Chapter 5

Structural neuroimaging markers in bipolar disorder

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5.1 Introduction

Human behavior may be one of the most complex entities in science and, because of that, clarifying its biological basis has been a significant challenge. Historically, the nature of mental disorders has been categorized as organic versus endogenous. Later in the process, animal models were developed to study human behavior, with several obstacles and translational issues. As neuroscience advanced, postmortem brain studies came along with cutting-edge genetic research techniques. All of these progressive developments resulted in a shift from the traditional dichotomous approach to the adoption of a multifactorial concept, with a strong focus on the pathophysiological and neurobiological aspects of mental illness. In that sense, neuroimaging techniques have been considered crucial as a tool to increase the understanding of the neurobiological basis for psychiatric disorders (Soares & Mann, 1997).

At the very early stages, pneumoencephalography, which is now considered extremely rudimentary, was used to assess patients with mental disorders. In 1976, considered the inauguration year of the neuroimaging era in psychiatry, the first brain imaging study conducted by Johnstone et al., utilizing computerized tomography (CT). Their finding of increased cerebral ventricular size and its correlation with cognitive impairment was one of the most prominent milestones and probably the most replicated finding in neuroimaging of mental disorders (Johnstone, Frith, Crow, Husband, & Kreel, 1976). Afterwards, consistent and increasing efforts have been put in by researchers in the field of neuroimaging in psychiatry. Over time, structural and functional magnetic resonance imaging (MRI), molecular imaging, and

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other imaging techniques were developed. Intensive progresses in the field of neuroimaging and other branches of biological psychiatry led psychiatrists to reconsider the structure of the Diagnostic and Statistical Manual of Mental Disorders (DSM), and to incorporate a biological basis and definition for diagnosing psychiatric disorders (Miller, 2010). However, to date, DSM has not yet been able to develop a biological approach to implement neuroimaging and genetic methods into the diagnosis of psychiatric disorders.

5.2 Biomarker concepts and neuroimaging markers in psychiatry

With all the challenges mentioned above and the numerous advances in neuroimaging, the urge to detect biomarkers for psychiatric disorders has never faded. An ideal biomarker is expected to have the features of detecting diagnosis, changing with treatment interventions, predicting prognosis, and classifying disease stage (Atkinson et al., 2001). Biomarkers can be utilized in different aspects, and different concepts have been proposed to categorize biomarkers in psychiatry. Proof of concept is based on the effects of a therapeutic intervention on the pathophysiology of the disorder (Soares, 2010). This concept has been utilized in neurodegenerative diseases and, to some extent, in clinical trials and research. Another concept for biomarkers is proof of mechanism, which is mainly based on the mechanism of action of a drug (Cummings, 2010). Applications of the biomarker concept in psychiatry have been limited to proof of mechanism of new drugs, with dopamine receptor occupancy of antipsychotics and serotonin transporter blockade of antidepressants corresponding to the major areas of focus. Besides, structural imaging modalities, evaluating white matter and gray matter changes, have been used to identify biomarkers for psychiatric disorders and bipolar disorder (BD).

5.3 Structural neuroimaging in psychiatry

The principle of MRI is based on the hydrogen (^{1}H) atom, whose nuclei have a small magnetic field and is the most abundant atom in the human body. The MRI acquisition process starts with a strong magnetic field, causing the small fields of ^{1}H nuclei to align, and then a brief electromagnetic field excites the nuclei. The receiver coil captures the energy released by the ^{1}H atoms during realignment, and these data are used to build the structural image. There are different parameters that can be used to acquire certain types of images for instance, T_1-weighted images, to obtain a good contrast between gray and white matter and T_2-weighted images to discern water and cerebral parenchyma (Bushong & Clarke, 2013).

Nowadays, MRI is the preferred structural imaging technique for several reasons, including; its high resolution, which provides a good contrast to asses infratentorial structures, its noninvasive nature, which allows the evaluation of children and the feasibility of repetitive assessments of the same patient, which is critical for longitudinal studies (Sassi & Soares, 2003).

5.3.1 Overview of existing literature

Starting in 1983, a large amount of structural imaging research in mental disorders has been published. Nonetheless, a general overview of the existing literature on neuroimaging findings in BD shows variable results. Several clinical and technical issues can further explain this variability. Clinical issues include variations in the subtypes of the BD diagnosis, severity of the disorder, number, and type of previous episodes, and current and past medication status. Technical issues correspond to differences in terms of MRI devices with different strength and slice size, as well as manual versus automated measurements (Brambilla, Glahn, Balestrieri, & Soares, 2005; Soares & Mann, 1997).

Still, despite these methodological, technical, and clinical challenges, certain findings have been consistently reported among patients with BD. Enlargement of the amygdala is classically considered one of the most replicated neuroimaging finding in BD (Brambilla et al., 2005). Moreover, decreased volume in the temporal lobe, dorsolateral prefrontal cortex, basal ganglia, and cingulate cortex volume, as well as enlarged third ventricle, and increased white matter hyperintensities have been consistently reported (Brambilla et al., 2005; Keener & Phillips, 2007; Soares & Mann, 1997; Strakowski, DelBello, Adler, Cecil, & Sax, 2000).

Most of the early neuroimaging studies had the limitation of a small sample size. As neuroimaging research in BD advanced, different approaches came into play to address weaknesses of small sample-sized studies; mega and metaanalyses and big research consortiums. Also, it must be taken into consideration that meta-analyses have limitations, including but not limited to methodological issues from the included studies, as well as variable patient inclusion criteria across studies.

While some meta-analyses showed a nonsignificant difference in the amygdala and subgenual frontal cortex (Hajek et al., 2009; Hajek, Kozeny, Kopecek, Alda, & Höschl, 2008), others denoted decreased gray matter volume in the inferior frontal cortex, insula, and anterior cingulate cortex (ACC) (Bora, Fornito, Yücel, & Pantelis, 2010; Ellison-Wright & Bullmore, 2010). As the data and results from metaanalyses still lacked, large research consortiums have been established with several sites' participation, forming a basis for mega-analyses. The findings of significance reported in those mega-analyses are increased lateral ventricle size, smaller corpus callosum (Kempton, Geddes, Ettinger, Williams, & Grasby, 2008), larger temporal lobe, and right putamen (Hallahan et al., 2011).

5.3.2 Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a relatively novel modality used in neuroimaging. It is used to assess white matter integrity. DTI is based on the characterization of tissue diffusivity as represented through axial and radial diffusivity. That is ultimately translated as a measure named fractional

anisotropy (FA), which ranges from 0 to 1. In general, DTI is utilized for assessing myelination, structure, and connectivity of white matter (Le Bihan et al., 2001). Besides, a method named DTI tractography is used to further evaluate white matter connectivity among various brain regions (Lin, Weng, Xie, Wu, & Lei, 2011).

Overall, DTI studies in BD patients have shown marked variability; however, decreased FA has been reported in several brain areas, including the parahippocampal gyrus, right ACC, and subgenual prefrontal cortex (SGPFC). Moreover, disrupted connectivity has been reported between the frontal cortex and the temporal and parietal cortices (Matsuo, Sanches, Brambilla, & Soares, 2012).

5.4 Neuroimaging as a tool to improve the diagnostic accuracy of bipolar disorder

As we discussed above, the concept of biomarkers includes a diagnostic and prognostic value. Psychiatric disorders are usually regarded as categorically distinct from each other but, while a disorder can present as in the spectrum of "solely" mood, psychotic, or anxiety, mostly there is an overlap in symptom dimensions. For example, mood disorders can often present with anxiety or psychotic features, or psychotic disorders can have comorbid mood disorders. Since the existing evidence mostly compares BD with unipolar depression (UD) and schizophrenia, we will discuss potential neuroimaging markers among these disorders in this chapter.

5.4.1 Distinguishing bipolar disorder from schizophrenia

Although BD is classified as a mood disorder and schizophrenia is usually included in the psychotic spectrum, there is a considerable overlap between both conditions in terms of symptomatology. It is not uncommon for BD to present with psychotic features and schizophrenia with mood symptoms. As a result of this overlap, distinguishing BD from schizophrenia has been both research and diagnostic challenging.

Many studies have been conducted to investigate neuroimaging differences and similarities in BD and schizophrenia. In this chapter, we will mostly focus on differences between them, with a limited emphasis on similarities. A meta-analyses utilizing anatomical likelihood estimation (ALE) showed prominent gray matter deficits in frontal, limbic, and subcortical regions of schizophrenia patients compared to healthy controls (Fornito, Yücel, Patti, Wood, & Pantelis, 2009). Another meta-analyses using ALE showed decreased gray matter in the insula and anterior cingulate of BD patients (Ellison-Wright & Bullmore, 2010). Birur et al. included 40 studies in their systematic review and concluded that patients with schizophrenia

demonstrated widespread cortical gray matter volume loss; however, the volume loss in BD was less intense or even lacking (Birur, Kraguljac, Shelton, & Lahti, 2017). In this context, gray matter volume reduction has been proposed as an intermediate phenotype, which seems to be more frequent and more prominent in schizophrenia and schizoaffective disorder but limited and less prominent in BD (Ivleva et al., 2013). Hippocampus, thalamus, and amygdala have been the most salient subcortical regions. Among these subcortical regions, the hippocampus has been widely investigated. Mathew et al. found that volume reduction in the hippocampus and the subfields of the hippocampus is more prominent in psychotic disorders and correlated with cognitive performance, pointing out a stronger association with the pathophysiology of psychosis (Mathew et al., 2014). A study comparing hippocampal volumes in schizophrenia and BD revealed significantly smaller volumes in schizophrenia, suggesting that volume reduction can be a potential distinguisher between these disorders (Knöchel et al., 2014). In addition to the hippocampus, the volume of the thalamus shown to be reduced in both BD and schizophrenia, with larger reductions reported in schizophrenia (Ivleva et al., 2013; Watson et al., 2012). Reports on other subcortical structures such as the amygdala and basal ganglia have been inconsistent and inadequate to propose a shared endophenotype or distinguishing marker (Hartberg et al., 2011; Molina et al., 2011; Pina-Camacho et al., 2016; Womer et al., 2014). Another challenge to consider is the presence of psychotic symptoms in BD and distinguishing BD with psychotic features from schizophrenia. A limited number of studies have focused on that aspect, and even more limited data are available for neuroimaging. In their systematic review, Buoli et al. reported that BD patients with psychotic features had larger ventricle size but similar hippocampal volumes compared to nonpsychotic BD patients and healthy controls (Buoli et al., 2016). While integrating the biomarker approach in light of existing neuroimaging literature, technical variations in data acquisition and data analysis, clinical variations such as medication exposure, severity, and illness duration should be considered as confounding factors. To control these factors, on the one hand, studies need to be performed with more homogeneous groups; on the other hand, machine learning modalities can be applied for better categorization and classification.

5.4.2 Distinguishing bipolar disorder from unipolar depression

Core symptoms of BD and schizophrenia are different. However, BD and UD share several core symptoms. The overlap in core symptoms challenges the interpretation of neuroimaging findings to distinguish BD from UD. Because of these shared features, initial neuroimaging studies of mood disorders tended to combine both disorders. This combination caused the initial misconception that UD and BD were pathophysiologically similar, but

current evidence supports that these disorders are distinct neurobiological entities. Neuroimaging research can be critical to explain both similarities and differences across UD and BD.

Decreased prefrontal cortex volume has been consistently reported in BD and UD as a common and one of the most replicated findings (Coffman, Bornstein, Olson, Schwarzkopf, & Nasrallah, 1990; Kumar, Jin, Bilker, Udupa, & Gottlieb, 1998). Specifically, subregions of the prefrontal cortex, including the dorsolateral prefrontal cortex, orbitofrontal cortex, SGPFC, ACC, have been analyzed and compared in UD and BD (Konarski et al., 2008).

The orbitofrontal cortex is an integral brain region in the regulation of behavior and emotions. Its volume has been widely explored in both UD and BD. Reports from UD studies have been mostly consistent and denoting reduced volume, but BD studies have shown inconsistency with regarding to that finding (Adler, Levine, DelBello, & Strakowski, 2005; Ballmaier et al., 2004; Farrow, Whitford, Williams, Gomes, & Harris, 2005; Lacerda et al., 2004). A limited number of studies that included SGPFC showed its volume is reduced both in BD and UD (Caetano et al., 2006; Haznedar et al., 2005; Konarski et al., 2008). It has been hypothesized that this reduction may be a result of multiple mood episodes, as it was not found in children with BD (Sanches et al., 2005).

The ACC is a critical brain region for the regulation of behavior and emotions. Lesions of the ACC can present with a wide variety of symptoms, including apathy, depression, or disinhibition (Devinsky, Morrell, & Vogt, 1995). A considerable amount of research pointed out the functional and structural alterations of ACC in BD and UD. Available evidence mainly indicates reductions in overall volume and gray matter as a shared feature (Konarski et al., 2008).

Temporal lobe studies have also been inconsistent within disorders themselves or between them, lacking the potential to reach a biomarker status. However, medial temporal regions such as the hippocampus and amygdala have demonstrated a distinctive potential. Hippocampus is probably one of the most investigated brain regions among psychiatric disorders. Many studies comparing hippocampal volumes in UD with healthy controls reported a decreased volume, whereas some of the studies lacked statistical significance (Janssen et al., 2004; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Videbech & Ravnkilde, 2004). Reports from BD have not shown a decreased hippocampal volume (Altshuler, Bartzokis, Grieder, Curran, & Mintz, 1998; Strakowski et al., 1999). Conclusion of an extensive research and metaanalyses was the reduction of hippocampal volume can be considered a feature of UD compared to BD (Konarski et al., 2008). The other medial temporal region is the amygdala, essential for fear recognition, and memory (Davis & Whalen, 2001). Lesions of the amygdala result in reduced fear recognition and emotional blunting. Overall comparison of amygdala volume showed smaller volumes in UD and larger volumes in BD, another candidate of a neuroimaging marker (Altshuler et al., 2000; Brambilla

et al., 2003; Caetano et al., 2004; Sheline, Gado, & Price, 1998). A further subcortical region with a biomarker potential is basal ganglia. Basal ganglia volumes are reported to be decreased in UD and increased in BD (Greenwald et al., 1997; Strakowski et al., 1999).

With respect to the cerebellum, cerebellar vermis volumes were reported to be reduced in BD but not in UD (Strakowski, Adler, & DelBello, 2002). Moreover, thalamic volumes have been extensively investigated in BD. However, results have been controversial, reporting increased, decreased, or unchanged volumes (Lochhead, Parsey, Oquendo, & Mann, 2004; Strakowski et al., 1999). The alteration of the results can be explained with the technical difficulties related to the anatomical location of the thalamus in the brain (Strakowski et al., 2002). Finally, a limited number of studies investigated pituitary volumes in BD and UD so far, and one reported increased pituitary volume in UD and other reported decreased volume in BD (MacMaster & Kusumakar, 2004; Sassi et al., 2001). With regard to white matter abnormalities, increased white matter hyperintensities, are a common finding for both BD and UD.

An overview of the results mentioned above denotes that there are shared findings and differences between BD and UD, particularly in the limbic system. On the one hand, the limbic system's differences might explain the different patterns of mood dysregulation found in BD and UD. On the other hand, there is a strong genetic relationship between these disorders, and the overlap observed in structural neuroimaging is expected, to some extent, to explain their interrelation.

5.5 Neuroimaging markers in high-risk populations

A further important utilization of structural neuroimaging markers in BD is determining high-risk populations and developing methods to prevent illness or improving prognosis with early interventions (Atluri et al., 2013; Frey, Fonseca, Machado-Vieira, Soares, & Kapczinski, 2004). This context is mainly described as endophenotypes, which refer to biological markers of vulnerability, present in affected individuals and observed in unaffected but high-risk populations such as relatives of BD patients. Ideally, endophenotypes are considered behavioral or neurobiological measures that are state-independent (Sanches, Keshavan, Brambilla, & Soares, 2008).

Neuroimaging research carries significant potential for the determination and classification of endophenotypes, especially in BD. A few studies focused on populations with high genetic risk for BD, but results have been inconsistent. Another ethical issue is the utilization of imaging techniques with ionizing radiation in children younger than 18 years old. Besides, individuals at high risk for BD tend to present with other psychiatric conditions, which causes a confounder effect on results, beclouds interpretation. Finally, a mood disorder in a proband refers to an increased risk of both BD and UD in the family.

Neuroimaging studies in high-risk populations, offspring of patients with BD, and focusing on brain regions associated with emotional regulation have been mostly insignificant (Frangou, 2019; Sanches & Soares, 2020). On the other hand, some noteworthy findings are as following; reduction of gray matter volume in superior and middle temporal regions (Hanford, Hall, Minuzzi, & Sassi, 2016), cortical thinning of temporal, frontal and supramarginal regions (Hanford, Sassi, Minuzzi, & Hall, 2016), increased volume of amygdala (Bauer et al., 2014), and reduction of gray matter in the hippocampus (Ladouceur et al., 2008). Lancaster reported reduced volume in the nucleus accumbens is associated with familial risk among offspring of BD patients (Lancaster, 2018). Besides, twin studies carry significant potential for endophenotype research. Noga et al. showed that hippocampal volumes were smaller in twins who had BD diagnosis compared to their respective twins who did not have BD (Noga, Vladar, & Torrey, 2001). Finally, abnormalities of white matter in frontal and temporal gyrus, and precuneus have shown to have potential in differentiating BD offspring from controls (Hajek et al., 2015).

In conclusion, research on populations at high risk for BD is still at the early stages. However, there is significant potential that neuroimaging may take place in that aspect. In the future, some neuroimaging findings can help identify prodromal stages and be a marker of disease development and vulnerability.

5.6 Summary and conclusions

The diagnosis of psychiatric disorders mainly relies on the patients' subjective reports, and historically biological (or organic) basis has been disregarded. Starting in the late 1970s and especially within the last couple of decades, consistently increasing effort has been put in biological psychiatry to unveil the neurobiology and pathophysiology of psychiatric disorders. These advances in neuroscience urged the DSM-5 to implement biological aspects, including neuroimaging, to distinguish mental disorders; however, it failed. Although no consensus has been reached out yet, the determination of biomarkers has been a long-standing need and challenge in the field of psychiatry.

In psychiatry, the concept and utilization of biomarkers have been mostly limited to proof-of-mechanism of the drugs, mainly based upon dopaminergic and serotonergic pathways. With a wide range of structural and functional techniques, neuroimaging modalities are currently the most state-of-the-art method to investigate the living brain. Structural neuroimaging is utilized to define brain regions' volume and shape, white matter tracts, and hyper/hypo intensities. A considerable amount of research has been done in BD to identify structural neuroimaging markers.

Contextually, distinguishing BD from healthy controls seems to be less problematic. On the other hand, differentiating BD from other psychiatric

disorders, especially UD and schizophrenia, may be challenging, in part due to considerable phenotypical overlap across these disorders.

A review of the existing literature comparing BD with schizophrenia reveals that overall gray matter volume loss is more widespread and prominent in schizophrenia. In terms of brain regions, the hippocampus and thalamus were reported to be smaller in schizophrenia patients compared to BD, and may represent a possible intermediate phenotype. Also, BD patients with psychotic features reported to have larger ventricle size compared to nonpsychotic BD patients.

The biggest obstacle to overcome is differentiating BD from UD with neuroimaging, because of the significant overlap in core depressive symptomatology. Besides, similar findings across BD and UD can help determine the basis for shared features. Decreased prefrontal cortex and ACC volume seem to be a consistent finding for both BD and UD. Further focusing on medial temporal regions, decreased hippocampal volume tend to concur with UD but not with BD. The amygdala volume has been shown to be reduced in UD and increased in BD, revealing a possible candidate marker. As a general perspective, overlapping findings across psychiatric disorders can be considered a representation of a shared feature or phenotype, and different findings can be identified as potential biomarker candidates, specifically when comparing BD with UD.

Another beneficial aspect of neuroimaging can be revealing potential structural markers by studying high-risk populations, and possibly improving prognosis. However, the literature is extremely limited on determining markers for high-risk populations. Available evidence suggests that hippocampus and ACC are potential regions to focus.

Finally, machine learning, a set of computational tools, can be coupled with neuroimaging data and used in the differential diagnosis of BD with other conditions, identification of BD subtypes, determination of prognosis, and characterization of predictors of response to certain treatments. (Nielsen, Barch, Petersen, Schlaggar, & Greene, 2019).

As neuroimaging research keeps growing for psychiatric disorders, especially for BD, it is reasonable to expect better results with more clear conclusions from large research consortiums. In the recent future, it can be expected that structural neuroimaging markers will play a role in diagnosis; however, right now, it is hard to speculate that it will be a unique diagnostic tool.

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