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Neuroplasticity in Bipolar Disorder: Insights from Neuroimaging

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Abstract

Background: Advances in neuroimaging techniques have produced evidence about disrupted frontolimbic circuits related to emotional regulation. These neuroimaging studies may suggest impairments in cellular plasticity in bipolar disorder (BD) patients. However, the long-term use of mood stabilizers may restore these dysfunctions by neurotrophic effects

Objectives: Review the major structures of the brain that underpin this disorder, synthesize the main findings in neuroimaging in BD, and debate neuroplastic effects of psychopharmacological treatment on findings from the neuroimaging studies.

Methods: We undertook a review from neuroimaging in BD. Search words entered were "bipolar disorder", "mania", "depression", "mixed states", "suicide", "psychosis" "lithium", "mood stabilizers", "neuroplasticity", magnetic resonance imaging", "functional magnetic resonance", "FDG-PET", "SPECT".

Results: The literature highlighted specific brain areas that support emotional regulation and processing. Moreover, there is heterogeneity across studies and some findings are controversial, but some results suggest neuroplastic effects from the long-term psychopharmacological treatment (particularly mood stabilizers) in bipolar disorder.

Conclusion: The findings in neuroimaging studies suggest there is fronto-limbic circuitry dysregulation in BD; changes in specific brain areas have been replicated in several studies, which may reflect impairments in neuroplastic phenomena. Evidence from neuroimaging studies have been also show that long-term treatment may be

associated with metabolic/functional compensation or structural restoration in bipolar responders.

Keywords: bipolar disorder, neuroimaging, treatment, neuroplasticity

1. Introduction

Bipolar disorder (BD) affects around 3% of the population [1] and is a serious multifactorial disease, caused by combination of genetic vulnerability and environmental stressors with abnormalities in neurotransmitter and neuroendocrine systems, and intracellular signaling pathways as well. Clinically, BD is characterized by recurrent changes of thought, behavior, cognition, mood, and desynchronization of circadian rhythm, which imply in affective phases—mania, hypomania, depression, and mixed states. As a result, BD is a condition often difficult to diagnose, since at least 50% of patients with BD have an initial episode of depression and 35% may have a delay in their diagnosis in up to 10 years [2]. In this context, samples more homogeneous in neuroimaging studies in BD may allow better understanding of BD pathophysiology, through the establishment of putative associations between areas and neuronal circuits and clinical phenotypes, and also to clarify the utility of the various neuroimaging methods for determining potential neurobiological markers of BD.

In this sense, some authors propose concepts in neuroimaging biomarkers for mood disorders, such as *prognostic biomarkers* that characterize the risk for onset or progression of the disease, *predictive biomarkers* associated with the likelihood of therapeutic response, and *pharmacodynamic biomarkers*, which show biological response related to drug treatment [3].

The majority of neuroimaging studies in BD have been demonstrated abnormalities in different cortical and subcortical areas involved in emotional processing and regulation, while *postmortem* histopathological studies of these regions have shown abnormal reductions of synaptic markers and glial cells in prefrontal cortex and hippocampus and point to a dysfunction of the complex intracellular mechanisms, which involve second messengers systems, regulation of the gene expression and synthesis of trophic factors [4]. Overall, these neuropathological and neuroimaging studies may suggest impairments in cellular plasticity and resilience in patients who suffer from mood disorders.

Conversely, a substantial body of evidence suggests that long-term psychopharmacological treatment with antidepressants and mood stabilizers—in particular lithium and valproate—may compensate for this dysfunction by reducing the pathological limbic activity subjacent to affective symptoms and by regulating gene expression of neurotrophic factors that exert neuroplastic effects within the pathways modulating emotional expression. Such effects may be associated with structural restoration or enlargement of specific brain areas in chronically treated BD patients evaluated in multiple neuroimaging studies, when compared to healthy controls [5–7].

Keeping these issues in mind, the purpose of this chapter is to review the major cortical and subcortical structures of the brain that underpin this disorder, describe the main findings in

structural and functional neuroimaging in BD, and synthesize impaired major cellular plasticity mechanisms and potential neuroplastic effects of mood stabilizers on structural and functional findings from the neuroimaging studies.

2. Circuits and neuronal models of emotion regulation

- Ventrolateral prefrontal circuit: Constituted by the ventrolateral prefrontal cortex (VLPFC)—Brodmann areas (BA) 10 and 47—which sends fibers to the ventromedial striatum (ventromedial caudate nucleus, ventral putamen, nucleus accumbens, and olfactory tubercle) and which projects to the globus pallidus (GP); pallidal fibers follow for ventral anterior and dorsomedial nuclei of the thalamus, which connects again to VLPFC. The anterior temporal cortex (areas comprising BA 20 and BA 38) maintains reciprocal connections with VLPFC and amygdala [8, 9].
- Ventromedial prefrontal circuit: Formed by the ventromedial prefrontal cortex (VMPFC), defined by BA 11 and 12, of which depart fibers to follow to the ventromedial striatum and ventral caudate nucleus. From these regions, projections run for ventral anterior, dorsomedial and ventrolateral nuclei of the thalamus, closing the circuit with thalamic pathways to the ventromedial cortex. It should be mentioned projections of these cortical areas also to the entorhinal cortex and amygdala—lesion in these areas produces impairment in the allocation of emotional valence of information, a process that facilitates storage of information—as well as reciprocal connections between the insula with the amygdala and the VMPFC [9].
- Anterior cingulate circuit: The ACC is the most part of BA 24, 25, and 32. These cortical areas maintain connections with the ventral medial striatum, of which follow fibers to the rostral lateral and ventral GP, which in turn sends projections for dorsomedial nucleus of the thalamus; fibers depart from this topography and return to the ACC, closing this circuit [8, 9].

The ACC is divided functionally into ventral or “affective” region (more anterior portions of BA 25 [paragenua] and BA 24 [subgenua]) and dorsal or “cognitive” region (posterior pre-limbic area [BA 32] and more posterior portions of BA 24).

The affective division of the ACC has connections with the amygdala, the periaqueductal gray matter, the anterior thalamic nuclei, the ventral striatum, and the insula; it contributes to the regulation of endocrine and autonomic functions, generation of appropriate social behavior, and part of the global emotional response by activation of somatic and visceral states relevant to emotional experience; cognitive division includes the posterior portions of BA 24 and 32 and connects to the periaqueductal gray matter and primary and associative cortical motor areas; it is associated with inhibition responses [10] and monitoring conflicts [11, 12].

- Dorsolateral prefrontal circuit (DLPFC) includes BA 10, 45, and 9/46 Brodmann, which covers part of the lateral surface of the frontal lobes. These regions depart fibers to the dorsolateral caudate nucleus, which in turn sends fibers to the GP and then to ventroanterior, dorsomedial, and ventrolateral nuclei of the thalamus; thalamic pathways from these nuclei return to DLPFC [8, 9].

Compounding these circuits, the cerebellum receives cortical projections from nuclei located in the base of the pons; the fibers of the pontine nuclei decussate and follow the middle cerebellar peduncle to specific cerebellar targets: while the motor cortex projects to the cerebellum (paravermian region) through lateral pontine nuclei, associative cortical areas of the prefrontal, parietal, and temporal regions as well as ACC reach the cerebellum through pontine nuclei medial [13].

The amygdala is divided into three major sections: basolateral, corticomедial, and central. The basolateral nucleus participates in the sensory information integration from external and internal environments, which are linked to learned information and are processed by associative cortical areas, with subsequent planning, selection, and implementation of the action; corticomедial nucleus contributes to the presence of emotional attributes related to sensory and nociceptive stimuli; and the central nucleus is the convergence site of all signs of the amygdala. The amygdala regulates the fight, flight, or freeze behaviors together with the periaqueductal gray matter and contributes to motor and autonomic responses to emotional stimuli [14].

Among several neural circuit models related to processes of emotional perception and regulation proposed in the literature, the Mary Phillips and coworkers' model highlights over others [15, 16]. This model proposes the existence of two neuronal systems: a ventral system comprising subcortical (the amygdala, the insula, the ventral striatum) and cortical structures (the hippocampus, the anterior cingulate, and prefrontal cortex) and would be linked to identification of the emotional meaning of a stimulus associated with generation of affective states and autonomic regulation; the dorsal system would be represented by dorsal regions of the anterior cingulate and PFC as well as the hippocampus and would support cognitive processes such as selective attention, planning, performance monitoring, and voluntary regulation of emotional states.

The assessment of neuroimaging findings in BD allows to corroborate the relevance of this model, from the identification of dysfunction in different cortical and subcortical areas—as already stated, structures involved in processing and emotion regulation—abnormal increase in activity of the amygdala during performance of emotional and non-emotional tasks; abnormal decrease in activity of the VLPFC and orbital frontal cortex (OFC); and abnormal decrease in functional connectivity between the amygdala and the prefrontal cortex during emotional regulation tasks. Moreover, in studies involving reward paradigms (anticipation of reward), there is abnormal increase in activity of the ventral striatum, the VLPFC and OFC [17, 18].

3. Main findings of neuroimaging in BD

3.1. White matter

The white matter (WM) hyperintensity is a change often described in BD patients, both in adult [19] and pediatric [20] samples. Among the WM association bundles, the corpus callosum (CC) is one of the structures of great interest in BD research. In this region, studies using diffusion tensor

technique (DTI) often show loss of structural integrity of the CC in its various segments (genu, body, or splenius) [21, 22]. Moreover, a recent study conducted by our group evaluated bipolar patients type I euthymic and showed reduction of CC in the areas of the genu and isthmus when compared to healthy controls, confirming data from other studies [23, 24], but with no significant difference between suicide and non-suicidal [25]; a meta-analysis documented the volume reduction of this structure in bipolar patients [26]. Finally, another study found that bipolar patients without suicide attempt had lower values of fractional anisotropy (FA) in the genu and body of the CC when compared to unipolar depressed and healthy controls, and bipolar suicide patients had reduction of FA in all regions of the CC when compared to healthy controls [27]. In addition, more recent studies have shown that in euthymic and non-euthymic bipolar patients with a history of psychotic symptoms was observed higher area of the rostrum of the CC [28] and lower FA in the body of the CC in bipolar euthymic or depressed patients [29]; importantly, changes of the CC have also been described in children and adolescents with BD [30] and in groups of risk for BD, such as first-degree relatives [31].

Furthermore, loss of functional integrity was verified in other associative bundles of white matter, for instance, uncinate fasciculus (which connects the orbital frontal cortex and areas of the ventromedial prefrontal cortex to the amygdala and hippocampus) was studied in some works, in which the results are inconsistent, with bilateral reduction of AF [32, 33] or increased AF to the left in this region [34]. Finally, lower FA in the left orbital frontal WM among patients with attempted suicide, a finding that correlated with higher impulsivity score [35].

Taken together, these findings suggest that WM abnormalities in BD may compromise the interhemispheric neuronal transmission and subsequent emotional processing/regulation—which may represent a potential anatomical biomarker of the disease—and precede the onset of bipolar disorder and predispose to brain development changes during the neurodevelopmental process of the central nervous system (CNS) in children and adolescents.

3.2. Frontal lobe

The anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and orbital frontal cortex (OFC) represent the most widely studied frontal lobe areas in BD research.

Studies assessed the ACC through MRI showed volumetric reduction of the subgenual AC (sgACC) (areas 24 and 25 Brodmann), a finding confirmed in a meta-analysis [36]. In studies with proton magnetic resonance spectroscopy (^1H -MRS), reduction of the N-acetyl-aspartate (NAA) and increase of the choline in the ACC are the most consistent results [37]. Interestingly, some studies showed that long-term treatment with lithium increased the sgACC volume [6] and was associated to higher levels of NAA in this region [38, 39]. Additionally, Functional changes on PET studies were observed both in patients at resting state as in those undergoing activation tasks in the CC: most of them show hyperactivity ACC, notably the sgACC in patients in depressive [40] and manic [41] states.

Studies that evaluated the pregenual ACC (pgACC) also reported abnormalities, with reduction of the left pgACC volume, both in adults [42, 43] and in adolescents [44].

Another H¹MRS study of this region detected in patients with mania increased relationship glutamine/glutamate, a finding that may be related to impairment of glial-neuronal cell interaction in the interpretation of the authors [45].

Some studies have demonstrated reduction in DLPFC volume in adults [46, 47] and pediatric samples [48], whereas other studies using H¹MRS reported reduction of NAA in this region [49, 50]. At last, hypometabolism of the DLPFC with ¹⁸FDG-PET and functional magnetic resonance imaging (fMRI) in patients with BD was found, both in mania [51] and in depression [52–54].

Other studies evaluating the OFC showed reduction of its volume both in adults [46, 55–57] and in pediatric patients [58, 59], but the heterogeneity of their samples may limit the interpretation of results. A H¹MRS study of this region demonstrated the decrease of the NAA and the choline in hospitalized non-euthymic bipolar patients (mixed or manic episode), but a minority was in use of lithium [60], whereas our group reported normal metabolic levels in medial orbital frontal cortex in BD I euthymic outpatients with and without suicidal behavior [7]. In fact, in our sample, 30.2% of the subjects were prescribed the first mood stabilizer in the year after the first affective episode, 22% after the first year before the fifth year, and 47.8% 5 years after the first affective episode, and it was demonstrated a higher prevalence of suicide attempts in the latter group [61]. These results support the protective clinical effect of the use of mood stabilizers on the suicidal behavior.

Finally, in patients with mania, hypoactivation of the VLPFC and the OFC in fMRI studies was documented [62, 63].

3.3. Amygdala

Volumetric abnormalities of amygdala are among the most common findings, especially in adolescent samples, in which smaller volumes were reported, but with controversial results among adults. While the reduction of the amygdala among adolescents may represent an anatomical characteristic finding of this clinical subgroup, inconsistent results in adults may result from clinical course, the proportion of adult patients with early BD compounding the sample or neuroplastic effects associated with treatment [15].

The studies of fMRI suggest abnormality of the amygdala in response to a variety of experimental paradigms (resting state, processing of emotional stimuli, and cognitive tasks with or without emotional valence) in the context of the various affective states [11]. On the other hand, some authors reported the absence of hyperactivity of the amygdala during euthymia, which may reflect normalization of the amygdala function induced by long-term treatment, possible evidence of neuroplasticity [64].

3.4. Cerebellum

Most structural neuroimaging studies of the cerebellum showed a reduction in the volume of sub-regions of the cerebellar vermis [65–68], and reduction of the cerebellar volume may be associated with genetic predisposition to BD [69]. Additionally, reduction of the density of the gray matter of the cerebellar vermis has been reported in untreated BD patients, but not in

patients under treatment, which may suggest possible neuroprotective effects associated with psychopharmacological drug use [70].

3.5. Hippocampus

Data from a meta-analysis that summarized the results of 25 studies of hippocampal structure have found reduced hippocampal volume, especially in bipolar adolescent samples and reported apparent relationship between increased hippocampal volume and lithium therapy, which may explain the non-significant difference in hippocampal volume in most studies with samples of adult patients when compared to healthy controls [71].

4. Evidence of impairment of cellular resilience and plasticity in BD

There is growing evidence in literature of changes of neuroprotective processes and cellular plasticity and resilience pathways in BD from morphometric and neuropathological studies. Particularly, several mechanisms have founded to be involved as putative etiologic theories that underlie the neurobiological basis of BD, including proinflammatory cytokines, intracellular signaling cascades, and disrupted neurotrophic factor pathways.

More specifically, inflammatory mediators, such as interleukins, tumor necrosis factor alpha (TNF- α), and C-reactive protein, may influence several aspects of the pathophysiology of BD through changes in regulation of neuronal excitability, neuronal survival, synaptic transmission, and plasticity [72, 73]. Several studies have demonstrated a low-grade proinflammatory state in BD during euthymia [74–77], whereas both mania and depression seem to be associated with even more increased circulating cytokines [78, 79]. In addition, it has been suggested that proinflammatory cytokines may be one of the mechanisms of progression of BD, according to some studies [77, 80].

In terms of dysfunction of intracellular signaling cascades, there is a solid evidence of impaired regulation of calcium signaling and increased intracellular calcium levels, with subsequent loss of modulation of neuronal and glial activity, increased oxidative stress, and shortened survival cell [81–83]. Besides, Bcl-2, a protein with both antiapoptotic and neuroprotective properties highly expressed in the limbic system [84, 85], is associated with calcium regulation, reducing its release; Bcl-2 polymorphism AA was associated with both higher cytosolic calcium levels in lymphoblasts [86] and age-related decreases in brain gray matter volume [87].

Additional important signaling cascades involved in BD pathophysiology are those associated with members of the neurotrophin family, especially brain-derived neurotrophic factor (BDNF), which exerts its biological effects through activation of intracellular systems, including the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway [88].

BDNF is essential for neuroplastic phenomena, such as neurogenesis, neuronal survival, normal maturation of neural development pathways, and synaptic plasticity and dendritic

growth in adulthood as well [89], and it has been demonstrated circulating BDNF is reduced during manic and depressive states [90, 91], while ERK/MAPK pathway is an important intracellular mediator of biological effects of neurotrophic factors, acting on several proteins involved in cellular plasticity, such as glycogen synthase K-3 (GSK-3)—a major regulator of apoptosis—and cAMP response element-binding protein (CREB), which is a facilitator of the expression of neurotrophic/neuroprotective proteins such as Bcl-2 and BDNF [92, 93].

Information about histopathological abnormalities of neuronal and glial cells from *postmortem* studies in mental illness is scarce and its interpretation may be limited due to employment of different techniques and presence of confounding factors such as illicit-drugs and alcohol abuse [94]. However, particularly in BD patients, these abnormalities seem to be concentrated on frontolimbic regions associated with emotional regulation, including the DLPFC and ACC [95].

Although histopathological findings vary among regions and layers of the prefrontal cortex in BD patients, the majority of *postmortem* studies points up reductions in the neuronal density and size, glial cell density and changes in protein expression (implicated in the regulation of synaptic plasticity), which likely result from a combination of dendritic atrophy and/or cell loss in the DLPFC and ACC [95].

In this context, it is possible to hypothesize a link among the neuropathological, neuroimaging, and clinical findings, which dendritic atrophy and cell loss may result in reductions of volume in prefrontal areas, as abnormal synaptic interactions among cortical and subcortical brain structures may result in structural and functional intra- and interhemispheric disconnections and culminate in more vulnerability to stressful stimuli from environment, emotional dysregulation, and BD-related affective, cognitive, and behavioral symptoms [96].

However, lithium and valproic acid, respectively, through inhibition of glycogen synthase kinase-3 (GSK-3) and the histone deacetylases (HDACs), regulate the transcription and expression of neurotrophic, angiogenic, and neuroprotective proteins, such as BDNF, glial cell line-derived neurotrophic factor (GDNF), and angiogenic vascular endothelial growth factor (VEGF). Also, lithium in particular acts on factors that affect apoptotic signaling, such as Bcl-2, p53, Bax, caspase, and heat shock proteins (HSP); both lithium and valproate activate ERK/MAPK pathway. Finally, lithium contributes to induction of the ubiquitin-proteasome system and autophagy, two major intracellular quality control mechanisms for protein clearance that prevent abnormal protein accumulation. Overall, these findings highlight the properties of lithium and probably other mood stabilizers to suppress cell death, attenuate neuroinflammation, and promote angiogenesis and cellular plasticity in BD patients, which contribute to the reduction of neuronal loss [5].

However, not all neuroimaging studies show benefits from long-term use of mood stabilizers. For instance, in a study that evaluated both medicated with antipsychotics or lithium manic (most hospitalized) and outpatient euthymic patients and healthy controls using fMRI demonstrated loss of functional connectivity between amygdala and ACC in manic, but not in euthymic patients;

according to its authors, these findings may suggest a state-dependent neuronal dysfunction [97], but these results may be a marker of treatment non-response, since all patients were medicated.

This latter hypothesis has been brought up a longitudinal study in which bipolar I patients were assigned to euthymic, responders, and non-responders to lithium therapy. When baseline and after treatment volumes of the hippocampus, amygdala, PFC, DLPFC, and ACC volumes were compared, there was a significant enlargement in the left PFC and DLPFC in bipolar I patients who responded to treatment, and the left hippocampus and right ACC volumes were decreased in non-responders [98].

5. Conclusion

In summary, the main findings in structural and functional neuroimaging studies suggest that there is frontolimbic circuitry dysregulation in BD, characterized by impairment of control of subcortical regions by cortical ones; changes in specific brain areas have been replicated in several studies, which may reflect impairments in physiological neuroplastic phenomena in the central nervous system. However, growing body of evidence from neuroimaging studies also shows that long-term treatment with mood stabilizers may be associated with metabolic/functional compensation or structural restoration, at least in bipolar responders, and neuroimaging techniques may be considered as a potential tool for establishing prognostic, predictive, or pharmacodynamic biomarkers in BD in the future.

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