

The Predictive Value of Neuroimaging Biomarkers in the Onset and Relapse of Bipolar Disorder

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Abstract

Bipolar disorder is a complex mood disorder characterized by recurring episodes of mania and depression, making early diagnosis and the prediction of the onset and relapse of bipolar disorder prove difficult to do reliably. However, neuroimaging biomarkers (specifically ones from structural magnetic resonance imaging (sMRI) and functional magnetic resonance imaging (fMRI)) can offer new ways to understand and predict the disorder. This paper aims to show the extent of which neuroimaging biomarkers can predict the onset and relapse of bipolar disorder and the limitations of their clinical application. A literature review was conducted using existing research consisting of function and structural abnormalities, longitudinal studies, and machine learning approaches. The aforementioned studies found differences in grey matter volume and cortical thickness, especially in areas concerning emotional regulation and cognitive control. Functional MRI scans also reported altered brain activation in the frontal-limbic circuits and larger neural networks. Overall, the evidence suggests that although neuroimaging biomarkers can identify brain patterns associated with bipolar disorder, current methods are not reliable enough to predict the onset or relapse of bipolar disorder on their own. However, future research combining brain imaging with biological and clinical data may improve treatment and support earlier intervention and personalized treatment.

Keywords

Behavioral and Social Sciences; Neuroscience; Bipolar Disorder; Neuroimaging biomarkers; Functional MRI scan; Structural MRI scan; Recurrence; Depressive episodes; Manic episodes; Neural predictors

Introduction

Bipolar disorder (BD), is one of the most serious and debilitating recurrent mood disorders, characterized by alternating cycles (or 'episodes') of mania, hypomania, and major depression alongside periods of euthymia. In terms of global population, it was recorded in 2019 that bipolar disorder affects approximately 2.4% people and contributes to decreased quality of life, decreased daily function, and cognitive impairment. Furthermore, individuals affected by bipolar disorder have a highly increased mortality rate, with the risk of suicide being 20-30 times greater for affected people compared to the general population.¹

However, although the effects are severe, diagnosis often happens years after the symptoms start surfacing, and even afterwards it is difficult to predict when another episode will occur. Additionally, it is common that bipolar disorder is misdiagnosed as a major depressive disorder in mental health settings, and is frequently left untreated or ignored.² Accordingly, there is a growing need for proper and precise ways to diagnose and treat bipolar disorder in people struggling from it.

Nevertheless, recent breakthroughs in neuroimaging bipolar disorder through fMRIs and sMRIs have opened pathways to understand the structural and functional neuroanatomy of bipolar disorder, focusing

on identifying biomarkers in relation to the pathophysiology of the presentation, development, and objective risk of BD. In this study, biomarkers refer to features of the brain identified through structural and function MRI scans that may help predict the onset and relapse of bipolar disorder. These include differences in brain structure (such as grey matter volume and cortical thickness), and differences in brain activity and connectivity through regions. With research regarding morphological abnormalities frequently present in affected persons rapidly progressing, personalized and effective treatment can become more feasible along with an earlier diagnosis and clinical progression.

Currently, sMRI research has found that there are certain structural differences associated with bipolar disorder, such as differences in grey matter volume between neurotypical people and people with bipolar disorder. For example, in a meta analysis directed by Wang et. al, there was evidence of lower grey matter volume in the bilateral superior frontal gyri, left anterior cingulate cortex, and right insula, all three being central to processes such as cognitive control, emotional regulation and awareness- therefore being areas of interest to understand the neural basis of bipolar disorder.³ However, while progress is being made in this field, it is not definite, as there were some discrepancies in the results- for many patients, the certain medications they were taking at the time affected their results, as did their current affective state (i.e. results differed for those in a state of euthymia and depression versus manic or otherwise).

While these structural findings provide evidence of abnormalities in certain brain regions, functional neuroimaging provides complementary information regarding the interplay between them during emotional and cognitive processing. For this reason, many studies have been done concerning functional MRI scans, which aim to examine irregularities in brain activity and connectivity. To cite an example, in a synthesis of existing fMRI studies conducted by Strakowski et al., found that bipolar 1 disorder is strongly linked to certain disruptions to the ventral prefrontal-striatal-pallidal-thalamic iterative networks as they affect the amygdala, leading to altered emotional regulation- which is a good indicator of the distinct episodes typically found in those with bipolar disorder.⁴ Nevertheless, more studies across diagnostic groups are needed to further solidify the evidence and further the research as of now.

Using structural and functional neuroimaging, researchers thus far have found unique differences associated with bipolar disorder (e.g. structural differences such as grey matter changes and functional differences through altered activity and connectivity), showing identifiable neurobiological patterns presented in a person with bipolar disorder. Nonetheless, it should be understood that although promising evidence and predictive models have been produced through various forms of neurological and clinical data, it is evident that larger samples and stronger validation in the form of accuracy and reliability is needed before these models can be considered reliable.⁵ However, if reliable biomarkers could predict the *onset*, they could potentially allow researchers to identify people with a higher risk earlier, and if they could predict *relapse*, it could potentially let clinicians and mental health providers to identify changes related to the risk of another mood episode and allow for earlier intervention and treatment.

The onset of bipolar disorder is the first occurrence of a diagnosable episode of bipolar disorder, such as a manic or a depressive episode. In this study, onset refers to the development of bipolar disorder that researchers aim to predict using neuroimaging biomarkers. Furthermore, relapse is defined by the return of significant mood symptoms (such as a manic or depressive episode) after a period of improvement or remission in an individual with bipolar disorder). In this study, relapse refers to the recurrence of an episode that neuroimaging biomarkers might help predict. These definitions provide a general framework for the basis of this study, but the criteria used to measure the onset and relapse of bipolar disorder vary throughout the literature reviewed. For example, while some researchers use clinical rating scale scores, others use a formal diagnosis of mood episode or the need of hospitalization as criteria.

Research on people with a higher risk for developing BD also emphasizes the high potentiality of longitudinal studies rather than cross-sectional because it can help specify whether a symptom precedes the condition rather than occurring alongside it⁶, substantiating the necessity for greater efforts considering it⁷. Although neuroimaging studies have identified recurring abnormalities, it remains unclear

whether these findings can reliably predict the onset and relapse, due to various factors like mood state, medication, and different methods used (cross-sectional v. longitudinal), and more.

Therefore, this study aims to critically evaluate existing research on neuroimaging biomarkers in bipolar disorders with specific emphasis on their ability to predict the onset and relapse. By analyzing various findings from structural MRI, functional MRI, and predictive modeling studies, this study focuses on assessing both the potential and limitations on neuroimaging as a predictive tool for the onset and relapse of bipolar disorder.

Methods

The main objective of this study is to synthesize the available information on neuroimaging biomarkers in bipolar disorder and the potential of using them to predict the onset and relapse using a qualitative literature review design. Rather than conducting an experiment or gathering newfound medical data, this study analyzes and compares findings from preexisting sources.

Relevant literature was gathered from academic databases and other scholarly sources, such as PubMed, ScienceDirect, National Institutes of Health, and more. The researcher used combinations of keywords such as “bipolar disorder”, “neuroimaging biomarkers”, “structural MRI”, “functional MRI”, “bipolar disorder onset prediction”, “bipolar disorder relapse prediction”, and “machine learning and bipolar disorder”. Priority was given to peer reviewed studies, meta-analyses, and original neuroimaging research that clearly examines structural or functional alterations associated with bipolar disorder.

The collected 19 pieces of literature are analyzed by comparing findings among different studies and finding recurring patterns, discrepancies, limitations, and the potential abilities. Focus is given to structural differences such as grey matter volume and cortical thickness, and functional differences such as altered brain activity and connectivity, and the ability of these traits to predict the onset and relapse. Additionally, factors that may influence the results are taken into account, for instance: medication, mood state, sample size, and differences in imaging methods. These comparisons are used to evaluate whether current evidence supports the use of neuroimaging biomarkers as predictive tools.

Because this study is a literature review, no physical tools, experiments, or materials were used, instead relying completely on previously published sources.

Results and Discussion

Structural MRI findings

The studies reviewed revealed that structural magnetic resonance imaging (sMRI) has been able to consistently find neuroanatomical abnormalities in individuals presenting bipolar disorder, most frequently involving grey matter volume and cortical thickness in various regions associated with emotional regulation, cognitive control, and stress processing. In the aforementioned voxel-based meta-analysis conducted by Wang et. al, involving 1,843 people with bipolar disorder and 2,289 controls, reduced grey matter volume was found in the bilateral superior frontal gyri, left anterior cingulate cortex, and right insula.³ Large scale research, led by Hibar et. al from the ENIGMA-BD similarly reported cortical abnormalities across different brain regions, supporting the conclusion that structural changes in bipolar disorder are distributed between multiple connected neural networks, rather than being confined to a single location.⁸

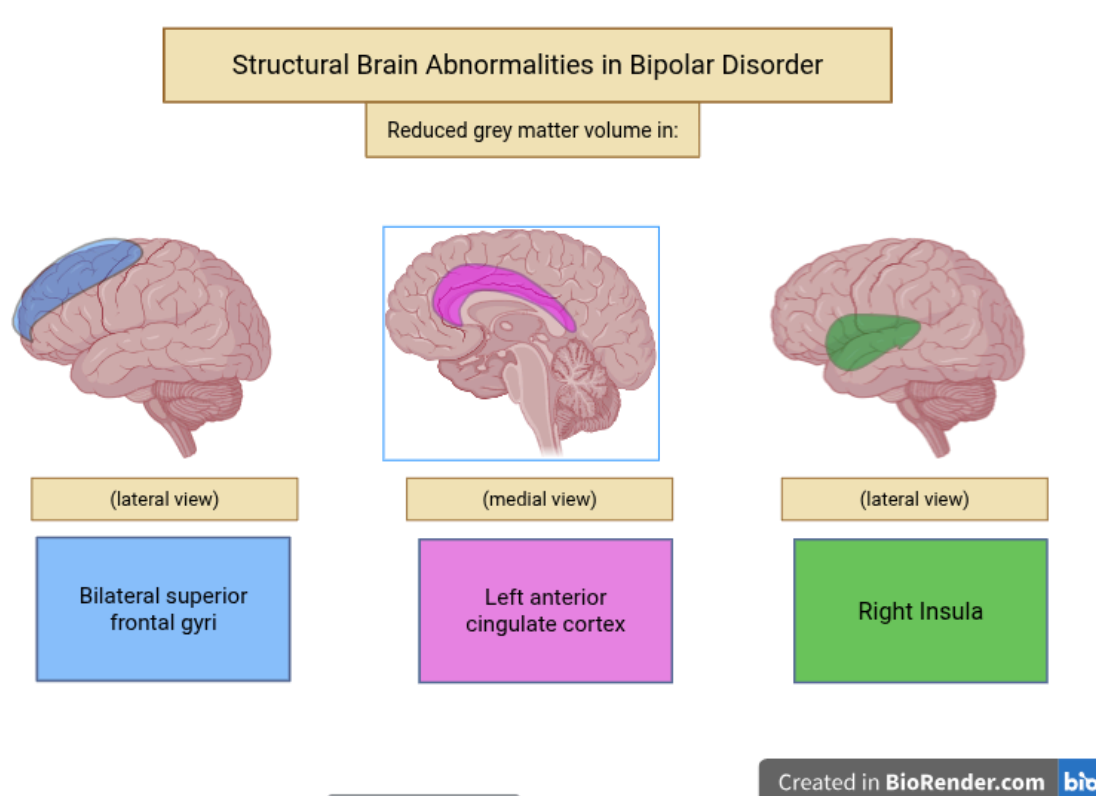


Figure 1. Structural Brain Abnormalities. Structural MRI scans have identified reduced grey matter volume in the bilateral superior frontal gyri, left anterior cingulate cortex, and right insula. Made in BioRender

These findings are important because the affected regions are closely involved in the functions disrupted in bipolar disorder. The prefrontal and cingulate regions contribute to emotional regulation and self control, while the insula is involved in internal states and the salience network. Therefore, structural abnormalities in these regions may reflect disruptions in the neural networks responsible for regulating mood and behavior. Earlier reviews of potential biomarkers also suggested that structural differences regarding the prefrontal and limbic area of the brain could also contribute to the development of clinically useful data in the subject.⁹

However, the results shown across structural studies are not always completely uniform. Recent research emphasizes that certain structural differences can be influenced by medication, age, illness duration, and even bipolar subtype. In fact, a recent study done by Parker et al. supports the idea that brain changes prevalent in people with bipolar disorder may occur over the course of the illness rather than be a fixed pattern present in everyone with it.¹⁰ This may explain why earlier studies might have provided seemingly inconsistent findings in regards to the exact location and magnitude of structural abnormalities found in the brain.

Therefore, the evidence suggests that sMRI provides a neurobiological basis of bipolar disorder, but structural abnormalities (as of now) have limited capabilities in the use of them as individual predictive markers. This limitation was demonstrated by a large scale machine learning study concerning 3020 individuals across 13 sites, conducted by Nunes et. al from the ENIGMA-BD Working Group. Although the model was able to distinguish people with bipolar disorder from neurotypical people above chance, the highest aggregate accuracy was 65.23%, 80% short of the clinically relevant accuracy threshold.¹¹ However, the results were still promising and provided a rational approximation of classification performance, which allows a possibility for future refinement and use. Currently, while SMRI findings may

contribute to a predictive model, present evidence shows that they are not yet capable of serving as a standalone or diagnostic marker for predicting the onset and relapse of bipolar disorder.

Functional MRI findings

The reviewed literature concerning functional magnetic resonance imaging (fMRI) revealed that bipolar disorder has been found to be associated with abnormalities regarding brain activity and connection to different neural regions. Unlike sMRI, which pinpoints anatomical abnormalities, fMRI scans allow researchers to identify brain activation and functional connectivity. Across the studies, the most commonly implicated systems involve the frontal limbic circuit, including the ventromedial and ventrolateral prefrontal cortex, the ACC, the orbitofrontal cortex, and the amygdala- all involved in emotional regulation - contributing to emotional instability in bipolar disorder. Along with this information, research has been conducted on other circuits too, such as the reward processing circuits and those for cognitive control.^{12,9}

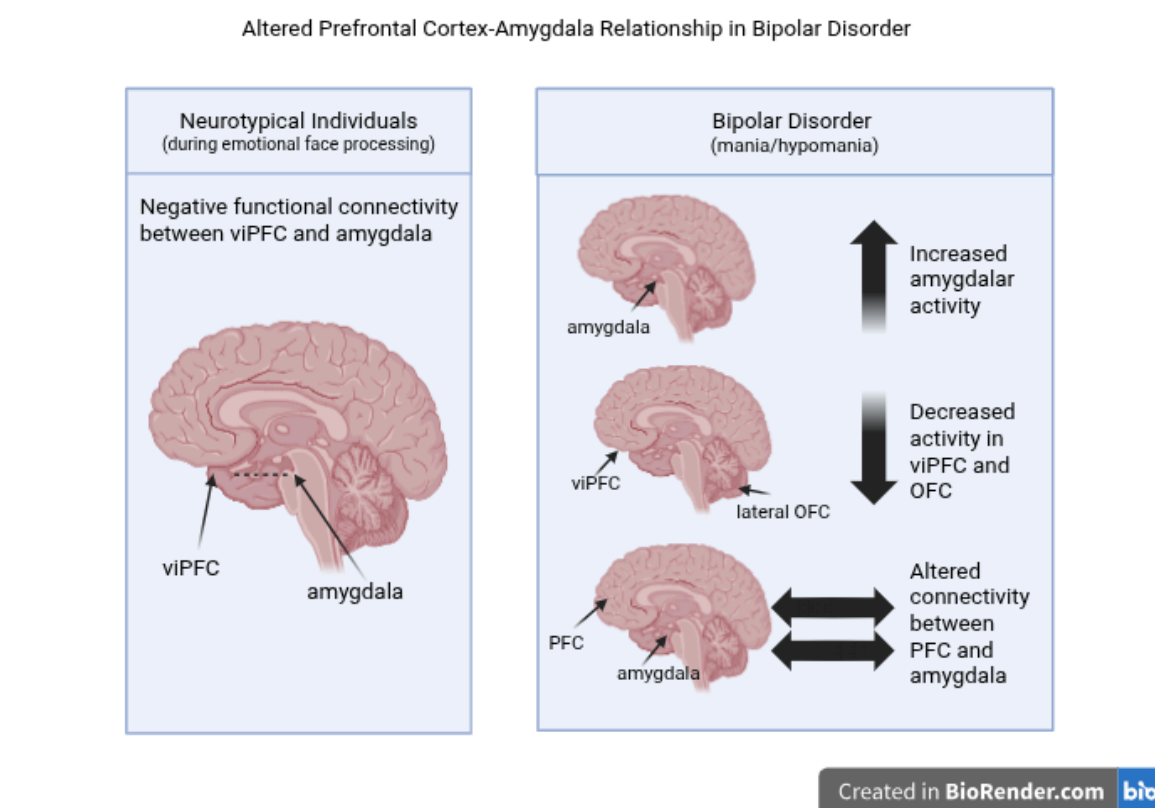


Figure 2. Altered prefrontal cortex-amygdala connectivity in bipolar disorder. Compared to neurotypical individuals, people with mania or hypomania may show increased amygdalar activity, reduced activity and altered connectivity in prefrontal regulatory regions, contributing to emotional dysregulation and mood instability. Made in BioRender

Specifically, relevant studies reveal a pattern of an abnormal relationship between the prefrontal cortex and amygdala in those with bipolar disorder. The prefrontal cortex normally specializes in the regulation of emotional responses, while the amygdala corresponds to the role of emotional processing. When tested on processing emotional faces, neurotypical individuals displayed a negative functional connectivity of the ventrolateral prefrontal cortex (viPFC) and the amygdala, providing the conclusion that the viPFC may suppress amygdalar reactivity.¹² However, in patients with mania/hypomania, there was a noted increase in activity in the amygdala¹³ and decreased activity in the ventrolateral and lateral orbitofrontal cortices¹⁴ during emotional processing. In addition, altered connectivity between these regions have been

associated with reduced mood control- stemming from an imbalance in the emotional processing and regulation of cortical systems seen in patients with BD.

Additionally, building on existing task-related studies, resting-state fMRI scans also demonstrate abnormalities beyond individual brain regions. Weaker functional connectivity along the frontoparietal network have been reported¹²; along with altered connectivity within and between the DMN¹⁵, FPN, and salience network.¹⁶ These findings suggest that bipolar disorder may be better understood as a disorder involving large scale neural networks rather than dysfunction in one isolated brain region. This interpretation is also supported by more recent work connecting sMRI and fMRI scans with broader biological mechanisms, including inflammation and mitochondrial dysfunction.¹⁷

Despite these promising findings, a pattern emerged from the reviewed literature- functional abnormalities are often dependent on the patient individual's mood state. Some differences may be present during depression, (hypo) mania, and euthymia, while other findings represent more stable characteristics of the disorder.¹² The distinction between a state marker (for mood state) and a trait marker (which can be used for the prediction of bipolar disorder) is particularly important to consider for the topic in hand. A brain abnormality associated with an active manic or depressive episode may help identify a person's current clinical state, but it does not produce a necessarily reliable prediction for a future episode. Consequently, fMRI findings are promising for revealing biomarkers, but additional longitudinal research is needed to determine which abnormalities predate mood changes and which occur as consequences of them.

Predictive neuroimaging findings

The strongest evidence for the potential predictive value of neuroimaging comes from studies that move beyond trying to identify group differences and instead attempt to predict individual clinical outcomes. In a longitudinal study conducted by Chen et al. of 61 patients with bipolar disorder, brain morphology, functional connectivity, and inflammatory biomarkers were used to predict changes over the course of one year, the predicted changes in measures of mania, depression, psychiatric symptoms, and medication side effects all strongly correlated with the actual changes observed during the follow up.¹⁸

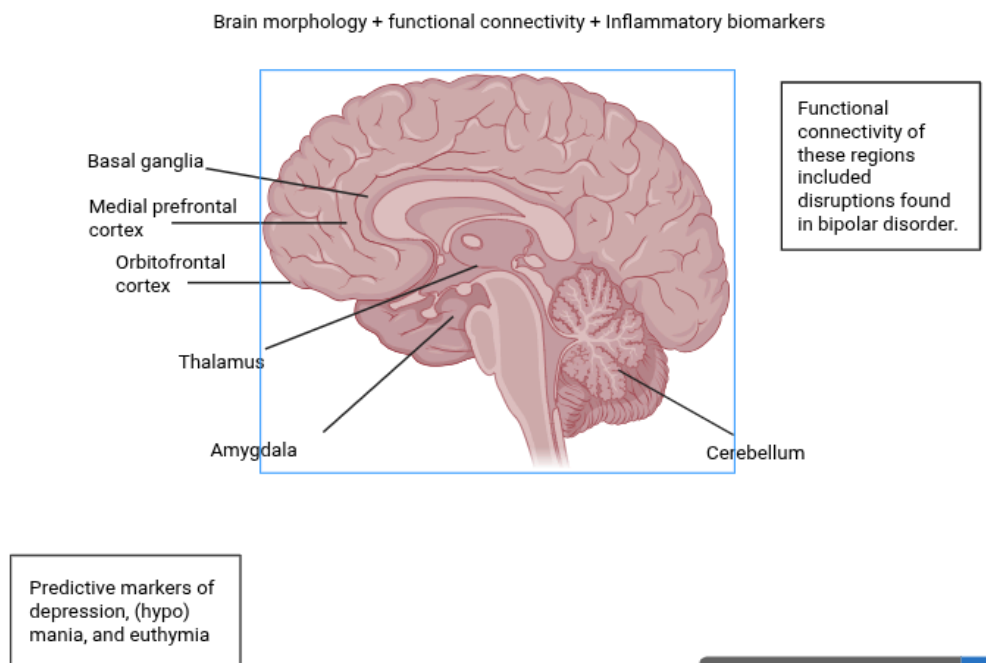


Figure 3. Functional connectivity disruptions over the course of a year. Brain morphology, functional connectivity, and inflammatory biomarkers are used to predict changes over the course of a year in mania, depression, psychiatric symptoms, and medication side effects, and relevant brain regions contribute to these predictions. Source: Made with BioRender

The regions and networks contributing to prediction included the subcortical and cerebellar regions, the basal ganglia, and regions of the limbic system (comprising the thalamus and amygdala, the cerebellum, oFC, and mPFC).¹⁸ However, the modest classification accuracy also demonstrates the difficulty of applying group level neuroimaging studies to individual patients.

More current literature suggests that predictive performance may improve when neuroimaging is combined with different forms of biological and clinical data. A recent review of molecular and neuroimaging research conducted by Oglodek et. al finds that the use of multimodal approaches integrating sMRIs, fMRIs, spectroscopy, inflammatory + metabolic biomarkers, and molecular analyses may better capture the heterogeneity of bipolar disorder.¹⁷ This interpretation is consistent with earlier biomarker reviews, which conclude that the development of a single, specific biomarker for bipolar disorder is unlikely because of the disorder's clinical and biological heterogeneity.^{19,9,18}

Neuroimaging Biomarkers Associated with Onset

Structural and functional MRI scans have identified recurring brain differences associated with bipolar disorder that could be connected to the onset of the disorder. For example, sMRI scans have identified differences in grey matter volume along with cortical thickness in areas such as the prefrontal cortex and anterior cingulate cortex.^{3,8} On the other hand, fMRI scans have identified altered brain activity and connectivity in networks involved in emotional regulation.¹² These findings, although they help researchers identify brain patterns associated with bipolar disorder, do not reliably predict who will develop bipolar disorder effectively. To evaluate predictive value, longitudinal studies are needed that follow people who have not developed bipolar disorder and note if their brain patterns are associated with a later diagnosis. Therefore, although sMRI and fMRI scans provide promising evidence of brain abnormalities related to bipolar disorder, their ability to predict the onset of it remains uncertain as of now.

Neuroimaging Biomarker Associated with Relapse

Neuroimaging may also be helpful in investigating relapse in individuals with bipolar disorder already present. Functional MRI scans have identified differences in brain activity and connectivity between mood states (such as mania or depression), helping researchers further understand the neural changes associated with mood instability.¹² In addition, a longitudinal study involving brain morphology, functional connectivity, and inflammatory biomarkers found that its models could predict changes in symptoms over a one year period.¹⁸ This suggests that combining neuroimaging with other biological measures could help researchers predict aspects over the course of bipolar disorder. However, predicting changes in symptom severity is not the same as predicting the recurrence of a full manic or depressive episode. Furthermore, functional brain abnormalities can vary depending on a person's mood state, so it is difficult to predict whether specific abnormalities can reliably predict a future relapse.¹² Therefore, more longitudinal studies that directly measure the recurrence of mood episodes are needed before neuroimaging can be reliably used as a means for the prediction of relapse.

Comparison with Previous Studies and Possible Mechanisms

Overall, the results of the reviewed literature strongly demonstrate correlation with previous neuroimaging research. While earlier studies primarily focused on differences between people with bipolar disorder and neurotypicals, more recent ones more increasingly use large datasets, longitudinal studies, and machine learning techniques to determine the predictive value of the differences found.^{9,11,18} This progression is relevant to the progression from identifying if bipolar disorder is associated with measurable brain differences to whether those differences can be useful to predicting clinically useful outcomes.

A possible mechanism underlying the findings is the disruption of the neural networks responsible for emotional processing, cognition, and regulation. Structural differences in the frontal, cingulate, insular, and limbic regions may affect the organization of these systems, while functional abnormalities affect the way these systems communicate and interact. During periods of mood instability, an imbalance between the limbic emotional processing and the prefrontal regulatory control may contribute to manic or depressive symptoms.^{12,9} Additionally, research indicates that these neural alterations may interact with inflammatory and mitochondrial processes, although these relationships require some further insight.¹⁷

Conclusion

Overall, these findings have important implications for the future of research and development in bipolar disorder. If reliable neuroimaging biomarkers could identify individuals before the full onset of the disorder or detect neural changes before a shift in a mood episode, earlier intervention and personalized treatment would become more possible for individuals to access. Furthermore, neuroimaging may contribute to predicting treatment response and monitoring changes throughout the course of the disorder.

Throughout the literature, several limitations were identified and acknowledged. Firstly, bipolar disorder is highly heterogeneous, and differences in age, medication, duration, current mood state, and more can negatively impact the consistency of both sMRI and fMRI results. In addition, many studies use small scale or cross-sectional designs which make it difficult to determine whether a brain abnormality is a cause, effect, or impermanent correlate of a mood episode. Predictive studies may also work well within a particular dataset, but do not generalize as effectively when applied to broader populations.

Taken together, the literature suggests meaningful evidence of structural and functional abnormalities associated with bipolar disorder. While structural MRI studies consistently find differences in grey matter volume and cortical anatomy, function MRI studies identify altered connectivity within networks involving emotional regulation, cognitive control, and reward systems. Predictive and machine learning studies also reveal combinations of neuroimaging features that can provide information about individual clinical outcomes.

Nevertheless, the central finding of this review is that identifying an abnormality associated with bipolar disorder is not sufficient to predict future onset or relapse because of the variability in the expression of the disorder. Current neuroimaging biomarkers demonstrate significant potential- especially when combined with other clinical or biological measures- but they remain insufficiently accurate for routine clinical application. Therefore, the evidence suggests a future where multimodal and longitudinal approaches may improve prediction, rather than the use of a single MRI measurement as a definitive biomarker.

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