects in terms of clinical improvement. Indeed, distinct classes of medications may influence brain functional activity and connectivity based on their specific mechanisms of action, leading to patterns of neural changes characteristic for each drug [35]. However, the exact molecular mechanisms by which different pharmacological agents exert their effects on specific brain structures are still unknown and therefore require further investigations.

Finally, the present review also included fMRI studies that examined the interactions between the immune system [55] or genetic polymorphisms (Homer 1) [53] and neural function in patients with BD treated with lithium. This is not surprising, especially because increasing evidence suggests that BD pathogenesis may be associated with immune dysfunction [71] and genetic factors [72].

From an immunological perspective, the evidence of an association between the circulating immune system natural killer cells and changes in brain connectivity of patients with BD treated with lithium found by Furlan et al. [55] aligned with previous findings reporting the effect of lithium on immune cell functions [73], such as the regulation of proliferation and apoptosis of lymphocytes [74]. In turn, this may suggest that the effect of lithium on the immune

system could be part of its mechanism of action in modulation of brain activity and connectivity in BD. Similarly, from a genetic point of view, the results reported by Benedetti et al. [53] of different patterns of brain activation in patients with BD receiving lithium associated with distinct Homer variants are in agreement with previous evidence showing that the gene variants of Homer 1 are associated with lithium responsiveness in patients with BD [57, 75], ultimately suggesting that genetic polymorphisms might play a role in response to lithium and its effects on brain function, possibly contributing to the choice of treatment in future clinical practice.

5 Limitations

The presented findings should be interpreted with caution and considered in light of several limitations. First, many studies used small samples, with heterogeneous clinical characteristics (e.g., illness phase, patients with bipolar type I and/or those with bipolar type II), which are not suitable to detect small fMRI signal differences and might be biased by other confounders, such as specific clinical variables. Second, included studies presented heterogeneous study designs (e.g., cross-sectional vs. longitudinal designs), which might have limited the generalizability of the findings. Third, some of the included studies also differed in terms of treatment duration, mean dosage, and type of other medications that were used to compare lithium effects, which may have had a confounding effect on neuroimaging findings. Finally, the heterogeneity in fMRI methodology and analysis led to difficulties in comparing the results of the included studies. For example, task-based fMRI studies focused on different brain regions that were functionally involved in a specific task performance, so the choice of a specific fMRI paradigm may have influenced the results. To address these limitations, future research needs to employ larger cohorts and homogeneous experimental designs.

6 Conclusion

Although the heterogeneity of samples, study designs, and methodologies limited the comparison of fMRI findings, the majority of reviewed studies found that lithium had normalizing effects on brain circuitries in patients with BD. Specifically, the available evidence suggests that lithium treatment regulates the activity and connectivity of brain regions involved in emotion regulation and processing, regardless of the task employed. Importantly, these functional changes might represent an indication of general clinical improvement in patients with BD.

Nonetheless, future research can shed more light on the underlying mechanisms responsible for the effects of lithium on brain function by employing larger cohorts of patients, including those treated with other mood stabilizers, which may be paramount to disentangle the specific effect of lithium in these areas. Prospectively, although the functional imaging research represents a unique approach to unraveling the neural mechanisms of medication effects and identifying specific biomarkers of treatment outcome, the utility of functional neuroimaging findings to predict individualized treatment response remains to be clarified. Indeed, large multicenter studies have only recently begun to investigate the prediction of treatment response and tolerability with the support of multi-modal biomarkers, including fMRI data [76].

Declarations

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Author contributions LDF and GD designed the literature review and methodology. EB and LDF searched the literature, selected, and reviewed the collected studies, and wrote the first draft of the manuscript. ADA, GD, and PB revised the manuscript. All authors agreed with the final content of the manuscript. All authors agree to be accountable for the information presented in the manuscript.

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