Examining Alterations in Brain Structure, Function, and Neurotransmitter Activity Among Those with Bipolar Disorder

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Bipolar disorder (BD) is a mental health disorder characterized by alternating manic and depressive episodes that significantly impact cognitive function, emotion regulation, and quality of life. Extensive research, inclusive of contrasting findings in part due to methodological limitations and to the inclusion of pharmacotherapy, add to the complexity of understanding the neurobiological underpinnings of BD. This narrative review examines the current literature on the neurobiological alterations in BD in adults, with a focus on brain structure, functional connectivity, and neurotransmitter activity. Structural neuroimaging studies reveal volumetric reductions and alterations in cortical thickness and surface area among key brain regions that may underlie symptoms of both depressive and mania episodes. Functional connectivity studies highlight disruptions within and between neural networks that underlie mood instability and impaired cognitive control observed among those with BD. Furthermore, neurotransmitter dysregulation across multiple neurotransmitter systems may contribute to the fluctuating mood states observed among those with BD. Future research, specifically longitudinal studies and studies replicating brain structure related findings, may deepen our understanding of the neural basis of BD and optimize the development of targeted pharmacotherapy treatments that address both mood states more efficaciously.

Keywords: Bipolar disorder, brain structure, volume, neural networks, functional connectivity, neurotransmitters

Abbreviations

- BD = bipolar disorder
- PFC = prefrontal cortex
- ACC = anterior cingulate cortex
- PCC = posterior cingulate cortex
- DMN = default mode network
- CEN = central executive network
- SN = salience network

Introduction

Bipolar disorder (BD) is a mental health disorder characterized by substantial changes in mood1. As defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and International Classification of Diseases (ICD-11), BD includes phases of manic episodes, depressive episodes, or mixed episodes with symptoms of both manic and depressive episodes[1,2]. Manic episodes may involve elation, irritability, sleeplessness while depressive episodes induce melancholy, lack of interest in activities, and restlessness[1]. Subtypes of BD include type I (BD-I), consisting of at least one full manic episode present for at least 1 week that may precede or be followed by depressive episodes, and type II (BD-II), which includes at least one major depressive episode and one hypomanic episode for at least 4 consecutive days. Both types of BD may greatly influence patients quality of life including diminished ability to carry out daily tasks and affect social relationships with others[3].

The impact of BD goes beyond the patient level, leading to substantial societal burdens. BD affects approximately 0.49% of the global population, with prevalence slightly higher in females compared to males[4]. In 2017, the global disability-adjusted life years (DALYs) for BD totaled 9.29 million, also higher for females than for males[5]. BD is associated with high costs, inclusive of pharmacotherapy and additional societal level costs such as increased rates of unemployment, with an estimated total annual cost of 342 million for the National Health Service (NHS) in the UK alone[6]. BD is the 17th leading cause of global burden of disease, according to results from the 2013 Global Burden of Disease[7]. Thus, the presence of multiple mood states renders BD a complex disorder with vast implications at the individual- and societal-level.

A multitude of factors may contribute to BD. Heritability rates are high among first-degree relatives of people with BD[8]. Neurobiological studies, using neuroimaging techniques to ex-

plore brain structure and function, show varying degrees of brain atrophy, altered brain development and connectivity, and impaired neuroplasticity among those with BD[9]. Alterations in neurotransmitters, specifically dopamine, GABA, and noradrenaline, among those with BD may further contribute to changes in mood[10]. The culmination of brain structure, function, and neurotransmitter-level factors across mood states from opposite ends of the spectrum render BD a unique disorder with a possibly overlapping and distinct neural origins.

Despite efforts examining neurobiological factors that contribute to BD, research is still limited and contains mixed findings[9]. BD among adolescents still face debates regarding misdiagnosis, possibly related to the added complexity of brain development still occurring throughout adolescence[11]. Establishing a clear understanding of neural alterations among adults with BD may shed light on initial neural markers of the disorder among adolescents and foster the development of more effective pharmacological treatments. Therefore, the aim of this narrative review is to summarize the existent literature that examines alterations in brain structure, function, and neurotransmitter activity, among adults with BD.

Methods

The present narrative review identified peer-reviewed articles from PubMed and Google Scholar to reflect updates on this topic from primarily the last 5 10 years, however a few older articles were included if they provided formative information. Results included herein include a variety of article types including randomized clinical trials and review articles.

Brain structure

Grey Matter

Volume

The most common metric of brain structure that has shown alterations in multiple brain regions among those with BD is grey matter volume. Below is a brief summary of alterations in key brain regions and how they related to symptoms observed among those with BD.

The hippocampus contributes to numerous cognitive functions and emotion regulation. Disruptions in the hippocampus may underlie depressive symptoms seen in BD[12]. Compared to healthy controls, BD patients have lower volumes[13–15] but greater variability of volumetric alterations[16] in the hippocampi. This may be due to heterogeneity in the pathophysiology underlying BD and potential sex-related differences[17]. Males may exhibit fewer reductions in grey matter volume, which may be associated with clinical presentation as males exhibit fewer depressive episodes compared to female[16]. Mixed findings may also be due to BD subtype or medication[16]. Lithium treatment may counteract the decrease in hippocampal grey matter volumes by increasing grey matter volume[18]. Reductions in gray matter volume may play an important role, most notably for sex-related differences in depressive symptoms among those with BD.

The amygdala is critical to processing emotions related arousal and affect[19] and has numerous connections with the prefrontal cortex (PFC) involved in executive functioning. Environmental stressors may alter the nuclei within the amygdala leading to mood dysregulation in BD patients[20]. Age-related differences in the amygdala may impact BD among younger populations. Children and adolescents with BD have smaller left amygdala volumes[20,21], however, adults with BD generally do not exhibit significant differences in amygdala volume compared to controls[16]. Of note, some studies have shown a trend towards increased amygdala volume in adult patients[21,22]. Amygdala volumes may increase in adults with BD as a compensatory reaction to having a smaller amygdala volume during youth[20]. Medication may again play an important role, as lithium or valproate can increase amygdala grey matter[23]. Amygdala volume alterations in BD are dynamic across the lifespan, potentially influenced by early structural differences, compensatory mechanisms, and the effects of medication.

The anterior cingulate cortex (ACC) integrates cognitive, emotional, and autonomic functions[24]. The PFC is also responsible for similar processes, therefore alterations in the PFC may be linked to emotional processing deficits and cognitive impairments seen in BD patients[25]. Multiple studies have reported decreased grey matter volumes of the left ACC[26], middle and superior left PFC, and middle and inferior right PFC[27] in individuals with BD compared to healthy controls. The reductions are particularly noted in pharmacologically untreated patients[26], and neuroimaging evidence shows that lithium treatment may counteract this change by increasing overall grey matter volumes.

The lateral ventricles, third ventricles, and thalamus have also shown altered grey matter volume in individuals with BD. The thalamus plays a key role in cognitive processing. While increased ventricular volume is generally correlated with aging[28], patients with BD tend to have enlarged ventricular and reduced thalamic volume[29].Variability in the lateral ventricles, third ventricles, and thalamus are similar to alterations that have been observed among those with schizophrenia[16,30]. Underlying structural heterogeneity in these regions could be a shared feature across both BD and schizophrenia, which may explain cognitive impairments observed in both conditions.

BD may have a neurodegenerative component. Longitudinal studies have found significant differences in progressive grey matter alterations in BD patients compared to healthy controls[31]. While mixed findings do exist, studies have shown that repeated mood episodes correlate with increase cortical thinning and grey

matter reduction from younger (18 years) to older adults (50-60 years)[32–34]. The consensus is that recurrent mood episodes contribute to grey matter loss, particularly in the amygdala, ACC, superior frontal and medial orbitofrontal regions[31–34]. Those with BD also have a larger brain age gap, the difference between an individual's chronological age and predicted age from brain imaging data, reflect the presence of neurodegenerative processes accelerating brain ageing. To moderate these aspects, neuroprotective treatments such as lithium may be helpful increase overall grey matter volume[35].

Cortical Thickness and Surface Area

BD is associated with widespread cortical thinning, particularly in regions critical for emotional regulation and executive function. Cortical thinning has been observed in the left insula, bilateral ACC, left inferior frontal gyrus, and the medial part of the left superior frontal gyrus[36]. Unaffected first-degree relatives have also shown cortical thinning in in the ACC, orbitofrontal cortex, dorsolateral PFC, and superior temporal cortex adding support for the hypothesis that abnormalities in these regions may represent trait markers of the disorder[37]. Structural changes in these regions likely contributes to disruptions in affective regulation and self-referential processing, all of which are hallmark cognitive and emotional deficits in BD[36,37]. Moreover, age-related analyses revealed that older BD patients exhibit greater cortical thinning in the insula[36], suggesting that BD may involve progressive neurostructural deterioration over time.

Compared to cortical thickness, findings on surface area are more heterogeneous potentially due to medication history, age, and inherited surface area differences. Across both BD-I and BD-II, studies have found shared surface area reductions in the medial prefrontal cortex, and more extensive and widespread surface area reductionsincluding in the superior temporal sulcus and fusiform gyrus specific to the BD-I subgroup[38]. Compared to healthy controls, those with BD-I have shown greater surface area of the left pars triangularis, a region implicated in language processing and affective regulation[37]. Alterations in cortical thickness and surface area offer complementary perspectives on BD pathophysiologywhere cortical thinning indicate progressive and symptomatic burden, and changes in surface area may reflect early neurodevelopmental divergence, compensatory reaction, or differences in BD subtype.

White Matter

White matter is extensively involved in cognitive function, connectivity and plasticity. Abnormalities in white matter volume are one of the most consistently reported findings in neuroimaging studies of BD[39]. Many studies show regionally specific white matter volumetric abnormalities in BD that do not progress with illness duration[31]. Alterations in white matter volume have been primarily observed in the corpus callosum, crucial for interhemispheric communication and cognitive functioning[39], and the cingulate gyrus, serving an essential role in emotion regulation and decision making[40]. Meta-analyses have shown decreased white matter volume in the corpus callosum and white matter adjacent to the cingulate gyrus[41,42]. Disruptions in interhemispheric communication may lead to impairments with emotional regulation, a hallmark symptom of BD. Impaired connectivity in the corpus callosum could lead to difficulties in coordinating cognitive and emotional processes[43], while abnormalities in the cingulate gyrus may result in mood instability, impulsivity[40], and impaired emotional processing. While the extant literature on white matter changes in BD is relatively consistent, it is limited in magnitude and given the importance of white matter functioning on cognitive and emotional processing, more research is needed to further replicate the existing findings.

Brain Function

The default mode network (DMN) is a major neuronal network consisting of the ventromedial PFC, dorsomedial PFC, posterior cingulate cortex (PCC), precuneus, and inferior parietal lobule, which deactivates during goal-directed tasks[44,45]. The DMN is typically active during rest and involved in self-referential thinking[46]. The salience network (SN) is a large paralimbic-limbic functional network anchored to the anterior insula and dorsal ACC, as well as the anterior PFC, the supramarginal gyrus, the striatum, and the thalamus; it is involved in detecting, processing, and integrating internal and external salient information[47]. The SN evaluates the importance of internal or external stimuli and to assist the coordination of the brains response to those stimuli[48]. The central executive network (CEN) is responsible for executing various executive functions, such as planning, decision-making, and problem-solving. The following paragraphs will discuss alterations in these neural networks among those with BD.

Resting-state Functional Connectivity

Resting-state functional connectivity studies examine the brains intrinsic activity during rest. These studies have shown abnormal connectivity within the DMN, and between the DMN and SN in early-onset BD[49]. Increased functional connectivity at rest between the insula of the SN and medial PFC of the DMN[50], the ACC of the SN and superior frontal gyrus of the DMN[51], the anterior insula cortex of the SN toward the middle frontal gyrus of the DMN[52], the ventral anterior insula of the SN and precuneus in the DMN[50], and the subgenual ACC of the SN and PCC of the DMN[53] has been observed among those with BD. Disruptions in connectivity within and between the DMN and SN may contribute to mood instability and manic or depressive symptoms[54]. Greater connectivity between DMN and

SN could lead to excessive focus on thoughts, emotions, and self-referential mental processes with reduced transition from idea to action. Alternatively, it could lead to excessive focus on external contents, for instance stimuli in social interactions, hence increasing expression of ideas as actions[49]. There are some mixed mixed findings[55] for intra-network connectivity between the DMN and SN, and this may be due to methodological differences[56] or illness duration[57]. Lastly, specific to the DMN, hypo-connectivity within the DMN among those with BD[55,57] has also been observed among those with schizophrenia[58], suggesting an overlap in the neural aberrations between these disorders that is likely related to manic symptoms observed in BD.

Alterations in cortico-limbic connectivity have also been observed among those with BD, specifically in the occipital and frontal lobes, amygdala, hippocampus, insula, thalamus, and striatum[49]. Decreased connectivity between the right orbital frontal cortex and left amygdala, between the left superior frontal gyrus and left putamen, and between the left superior frontal gyrus and left insula in patients compared to controls, and an increase in connectivity between right superior occipital gyrus and right hippocampus[59]. One hypothesis is that an imbalance between the activity of these cortical areas functioning in emotional regulation and the activation of the limbic system might cause unstable cognitive control of emotions, typically observed in adults with BD[60]. Therefore, alterations in the DMNs connectivity within and with SN, and the connectivity of cortico-limbic structures, may contribute to manic symptoms among those with BD.

Default Mode Network

Intra-network and inter-network changes in the DMN are among the most prevalent alterations noted in BD. Key regions that demonstrated altered resting-state functional connectivity were the medial PFC[55,61], PCC[55,62], and superior frontal gyrus[63]. The medial PFC was found to have lower global brain connectivity with respect to other regions of the frontal cortex, as well as reduced functional connectivity with other regions of the DMN such as the PCC[50]. The medial PFC is involved in self-reflection and is associated with cognitive and affective functions such as emotional facial recognition. The superior frontal gyrus, a region that contributes to higher cognitive functions such as working memory, was found to contain hyper-connectivity between select subregions, such as the medial and dorsolateral aspects of the left superior frontal gyrus among those with BD[63]. Lastly, studies using task-based stimuli such as emotion recognition or cognitive tasks showed results in opposite in polarity with respect to at rest, showing increased intra-network functional connectivity in individuals with BD compared to healthy controls in non-resting states[64]. These results showcase the intricate role of the DMN in BD, where altered intra- and inter-network connectivity may contribute to disruptions in self-referential processing, emotional regulation, and cognitive function, influencing mood instability.

Salience Network

Intra-network functional connectivity of the SN has been shown to decrease at rest in those with BD compared to healthy controls[55,65]. More specifically, functional connectivity was decreased between the anterior insula and ventrolateral PFC[57,65], between the subgenual ACC and inferior temporal gyrus[50,52], and between the perigenual ACC and the ventrolateral PFC[54]. There was also reduced functional connectivity between subregions of the ACC when lower supragenual and perigenual ACC connectivity was observed[54]. The SN, particularly the anterior insula, is involved in communication between different neural networks, specifically the DMN during cognitive leisure and CEN during cognitive exertion, which is crucial for adaptive mood regulation[66]. Thus, the SN is implicated in the dynamic process of switching between depressive and manic states in BD[67]. The SN serves a critical role in salience detection and network switching, therefore disruptions in the SN among those with BD may contribute to impaired mood regulation and specifically the transition between affective states.

Triple Network

The triple network, composed of the DMN, SN, and CEN[68], has shown altered patterns of connectivity among those with BD. Those with BD have shown hyper-connectivity between the DMN and SN as previously noted, however, reduced connectivity between the CEN-SN and CEN-DMN has also been observed. For the CEN-SN, reduced functional connectivity between the insula of the SN and inferior parietal lobule of the CEN was associated with greater impairment in perceived emotion control and inhibition[57], often seen in manic episodes[69]. Mixed findings have been reported with some showing increased connectivity between the dorsal anterior insula of the SN and inferior parietal lobule of the CEN at rest[65]. For the CEN-DMN, functional decoupling has been observed between the dorsolateral PFC and inferior frontal gyrus of the CEN and the medial PFC of the DMN at rest in those with BD compared to healthy controls[50,56,70], meaning that the networks are lacking synchronization or functioning independently when their activity should be coordinated. While healthy controls show anticorrelation between the CEN and DMN[68], weakened or reversed functional connectivity between the two may indicate an imbalance in the brains ability to segregate between a state of rest and a task-positive state (when the brain is engaged in goal-directed cognitive tasks) in those with BD. Functional connectivity among those with BD shows dysregulation of large-scale brain networks in BD, in addition to altered connectivity

within and between the DMN, SN, and CEN leading to disruptions cognitive and emotional processing, leading to mood instability and impaired executive function.

Neurotransmitter Activity

Dopamine

Dopamine regulates various physiological and cognitive functions and plays an essential role in the brains reward system, reinforcing goal-directed behaviors[71]. In BD, dysregulation of dopamine receptorsparticularly D2 and D3 receptorshas been observed, particularly in limbic and striatal brain regions leading to heightened motivation, reward sensitivity, and impulsive behaviors[71,72]. This may cause increased striatal dopamine transporter levels as compensation, lowering dopaminergic transmission. These fluctuations influence dopamine turnover, and disrupt the balance of signaling across mood states, explaining the alternating manic and depressive symptoms characteristic of BD[73]. Increases in homovanillic acid (HVA), a metabolite used to assess dopamine activity, provides more support for an overactive dopaminergic system in BD during manic episodes[74,75]. Dopamine depletion is thus associated with depressive symptoms, including lack of motivation and cognitive impairment.

Medication provides additional support for the role of dopamine. Dopamine receptor antagonists, such as atypical antipsychotics, are commonly used to manage mania by reducing excessive dopamine activity[10]. On the other hand, some dopaminergic medications, like psychostimulants and certain antidepressants, have been reported to trigger manic episodes in susceptible individuals, reinforcing the link between dopamine dysregulation and BD symptomatology[76]. Noradrenaline

Noradrenaline (also named norepinephrine) is involved in the brains arousal and stress response systems, playing a crucial role in regulating mood[77]. Fluctuations in noradrenaline levels have been directly linked to symptomatic shifts in BD, as changes in its metabolism correlate with different mood states[78]. The primary metabolites of noradrenaline, 3-methoxy-4-hydroxyphenylglycol (MHPG) and 3,4-dihydroxyphenylglycol (DHPG), serve as biomarkers for noradrenergic activity. Higher concentrations of MHPG levels have been detected during manic episodes and lower concentrations during depressive phases[78], suggesting MHPG may serve as a potential biomarker for mood fluctuations. Alterations in adrenergic receptors, including downregulation of β-adrenergic receptors, may impair feedback regulation of noradrenaline release and contribute to emotional dysregulation and heightened stress sensitivity[79].

Pharmacological interventions targeting the noradrenergic system further highlight its role in BD. Selective noradrenaline reuptake inhibitors (NRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are commonly used to treat depressive symptoms[10]. However, they may increase the risk of manic episodes, as they elevate synaptic noradrenaline levels, which may overstimulate neural circuits[10,80]. Given noradrenalines strong association with BD symptomatology, future research aims to refine treatment strategies by developing biomarker-driven interventions.

GABA

Gamma-aminobutyric acid (GABA) is the brains primary inhibitory neurotransmitter[81,82]. It counterbalances excitatory neurotransmitters preventing excessive neural activity that could lead to mood disturbances[83]. Neuroimaging and postmortem studies have revealed altered GABAergic signaling in BD, particularly in the prefrontal cortex, amygdala, and hippocampus, regions involved in mood regulation, impulse control, and emotional processing[84]. Individuals with BD often exhibit lower GABA levels, particularly during depressive episodes, suggesting that GABA deficits may contribute to heightened neural excitability, which in turn leads to mood instability, anxiety, and cognitive impairments[85,86]. Conversely, some evidence suggests that GABA levels may increase during manic episodes, potentially reflecting a compensatory mechanism in response to excessive excitatory activity[10].

Medications that modulate GABAergic activity, such as Valproate and lithium, enhance GABAergic transmission, helping to restore neural balance and prevent mood swings[87]. Benzodiazepines, which directly enhance GABA receptor function, are occasionally prescribed as adjunctive treatments for managing acute mania or anxiety symptoms[87]. Changes in GABA receptor composition have also been observed. Postmortem studies report reduced expression of $GABA_A$ receptor subunits $\alpha 2$, $\beta 1$, and in the cerebellum of individuals with BD[88], while increased benzodiazepine site binding in the hippocampus suggests regional upregulation or altered receptor configuration, possibly involving the $\alpha 5$ subunit[89] . GABAB receptor expression has also been found to be reduced[88,90], further implicating receptor-level dysfunction and underscoring the potential of GABA receptor modulators as promising targets for future BD treatments.

Glutamate

Glutamate serves as the main excitatory neurotransmitter and is critical for neural circuit function[91]. Balancing the ratio of glutamine (the primary metabolite of glutamate) / glutamate levels is necessary to prevent neuronal damage[92]. Those with BD have shown higher levels of glutamate and glutamine, particularly in the ACC and the PFC[93,94], and higher glutamine/glutamate ratio suggesting hyperactivity in glutamatergic neurotransmission and potential disruptions in neuronal-glial interactions[93,95]. Some studies have noted this heightened ratio is present primar-

ily when BD patients are experiencing a manic episode[93,95,96], consistent with the elevated cerebral metabolic rate that accompanies racing thoughts, irritability and distractibility observed in mania[94]. Glutamate dysregulation may also affect synaptic function and neuroplasticity through structural alterations in the synapse[97]. This corresponds to the recent reconceptualization of BD as a synaptic plasticity-related disorder instead of as one simply due to neurotransmitters in deficit or excess[97].

Abnormalities in glutamate receptors are also observed. Overactivation of NMDA receptors can increase calcium influx and oxidative stress, potentially leading to neuronal damage[94]. On the other hand, reduced expression of AMPA receptorsanother type of glutamate receptorcan impair synaptic transmission and plasticity, further contributing to cognitive and emotional symptoms in BD[95]. These changes not only affect glutamate metabolism and clearance but also alter the excitatory/inhibitory balance across functional networks. In reference to medications that modulate glutamate, Ketamine may increase in glutamate neurotransmission, rapidly rebooting synaptic connectivity that leads to antidepressant effects[98]. Lamotrigine and other mood stabilizers prevent glutamate release, dampening overactive excitatory circuits to avoid manic switching and to potentially have neuroprotective benefits[99]. These findings underscore glutamates multifaceted involvement in BD, acting as both a potential driver of excitotoxic damage and a key modulator of synaptic plasticity, mood regulation, and treatment response.

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is involved in mood regulation, sleep, and impulse control[100]. Serotonin activity is typically reduced during depressive episodes, leading to symptoms such as low mood, fatigue, and emotional dysregulation[85]. Lower rates of the main metabolite and indicator of serotonin turnover rate in the brain, 5-hydroxyindoleacetic acid (5-HIAA), have also been observed[101]. However, others have also found a lack of correlation between 5-HIAA levels and BD, suggesting mixed results[10], that may be due to medication correcting for serotonin dysregulation. Additionally, serotonin transporter (SERT) function is altered in BD, with studies showing higher SERT availability during depressive states, which may lead to excessive serotonin reuptake and decreased serotonin signaling[102].

Selective serotonin reuptake inhibitors (SSRIs), commonly used for depression and increase serotonin levels by blocking its reuptake, can trigger manic episodes among those with BD, especially when used without a mood stabilizer[103]. This phenomenon, known as an antidepressant-induced switch, highlights serotonins role in mood destabilization. Mood stabilizers such as lithium and atypical antipsychotics help regulate serotonin signaling, preventing extreme mood fluctuations[104]. Continued research is needed to understand how these medications can be effectively used while reducing the risk of inducing mania.

Integration of Brain Structure, Brain Function, and Neurotransmitter Alterations

A growing body of research highlights the interconnected nature of structural abnormalities, functional network disruptions, and neurotransmitter imbalances in BD. Table 1 briefly summarizes key findings from each domain. Key regions such as the ACC, dorsolateral PFC, ventromedial PFC, and hippocampus are also central nodes in functional networks like the DMN, SN, and fronto-limbic circuit[105]. These regions are embedded in systems responsible for emotional regulation, cognitive flexibility, and motor behavior, and densely populated with neurotransmitter receptors, particularly for serotonin, dopamine, and GABA[84]. Reduced gray matter volumes and impaired white matter tracts between the PFC and amygdala have been observed particularly among those with rapid cycling or mixed episodes of BD[85]. Functionally, this circuit shows state-dependent dysregulation: during manic states, hyperconnectivity between the ventromedial PFC and amygdala coincides with heightened emotional intensity, while depressive phases are marked by hypoactivity and emotional blunting. At the neurochemical level, the same fronto-limbic areas are influenced by serotonergic and glutamatergic signaling. Abnormal serotonin activity in the ventromedial PFC and heightened glutamate levels in the limbic system may underlie the emotional instability that characterize BD[106].

The DMN further illustrates this multilevel disruption. Structurally, regions such as the PCC and ventromedial PFCcore DMN nodesshow volume reductions and reduced myelination[85]. Functionally, these same areas exhibit hyperconnectivity and hyperactivation during depressive states, contributing to ruminative thought patterns and cognitive inflexibility[85]. Neurochemically, serotonin and GABA signaling modulate DMN activity and when they fail to adequately suppress DMN overactivity, the result is persistent self-focused rumination and emotional dysregulation. This triple convergencestructural atrophy, functional hyperconnectivity, and neurotransmitter imbalancehelps explain why the DMN has been proposed as a potential biomarker for BD diagnosis and severity[107]. Evidence across networks underscores the necessity of viewing BD as a disorder of systems-level dysregulation rather than dysfunction in any single domain.

Manic versus Depressive Episodes

Neurobiological alterations in BD are not static but vary significantly across manic and depressive episodes. Structurally, certain regions such as the amygdala and prefrontal cortex show mood-state dependent activation. Functional MRI studies have

revealed hyperactivity in the amygdala and decreased activation in the ventrolateral prefrontal cortex during manic episodes, suggesting impaired top-down emotional regulation and heightened salience detection[108]. In contrast, depressive episodes are associated with hypoactivity in reward-related areas and heightened connectivity within the DMN, potentially reflecting increased self-referential thought. Cortical thinning and volumetric reductions in regions like the ACC have been associated with depressive states, while manic episodes may involve more dynamic alterations in limbic-prefrontal circuits[109,110].

On a functional level, brain arousal regulation also appears to differ between mood states. Depressive episodes are marked by sustained arousal whereas manic episodes demonstrate unstable arousal regulation, with rapid fluctuations toward lower arousal states[111]. These findings support the arousal regulation model, which asserts that the contrasting behavioral features of mania and depression may reflect compensatory responses to unstable or hyper-stable arousal states, respectively. Neurochemically, dopamine and norepinephrine signaling fluctuate with mood states: manic episodes often feature heightened dopaminergic and noradrenergic activity, while depressive episodes show attenuated transmission, as evidenced by variations in receptor availability and neurotransmitter turnover[112]. These dynamic, state-dependent alterations offer insight into the episodic nature of BD and highlight the need for phase-specific diagnostic and therapeutic strategies.

Other Relevant Factors

Genetic and Epigenetic Components

BD, particularly the type I subtype, is one of the most heritable psychiatric conditions. Heritability estimates have been shown to be as high as approximately 80% among type I subtype[8]. Linkage and association studies have revealed several chromosomal regions of interest, including 18q2123, 4p1213, and 13q3133. Rather than being driven by a single major gene, BD is most often discussed in the context of oligogenic epistatic models involving multiple interacting loci[9]. Genome-wide association studies (GWAS) and candidate gene analyses have highlighted the following genes: DRD1, DRD4, and DAT1, which regulate dopamine neurotransmission; HTTLPR and HTR2A, involved in serotonergic signaling; and BDNF and NCAM1, which are linked to neural development and synaptic plasticity[9]. Moreover, the involvement of genes governing circadian rhythms (e.g., CLOCK, ARNTL) provide compelling evidence linking disruptions in sleep-wake cycles to the pathophysiology of BD. These findings show that BD risk is polygenic, with multiple variants of small effect contributing to susceptibility.

In addition to genetic vulnerability, epigenetic mechanismswhich regulate gene expression without altering the underlying DNA sequenceare increasingly recognized as key contributors to BD. Altered DNA methylation in the promoter region of the catechol-O-methyltransferase (COMT) gene in the frontal cortex of BD patients is associated with increased gene expression and dopamine degradation in regions implicated in mood regulation[9]. In individuals with a high familial risk of BD, specific DNA methylation signatures have been detected in genes such as VARS2, which is involved in mitochondrial function, pointing to an epigenetic response to underlying polygenic risk[8]. These epigenetic alterations appear to overlap with genetic risk loci associated with BD and related disorders, reinforcing the complex gene-environment interplay in shaping disease trajectory.

Sex Differences

Select symptoms and features of BD have been shown to differ in prevalence and presentation between males and females. Women are more likely to experience frequent depressive episodes, rapid cycling between mood states, and higher rates of suicide attempts, while men are more likely to show symptoms of mania and earlier onset of the disorder[113,114]. Sex differences in BD are reflected in brain structure and function. Females have shown smaller volume in the right hippocampus[115], while males have shown larger grey matter volumes in the thalamus and caudate, as well as altered resting-state functional connectivity between the left thalamus and the right angular gyrus[116]. The angular gyrus is involved with processing language, number information, and memory, suggesting that in males, information routing through the thalamus may be reorganized in a way that could cause some of the cognitive symptoms observed in BD. Dysfunctional genomics among males in the dorsolateral PFC, involved with higher-level thinking and emotional control, may influence mood symptoms, namely mania and risk for psychosis[117]. These differences in brain and behavior highlight the importance of considering sex as a meaningful factor when studying BD and developing more personalized treatment strategies.

Neurobiological Mechanisms

Blood Brain Barrier (BBB) Permeability

The BBB, a protective structure that control which substances can pass from the bloodstream into the brain, and may be implicated in the progression of BD. When this barrier becomes weakened or disrupted, harmful moleculesincluding inflammatory proteins and toxinscan enter the brain and potentially disturb its normal functioning[118]. Individuals with BD show increased levels of markers in the blood that suggest BBB dysfunction, such as elevated S100B protein and matrix metalloproteinases[119]. These markers are linked to neural inflammation in regions such as the hippocampus and prefrontal cortex and have been observed more frequently in patients during mood episodes compared to euthymia. Understanding the connection between BBB

breakdown and mood instability may open new paths for treatment, such as therapies that focus on strengthening the barrier or reducing inflammation in the brain[84].

Circadian System Dysfunction

Circadian rhythm disturbances have been strongly linked to the development and course of BD. Those with BD that show alterations in key circadian genessuch as CLOCK, BMAL1, and PER3[120]. Abnormalities in these genes may lead to irregular sleep patterns, increased vulnerability to mood episodes, and difficulty stabilizing mood across time. Furthermore, BD patients often experience changes in sleep-wake cycles even before full mood episodes occur[121], suggesting that circadian rhythm disruption may be a potential early trigger of the disorder. Improving sleep hygiene and stabilizing daily routines could be valuable strategies in managing BD symptoms. This is a growing body of research, with potentially large implications in our understanding of the etiology and possible behavioral treatment strategies.

Mitochondrial Dysfunction

Mitochondrial dysfunction has been increasingly recognized as a contributing factor in the pathophysiology of BD. Patients with BD have shown altered mitochondrial DNA content, impaired oxidative phosphorylation, and elevated levels of lactate in the brain, especially the cingulate cortex, which signals inefficient energy metabolism[122]. These abnormalities can lead to impaired neuronal signaling, increased oxidative stress, and disruptions in calcium homeostasisall of which are implicated in BD symptoms such as mood swings, cognitive instability, and fatigue[122]. Mitochondrial dysfunction is closely tied to the regulation of apoptosis and neuroplasticity, suggesting that long-term mitochondrial abnormalities may contribute to the structural and functional brain changes observed in BD[9].

Oxidative Stress

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS)which are harmful byproducts of normal cellular metabolismand the bodys ability to neutralize them using antioxidants. Those with BD show increased levels of lipid peroxidation and protein oxidation, both signs of oxidative damage to cells[118], and are most noticeable during manic and depressive episodes, suggesting a link between mood instability and oxidative imbalance. Damage caused by ROS can impair mitochondrial function, disrupt neurotransmitter systems, and lead to neuronal cell deathall of which are processes believed to play a role in the unstable symptoms of BD. Antioxidant defense systems, including enzymes like superoxide dismutase (SOD), are also altered in individuals with BD, further contributing to oxidative burden[118]. Treatments targeting oxidative stresssuch as antioxidant supplementationmight offer new therapeutic avenues in the management of BD.

Discussion

The present narrative review aims to provide an overview of abnormalities in brain structure, function, and neurotransmitter activity in those with BD. Grey matter alterations include reduced volumes in key regions such as the hippocampus, amygdala, ACC, and PFC, all of which play a crucial role in emotion regulation, cognitive function, and mood stability. Longitudinal studies, while limited, suggest that repeated mood episodes contribute to progressive grey matter loss, particularly in the amygdala, ACC, and PFC, highlighting the potential neurodegenerative aspects of BD. In contrast, white matter abnormalities, particularly in the corpus callosum and cingulate gyrus, disrupt interhemispheric communication and emotional regulation, further exacerbating BD symptoms.

Functional connectivity research consistently shows disruptions in the DMN, SN, and CENthe triple network model. Altered DMN connectivity may underlie depressive symptoms. Hypo- and hyper-connectivity patterns in the SN contribute to the emotional instability observed in BD. Reduced connectivity within the CEN impairs cognitive control and executive functioning, leading to difficulties in impulse regulation and decision-making. Disruptions in communication between these networks may explain the abrupt shifts between manic and depressive states. Thus, BD is characterized by both intra-network and inter-network dysconnectivity disrupting emotional and cognitive processes.

Neurochemical research highlights the role of neurotransmitter dysregulation in BD. Dopamine and norepinephrine are often elevated during manic episodes and depleted during depressive states, contributing to the fluctuating mood patterns. GABA appears to be reduced in BD patients, particularly during depressive episodes, while heightened glutamine / glutamate ratio may underlie symptoms of mania. Lastly, reduced serotonergic activity linked to depressive symptoms and increased serotonin receptor sensitivity potentially contributing to mania.

While significant progress has been made in elucidating the neurobiological basis of BD, many questions remain unanswered. Other related factors outside of the direct scope of this review but are worth noting include the role of multiple genes associated with BD, sex-differences across brain structure and brain function, and various neurobiological mechanisms that may interact with alterations in brain structure, function, and neurotransmitter activity. Understanding BD as a disorder of disrupted brain structure, networks, and neurotransmitter imbalances, rather than focusing solely on individual brain regions or chemicals, may pave the way for more comprehensive treatment approaches.

Limitations

While this review provides an overview of neurobiological alterations in BD, it is not an exhaustive examination of BD etiology. Variability in episode severity, inclusion of patients across manic and depressive states, and subtypes make it difficult to establish universal neurobiological markers. Differences neuroimaging techniques and task paradigms, in addition to neurotransmitter studies using varying sample collection methods, may contribute to mixed findings. Additionally, cross-sectional studies dominate the literature, limiting the ability to establish causal relationships between brain alterations and disease progression. The lack of studies distinguishing medicated from unmedicated patients makes it difficult to isolate BD-specific alterations from medication effects. Environmental and genetic factors also play a role in BD, but few studies integrate these factors leading to difficulties in reproducibility.

Future Research Directions

Future research should aim for large-scale, multi-center longitudinal studies to address the limitations of cross-sectional designs, include thorough assessment of additional factors that may alter neurobiological components (i.e., genetic predisposition, environmental stressors), and analyze data in a way that accounts for additional variables such as sex, medication status, or BD subtype. Additionally, recruiting medication-nave patients would help distinguish BD-specific alterations from medication effects. Standardized methodologies across studiessuch as consistent imaging techniques, neurotransmitter measurement protocols, and diagnostic criteriawould enhance comparability and reproducibility of findings. Lastly, examining interactions between genetic predisposition, life stressors, age (expanding studies among adolescents), and comparisons with pre-clinical models may offer deeper insights into BDs etiology.

Conclusion

BD is a highly complex and heterogeneous psychiatric disorder with significant alterations in brain structure, functional connectivity, and neurotransmitter activity. While extensive research has sought to identify neurobiological markers of BD, findings remain inconsistent due to methodological challenges, patient heterogeneity, and medication effects. This narrative review focused on adults with BD integrates the current literature to provide a comprehensive understanding of the neurobiological basis of BD. Future research is needed to further understand how the neural basis of BD may be used to optimize pharmacological treatment options.

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Brain Structure			
Brain Region	**Cortical Metric**	**Relationship to BD**	**Reference**
Hippocampus	Volume	Reduced volume, high variability; possibly sex- and treatment-related	Cao et al., 2017; Haukvik et al., 2020; Han et al., 2019; Angelescu et al., 2021; Lyoo et al., 2010
Amygdala	Volume	Developmental changes; increase in adults, decrease in youth	Hajek et al., 2008; Pfeifer et al., 2008; Chen et al., 2004; Chang et al., 2005; Sun et al., 2017
ACC	Volume	Decreased volume; related to emotional and cognitive dysfunction	Sassi et al., 2004; López-Larson et al., 2002; Shackman et al., 2011
Lateral ventricles	Volume	Increased volume; associated with aging and cognitive impairments	Luciano et al., 2022; Hibar et al., 2016
Corpus callosum	Volume	Decreased volume; impairs interhemispheric communication	Wang et al., 2008; Pezzoli et al., 2018; Favre et al., 2019
Cingulate gyrus	Volume	Decreased volume; linked to mood instability and impulsivity	Poletti et al., 2015; Matsuo et al., 2009
Brain Function			
Neural Network	**Brain Regions Involved**	**Relationship to BD**	**Reference**
Default Mode Network	Ventromedial PFC, dorsomedial PFC, PCC, precuneus	Hypoconnectivity at rest; hyperconnectivity during tasks	Chai et al., 2011; Favre et al., 2014; Magioncalda et al., 2014
Salience Network	anterior insula, dorsal ACC, anterior PFC, supramarginal gyrus, striatum, thalamus	Hypoconnectivity at rest; affects salience processing and state switching	Rey et al., 2016; Hu et al., 2016; Ellard et al., 2018
DMN-SN	Combined nodes of DMN and SN	Hyperconnectivity; excessive internal or external focus	Cattarinussi et al., 2022; Gong et al., 2019
CEN-SN	Insula (SN) and inferior parietal lobule (CEN)	Reduced connectivity; relates to impaired emotion control and inhibition	Roberts et al., 2017; Zhang & Zhong, 2023
CEN-DMN	Dorsolateral PFC and inferior frontal gyrus (CEN) and medial PFC (DMN)	Functional decoupling; impairs task-positive/resting-state transitions	Magioncalda et al., 2014; Menon, 2011
Neurotransmitter Activity			
Neurotransmitter	**Area of Alteration**	**Relationship to BD**	**Reference**
Dopamine	Striatum, limbic system	Increased during mania, decreased during depression; drives mood switching	Speranza et al., 2021; Cousins et al., 2009; Ashok et al., 2017; Palsson et al., 2023
Noradrenaline	MHPG levels in plasma/CSF	Higher in mania, lower in depression; linked to arousal and stress response	Kurita, 2016; Hussain et al., 2023; van Enkhuizen et al., 2015
GABA	PFC, amygdala, hippocampus	Low in depression; increased excitability and mood instability	Kaufman et al., 2009; Brambilla et al., 2003; Fatemi et al., 2013; Wang & Ketter, 2005
Glutamate	ACC, PFC	Elevated in mania; contributes to excitotoxicity and emotional dysregulation	Kubo et al., 2016; Ino et al., 2023; Dost Öngür et al., 2008; Guglielmo & Hasler, 2022
Serotonin	PFC, brainstem nuclei	Reduced in depression; altered receptors affect emotional reactivity	Bakshi & Tadi, 2022; Manji et al., 2003; Bartlett et al., 2022; Viktorin et al., 2014
Other Relevant Factors			
Factor	**Relationship to BD**		**Reference**
Genetic	High heritability; polygenic with risk genes affecting neurotransmission		James & McMahon, 2020; Sigitova et al., 2016
Epigenetic	Environmental factors influence gene expression; treatment may modify epigenetics		Angelescu et al., 2021; James & McMahon, 2020
Sex differences	Affects brain volume, functional connectivity, and symptom presentation		Shi et al., 2018; Lee et al., 2024; Zhang & Swaab, 2024
Blood Brain Barrier	Disruption allows harmful proteins into brain; linked to inflammation		Wakonigg Alonso et al., 2024
Circadian System Dysfunction	Gene mutations and rhythm misalignment can trigger mood episodes		Melo et al., 2016; McClung, 2007
Mitochondrial Dysfunction	Impaired energy production and calcium regulation affect neuronal function		Kato, 2022
Oxidative Stress	Excess ROS causes cell damage		Andreazza et al., 2008

Table 1. Summary of Neurobiological Factors Underlying Bipolar Disorder