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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 genic 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 prefrontal 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, corticomedial, 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; corticomedial 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 DLPF 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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References

- [1] Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med.* 2005 Jun 16; 352(24):2515-2523.

- [2] Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry*. 2003 Feb; 64(2):161-174.
- [3] Savitz JB, Rauch SL, Drevets WC. Clinical application of brain imaging for the diagnosis of mood disorders: the current state of play. *Mol Psychiatry*. 2013 May; 18(5):528-539.
- [4] Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry*. 2001 May 1; 49(9):741-752.
- [5] Chiu TC, Wang Z, Hunsberger JG, Chuang DM. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. *Pharmacol Rev*. 2013 Jan 8; 65(1):105-142.
- [6] Moore GJ, Cortese BM, Glitz DA, Zajac-Benitez C, Quiroz JA, Uhde TW, Drevets WC, Manji HK: A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. *J Clin Psychiatry*. 2009 May; 70(5):699-705.
- [7] Rocha MV, Nery-Fernandes F, Guimarães JL, Quarantini L de C, de Oliveira IR, Ladeia-Rocha GG, Jackowski AP, de Araujo Neto C, Miranda-Scippa Â. Normal metabolic levels in prefrontal cortex in euthymic bipolar I patients with and without suicide attempts. *Neural Plast*. 2015; 2015:165180.
- [8] Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical psychiatry: an update. *J Psychosom Res*. 2002 Aug; 53(2):647-654.
- [9] Strakowski SM, Adler CM, Almeida J, Altshuler LL, Blumberg HP, Chang KD, et al. The functional neuroanatomy of bipolar disorder: a consensus model. *Bipolar Disord*. 2012 Jun; 14(4):313-325
- [10] Zald DH, Kim SW. Anatomy and function of the orbital frontal cortex, I: anatomy, neurocircuitry, and obsessive-compulsive disorder. *J Neuropsychiatry Clin Neurosci*. 1996 Spring; 8(2):125-138.
- [11] MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*. 2000 Jun 9; 288(5472):1835-1838.
- [12] Kerns JG, Cohen JD, MacDonald AW 3rd, Cho RY, Stenger VA, Carter CS. Anterior cingulate conflict monitoring and adjustments in control. *Science*. 2004 Feb 13; 303(5660):1023-1026.
- [13] Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR. Pathological laughter and crying: a link to the cerebellum. *Brain*. 2001 Sep; 124(Pt 9):1708-1719.

- [14] LeDoux J. The amygdala. *Curr Biol*. 2007 Oct; 17(20):R868-R874.
- [15] Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol Psychiatry*. 2003 Sep 1; 54(5):504-514.
- [16] Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotional regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry*. 2008 Sep; 13(9):829, 833-857.
- [17] Blond BN, Fredericks CA, Blumberg HP. Functional neuroanatomy of bipolar disorder: structure, function, and connectivity in an amygdala-anterior paralimbic neural system. *Bipolar Disord*. 2012 Jun; 14(4):340-355.
- [18] Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry*. 2014 Aug; 171(8):829-843.
- [19] Soares JC, Mann JJ. The anatomy of mood disorders – review of structural neuroimaging studies. *Biol Psychiatry*. 1997 Jan 1; 41(1):86-106.
- [20] Lyoo IK, Lee HK, Jung JH, Noam GG, Renshaw PF. White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Compr Psychiatry*. 2002 Sep-Oct; 43(5):361-368.
- [21] Wang F, Kalmar JH, Edmiston E, Chepenik LG, Bhagwagar Z, Spencer L, et al. Abnormal corpus callosum integrity in bipolar disorder: a diffusion tensor imaging study. *Biol Psychiatry*. 2008 Oct 15; 64(8):730-733.
- [22] Bruno S, Cercignani M, Ron MA. White matter abnormalities in bipolar disorder: a voxel-based diffusion tensor imaging study. *Bipolar Disord*. 2008; 10(4):460-468.
- [23] Brambilla P, Nicoletti MA, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, et al. Magnetic resonance imaging study of corpus callosum abnormalities in patients with bipolar disorder. *Biol. Psychiatry*. 2003; 54(11):1294-1297.
- [24] Atmaca M, Ozdemir H, Yildirim H. Corpus callosum areas in first-episode patients with bipolar disorder. *Psychol Med*. 2007 May; 37(5):699-704.
- [25] Nery-Fernandes F, Rocha MV, Jackowski A, Ladeia G, Guimarães JL, Quarantini L de C, et al. Reduced posterior corpus callosum area in suicidal and non-suicidal patients with bipolar disorder. *J Affect Disord*. 2012 Dec 15; 142(1-3):150-155.
- [26] Arnone D, McIntosh AM, Chandra P, Ebmeier KP. Meta-analysis of magnetic resonance imaging studies of the corpus callosum in bipolar disorder. *Acta Psychiatr Scand*. 2008; 118(5):357-362.
- [27] Cyprien F, de Champfleur NM, Deverdun J, Olié E, Le Bars E, Bonafé A, et al. Corpus callosum integrity is affected by mood disorders and also by the suicide attempt history: a diffusion tensor imaging study. *J Affect Disord*. 2016 Jul 19; 206:115-124.

- [28] Sarrazin S, Poupon C, Linke J, Wessa M, Phillips M, Delavest M, et al. A multicenter tractography study of deep white matter tracts in bipolar I disorder: psychotic features and interhemispheric disconnectivity. *JAMA Psychiatry*. 2014 Apr; 71(4):388-396.
- [29] Sarrazin S, d'Albis MA, McDonald C, Linke J, Wessa M, Phillips M, et al. Corpus callosum area in patients with bipolar disorder with and without psychotic features: an international multicenter study. *J Psychiatry Neurosci*. 2015 Sep; 40(5):352-359.
- [30] Caetano SC, Silveira CM, Kaur S, Nicoletti M, Hatch JP, Brambilla P, et al. Abnormal corpus callosum myelination in pediatric bipolar patients. *J Affect Disord*. 2008; 108:297-301.
- [31] Versace A, Ladouceur CD, Romero S, Birmaher B, Axelson DA, Kupfer DJ, et al. Altered development of white matter in youth at high familial risk for bipolar disorder: a diffusion tensor imaging study. *J Am Acad Child Adolesc Psychiatry*. 2010; 49:1249-1259.
- [32] McIntosh AM, Muñoz-Maniega S, Lymer GK, McKirdy J, Hall J, Sussmann JE, et al. White matter tractography in bipolar disorder and schizophrenia. *Biol Psychiatry*. 2008 Dec 15; 64(12):1088-1092.
- [33] Sussmann JE, Lymer GK, McKirdy J, Moorhead TW, Muñoz-Maniega S, Job D, et al. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. *Bipolar Disord*. 2009 Feb; 11(1):11-18.
- [34] Houenou J, Wessa M, Douaud G, Leboyer M, Chanraud S, Perrin M. Increased white matter connectivity in euthymic bipolar patients: diffusion tensor tractography between the subgenual cingulate and the amygdalo-hippocampal complex. *Mol Psychiatry*. 2007 Nov; 12(11):1001-1010.
- [35] Mahon K, Burdick KE, Ardekani BA, Szeszko PR. Relationship between suicidality and impulsivity in bipolar I disorder: a diffusion tensor imaging study. *Bipolar Disord*. 2012 Feb; 14(1):80-89.
- [36] Heng S, Song AW, Sim K. White matter abnormalities in bipolar disorder: insight from diffusion tensor imaging studies. *J Neural Transm*. 2010 May; 117(5):639-654.
- [37] Yildiz-Yesiloglu A, Ankerst DP. Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the in vivo proton magnetic resonance spectroscopy findings. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006 Aug 30; 30(6):969-995.
- [38] Moore GJ, Galloway MP. Magnetic resonance spectroscopy: neurochemistry and treatment effects in affective disorders. *Psychopharmacol Bull*. 2002 Spring; 36(2):5-23.
- [39] Forester BP, Finn CT, Berlow YA, Wardrop M, Renshaw PF, Moore CM. Brain lithium, N-acetyl aspartate and myo-inositol levels in older adults with bipolar disorder treated with lithium: a lithium-7 and proton magnetic resonance spectroscopy study. *Bipolar Disord*. 2008 Sep; 10(6):691-700.

- [40] Drevets WC. Neuroimaging studies of mood disorders. *Biol Psychiatry*. 2000 Oct 15; 48(8):813-829.
- [41] Blumberg HP, Stern E, Martinez D, Ricketts S, de Asis J, White T, et al. Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry*. 2000 Dec 1; 48(11):1045-1052.
- [42] Fornito A, Malhi GS, Lagopoulos J, Ivanovski B, Wood SJ, Saling MM, et al. Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I patients. *Psychiatry Res*. 2008 Feb 28; 162(2):123-132.
- [43] Matsuo K, Nicoletti MA, Peluso MA, Hatch JP, Nemoto K, Watanabe Y, et al. Anterior cingulate volumes associated with trait impulsivity in individuals with bipolar disorder. *Bipolar Disord*. 2009 Sep; 11(6):628-636.
- [44] Kalmar JH, Wang F, Spencer L, Edmiston E, Lacadie CM, Martin A, et al. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. *J Int Neuropsychol Soc*. 2009 May; 15(3):476-481.
- [45] Ongur D, Jensen JE, Prescott AP, Stork C, Lundy M, Cohen BM, et al. Abnormal glutamatergic neurotransmission and neuronal-glial interactions in acute mania. *Biol Psychiatry*. 2008 Oct 15; 64(8):718-726.
- [46] Frangou S. The Maudsley Bipolar Disorder Project. *Epilepsia*. 2005; 46(Suppl 4):19-25.
- [47] Brooks JO 3rd, Bonner JC, Rosen AC, Wang PW, Hoblyn JC, Hill SJ, et al. Dorsolateral and dorsomedial prefrontal gray matter density changes associated with bipolar depression. *Psychiatry Res*. 2009 Jun 30; 172(3):200-204.
- [48] Dickstein DP, Miham MP, Nugent AC, Drevets WC, Charney DS, Pine DS, et al. Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. *Arch Gen Psychiatry*. 2005 Jul; 62(7):734-741.
- [49] Molina V, Sánchez J, Sanz J, Reig S, Benito C, Leal I, et al. Dorsolateral prefrontal N-acetyl-aspartate concentration in male patients with chronic schizophrenia and with chronic bipolar disorder. *Eur Psychiatry*. 2007 Nov; 22(8):505-512.
- [50] Kalayci D, Ozdel O, Sözeri-Varma G, Kiroglu Y, Tümkaya S. A proton magnetic resonance spectroscopy study in schizoaffective disorder: comparison of bipolar disorder and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012 Apr 27; 37(1):176-181.
- [51] Brooks JO 3rd, Hoblyn JC, Ketter TA. Metabolic evidence of corticolimbic dysregulation in bipolar mania. *Psychiatry Res*. 2010 Feb 28; 181(2):136-140.
- [52] Altshuler L, Bookheimer S, Townsend J, Proenza MA, Sabb F, Mintz J, et al. Regional brain changes in bipolar I depression: a functional magnetic resonance imaging study. *Bipolar Disord*. 2008 Sep; 10(6):708-717.

- [53] Brooks JO 3rd, Wang PW, Bonner JC, Rosen AC, Hoblyn JC, Hill SJ, et al. Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. *J Psychiatry Res.* 2009 Jan; 43(3):181-188.
- [54] Hosokawa T, Momose T, Kasai K. Brain glucose metabolism difference between bipolar and unipolar mood disorders in depressed and euthymic states. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009 Mar 17; 33(2):243-250.
- [55] Lyoo IK, Sung YH, Dager Sr, Friedman SD, Lee JY, Kim SJ, et al. Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disord.* 2006 Feb; 8(1):65-74.
- [56] Nugent AC, Miham MP, Bain EE, Mah L, Cannon DM, Marret S, et al. Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. *Neuroimage.* 2006 Apr 1; 30(2):485-497.
- [57] Narita K, Suda M, Takei Y, Aoyama Y, Majima T, Kameyama M, et al. Volume reduction of ventromedial prefrontal cortex in bipolar II patients with rapid cycling: a voxel-based morphometric study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011 Mar 30; 35(2):439-445.
- [58] Wilke M, Kowatch RA, DelBello MP, Mills NP, Holland SK. Voxel-based morphometry in adolescents with bipolar disorder: first results. *Psychiatry Res.* 2004 May 30; 131(1):57-69.
- [59] James A, Hough M, James S, Burge L, Winmill L, Nijhawan S, et al. Structural brain and neuropsychometric changes associated with pediatric bipolar disorder with psychosis. *Bipolar Disord.* 2011 Feb; 13(1):16-27.
- [60] Cecil KM, DelBello MP, Morey R, Strakowski SM. Frontal lobe differences in bipolar disorder as determined by proton MR spectroscopy. *Bipolar Disord.* 2002 Dec; 4(6):357-365.
- [61] Nery-Fernandes F, Quarantini L de C, Galvão-de-Almeida A, Rocha MV, Kapczinski F, Miranda-Scippa A. Lower rates of comorbidities in euthymic bipolar patients. *World J Biol Psychiatry.* 2009; 10(4 Pt 2):474-479.
- [62] Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, et al. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. *Biol Psychiatry.* 2005 Nov 15; 58(10):763-769.
- [63] Mazzola-Pomietto P, Kaladjian A, Azorin JM, Anton JL, Jeanningros R. Bilateral decrease in ventrolateral prefrontal cortex activation during motor response inhibition in mania. *J Psychiatr Res.* 2009 Jan; 43(4):432-441.
- [64] Blumberg HP, Donegan NH, Sanislow CA, Collins S, Lacadie C, Skudlarski P, et al. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. *Psychopharmacology (Berl).* 2005 Dec; 183(3):308-313.

- [65] DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. *Neuropsychopharmacology*. 1999 Jul; 21(1):63-68.
- [66] Mills NP, DelBello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *Am J Psychiatry*. 2005 Aug; 162(8):1530-1532.
- [67] Monkul ES, Hatch JP, Sassi RB, Axelson D, Brambilla P, Nicoletti MA, et al. MRI study of the cerebellum in young bipolar patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008 Apr 1; 32(3):613-619.
- [68] Baldaçara L, Nery-Fernandes F, Rocha M, Quarantini L de C, Rocha GG, Guimarães JL, et al. Is cerebellar volume related to bipolar disorder? *J Affect Disord*. 2011 Dec; 135(1-3):305-309.
- [69] Sariçiçek A, Yalin N, Hidiroglu C, Çavusoglu B, Tas C, Ceylan D, et al. Neuroanatomical correlates of genetic risk for bipolar disorder: a voxel-based morphometry study in bipolar type I patients and healthy first degree relatives. *J Affect Disord*. 2015 Nov 1; 186:110-118.
- [70] Kim D, Cho HB, Dager S, Yurgelun-Todd DA, Yoon S, Lee JH, et al. Posterior cerebellar vermal deficits in bipolar disorder. *J Affect Disord*. 2013 Sep 5; 150(2):499-506.
- [71] Danzer R, Kelley K. Twenty years of research in cytokine-induced sickness behavior. *Brain Behav Immun*. 2007 Feb; 21(2):153-160.
- [72] Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav Immun*. 2011 Feb; 25(2):181-213.
- [73] Kapcsinski F, Dal-Pizzol A, Teixeira AL, Magalhães PV, Kauer-Sant'Anna M, Klamt F, et al. Peripheral biomarkers and illness activity in bipolar disorder. *J Psychiatr Res*. 2011 Feb; 45(2):156-161.
- [74] Hope S, Dieset I, Agaitz I, Steen N, Ueland T, Melle I, et al. Affective Symptoms are associated with markers of inflammation and immune activation in bipolar disorder but not schizophrenia. *J Psychiatr Res*. 2011 Dec; 45(12):1608-1616.
- [75] Kim YK, Jung HG, Mint AM, Kim H, Park SH. Imbalance between proinflammatory and anti-inflammatory cytokines in bipolar disorder. *J Affect Disord*. 2007 Dec; 104(1-3):91-95.
- [76] Doganavsargill-Baysal O, Cinemre B, Aksoy UM, Akbas H, Metin O, Fettahoglu C, et al. Levels of TNF- α , Soluble receptors (sTNFR1, sTNFR2), and cognition in bipolar disorder. *Hum Psychopharmacol*. 2013 Mar; 28(2):160-167.
- [77] Maes M, Bosmaus E, Calabrese J, Smith R, Meltzer HY, et al. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. *J Psychiatr Res*. 1995; 29(2):141-152.
- [78] Kauer Sant'Anna M, Kapczinski F, Andreazza AC, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. *Int J Neuropsychopharmacol*. 2009; 12(4):447-458.

- [79] Grande I, Magalhães PV, Chendo I, et al. Staging bipolar disorder: clinical, biochemical and functional correlates. *Acta Psychiatr Scand*. 2014; 129(6):557-567.
- [80] Kato T, Ishiwata M, Mori K, Washizuka S, Tajima O, Akiyama T, et al. Mechanisms of altered Ca^{2+} signalling in transformed lymphoblastoid cells from patients with bipolar disorder. *Int J Neuropsychopharmacol*. 2003 Dec; 6(4):379-389.
- [81] Akimoto T, Kusumi I, Suzuki K, Koyama T. Effects of calmodulin and protein kinase C on transient Ca^{2+} increase and capacitative Ca^{2+} entry in human platelets: relevant to pathophysiology of bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007 Jan; 31(1):136-141.
- [82] Andreazza AC, Kauer-Sant'Anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative Stress markers in bipolar disorder: a meta-analysis. *J Affect Disord*. 2008 Dec; 111(2-3):135-144.
- [83] Bernier PJ, Parent A. The anti-apoptosis bcl-2 proto-oncogene is preferentially expressed in limbic structures of the primate brain. *Neuroscience*. 1998 Feb; 82(3):635-640.
- [84] Liu L, Schulz S, Lee S, Reutiman TJ, Fatemi SH. Hippocampal CA1 pyramidal cell size is reduced in bipolar disorder. *Cell Mol Neurobiol*. 2007 May; 27(3):351-358.
- [85] Machado-Vieira R, Pivovarov N, Stanika R, Yuan P, Wang Y, Zhou R, et al. The bcl-2 gene polymorphism rs956572AA increases inositol 1,4,5-triphosphate receptor mediated endoplasmic reticulum calcium release in subjects with bipolar disorder. *Biol Psychiatry*. 2011 Feb; 69(4):344-352.
- [86] Liu M, Huang CL, Yang AC, Tu PC, Yeh HL, Hong C, et al. Effect of bcl-2 rs956572 polymorphisms on age related-gray matter volume changes. *PLoS One*. 2013; 8(2):e56663.
- [87] Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Prog Neurobiol*. 2005 Jun; 76(2):99-125.
- [88] Post RM. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. *J Psychiatr Res*. 2007 Dec; 41(12):979-990.
- [89] Cunha AB, Frey BN, Andreazza AC et al. Serum brain derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. *Neuroscience Lett*. 2006 May; 398(3):215-219.
- [90] Machado-Vieira R, Dietrich MO, Leke R et al. Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. *Biol Psychiatry*. 2007 Jan; 61(2):142-144.
- [91] Chen G, Manji HK. The extracellular signal-regulated kinase pathway: an emerging promising target of mood stabilizers. *Curr Opin Psychiatry*. 2006 May; 19(3):313-323.
- [92] Engel SR, Creson TK, Hao Y, et al. The extracellular signal-regulated kinase pathway contributes to the control of behavioral excitement. *Mol Psychiatry*. 2009 Apr; 14(4):448-461.

- [93] Dorph-Petersen KA, Lewis DA. Stereological approaches to identifying neuropathology in psychosis. *Biol Psychiatr*. 2011 Jan; 69(2):113-126.
- [94] Gigante AD, Young LT, Yatham LN, Andreazza AC, Nery FG, Grinberg LT, et al. Morphometric post-mortem studies in bipolar disorder: possible association with oxidative stress and apoptosis. *Int J Neuropsychopharmacol*. 2011 Sep; 14(8):1075-1089.
- [95] Otten M, Meeter M. Hippocampal structure and function in individuals with bipolar disorder: a systematic review. *J Affect Disord*. 2015 Mar 15; 174:113-125.
- [96] Soeiro-de-Souza MG, Dias VV, Figueira ML, Forlenza OV, Gattaz WF, Zarate CA Jr, et al. Translating neurotrophic and cellular plasticity: from pathophysiology to improved therapeutics for bipolar disorder. *Acta Psychiatr Scand*. 2012 Nov; 126(5):332-341.
- [97] Brady RO Jr, Masters GA, Mathewa IT, Margolus A, Cohen BM, Öngür D, Keshavan M. State dependent cortico-amygdala circuit dysfunction in bipolar. *J Affect Disord*. 2016 Sep 1; 201:79-87.
- [98] Selek S, Nicoletti M, Zunta-Soares GB, Hatch JP, Nery FG, Matsuo K, et al. A longitudinal study of fronto-limbic brain structures in patients with bipolar I disorder during lithium treatment. *J Affect Disord*. 2013 Sep 5; 150(2):629-633.