Neuroanatomic and Functional Neuroimaging Findings

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Abstract The search for brain morphology findings that could explain behavioral disorders has gone through a long path in the history of psychiatry. With the advance of brain imaging technology, studies have been able to identify brain morphology and neural circuits associated with the pathophysiology of mental illnesses, such as bipolar disorders (BD). Promising results have also shown the potential of neuroimaging findings in the identification of outcome predictors and response to treatment among patients with BD. In this chapter, we present brain imaging structural

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and functional findings associated with BD, as well as their hypothesized relationship with the pathophysiological aspects of that condition and their potential clinical applications.

Keywords Bipolar disorder · Diffusion tensor imaging · Functional neuroimaging · Magnetic resonance imaging

1 Introduction

The search for brain morphology findings that could explain behavioral disorders has gone through a long path in the history of psychiatry. The German physician Theodor Meynert, one of the representatives of the so called "first biological psychiatry movement" in the nineteenth century, once said: "The study of human anatomy in its current form has passed from a solely descriptive science to something higher, to a form of knowledge that attempts to explain. . . The more psychiatry seeks, and finds, its scientific basis in a deep and finely grained understanding of the anatomical structure [of the brain], the more it elevates itself to the status of science that deals with causes" (Shorter 1997). Almost 130 years after his words, the psychiatric field has witnessed astonishing progress in the way we see the brain, both structurally and functionally, which has provided valuable insights on the neurophysiological processes that underlie the abnormalities in behavior, cognition, and emotion we observe in patients with psychiatric disorders. With the advances in brain imaging technology, studies have been able to identify patterns in brain circuitry associated with fundamental characteristics found in patients with bipolar disorders (BD), as alterations in emotional processing and regulation and reward processing (Phillips and Swartz 2014). Here, we critically analyze the brain imaging structural and functional findings associated with BD, not only regarding their correlation with pathophysiological aspects of the disease but also their potential clinical applications.

2 Structural Neuroimaging and Diffusion Tensor Imaging Studies

2.1 Structural Magnetic Resonance Imaging MRI (sMRI) Findings in BD

The use of sMRI in the study of brain abnormalities in individuals with BD has accumulated evidence over more than three decades of research, with countless studies. In one of the first of these studies, Johnstone et al. (1989) compared the

temporal lobe structure in patients with BD, patients with schizophrenia, and healthy controls (HC). All participants with BD had a history of psychosis (Johnstone et al. 1989). With a scanning magnetic resonance imaging system that operated at 0.15 Tesla (T), the authors found a trend towards significance on the association between diagnosis and temporal lobe size, with lower measures among individuals with schizophrenia compared to the other two groups. Actually, in this study the authors did not find significant brain structural differences between participants with BD and HC. However, an association between increased ventricular size and poor outcome when evaluating participants with schizophrenia and BD together was reported, suggesting neuroprogression associated with severe psychiatric disorders (Johnstone et al. 1989; Gama et al. 2013). In a review of the literature comprising the first decade of sMRI studies in individuals with mood disorders, Soares and Mann (1997) reported a consistent finding of enlargement of the third ventricle in participants with BD. In addition, the majority of the studies that evaluated temporal lobe findings in individuals with BD identified abnormalities, especially decreased temporal lobe volumes. There were conflicting sMRI results related to amygdala, hippocampus, and basal ganglia (Soares and Mann 1997).

More recently, an analysis from the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Bipolar Disorder Working Group (2018) compared sMRI cortical gray matter thickness and surface area between adults with BD (n = 1,837) and HC (n = 2,582) (Hibar et al. 2018). The comparisons were controlled for age and sex (for the cortical thickness analysis) and also intracranial volume (for surface area analysis). The results showed a significant and diffuse pattern of reduced cortical thickness in individuals with BD compared with HC. The findings were more accentuated for the left pars opercularis, left fusiform gyrus, and left rostral middle frontal cortex regions. Regarding surface area comparisons, there were no significant differences between BD and controls. The authors also investigated associations between sMRI measures and clinical variables, such as illness duration and history of psychosis. The duration of illness was associated with a broader pattern of reduced cortical thickness. The surface area of regions of interest (ROIs) was not correlated with disease duration in this study. History of psychosis, however, was associated with reduced surface area in the right caudal anterior cingulate cortex and in the left inferior temporal gyrus (Hibar et al. 2018). The same working group also investigated subcortical volumetric brain abnormalities among individuals with BD compared with HC, including nucleus accumbens, amygdala, caudate, globus pallidus, putamen, thalamus, and lateral ventricles (Hibar et al. 2016). The results showed significantly lower mean volumes of the hippocampus, thalamus, and a trend towards significance regarding the lower mean volume of amygdala in participants with BD, bilaterally, as well as larger lateral ventricles. Decreased hippocampal volumes were also associated with older age (Hibar et al. 2016). DelBello et al. (2004) found volumetric differences related to subcortical brain regions in patients with BD already during adolescence. The authors compared adolescents with BD (mean age 16.3 years) and HC (mean age 17.2 years) regarding amygdala, globus pallidus, caudate, putamen, and thalamus volumes. In this study, in addition to lower total cerebral volume, adolescents with

BD presented significantly reduced volumes of amygdala and larger putamen (DelBello et al. 2004). Sanches et al. (2005) did not find striatal volumetric differences between adolescents with BD compared with controls. However, among the adolescents with BD, there was a significant inverse relationship between age and volumes of left caudate, right caudate, and left putamen, which were not found for the HC (Sanches et al. 2005). Studies with individuals at high genetic risk for BD also found smaller anterior cingulate cortex (ACC) and larger amygdala volumes in unaffected relatives of patients with BD compared with controls, suggesting potential brain imaging markers of disease vulnerability (Bauer et al. 2014; Sanches et al. 2019).

2.2 Diffusion Tensor Imaging (DTI) Findings in BD

DTI maps characterize the three-dimensional diffusion of water as a function of spatial location, which may be used to estimate the pattern of connectivity in the brain and to study the integrity of white matter tracts (Alexander et al. 2007; Benedetti et al. 2011). Adler et al. (2004) hypothesized that changes in prefrontal function found in individuals with BD are associated with a dysconnectivity syndrome due to impairment in the white matter tract integrity. The authors compared fractional anisotropy (FA) of ROIs, more specifically above anterior commissure, which was chosen a priori, according to previous findings from the group. Nine patients with bipolar disorder were compared with nine HC, controlling for age and education. The authors found significantly reduced FA in two of the four ROIs in patients with BD and medium-to-large effect sizes when all ROIs were combined (Adler et al. 2004). Mean FA and apparent diffusion coefficient (ADC) of four axonal pathways were compared between euthymic patients with BD type I (BDI), healthy first-degree relatives of these patients, and HC in the study of Mahapatra et al. (2017). The results showed a significantly lower FA for individuals with BD type I when compared with first degree relatives, who in their turn presented significantly lower FA compared with HC for the following regions: corpus callosum, dorsal part of the right cingulum bundle, hippocampal part of right cingulum bundle, hippocampal part of the left cingulum bundle, right uncinate fasciculus, and left uncinate fasciculus (Mahapatra et al. 2017). Duarte et al. (2016) reviewed studies of DTI with participants with BD focusing on FA in white matter tracts. Among the 18 studies included in this systematic review, decreased FA in commissural and association tracts, especially in the fronto-limbic tracts, was the most common finding (Duarte et al. 2016). Favre et al. (2019) compared FA from 43 ROIs between 1,482 participants with BD and 1,551 HC from 26 cohort studies. The authors found significant differences in most of the regions compared with higher effect sizes for corpus callosum and cingulum. In addition, there was a significant positive relationship between FA in the inferior fronto-occipital fasciculus and the age of onset within participants with BD. Moreover, similar to volumetric brain abnormalities, changes in white matter

can be found in an early stage of the disease. Adler et al. (2006) reported that adolescents in their first episode of mania presented significantly decreased FA in the prefrontal white matter (more specifically in superior-frontal tracts) when compared with healthy participants.

2.3 Longitudinal sMRI and DTI Findings

Longitudinal neuroimaging studies are useful for the investigation of abnormalities in the brain maturation trajectories among individuals with BD, as well as to identify potential risk factors of neuroprogression and its clinical correlates. Abe et al. (2019) followed 90 patients with BD and 61 HC for 6 years to investigate putative alterations in cortical thickness. The results showed that patients with BD presented with increases in cortical thickness in visual/somatosensory areas and abnormal cortical thinning in bilateral middle temporal cortices compared with controls. While the decreases in cortical thickness suggest an expected neuroprogression of the disease, reflecting a gray matter loss, the increase in the cortical thickness of the medial occipital cortex and central sulcus was unexpected, especially considering that controls showed a decrease in the cortical thickness in these regions (Abe et al. 2019). Zak et al. (2019) also reported decreased cortical thickness in the left and right prefrontal and left temporal cortex of individuals with BD type II in a follow-up study. Both patients and controls displayed cortical thinning over the follow-up period, but patients with BD showed greater thinning in inferior temporal and left posterior cortices. Adolescents with BD, compared with HC, showed more reductions in the insula, orbitofrontal, and dorsolateral prefrontal cortices over a 2-year follow-up study (Najt et al. 2016). Bootsman et al. (2015) have investigated brain changes in subcortical regions in a twin study with individuals with BD. Despite significant differences between patients with BD and controls regarding thalamus, putamen, and nucleus accumbens at baseline, the authors did not find differences overtime after correction for multiple comparisons (Bootsman et al. 2015).

Furthermore, adolescents and young adults with BD (17.6 mean years old) and HC (16.6 mean years old) were part of a longitudinal study with DTI data at baseline and after 2.5 years of follow-up (Weathers et al. 2018). The authors investigated differences between the groups regarding uncinate fasciculus (UF), a tract that connects the amygdala and ventral prefrontal cortex, a brain network associated with emotion regulation (Weathers et al. 2018). In the patient group, there was no significant association between FA at the UF and age and no differences between the two time points, while in HC the authors did find positive associations between UF FA and age, as well as increases in UF over the follow-up period (Weathers et al. 2018). Finally, in another study, individuals at high risk for bipolar disorder (including a high-risk subgroup who later developed major depressive disorder) were compared with HC with respect to change in white matter integrity over a 2-year follow-up period (Ganzola et al. 2017). The authors hypothesized that patients, compared to controls, would show FA decreases in the corpus callosum and

fronto-limbic connections. However, the results showed that, despite reductions in FA found in the whole sample, there were no statistically significant differences between groups (Ganzola et al. 2017).

3 Functional Neuroimaging

3.1 Positron Emission Tomography (PET)

PET uses radioactive tracers to investigate distinct neural functions, providing quantitative images of the spatial distribution of the compound. One highly used radioactive tracer, F-fluorodeoxyglucose (FDG), is a glucose analog and is, therefore, useful for the measurement of brain metabolism (Gonul et al. 2009). Mah et al. (2007) performed a PET study in individuals with BD type II and a current major depressive episode and HC. The authors did not find differences regarding whole-brain metabolism. However, for ROIs analysis, the results showed higher metabolism in the amygdala, left orbitofrontal cortex, right anterior cingulate cortex, accumbens area, left and right putamen, and left caudate regions in patients compared with controls (Mah et al. 2007). In another study, the FDG PET findings among BD patients with and without psychotic symptoms and HC were analyzed (Marotta et al. 2019). Patients with BD and no history of psychotic symptoms presented decreased FDG uptake in the middle occipital gyri bilaterally, as well as increased uptake in insula and temporal regions, compared with controls. However, in comparison with patients with BD and a history of psychotic symptoms, those without psychosis presented an increase in FDG uptake in the right fusiform gyrus (Marotta et al. 2019). The central serotonin transporter (5-HTT) system was also investigated in individuals with BD in comparison with HC by measuring a PET radioligand for the 5-HTT, the [^{11}C]DASB (Cannon et al. 2006). In this cross-sectional study, Cannon et al. (2006) found higher levels of the ligand in the insula, medial PFC, thalamus, caudate, and dorsal cingulate cortex and reduced levels in the brainstem of the patients. There were no significant correlations between 5-HTT binding and depression scores, illness duration, and age of onset (Cannon et al. 2006). Radioligand binding associated with microglia activation, which is suggestive of neuroinflammation, was reported as significantly increased in patients with BD compared with HC in the study of Haarman et al. (2014). Anand et al. (2011) investigated the dopaminergic system in individuals with BD by measuring the striatal binding potential of the dopamine transporter (DAT)-selective radiotracer [(11) C]CFT in individuals with BD (euthymic or depressed) and HC. The striatal binding potential was found to be significantly decreased among patients, particularly in the left and right dorsal caudate (Anand et al. 2011). These results are in agreement with previous reviews of the literature (such as the one by Berk et al. 2007), which highlight the evidence supporting the hypothesis that dysfunctions in the dopaminergic function seem to be involved in the pathophysiology of BD (Berk et al. 2007). Interestingly, a recent systematic review and meta-analysis indicated

that a previous diagnosis of BD shows a more than threefold odds ratio associated with a subsequent diagnosis of idiopathic Parkinson's disease, an illness associated with degeneration of dopaminergic neurons in the substantia nigra (Kalia and Lang 2015; Faustino et al. 2019).

3.2 Resting-State Functional MRI (rsfMRI)

fMRI generates images using blood oxygen level-dependent (BOLD) contrast, which provides a spatial resolution that allows the localization and delimitation of activated brain areas. Thus, fMRI helps evaluate brain activity changes in specific areas, associated with the performance of specific tasks (Chow et al. 2017). Moreover, fMRI also allows the assessment of anatomically separated brain regions that are nevertheless related with respect to patterns of neuronal activity and are, therefore, functionally connected, even during "resting states" of the brain (van den Heuvel and Hulshoff Pol 2010). These complex set of neural networks mediate emotions, cognitions, and behaviors, whose dysfunction probably underlies the psychiatric manifestations are observed in the patients (Steinberg et al. 2015). Thus, brain imaging techniques that map brain regions functionally interconnected are fundamental tools to investigate neurobiological brain mechanisms of psychiatric illness.

For instance, Liu et al. (2012) investigated resting-state functional connectivity within the default mode network (DMN) in individuals with BD and HC. The DMN is related to self-oriented patterns of thought, which include rumination and introspective states, and comprise the medial, lateral, and inferior parietal cortices, the medial prefrontal cortex (mPFC), and the precuneus/posterior cingulate cortex (PCC) (Langenecker et al. 2014; Mak et al. 2017). The results showed that patients with BD displayed abnormal brain activity with significantly increased regional homogeneity (ReHo) in the left medial frontal gyrus and the left inferior parietal lobe, which could be interpreted as an enhancement of the local synchronization in those regions (Liu et al. 2012). The authors pointed out that hyperactivity of the medial frontal gyrus could be related to cognitive-emotional interference in patients with BD, as this region is implicated in cognitive regulation and emotion perception. Frontal-limbic connectivity dysfunction has been associated with the pathophysiology of BD, especially with respect to mood dysregulation due to impairment in the prefrontal cortex inhibitory control over subcortical structures as amygdala (Anticevic et al. 2013). Vizueta et al. (2012) showed that patients with BD type II and depression presented with significantly decreased activation in the left and right ventrolateral prefrontal cortices and the right amygdala, as well as reduced functional connectivity between the right amygdala and the orbitofrontal and dorsolateral prefrontal cortices in comparison with HC. In a systematic literature review, Vargas et al. (2013) reported that the most common findings from rsfMRI studies in individuals with BD were in the brain connectivity of the PFC areas and anterior cingulate cortex with meso-limbic areas as thalamus, insula, and amygdala in

comparison with HC. Furthermore, altered connectivity between prefrontal and subcortical regions may already be present early in life. For instance, Singh et al. (2014) found that high-risk youth for BD were found to have decreased connectivity between pregenual cingulate and left amygdala and between left ventral lateral PFC and caudate compared with low-risk youth.

4 Summary of Main Findings

The advances in neuroimaging technology have allowed the noninvasive study of the brain, both structurally and functionally. Different study designs have helped to address distinct research questions, such as brain biomarkers related to BD, including information on cortical thickness, surface area, subcortical volumes, white matter integrity, and connectivity of neural circuits. They have also attempted to characterize longitudinal neuroprogression patterns that are potentially specific to individuals with BD in comparison with healthy individuals. Despite the high heterogeneity of the studies from a methodological standpoint, including sample size, sociodemographic factors, and clinical characteristics, some findings could be pointed out. Structural studies have shown associations between duration of illness and reduced cortical thickness, in addition to increased third ventricle size and reduced volume of hippocampus and amygdala. DTI studies show decreased connectivity in fronto-limbic tracts, corpus callosum, uncinate fasciculus, and cingulum. Longitudinal studies found reduced cortical thickness in prefrontal and temporal regions.

In contrast, PET studies show higher metabolism in the amygdala, orbitofrontal cortex, cingulate and accumbens with 18-FDG, increased 5-HTT binding in the insula, medial PFC, thalamus and cingulate cortex, as well as decreased striatal binding potential in caudate and putamen regions. Imaging findings also point to microglia activation, suggesting the involvement of neuroinflammation in patients with BD. Resting-state fMRI studies show enhancement of local synchronization within the default mode network, as well as reduced connectivity in fronto-limbic regions. Studies with early age individuals found a reduced volume of amygdala and increase putamen volume, as well as gray matter reductions in the insula, orbitofrontal and dorsolateral PFC regions and decrease FA in PFC white matter. Finally, individuals at high genetic risk for BD also show structural and functional abnormalities that suggest disease vulnerability. In summary, structural and functional studies indicate abnormalities in brain regions associated with emotion-processing, emotion-regulation, and reward-processing neural circuits in the pathophysiology of BD (Phillips and Swartz 2014).

5 Diagnostic Specificity of Neuroimaging Findings

Neuroimaging studies have been used to investigate the heterogeneity of BD, including potential differences between illness subtypes according to categorical classifications (for instance, Diagnostic and Statistical Manual of Mental Disorders [DSM] Bipolar disorders type I and II) (American Psychiatric Association 2000), and with other psychiatric disorders that could share similar clinical symptoms despite distinctions in terms of prognosis and responses to treatment (for example, unipolar depression).

5.1 Structural Neuroimaging and DTI Findings

A longitudinal study that evaluated cortical thickness among patients with BD and HC did not find differences between BD I and II subtypes (Abe et al. 2019). Similar results were found for the ENIGMA study, which compared 1,275 adults with BD type I and unrelated 345 adults with BD type II. The authors did not find differences regarding cortical thickness or the surface area between the BD subtypes I and II (Hibar et al. 2018). Subcortical volumetric regions, including lateral ventricles, thalamus, putamen, globus pallidus, hippocampus, caudate, amygdala, and nucleus accumbens, were similar between BD type I and II in the study of Hibar et al. (2016). In a systematic review, Hanford et al. (2016) reported that most of the studies comparing patients with BD type I and II regarding cortical thickness did not find significant differences (Hanford et al. 2016)

Foley et al. (2018) compared FA in the uncinate fasciculus in individuals with BD type I and II. In this study, patients with BD type I were found to have lower FA than those with BD type II, which, in turn, did not differ from HC. Similar results were found in the study of Caseras et al. (2015), in which FA in the left uncinate fasciculus of patients with BD type I was significantly reduced in comparison with patients with BD type II. Ambrosi et al. (2016) compared axial diffusivity (AD) and radial diffusivity (RD) besides FA in patients with subtypes of BD and HC. The authors found that patients with BD type II presented lower FA in the right inferior longitudinal fasciculus compared with both BD type I and HC (Ambrosi et al. 2016). Diffusion tensor images of patients with BD type I and II were also investigated by Liu et al. (2010), who reported that individuals with BD II had lower FA in the right inferior frontal gyrus, left inferior prefrontal area, and right precuneus in comparison with BD I.

Han et al. (2019) reviewed studies assessing structural and functional MRI findings in patients with unipolar depression (UP) and bipolar depression. BD were reported as showing greater cortical thickness in the right precuneus, left inferior parietal gyrus, and right dorsolateral prefrontal cortex, as well as a smaller hippocampus and amygdala volumes and increased anterior cingulate cortex volume, compared with individuals with UP (Han et al. 2019). Differences in cortical

thickness were also found in the comparison between patients with schizophrenia (SCZ) and patients with BP in the study of Godwin et al. (2018), with respect to the frontal, parietal, and temporal cortices regions. In a study evaluating young individuals at high genetic risk for BD and SCZ, however, the authors did not find cortical thickness differences between groups, despite the high-risk SCZ group presenting significantly decreased surface area in the occipital lobe compared with those at high risk for BD (Sugranyes et al. 2017). Regarding volumetric structural neuroimaging findings, Ho et al. (2019), in a literature review, reported lower left, right, and total amygdala volumes in patients with schizophrenia compared with BD.

In the mentioned review of Han et al. (2019), the authors also reported differences regarding DTI measures, with patients with BD showing decreased FA in the posterior cingulum bundle and the genu of the corpus callosum compared with UP. Sexton et al. (2012) compared FA within the corpus callosum between participants with late-life BD and UP depression. The results showed that patients with BD had reductions in FA within the genu, body, and splenium of the corpus callosum, suggesting that altered inter-hemispheric connectivity might be a feature of late-life bipolar disorder (Sexton et al. 2012). Ho et al. (2019) reported no differences between patients with BD and SCZ regarding the FA of the uncinate fasciculus tract, a finding previously reported by studies comparing HC and BD (Ho et al. 2019; Mahapatra et al. 2017). On the other hand, comparisons on the corpus callosum white matter did not show differences between individuals with BD and SCZ diagnosis (Li et al. 2014). Negative findings were also found in the study of Skudlarski et al. (2013), which included patients with BD, SCZ, and their first-degree relatives. Positive findings were reported in the study of Tonnesen et al. (2018), in which patients with SCZ showed lower FA in the right inferior longitudinal fasciculus and right inferior fronto-occipital fasciculus compared with patients with BD.

5.2 Functional Neuroimaging Findings (PET, rs-fMRI)

Hosokawa et al. (2009) compared resting-state PET findings between patients with BD and UP and found a distinct pattern of decreased glucose metabolism related to HC, suggesting brain metabolism particularities in comparison with healthy individuals. However, the authors did not find differences between unipolar and bipolar depressed patients (Hosokawa et al. 2009). Altamura et al. (2017) used 18-FDG-PET scanning to compare brain metabolism differences between patients with BD type I and history of psychosis with or without substance use, and patients with substance-induced psychosis. The results showed that patients with substance-induced psychosis presented decreased glucose metabolism in the left posterior cingulate compared with patients with BD and history of psychosis with no substance use (Altamura et al. 2017). A study with fluorodihydroxyphenyl-l-alanine ([18F]-DOPA) PET did not show differences regarding dopamine synthesis capacity between patients with BD and history of psychosis and patients with SCZ. When both groups were

combined, however, the findings showed a significant positive correlation between psychotic symptom severity and dopamine synthesis capacity, suggesting a transdiagnostic role for dopamine dysfunction in BD and SCZ (Jauhar et al. 2017). Glucose metabolism differences between psychiatric diagnosis were also investigated by Boen et al. (2019). In this study, patients with borderline personality disorder (BPD) and no comorbid BD were compared with patients with BD type II and HC. Both groups of patients (BPD and BD) showed decreased metabolism in similar regions, such as insula, brainstem, and frontal white matter compared to HC, which could, in part, explain the high comorbidity between these two psychiatric diagnoses (Frias et al. 2016). The results also showed that patients with BD presented higher metabolism in some cortical areas compared with those with BPD (Boen et al. 2019).

In a literature review with fMRI studies, McGrath et al. (2004) did not find evidence of differences between patients with BD type I and type II. When compared with patients with UP depression, however, patients with BD presented a distinct pattern of connectivity in the study of Goya-Maldonado et al. (2016). While the former showed increased connectivity in the DMN in the precuneus and hippocampus bilaterally, patients with BD showed increased functional connectivity in the frontoparietal network, especially in the dorsolateral and ventrolateral PFC compared with participants with UP depression (Goya-Maldonado et al. 2016). Karcher et al. (2019) investigated corticostriatal connectivity in individuals with SCZ and BD with a history of psychotic symptoms compared with HC. Both patient groups presented with reduced connectivity between the putamen and the medial prefrontal cortex and reduced salience network connectivity, suggesting a common pattern of corticostriatal dysconnectivity in patients with primary psychotic disorders (Karcher et al. 2019). Similar transdiagnostic findings were reported in the study of Ma et al. (2019), in which patients with SCZ, BD, and UP depression presented common network dysfunction.

5.3 Neuroimaging and Pattern Classification Methods and the Diagnosis of BD

Machine learning (ML) techniques are able to analyze multiple sources of data, which can provide information from an individual level, rather than between-groups average differences, with a potential role in terms of diagnostic prediction and accuracy (Nunes et al. 2018).

Nunes et al. (2018) analyzed clinical and neuroimaging data (including regional cortical thickness, surface area, and subcortical volumes) of 853 participants with a diagnosis of BD and 2,167 HC using support vector machines (SVM), aiming at discriminating patients from controls. In this study, despite the accuracy of 65.23% (95% CI = 63.47–67.00) was below the considered clinically relevant (80%), taking into account the high heterogeneity of the sample, from 13 cohort studies over the

world, the results suggest ML approaches as a potential technique for improvement of diagnosis accuracy (Nunes et al. 2018). With DTI data, Mwangi et al. (2015) investigated the potential of SVM to accurately discriminate individuals with pediatric BD from HC (both groups with approximately 12 years old on average). The authors reported accuracy of 78.12%, with a sensitivity of 68.75% and specificity of 87.5%, with the most relevant regions discriminating patients from controls showing a consistent reduced pattern of FA (Mwangi et al. 2015).

The discrimination between UP depression and BD depression was also investigated by studies using SVM algorithms. Matsuo et al. (2019) found that gray matter volumes of the dorsolateral PFC bilaterally and anterior cingulate cortex contributed to the diagnosis classification of UP depression and BD depression with SVM models. Brain structural neuroimaging data was also used by Rubin-Falcone et al. (2018) to differentiate individuals with BD and UP depression, with results showing a combined accuracy of 75% using SVM for gray matter volume data. Li et al. (2017) used resting-state fMRI with SVM approach to test its accuracy to discriminate individuals with BD from unipolar depression. Results showed an accuracy of 86%, as well as a large proportion of disease-specific information, with a low overlap between individuals with UP depression and BD depression with respect to topographic abnormalities (Li et al. 2017).

Machine learning methods can help not only in terms of diagnostic discrimination but also in predicting specific outcomes and identifying specific clinical phenotypes in bipolar disorder, which can be useful for approaching the clinical heterogeneity of the illness. Sartori et al. (2018) used volumetric brain imaging data to predict functioning in patients with bipolar disorder and HC, utilizing an ML approach. Both groups displayed significantly different functional outcomes, which included the Functioning Assessment Short Test (FAST) scores and employment status (Reisberg 1988; Sartori et al. 2018). Left superior frontal cortex volume and left rostral middle frontal cortex were the central regions able to predict FAST scores in patients with BD (Sartori et al. 2018; Phillips and Swartz 2014). There were no significant findings in the HC group (Sartori et al. 2018). Neuroimaging and neurocognitive data were used to investigate clinical phenotypes in patients with BD in the study of Wu et al. (2017). The cognitive evaluation included measures associated with arousal, cognitive control, declarative memory, social communication, and valence systems according to the Research Domain Criteria (RDoC) Initiative (Wu et al. 2017; National Institute of Mental Health 2008). The authors found two phenotypes, which did not overlap with the DSM BD classifications. The ML algorithm, using FA, discriminated these phenotypes with 75.9% accuracy (the inferior frontal-occipital fasciculus and the minor forceps of the corpus callosum were the most relevant brain regions) (Wu et al. 2017).

Taken together, these studies show that ML techniques are very promising approaches not only for the improvement of diagnostic accuracy and prediction but also for the better characterization of the phenotypical heterogeneity in BD (Librenza-Garcia et al. 2017). In a position paper from the International Society for Bipolar Disorders Big Data Task Force, Passos et al. (2019) enumerated some of the challenges faced by ML, including model validation, computational power,

multimodality, and lack of a uniform pipeline for ML studies. However, once overcome, these techniques, combined with big data analyze, could help with the aim of improving prognosis in the management of BD, with better prediction of clinical outcomes and response to treatment (Passos et al. 2019).

6 Perspectives on the Role of Neuroimaging in the Management of BD Patients

6.1 Neuroimaging Studies and Bipolar Disorders Mood States

In a longitudinal study, Zak et al. (2019) reported greater cortical thinning in the left temporal cortical among patients with BD with more than two depressives episodes from baseline to the follow-up, compared with patients with fewer depressive episodes. Another longitudinal study found a greater cortical thinning in the inferior frontal cortex of patients with mania compared with patients with non-manic BD type I. In addition, patients with BD type II that experienced hypomanic episodes during the follow-up showed more pronounced decreases in the inferior frontal cortex compared with patients with BD type II who did not have hypomanic episodes during the longitudinal evaluation (Abe et al. 2019). Using an FDG PET scan, Brooks et al. (2009) found a significant inverse correlation between global metabolic rates and scores in the Hamilton depression scale (HAM-D) (Brooks et al. 2009; Hamilton 1960). Brady et al. (2016) investigated rsfMRI activity in regions associated with affect perception, affect regulation, and reward-seeking behavior during different mood states in patients with BD type I, mania and euthymia, as well as in HC. The results showed that, compared with patients with BD in euthymia, those with mania presented with significantly increased connectivity between the right amygdala and the bilateral supplemental motor area in the frontal cortex, as well as decreased connectivity with the ACC, suggesting altered emotion regulation neural circuits associated with mania states. There were no significant differences regarding connectivity with the ventral striatum between patients with BD in mania or euthymia (Brady et al. 2016). In a longitudinal design, these authors were able to replicate these findings, suggesting that cortico-amygdala resting-state connectivity could be a biomarker of mood state in patients with BD (Brady et al. 2017).

6.2 Neuroimaging Studies, Bipolar Disorders, and Pharmacological Treatment

Hibar et al. (2018) found significant increases in cortical thickness associated with the use of lithium in patients with BD, mainly in the left paracentral gyrus and the left

and right superior parietal gyrus, as well as increased surface area in the left paracentral lobe. The use of typical and atypical antipsychotic medications seemed to show different types of associations with the imaging findings. While the use of typical antipsychotics was associated with increased cortical surface area (especially in the left middle temporal gyrus, left inferior parietal gyrus, and right temporal pole), atypical antipsychotic use was associated with decreased cortical surface area in the right rostral middle frontal gyrus and right superior frontal gyrus (Hibar et al. 2018). Li et al. (2019) compared cortical thickness and subcortical volumes in HC with patients with BD taking valproate and patients with BD on lithium. Results showed that participants with BD on lithium had significantly increased cortical thickness in the right superior frontal cortex and in the left rostral middle frontal cortex compared with those taking valproate. The authors did not find differences in subcortical regions. In patients with pediatric bipolar disorder, a preliminary study showed decreases in the amygdala volume after a 6-week treatment period with sodium valproate (Cazala et al. 2018). Further, in the mentioned follow-up study by Abe et al. (2019), the authors reported that patients who used lithium presented with an increase in the cortical thickness of the medial occipital, which was not found for patients who were not on that medication. Brain structure changes with lithium use may also be related to duration of medication exposure, as showed by the study of Sani et al. (2018), in which short-term use was related to changes in amygdala volume and long-term use with changes in hippocampus and amygdala volumes.

Favre et al. (2019) reported associations between FA findings and use of medications in a cross-sectional study with 1,482 participants with BD. In this study, antipsychotics were associated with lower FA within the genu of the corpus callosum. The authors did not find differences related to antidepressant use. Regarding lithium, the authors reported higher FA in several ROIs among the patients who were on that medication, which may be related to the potential of lithium in promoting myelination (Favre et al. 2019; Brambilla et al. 2009). FA in the corpus callosum was significantly higher among patients on lithium in the study of Abramovic et al. (2018), with no significant differences in FA associated with antipsychotic medication.

Valproate treatment (in monotherapy or combination with lithium) was not associated with brain 5-HT2A receptor binding patterns in adult patients who met DSM criteria for a manic episode, in a study by Yatham et al. (2005). Using resting-state fMRI, Spielberg et al. (2019) investigated lithium effects on neural circuits related to mania and depression in BD. The results showed that treatment with lithium was associated with normalization of connectome indices observed during mania. In addition, changes in connectome indices associated with both mania and depression were correlated with symptom changes (Spielberg et al. 2019). Moreover, the velocity of normalization of neural circuits associated with pharmacological treatment seems to be distinct, depending on the medication considered. Dandash et al. (2018) reported that treatment with lithium showed a faster normalization of hyperconnectivity in the ventral striatum with the cerebellum compared to treatment with quetiapine.

6.3 Neuroimaging to Predict Pharmacological Treatment Response

Baseline FA connectivity of the cingulate and hippocampal regions significantly predicted 8-week global clinical impression (CGI) severity scores after treatment with lithium (4 weeks of treatment) in pediatric patients with BD, an effect found for both severity of mania and depression (Kafantaris et al. 2017). DTI was also used to investigate white matter connectivity as a possible predictor of response to antidepressant treatment in adult patients with BD type I. The results showed an inverse correlation between clinical improvements and white matter microstructure integrity of tracts, including corpus callosum, cingulum bundle, and inferior fronto-occipital fasciculus (Bollettini et al. 2015). Clinical response to ketamine infusion in patients with bipolar depression was associated with increased 18-FDG metabolism in the subgenual anterior cingulate cortex after placebo infusion in the study of Nugent et al. (2014). In addition, changes in metabolism in the right ventral striatum between placebo and ketamine infusions showed significant inverse correlations with changes in depression scores (Nugent et al. 2014). In another study, subgroups of patients defined by cluster analysis according to cortical thickness were associated with different responses to treatment in a randomized clinical trial, suggesting that neurobiological measures could address the clinical heterogeneity of bipolar disorder with respect to treatment response patterns (Zhang et al. 2018).

Furthermore, given the high complexity of bipolar disorder pathophysiology, improvements in the prediction of treatment response could be achieved by the inclusion of different clinical and neurobiological variables in addition to neuroimaging findings. The Response to Li Network (R-LiNK) initiative is a prospective multidisciplinary, international project which aims to identify individual predictors of clinical response to lithium. Data collection will include a combination of molecular, metabolic, structural, functional, and clinical biomarkers, with an ecological momentary assessment approach to monitor core BD symptoms, coupled with the investigation of moderators and mediators of response (Scott et al. 2019). Given the promising results on neuroimaging findings and treatment response prediction, such initiatives may provide precise and accurate information for the early and effective treatment of BD, which could potentially impact not only the burden associated with this illness but also psychiatric disorders in general.

6.4 Neuroimaging and Psychotherapy in Bipolar Disorders

Despite including principles of cognitive behavior therapy (CBT), such as extinction learning, identification and modification of maladaptive cognitions, and behavioral exposure (Ellard et al. 2010), transdiagnostic CBT focuses on maladaptive emotion processing. Ellard et al. used fMRI to investigate the association of brain connectivity of regions associated with emotion regulation and clinical outcomes of

transdiagnostic CBT intervention in patients with BD (Ellard et al. 2018). The results showed that changes in affective control scores were predicted by weaker connectivity between the left anterior insula and the right ventrolateral PFC (salience network), and by stronger connectivity between the bilateral dorsal anterior insula and bilateral amygdala at baseline (Ellard et al. 2018).

According to Teasdale et al. (2000), mindfulness-based cognitive therapy (MBCT) aims at teaching individuals "to become more aware of thoughts and feelings and to relate to them in a wider, decentered perspective as 'mental events' rather than as aspects of the self or as necessarily accurate reflections of reality." (Teasdale et al. 2000). This therapy has shown promising results in the treatment of patients with BD and has a first-line indication for preventing depression relapse (Lovas and Schuman-Olivier 2018; Parikh et al. 2016). Ives-Deliperi et al. (2013) reported significant decreases in anxiety and emotion dysregulation, improvement in mindfulness, and executive performance associated with MBCT in patients with BD comparing with those in a waiting list group. In addition, there was a significant correlation between signal change in the medial PFC after the intervention, suggesting a potential action mechanism of MBCT (Ives-Deliperi et al. 2013).

7 Conclusions

Neuroimaging studies have contributed to a better understanding of the pathophysiology of BD as a brain disease, pointing to dysfunctions in neural circuits associated with emotion regulation and reward processing. Despite the limited validity of categorical diagnosis, as shown by genetic studies, scientific literature has consistently shown significant structural and functional findings among patients with BD (defined according to DSM criteria) and individuals at high genetic risk for BD. The heterogeneity of BD might be addressed with the association of different sources of biological and clinical information, in addition to neuroimaging techniques, allowing the better characterization of phenotypes and the identification of biomarkers, ultimately resulting in potentially important clinical implications.

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