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REVIEW

Reviewing applications of structural and functional MRI for bipolar disorder

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Abstract

Bipolar disorders (BDs) represent one of the leading causes of disability and morbidity globally. The use of functional magnetic resonance imaging (fMRI) is being increasingly studied as a tool to improve the diagnosis and treatment of BDs. While morphological biomarkers can be identified through the use of structural magnetic resonance imaging (sMRI), recent studies have demonstrated that varying degrees of both structural and functional impairments indicate differing bipolar subtypes. Within fMRI, resting-state fMRI has specifically drawn increased interest for its capability to detect different neuronal activation patterns compared to task-based fMRI. This study aims to review recently published literature regarding the use of fMRI to investigate structural–functional relationships in BD diagnosis and specifically resting-state fMRI to provide an opinion on fMRI's modern clinical application. All sources in this literature review were collected through searches on both PubMed and Google Scholar databases for terms such as 'resting-state fMRI' and 'functional neuroimaging biomarkers of bipolar disorder'. While there are promising results supporting the use of fMRI for improving differential accuracy and establishing clinically relevant biomarkers, additional evidence will be required before fMRI is considered a dependable component of the overall BD diagnostic process.

Keywords Neuroimaging · fMRI · Biomarkers · Grey matter · White matter · Resting-state fMRI · Psychiatric disorders · Bipolar depression disorder · Mood disorder

Introduction

Psychiatric disorders are a series of mental health conditions that have historically been diagnosed on the basis of behavioral observation. This process is often highly inaccurate, as it relies upon a variety of subjective factors such as self-reporting, communication, and symptom awareness. With the multitude of inaccuracies and uncertainties that stem from this diagnostic pipeline, there is a clear need for more reliable diagnostic measures. Compounding the difficulty in identifying psychiatric disorders, there is a potential problem when a patient who has already been screened begins to demonstrate new symptoms or changes in presentation, also called diagnostic overshadowing [1]. Furthermore, patients that cannot be thoroughly examined or refuse to cooperate interfere with examinations that rely on active participation.

Bipolar depression disorder (BD) is considered one of the leading disabling psychiatric conditions. There are many questions regarding its pathophysiology as it is an affective disorder that undergoes varying fluctuation levels [2]. Its etiology is also unknown, although both genetic and environmental factors have been determined to contribute to risk of development. To further complicate the issue, bipolar depression disorder (BD) and unipolar depression disorder (UD) are frequently miscategorized. Although 20% of BD individuals receive the correct diagnosis during a depressive episode within the first year of seeking treatment, nearly 60% of BD individuals are initially diagnosed with UD depression [3]. In attempts to refine the diagnostic process, researchers are investigating neuroimaging as a method of establishing a solidified relationship between specific brain

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structures and understanding the neural substructure of psychiatric disorders. Over the last decade, there has also been increased interest in establishing clinically pertinent biomarkers for psychiatric disorders. These biomarkers have multiple clinical applications, including improving the diagnostic accuracy of BD and providing supplemental information for observations and interviews [4]. Additionally, biomarkers may also illustrate varying progressive stages of BD, which can help streamline treatment options depending on its severity. While structural magnetic resonance imaging (sMRI) has repeatedly identified potential biomarkers for bipolar disorder, a lack of understanding regarding the pathophysiology of this psychiatric disorder and its subtypes has obstructed the establishment of legitimate biomarkers from a united perspective.

Functional magnetic resonance imaging (fMRI) is considered to be a useful methodology for identifying biomarkers in both diagnostic and therapeutic processes [5]. This imaging technique is currently one of the most used neuroimaging modalities, alongside sMRI and positron emission tomography (PET) scans [6]. While task-based fMRI has been widely utilized to discern cognitive abnormalities in functional activation, the conduction of resting-state fMRI has garnered significant interest as a pathway towards discerning legitimate biomarkers. Hohenfeld et al. describe this imaging modality as a "biomarker-surrogate" that can be used to gain insight into obtaining true biomarkers [7]. Functional MRI focuses on the blood oxygen level-dependent (BOLD) signal to map neuronal activity as a function of external oxygen uptake. Resting-state fMRI expounds on this imaging method by monitoring changes to the BOLD signal when there are no stimulus or explicit tasks being done [8]. This methodology is capable of exploring the intrinsic segregation and specialization of brain neural networks.

In this review, we aim to scrutinize the recent literature to determine the diagnostic applications and limitations of task-based and resting-state fMRI in BD. More specifically, we report on the use of fMRI to determine structural–functional relationships, and we collect analysis results of resting-state fMRI in investigating limbic-system-specific biomarkers for accurate and specific diagnosis for BD.

Methods

The search for relevant literature involved both PubMed and Google Scholar databases. Our search included terms related to fMRI and neuroimaging for psychiatric disorders, such as 'Neuroimaging', 'fMRI', 'biomarkers', 'grey matter', 'white matter', 'resting-state fMRI', and 'psychiatric disorders' among others. We excluded studies published before 2000, as well as preprints, pre-clinical trials, duplicates, and studies with redundant information such as those with overlapping patient cohorts. The remaining 40 studies were selected for synthesis by the authors based on their relevance to the topic in question. Table 1 below shows the number of subjects and mean age of the included studies (Table 1).
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Results

Structural findings and biomarkers

Structural neuroimaging has concretely established multiple brain abnormalities in varying BD subtypes. Recent findings indicate that BD patients demonstrate morphological abnormalities in both grey and white matter. For example, grey matter atrophy has been recorded in both the inferior and left superior frontal gyrus, while white matter integrity was seen to be reduced in the superior longitudinal fasciculus and the corticospinal tract [9]. Grey matter volume reductions in the lateral orbitofrontal cortex have also been recorded in

Table 1 Number of subjects and mean age (±standard deviation) in years for the studies included in the "Results"

Study	Number of bipolar subjects	Mean age (±SD)
Syan et al. (2018) [8]	897	34 ± 5.26
Tang et al. (2020) [9]	35	31.49 ± 8.05
Nugent et al. (2006) [10]	36	39 ± 8.1
Lan et al. (2020) [11]	32	35.9 ± 11.7
Ott et al. (2019) [12]	29	43.97 ± 10.40
Hibar et al. (2018) [13]	1837	38.3 ± 11.7
Koshiyama et al. (2020) [14]	211	45.7 ± 11.6
Velakoulis et al. (2006) [15]	89	34.9 ± 9.6
Tang et al. (2018) [16]	43	32.51 ± 5.31
Rosso et al. (2007) [17]	20	23 ± 3
Damme et al. (2020) [18]	114	20.71 ± 2.00
Maletic et al. (2014) [19]	–	–
Nunez et al. (2011) [20]	19	11.1 ± 2.6
Lu et al. (2009) [21]	24	10.54 ± 2.81
Joshi et al. (2016) [22]	45	39.9 ± 12.1
Townsend et al. (2012) [23]	32	37 ± 13
Altshuler et al. (2005) [24]	11	36 ± 7.6
Radua et al. (2012) [25]	965	24, range 15–35
Calhoun et al. (2009) [26]	–	–
Chen et al. (2011) [27]	1040	–
Ambrosi et al. (2017) [28]	36	31.0 ± 11.3
Yu et al. (2020) [29]	23	28.52 ± 10.17
Du et al. (2019) [30]	32	–
Brady et al. (2017) [31]	47	29.3 ± 11.5
Wang et al. (2020) [32]	1047	–

individuals receiving medication for both bipolar I and II [10]. BD patients also present a deficit of axial diffusivity compared to major depressive disorder or healthy volunteer populations [11]. The hippocampus has also been targeted as a potential biomarker for BD, and sMRI has repeatedly observed hippocampal volume reduction across multiple neuropsychiatric disorders [12]. In a multicenter study of 1837 adults with BD, Hibar et al. noted markedly thinner cortical grey matter in the temporal, parietal, and frontal regions in both hemispheres. Additionally, BD was associated with reduced surface area and thickness in the supramarginal gyrus and insula [13]. Furthermore, Koshiyama et al. observed lower fractional anisotropy in the cingulate gyrus and white matter irregularities in the fornix and corpus callosum in individuals with BD when compared to healthy control subjects [14].

The amygdala has been a popular region of interest in characterizing BD and other psychiatric disorders. More generally, lesions of the amygdala are connected to deficits in emotional expression and memory. Although most studies report decreased amygdala volumes in bipolar youths, this has not been the case for adults. Recent examinations of BD adult individuals have been varied, demonstrating both increased and decreased amygdala volumes [15–17]. In a meta-analysis of literature focusing on this topic in adolescents with BD specifically, it was concluded that structural amygdala abnormalities are present in bipolar youths, but the same irregularities did not appear to be present in adults. These results suggest that there are age-specific changes in structural and functional connectivity. Tang et al. recently published a cross-sectional study examining structural and functional connectivity in the prefrontal–amygdala circuitry of women placed in different age groups and found that changes in the structural composition of this circuitry are associated with BD in women aged 26–45 years [16]. Interestingly, because amygdala volume is generally measured following the onset of BD, it is not concretely known whether abnormal volume levels predate BD risk or are merely associated with the disorder. Additionally, a significant amount of past literature has treated this region of interest as a homogenous structure without considering the potential issues that may arise due to its many differences in connectivity to other areas of the brain [18]. These observations coupled with treatment-related improvement across BD, schizophrenic, and unipolar disorder patients illustrate how structural neuroimaging has firmly contributed to improving clinical treatment of BD.

A wide majority of recent studies have utilized single-modality MRI, whether solely structural or functional. As this understandably limits the amount of the brain that can be seen, a combined structural–functional multimodal imaging analysis has been seen to provide deeper, more extensive insight. While revealing promising results through structural neuroimaging, Tang et al. discussed how the incorporation of functional imaging data could help explore a potential structural–functional covariant pattern in BD [9]. This is not to discredit the usefulness of structural neuroimaging, as there have been many positive morphological abnormalities identified in BD patients. However, the importance of understanding intrinsic functional irregularities cannot be overstated. Identifying deviations from expected connectivity may provide information on BD progression, as well as give information regarding potential vulnerability to developing BD.

Standard fMRI findings

Structural and functional distinctions are increasingly being recognized as a more precise and objective assessment tool for diagnosis compared to behavioral evaluation. While potential structural biomarkers in bipolar disorder have been obtained through sMRI, it is hypothesized that the structural reductions in grey matter may correlate to functional deficits. An observed decrease in prefrontal cortical activity may contribute to inadequate management of the default mode network (DMN), which has an effect on mood and cognitive processing. Furthermore, both grey and white-matter differences have been reported in the early stages of BD progression [19]. Decreased thickness is not the only factor that may impact neuronal processing; multiple studies have already published examples of reduced activation stemming from increased inferior frontal cortex (IFC) thickness. Nuñez et al. reported that decreased activation intensity in the right inferior frontal gyrus (IFG) was associated with a pattern of increased thickness in the right pars triangularis [20]. Reduced activation was also linked to increased IFC region thickness during orthographic processing tasks in a study examining the relationships between brain activation and structure in cohorts of normally developing children [21]. Furthermore, Joshi et al. report that reduced cortical thickness is associated with reduced cingulate fMRI activation, as well as a thinner cortex being associated with increased fMRI activation in bipolar patients [22]. Together, these findings suggest that reduced activation in the cingulate region may possess an underlying structural etiology, highlighting the importance of future research to simultaneously assess both structure and functionality. In stable mood state patients with bipolar I disorder, functional neuroimaging during the performance of a response inhibition task showed significantly reduced activation in the region of interest compared to healthy subjects [23]. Additionally, an evaluation of activation in the lateral orbitofrontal cortex found robust activation of the right orbitofrontal cortex in control subjects only [24]. Radua et al. used a multimodal meta-analysis to characterize a close relationship between structural and functional brain alterations, albeit in individuals with the

first episode of psychosis. An abnormal functional response was also demonstrated in the bilateral insulae as well as the medial anterior cingulate cortices [25].

Relationships between structural and functional observations should continue to be explored, as multiple studies have shown reduced regional activation to be connected with response inhibition. Future results can potentially provide information regarding the clinical progression and illness severity of BD. To better analyze information and improve the diagnostic process, utilization of multimodal imaging data is becoming increasingly popular. Calhoun et al. reported on combining independent component analysis with fMRI data to accurately differentiate between BD, schizophrenia, and healthy control patients [26]. Functional neuroimaging has been used to more precisely diagnose and classify BD disorder. For example, through functional neuroimaging, researchers have been able to better discern the nuanced differences between BD subtypes and differences between BD subtypes and psychiatric disorders [3]. Additionally, identifying the specific functional ramifications that accompany identified abnormalities in gray matter, white matter, and neurological bodies may result in the development of legitimate biomarkers; therefore, contributing information for utilization in various intervention methods.

While functional MRI has broadly improved neuroimaging in diagnosing patients, studies have utilized two types of fMRI patient environments for collecting data. Both resting-state and task-based fMRI highlight the patient's condition during collection of BOLD signals. With task-based fMRIs, neuronal BOLD signals are tracked while the participant performs a task. This form of functional mapping has been successful in identifying some biomarkers and differentiating psychiatric disorders. However, resting-state fMRI, during which the participant is not being neuronally stimulated and the BOLD signals are collected when the patient is in a resting state, has been shown to be a different avenue for determining more legitimate biomarkers. Signals detected in the absence of neuronal stimulation better reflect intrinsic functional brain networks and regions.

Resting-state and task-based MRI

Research has used both resting-state and task-based fMRI for diagnosing and categorizing BD. For example, researchers have observed attenuated activation of the inferior frontal cortex with emotional and cognitive tasks as well as enhanced limbic activation with emotional tasks [27]. While results like those from task-based fMRI have been helpful, many researchers are looking towards increased utilization of resting-state fMRI. Because resting-state fMRI results are collected in an unstimulated state, the neuronal functional connectivities can indicate disease progression. Furthermore, resting-state fMRI emphasizes the 'background' noise and spontaneous brain activity that task-based imaging regularly tries to minimize. Hohenfeld et al. investigated biomarkers for Alzheimer's and Parkinson's disorders using resting-state fMRI. While this study focuses on BD, its findings demonstrate that resting-state fMRI can be used as a "biomarker-surrogate." That is, although resting-state fMRI does not detect the neural network activation patterns seen in the presence of stimulus, it does detect the characteristic networks and spontaneous brain activation that give insight into neuronal activation patterns [7]. Because BD has been linked to dysregulation in emotional processing and regulation, resting-state fMRI would also be a better avenue compared to task-based for further investigations. Furthermore, there has been extensive investigation of a brain region called the default mode network (DMN) that routinely decreases activation during attention-demanding tasks. This region has been tied to BD subtype categorization and targeted imaging of the DMN provides insight task-based fMRI could not provide.

When imaging BD patients, resting-state fMRI has uncovered a multitude of biomarkers linked to BD and its subtypes. Ambrosi et al. observed differences including lower levels of resting-state functional connectivity between the left insula and mid-dorsolateral prefrontal cortex in BD patients compared to individuals with major depressive disorder or healthy controls, indicating the possibility of varying pathophysiological mechanisms producing emotional dysfunction in these disorders [28]. While both unipolar depression and bipolar depression demonstrate abnormal frontal and sensorimotor network functional connectivity, Yu et al. determined that bipolar depression exhibited more widespread affected connectivity patterns that primarily encompassed the sensorimotor network [29]. "Neuromark" is a newly developed framework that utilizes independent component analysis (ICA) to extract functional network information; usage deriving functional network measures was demonstrated to classify BD with an individual-class accuracy of 89%. This study also reported > 90% classification accuracy between BD and UD patients with overlapping depressive symptoms, highlighting the promise of potential brain imaging biomarkers compared to traditional behavioral evaluation [30]. Within BD patients, studies have also shown resting-state fMRI can be used to differentiate functional connectivity of the DMN across BD mood and trait states [31, 32]. Further, abnormal functional connectivities have been observed in the amygdala, ventrolateral prefrontal cortex, cingulate cortex, and medial prefrontal cortex among BD patients compared to healthy controls. A recent study suggests that stability in the default mode network, salience network, and frontoparietal network may be indications of BD patients in remission [8]. In general, while task-based fMRI has revealed many neurological markings of BD, resting-state fMRI utilization has provided a new avenue for a

more comprehensive evaluation of the BD patient's underlying pathology. The key results and limitations of these studies are summarized below (Table 2).

Discussion

At present, the determination of fMRI's true clinical and diagnostic applicability should remain a subject of extensive research going forward. This review examines the most recent findings regarding potential biomarkers located within the limbic system and the potential utility of resting-state fMRI in identifying legitimate biomarkers. While many studies contend that sMRI plays a significant role in the identification of structural irregularities in bipolar patients, the importance of developing a deeper understanding of the relationship between structural and functional abnormalities should not be undervalued. By utilizing neuroimaging for the purpose of identifying disease biomarkers, this will in turn affect the implementation of various treatment modalities and elucidate biological pathways within the brain [33].

However, although studies have yielded promising results, resting-state fMRI is still at times viewed with skepticism within the neuroradiology community [34]. One reason for this is that the fMRI blood oxygen level-dependent activity (BOLD) signal develops at a gradual pace and can result in poor temporal resolution. However, this tradeoff can be considered necessary to obtain real-time functional data [35]. While there is promise to the idea of identifying structural–functional relationships in individuals with bipolar disorder, it is possible that these functional deficits and abnormalities are correlated to the structural disturbances of connected areas, rather than the region of interest itself.

The aforementioned Du et al. study detailing Neuromark as a method for extracting functional network biomarkers utilizes multivariate source-based morphometry (SBM) with an ICA component [30]. SBM has been increasingly utilized as an alternative to voxel-based morphometry (VBM) when investigating functional connectivity due to the fact that VBM is limited as a univariate method. Ashburner and Friston detail the assumptions of voxel-based morphometry including correct identification of the structures being evaluated and the elimination of confounding effects, while discussing potential improvements to the segmentation process. [36]. In a study incorporating ICA to determine gray matter variations respective to schizophrenia (SZ), Xu et al. present their SBM approach as an alternative to VBM and reported a difference in results when comparing the two methods of harrianalysis. The most significant source of gray matter changes identified by the SBM approach occurred in the bilateral temporal lobe; conversely, the VBM approach identified the thalamus as the location of these changes. Furthermore, SBM was able to identify changes in other brain structures such as the basal ganglia and parietal lobe, demonstrating how it can be a viable alternative to VBM [37]. Related to Xu et al.'s schizophrenic focus, Sorella et al. used SBM to examine dissimilarities in gray matter between BD and SZ patients, finding that SZ is characterized by deficits in a specific network (IC 6). This study represented the first usage of SBM to investigate the neural bases in a comparative manner between BD and SZ patients, and the discovery of this observation encourages the continued use of SBM to examine the relationship between these disorders [38]. In a recent study, SBM was used to examine the relationship between tumor necrosis factor (TNF)-α and gray matter networks in major depressive disorder (MDD) patients [39]. Although conducted with small sample sizes, the authors were still able to identify an association between elevated serum TNF-α levels in early MDD progression with changes within the prefrontal network [39]. When taken together, these studies demonstrate the practicality of multivariate source-based morphometry in the analysis of psychiatric disorders and encourage the continued use of SBM to identify more relationships among the various brain networks.

Furthermore, one of the hallmarks involving the definition of a biomarker is reliability, and there is still uncertainty regarding how results involving reproducible networks can be applied on an individual basis. Even cooperative patients can cause physiological noise that can confound data. For example, respiration, though unavoidable, can produce inaccurate connectivity patterns if abnormal and may not completely get filtered out [34]. Still, enthusiasm regarding this imaging modality should not be tempered, provided that focus is directed on overcoming standardization issues, minimizing physiological noise, and improving the reliability and reproducibility of results. Although this methodology has the potential to elucidate the mechanistic underpinnings of psychiatric disorders, the absence of an externally mediated behavior means that it will likely continue to work in conjunction with, rather than in lieu of, standard task-based imaging.

Neuroimaging as a whole should continue to play a large role in the search for biomarkers of bipolar disorder. While sMRI has produced promising results, functional neuroimaging has demonstrated strong clinical utility, as well as variations in functional activity, that appear to be roughly tied to a potential structural etiology [19, 40]. To evaluate potential abnormalities in the frontal cortex, resting-state fMRI has emerged as a preferred imaging modality over traditional task-related fMRI from a clinical perspective. Any abnormalities discovered may help define intervention targets with increased precision. Future research should continue to work towards determining the full clinical utility of resting-state fMRI methods of analysis. A standardized method of data collection is required for any evidence to be considered significant going forward. Observed functional abnormalities

Table 2 Results and limitations of fMRI studies on bipolar disorder

Study focus	Study name	Results	Limitations
sMRI	Syan et al. (2018) [8]	Stability of DMN, FPN, and SN may be indicative of remission rsFC changes between prefrontal cortex, cingulate cortex, and amygdala may indicate neural correlation to symptoms experienced in BD euthymia	Relies on ability of patients to keep a "clear mind" Lack of existing studies on women of reproductive age affected by hormonal fluctuations Variation in size and location of ROIs
	Brady et al. (2017) [31]	DMN and dorsal attention network display significant connectivity alterations associated with bipolar mood states These patterns also distinguish BD euthymia from healthy controls Behavioral pathology related to increased connectivity	Patients not studied longitudinally Medication effects between patients was variable Study meant to serve as a complementation to existing BD models
	Du et al. (2019) [30]	Potential to be expanded to multimodal imaging data Can be utilized to differentiate BD and MDD with high accuracy using spatial networks Detected subtle dynamic functional connectivity differences that can assist with progression in dementia	Study utilized two independent datasets Did not explore network estimation at different parcellation levels
	Hibar et al. (2018) [13]	Decreased cortical grey matter in the temporal, parietal, and frontal regions bilaterally Reduced supramarginal gyrus and insula surface area and thickness Decreased frontal, medial parietal, and occipital cortical thickness associated with longer duration of illness	Moderating factors of BD (e.g., substance use) were not accounted for in this study Sample populations came from heterogeneous datasets from all over the world
	Koshiyama et al. (2018)	Decreased fractional anisotropy in the cingulate gyrus in BD patients Increased mean diffusivity in the body and fornix of the corpus callosum in BD patients Decreased radial diffusivity in the fornix and whole-brain white matter skeleton in BD patients	Differences in MRI scanning techniques across study subpopulations Environmental and genetic effects were not investigated
	Wang et al. (2020) [32]	BD patients present decreased connectivity within affective network in acute episodes specifically DMN displays decreased connectivity in acute state, increased connectivity in remitted state Altered connectivity within DMN implies trait-related cognitive impairments	Insufficient complete datasets for BDM and BDD May have missed alterations between BDM and BDD due to combining the results Meta-analysis did not cover alternative analytic methods such as independent component analysis Varying physiological states, physical movement of patients
	Ambrosi et al. (2017) [28]	Lower rsFC between bilateral insula and right frontopolar prefrontal cortex (FPPFC) Lower rsFC between left insula and left mid-dorsolateral prefrontal cortex Reported 78% accuracy differentiating BD and MDD in left posterior insula/right FPPC	Did not exclude depressed patients with comorbid substance use Utilized seed-based approach which can limit detection Unclear whether rsFC findings reflect emotional states or diagnosis-specific characteristics

Table 2 (continued)

Study focus	Study name	Results	Limitations
fMRI	Tang et al. (2020) [9]	GM atrophy in inferior frontal gyrus and left superior frontal gyrus associated with WM integrity reduction in corticospinal tract No statistical correlation between mixing coefficients of GM and WM components Showed age-associated GM changes in Bd patients compared to healthy individuals	Validation could be supported by expanded sample size Potential confounding effects due to medication prescribed to BD patients Structural–functional relationship could have been further explored through functional imaging
	Nugent et al. (2006) [10]	Revealed morphometric abnormalities in BD patients in regions such as medial and orbital PFC, STG, and PCC Observed that reductions in GM in BD patients appear to be left-lateralized; consistent with previous studies	Limitations of the VBM method include increased likelihood of Type I error and reduction in sensitivity for detecting volumetric abnormalities Inclusion of subjects with remote history of substance abuse
	Lan et al. (2020) [11]	Identified cluster of lower axial diffusivity (AD) in BD patients compared to healthy volunteers in the superior longitudinal fasciculus, inferior longitudinal fasciculus, and fronto-occipital fasciculus Results indicate deficit of AD in BD compared to both MDD and HV groups No association between AD in BD compared to cerebral perfusion, BMI, or blood pressure	Study design is a secondary analysis; data were not streamlined towards target information Potential confounding effects due to medication prescribed to BD patients As some analyses were post hoc, these need to be replicated in a prospective fashion
	Ott et al. (2019) [12]	Positive association between hippocampal change and treatment-specific cognitive improvements observed for lithium in BD patients Treatment with EPO, lithium, and exercise resulted in augmentation of hippocampal volume	Three studies used in the review were open-label, which increased risk of repeated testing effects Generalizability of results limited due to small subset of patients that underwent MRI assessment MRI analysis method used in this study may potentially exclude hippocampal sub-regional changes

Table 2 (continued)

Study focus	Study name	Results	Limitations
Both sMRI and fMRI	Nunez et al. (2011) [20]	fMRI testing revealed increased thickness in right IFG associated with decreased activation intensity No significant correlations between cortical thickness in pars orbitalis and pars opercularis in either left or right hemisphere inferior frontal regions Both age and proficiency with syntactic processing are tied to cortical activation	Potential physiological limits on intensity of activation in the left IFG due to the age range studied Limited normative data across age group in CELF-4 standardized testing
	Lu et al. (2009) [21]	Combined functional activity results with structural morphology to identify brain regions in which functional activation is related to cortical thickness Data consistent with hypothesis of mature cortical thickness patterns being related to mature activation patterns	Limited cross-sectional sample size may have affected cortical thickness results Potential relationships between mature patterns of activation and morphology of other brain anatomy that this study failed to detect Correlational design does not concretely address if structural maturation is the foundation for learning
	Joshi et al. (2016) [22]	Identified significant interaction effect ($p=0.047$) of fMRI activations as predictors for left IFC cortical thickness Found that euthymic BD patients displayed significant hypactiviation in core areas of inhibitory control circuits	Acknowledged lower spatial resolution of fMRI data combined with spatial smoothing makes for potential confounding variables in structure–function mapping studies Functional deficits can be attributable to structural disturbances in surrounding connected areas as well Lack of structure–function relationships in IFC could be tied to methodological limitations
	Radua et al. (2012) [25]	Identified functional and structural differences in the medial frontal/anterior cingulate cortex and insula/superior temporal gyrus in BD patients Noted that patients receiving antipsychotic medication were more likely to exhibit grey matter volume reduction in these regions	Difficult to exclude false negatives using voxel-wise analytics Studies utilized reported GM density instead of volume Functional imaging studies used employed a variety of cognitive tasks, potentially resulting in heterogeneity

should be emphasized, as these may contribute information that may contribute towards concretely establishing the structural etiology of bipolar disorder. Additionally, as many studies are being conducted in a cross-sectional manner, an increased number of longitudinal studies will serve to help clarify the true relationship between structural and functional abnormalities and bipolar disorder.

Conclusion

Recent literature on the utility of fMRI to determine biomarkers for patients with bipolar disorder demonstrate its potential to become a clinically dependent component of the diagnostic and therapeutic processes. Before this becomes concretely assimilated into practice, however, more consistent high rates of classification accuracy are necessitated for distinguishment between the various bipolar subtypes and psychiatric disorders such as major depressive disorder (MDD). In addition, while resting-state fMRI has exhibited promise towards identifying corticolimbic biomarkers in particular, there is still a need for additional studies to establish reliable and clinically legitimate biomarkers in bipolar patients.

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Compliance with ethical standards

Conflict of interest None of the authors declare conflicts of interest.

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