Neurobiology of Bipolar Disorder: Abnormalities on Cognitive and Cortical Functioning and Biomarker Levels

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Abstract: Bipolar disorder (BD) affects 1 to 1.5% of the world population and consists of at least one manic episode (or hypomanic) associated with depressive episodes, interspersed with periods of euthymic mood. Recurrent crises lead to significant disability in BD patients, and correlates negatively to social and occupational adjustment. Such disability can be explained by a series of events, such as cortical and altered metabolic activity, impairments in cognitive functions, and in core anatomical structures involved in mood modulation. Therefore, our review aims to provide information on the current research related to the pathophysiology of BD. We will review the cognitive and brain functioning, and biomarkers of BD. The current literature shows that cognitive deficits are commonly observed in all phases in BD patients, independent of a remissive state. These deficits are assigned to functional, structural and metabolic changes, particularly in the pre-frontal cortex region, hippocampus and amygdala, along with the connections between them, as well as decreased baseline brain-derived neurotrophic factor levels or imbalance between pro- and anti-inflammatory cytokines, implying a lower physical ability to reestablish from a stressful stimulus. BD patients effectively present a differentiated pattern of cortical, neuroanatomical and functional responses. It is suggested that physiological processes occur differently in bipolar subjects compared to healthy individuals, affecting behavior and brain function in such patients. Future directions are yet necessary to establish the best way to neutralize or reverse these events.

Keywords: Bipolar disorder, brain-derived neurotrophic factor, depression, mania, neuroplasticity.

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INTRODUCTION

Bipolar disorder (BD) affects 1 to 1.5% of the world population [1] and consists of at least one manic episode (or hypomanic) associated with depressive episodes, interspersed with periods of euthymic mood [2]. Recurrent crises lead to significant disability in BD patients and correlate negatively to social and occupational adjustment [3]. Such disability can be explained by a series of events, such as, cortical and altered metabolic activity, impairments in cognitive functions, and in core anatomical structures involved in mood modulation [3, 4].

Thus, BD patients show particularities in cortical activity compared to other psychiatric illnesses [4, 5], including differences among phases [6-8]. These cortical patterns are closely associated with poor cognitive performance [5], supporting the notion that BD patients exhibit cognitive dysfunction. This problem seems to occur in different cognitive

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domains, even during periods of clinical remission [3, 9], and may be explained by a significant volume reduction of white and gray matter [10, 11]. Therefore, the chronic state has been consistently attributed to functional and neuroanatomical changes in the cortex and may occur with different magnitudes of impact [4, 10, 12-14].

The prefrontal cortex (PFC) has an important role in BD pathophysiology, and has been also directly involved in changes of cognitive function [10, 15]. Neural connections between PFC and structures such as the hippocampus [16] and amygdala [11, 12] may explain the manifestation of mood events linked to BD, and seem to represent specific features of the disorder. For instance, manic patients have reduced activity of specific portions of PFC and increased reactivity of the amygdala in front of facial expressions of emotion, reflecting a state-dependent excitatory nature. The opposite is also observed in depressive phase of BD.

Moreover, the neurotransmission system and hormonal metabolic abnormalities such as elevated cortisol levels, or reduced levels of neurotrophic factors, are commonly observed in several mental disorders, as well as in BD patients. These changes strongly contribute to the worsening of the disorder, and they are connected to negative disease neuroprogression [17-20]. Thus, it makes sense to believe that a cascade of physiological events is integrated and forms a complex system, supporting concurrent level of damage from the disorder. Therefore, our review aims to provide information on current research related to the pathophysiology of BD. We will review cognitive and brain functioning and biomarkers of BD.

Cognitive Impairments in Bipolar Disorder Patients

Special attention has been given to cognitive deficits in patients with BD, which influence social and behavioral aspects of these subjects [21]. The literature is consistent and unidirectional in presenting cognitive deficits in bipolar patients [3, 9, 15, 22, 23], and that seems to be independent of a remitting phase of the disorder [3]. Martínez-Arán *et al*. [3] and other authors [9] further argue that negative effects over cognitive function do not seem to differ from patient's clinical status (i.e., depression, hypomania/maniac or euthymia).

There is a strong association between some neuropsychological and clinical characteristics presented by bipolar patients and cognitive performance variables. Clark, Iversen and Goodwin [24] suggest negative associations between the number of depressive episodes and poor performance in spatial working memory, California verbal learning test, tower of London problem solving task and tasks of speed process of visual information ($P<0.05$). Similarly, manic episodes are negatively associated to the same California verbal learning test and rapid visual information processing ($P<0.05$). These responses represent a large deficit of sustained attention in bipolar patients [3, 24]. Recurrence, in a large number of episodes, is also negatively correlated to poor cognitive performance [24] making them more vulnerable and increasing the effects of disorder cycles. Cognitive deficit independence during the remission phase of symptoms is mentioned in the meta-analysis of Robinson *et al*. [22]. These authors reported a moderate magnitude of effect size (ES – *"d index"*) (0.5 a 1.0) with important clinical significance on reducing cognitive function in euthymic patients. Thompson *et al*. [23], also presented persistent cognitive reduction on euthymic patients in different psychomotor, executive function, attention, immediate and declarative tests compared to control group. It seems that clinical status is quite independent of the performance in these cognitive domains [3, 9, 22, 25-27].

It is also suggested that patients with psychosis diagnosis in BD are significantly affected with higher cognitive decline compared to bipolar patients without psychotic traits [28]. However, these responses seem still uncertain. Preliminary comparisons demonstrate the existence of cognitive declines of similar magnitude for the same domains previously discussed [29, 30]. In this same meta-analysis of Bora, Yucel and Pantelis [29] the highest ES was found in the Symbol Coding Test – ES = 1.02. Eleven of the cognitive tests (Stroop test, Category Fluency, Verbal Memory Immediate, Wisconsin Card Sorting Test, Continuous Performance Test, Trail Making Test A and B, verbal memory delayed, Wisconsin Card Sorting Test Categories") obtained ES > 0.8 and moderate ES for two of the tests (visual memory e letter fluency) [29].

Exploring Mechanisms

The responsible mechanisms for poor cognitive performance despite not yet totally understood seem to be multifactorial, therefore, related to different functional implications [14], neuroanatomical [31], and regional cerebral blood flow abnormalities [32, 33]. In this sense, the PFC region and its subdivisions are directly affected in its functioning [4, 31, 34] and volume [11, 35, 36], and some areas become inefficiently activated during the cognitive assessment [4]. The changes in cortical activity can be associated to pre-existing cognitive alterations in these patients, loss of functionality, or efficiency of synaptic circuities in question [12, 13, 31]. For example, it was observed that manic patients, who had a poor performance in the Continuous Performance Test (i.e., reduction in attentional functioning), also had a lower volume in PFC and hippocampal areas, indicating an association between cognitive and brain functions [31]. Abnormalities in the activation of the ventral region of PFC observed in functional magnetic resonance imaging (fMRI) during the Color-Word Stroop test", suggest that cognitive processing is different in bipolar subjects when compared to healthy subjects [13].

A strong relationship was established between the cognitive decline and neuroanatomical changes in different brain areas such as hippocampus, amygdala, gray matter, and the PFC, as seen in the longitudinal multicenter study by Mungas *et al*. [37]. The mechanism responsible for the loss of volume or density in a given brain region seems to be related to a reduction in dendritic arborization, loss of myelination or synaptic connections, as observed in other mental disorders such as schizophrenia or Alzheimer disease [38]. These negative outcomes may be explained by a lower serum level of substances related to trophic processes, biomarker promoters of neuronal cell proliferation and survival, i.e., neurogenesis, such as brain-derived neurotrophin

factor (BDNF), or insulin-like growth factor-1 (IGF-1) which also participate of this pathophysiological mechanism [39]. The massive activation of the immune system is also closely linked to this process, and could also explain this cascade of events [40-42] and inhibition of neurogenesis. This relationship will be discussed in more detail below.

In another perspective, cerebrovascular metabolism and regional cerebral blood flow may reflect a neuronal cell deficient and poor nutrition in certain brain areas and seem to suppress the demand of activation on simple or complex cognitive tasks, and are strongly associated with cognitive decline [32, 33]. Dolan *et al*. [33], for example, reported a significant reduction of cerebral blood flow in the left PFC in depressed patients compared to healthy subjects. These authors also maintain the idea that these abnormalities are highly associated with neuropsychological functions. Other findings showed similar reductions in the anterior cingulate cortex, and the left dorsolateral prefrontal cortex [32].

In turn, treatment with specific drugs or engagement in physical exercise can induce the production of substances related to growth and vascular proliferation (e.g. vascular endothelial growth factor - VEGF). VEGF is produced due to the need of oxygen and increased metabolism [43], which is directly associated with improved cognition [43, 44]. In an important recent study conducted by Hohman *et al*. [44], the authors argue that hippocampal volume (p = 0.009), longitudinal hippocampal atrophy (p = 0.01), longitudinal decline of memory (p = 0.01), and reduction in executive function (p = 0.003) are highly associated with the amount of VEGF available in cerebrospinal fluid [44]. In this sense, the bioavailability of VEGF is essential for neurogenic effects [45].

β-amyloid plaque deposition appears to exert a similar influence on cognitive performance in bipolar patients [46, 47], like observed in Alzheimer disease patients [48]. The interaction of VEGF/β-amyloid peptide (1-42) has proven be a predictor of longitudinal memory decline [44]. β-amyloid plaques are formed by the action of β-secretase and γ-secretase cleavage of a transmembrane protein called amyloid precursos protein [49]. The regulation of β-amyloid seems to be influenced by the serum level of growth factors such as IGF-1 and other neurotrophins that are directly linked to neurogenesis [50]. Thus, high concentrations of β-amyloid are inversely related to IGF-1 concentrations [50]. Therefore, within this scenario, an efficient cognitive processing seems contradictory (Fig. **1**).

Cortical and Structural Changes in Bipolar Disorder Patients

PFC plays an important role on different functions, from the synthesis of information to behavioral execution, supported by innumerous connection networks [7, 8]. PFC is, perhaps, the most relevant structure to be studied in order to understand the physiopathology of patients with BP in the different domains of the illness [11, 13]. Abnormalities in the PFC are directly related to emotional and behavioral dysfunctions and poor cognitive performance [11, 51]. Thus, changes in metabolism and regional cerebral blood flow can alter the level of cortical activation in this particular area of interest, and thus modify the interaction with the limbic system [52]. For example, Blumberg *et al*. [13] associated elevated state of positive mood in patients with BD mainly due to reduction in the activation of the PFC right ventral portion. The left portion of the same structure was more activated in depressive patients, both determined via fMRI. Amygdala, in particular, a structure related directly with mood disorders and responsible for emotional processing, although still controversial, exhibits a bilateral reduction in activation in bipolar depressive patients [53]. In contrast, an opposite cortical response occurs in manic patients [8, 53]. It is suggested, generally, that these different responses of PFC, together with other structures, could reflect a specific trait in each BD cycle [13].

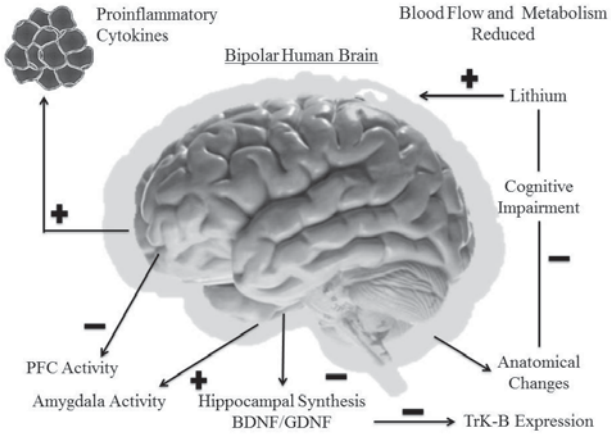

Fig. (1). Typical cortical, neuroanatomical, and biomarker alterations observed in patients with bipolar disorder.

In addition to particular cortical responses, fMRI also show implications on the volume and density of structures such as the hippocampus [16, 31, 36], amygdala [12, 36], hypothalamus [35] and cingulated cortex [11, 54]. This brain general dysfunction does not depend on the clinical state. Considering the field of emotional processing, the amygdala and hippocampus play an important role in BD, and these structures have its volume significantly reduced [12, 36]. Similarly, white and grey matters, mainly in frontal area of the brain, are also reduced on its volume [11]. The abnormality of these structures is associated to a strong genetic predisposition to develop BD and may explain diverse chronic cognitive alterations. Research point toward glial cells reduction, specifically in Broadman area 24, as well as blood flow reduction and cerebral metabolism alterations [55] in unipolar and bipolar depression [56]. All these responses seem to be higher when patients have previous familiar history compared to those who don't have familiar history, which probably makes them more vulnerable to the large spectrum illness symptoms [56].

Mania/Hypomania

Cortical activity in manic patients manifests in different pattern compared to bipolar patients in depressive and euthymic phase [6, 8, 13, 57-60]. As mentioned earlier, PFC

and its subdivisions have a great expressivity on symptoms developed by bipolar patients. There is data convergence toward a cortical activity reduction, mainly in PFC ventral portion in manic patients. The reduction of activity in this portion of the brain reflects mainly an excitatory state [13].

The functional network of cortical connections in manic bipolar patients, exhibits inverse modulation between PFC ventrolateral region and amygdala [8]. Foland *et al*. [8] found in a group of 9 manic and hypomanic patients and 9 healthy subjects, a higher activation of left portion of amygdala and concomitant reduction of PFC ventrolateral region from tests of facial matching of emotional expressions (labeling and emotional perception tasks). Amygdala reactivity seems to be state-dependent, however, these result are still questionable [6, 8]. Additionally, cortical activity increase of the inferior part of anterior frontal gyrus with concomitant reduction of cingulated cortex activity was also task dependent. The alterations in cortical activation pattern in manic patients compared to healthy individuals are shown in Table **1**.

Hippocampal region, also of great interest for BD, plays an important function on mood disorders and cognitive domains of attention, memory and learning. Abnormalities in this structure are consistently expressed both in depressive and bipolar depressive patients [61], however not in manic patients. Although still controversial, literature shows significant association between abnormal hippocampal volume and poor performance in cognitive tests ("Continuous Performance test"- $p=0,002$) [35], especially for smaller attention functioning in manic patients [31].

Drug interventions based on lithium exerts positive effects on both amygdala and hippocampus structures compared to patients who did not use medication [36]. Foland *et al*. examined 49 BD patients (22% manic at the scanning moment) and observed significant increasing of amygdala ($p=0.0258$) and hippocampus ($p=0.0356$ – left portion; $p=0.005$ – right portion) volumes, for patients who were administered lithium in treatment. In fact, these responses did not depend of the patients' clinical status ($p = 0.23$). Therefore, one must be careful when analyzing studies that did not make a rigorous pharmacological control, because lack of control could derail results extrapolation, given that there is a great influence in cerebral neuroanatomy [36]. The meta-analysis produced by Hajek *et al*. [62] compared patients who were long-term users of lithium to patients without use of the medicament and healthy controls. A smaller hippocampal volume was observed in patients who not used lithium, while a larger volume of both sides of hippocampus was noticed in patients treated with drugs. Lithium seems to protect patients from the deleterious effects of bipolar disorder [36], and this phenomenon is linked to the

Table 1. Cortical Changes in Manic Patients Compared to Healthy Subjects.

Author		Features			Results	
		Sample	Objective	Task	Outcomes	Conclusion
Mazzola-Pomietto *et al*. [57]	A	16 (manics)	Identify brain functional abnormalities in mania	Go-NoGo Task	VLPFC (R/ L) ↓	Response inhibition in mania is associated with a lack of engagement of the bilateral VLPFC
		16 (healthy)			VLPFC (R/ L) ↑	
Altshuler *et al*. [58]	A	11 (manics)	Investigate neural activity in the lateral orbitofrontal cortex in mania	Go-NoGo Task	RL Orbitofrontal Cortex ↓; Hippocampus ↓; Cingulate ↓	Mania is associated with a significant attenuation of task-related activation of RL orbitofrontal function
		13 (healthy)			RL Orbitofrontal Cortex ↑↑↑	
Elliott *et al*. [59]	A	11 (manics)	Investigate the neural activity orbitofrontal in mania	Go-NoGo Task	Orbitofrontal Cortex ↓; VLPFC/VMPFC ↑	Critical role for ventral and medial dysfunction in the pathology of mania
		13 (healthy)			Orbitofrontal Cortex ↔; VLPFC/VMPFC ↔	
Kaladjian *et al*. [60]	C	10 (manics)	Examine the functional changes associated with symptomatic remission in mania	Go-NoGo Task	Amygdala ↑; ↓(after mania);	Decrease in left amygdala responsiveness is a critical phenomenon associated with remission from mania
		10 (healthy)			Amygdala ↔	
Foland *et al*. [8]	A	9 (manics)	Evaluate functional connectivity between VLPFC and amygdala during the cognitive evaluation of affective stimuli	Perceive & label emotion	Amygdala (L)↑; VPFC (R)↓; inferior frontal gyrus ↑; ventral ACC ↓	Bipolar mania suggest that reductions in inhibitory frontal activity in these patients may lead to an increased reactivity of the amygdala
		9 (healthy)			Amygdala (L) ↓; VPFC (R) ↑; inferior frontal gyrus; (R) ACC ?	
Blumberg *et al*. [13]	A	11 (manics)	Characterize state/trait-related functional impairment in frontal systems in bipolar disorder	Strop Task	(R) VPFC ↓	VPFC abnormalities may be associated with specific acute mood states
		20 (healthy)			VPFC ↔	

Subtitles: ↑- increased activation compared to control; ↓- reduced activation compared to control; ↑↑↑ - greater intensity compared to other groups; ↓↓↓ - lower intensity compared to other groups; ↔ - small percentage of activation; VLPFC - Ventral Lateral Prefrontal Cortex; R - Right; L - Left; RL - Right Lateral; VMPFC - Ventromedial Prefrontal Cortex; ACC - Anterior Cingulate Cortex; A - Acute Research; C - Chronic Research; All studies used functional magnetic resonance imaging (fMRI).

increase, or restoration of normal levels of serum concentration of neurotrophins as mentioned before, thereby increasing neuronal resilience and reducing the perception of symptoms [19, 20, 63].

Depression

PFC is also directly implicated in the physiopathology of bipolar depressive patients. Patients with BD, in their depressive phase, exhibit a particular cortical activation pattern in relation to euthymic, manic and unipolar depressive patients [53, 64-68]. Negative mood state observed in depressive patients is associated with altered cortical responses, particularly a hemispheric asymmetry of PFC area, presenting a greater activation in the right side compared to manic patients. However, the ventral portion of the PFC becomes significantly more activated, as well as subcortical regions when observing positive and/or negative emotional expressions, when compared to unipolar depressive patients and healthy controls [64]. Given these characteristics, it is possible to have a differential diagnostic between unipolar and bipolar depression, since unipolar depressive patients have depressed activation in these regions using the same procedure [64].

Abnormal activation of structures related to frontal-subcortical circuit (frontal cortex, striatum, globus pallidus, substancia nigra and thalamus) [69] are directly associated to bipolar depression physiopathology [68]. This circuit is divided in different routes and is responsible for motor activity and some human behaviors, including emotion [69]. The responses of subcortical activation seem clear and some of them are defined as predominant traits in BD, compared to major depression. Lawrence *et al*. [64] showed increased striatal ventral, thalamic, hippocampal and amygdala activation in response to different facial expressions (fear or happiness) while patients with major depression presented less activation in the same areas. Almeida *et al*. [6] observed significant amygdala reactivity when comparing neuroimaging data between groups of patients with bipolar depression, major depression and healthy subjects exposed to faces of happiness (no interaction between depressive groups in amygdala activity), fear and sadness (reactivity in amygdale left portion in BP - $p=0.012$). These patients also tended to exhibit negative and deficient connectivity between the right portion of amygdala and dorsolateral right regions, as well as the right orbitofrontal area of PFC [53]. This directly implies in incapacity to regulate mood and emotions. The alterations in cortical activation pattern in bipolar depressive patients compared to healthy individuals are shown in Table **2**.

In addition to functional alterations observed in the depressive phase of BD, there are also neuroanatomical modifications, mainly in limbic/subcortical regions. According to what happens in the other phases of BD, volumetric relations are normally reduced when compared to healthy subjects [12, 70]. The volumetry of PFC, thalamus, hippocampus, amygdala, pallidal and striatal regions of patients with BD are reduced when compared to healthy subjects, with an effect size moderate to large [12]. Correspondingly, white matter linked to PFC and subcortical regions are also significantly reduced compared to healthy subjects, with moderate to large ES.

Biomarkers in BD Patients

Numerous studies have pointed out a strong and inverse association between BD symptoms and serum levels of some physiological biomarkers [71-74]. As a rule, the biomarkers can express a general neuroprogression of mental disorders, such as in the case of BD, or the degree of deterioration for repeated events related to the symptoms of disease. There are distinct biomarkers represented in the literature, and we can name a few with significant emphasis on BD, i.e., BDNF [20], glial cell line-derived neurotrophic factor (GDNF) [74], cortisol level [75], and cytokines [76]. Concerning BDNF and GDNF, these have an extensive role in the physiopathology of BD, and therefore will be addressed first. In this sense, the neuroanatomical and related brain functional circuit alterations do not comprise the whole set of abnormalities observed in BD. Neurotrophin deregulation in brain structures (hippocampal) and to a lesser extent in other body tissues suggests a mediator of illness progression [19]. Improvement of these biomarkers can reflect a positive and momentary reorganization of the illness course. These neurotrophins are then sustained as orchestrated substances during neuroplasticity, promoting greater synaptic efficiency/ connectivity, dendritic arborization, and are also mediators of important neurotransmitters implicated in the pathophysiology of BD [77].

Reduced circulating levels of BDNF, for example, are commonly observed in patients with BD [71]. Cunha *et al*. [71] compared serum levels of BDNF between bipolar depressive, manic, euthymic and healthy subjects. The results showed a significant reduction of serum concentration of BNDF (ELISA method) for depressive ($p=0.027$) and manic ($p=0.019$) patients, compared to healthy subjects; however, there was no interaction in euthymic and healthy subjects. Similar effects were demonstrated between BDNF levels in bipolar depressive compared to unipolar depressive patients [78]. Finally, a meta-analysis by Fernandes *et al*. [72] demonstrated a significant reduction of serum levels of BDNF in manic bipolar (ES =0.81) and depressive (ES =0.97) patients, but not in euthymics (ES =0.20) in relation to a healthy control group. Despite these consistent data, recent studies contradict previous results [79].

Decrease in BDNF levels implies a lower physical ability to reestablish from a stressful stimulus, i.e. allostasis [19]. An increased allostatic load seems to maintain cortisol levels chronically more elevated in BD patients [19]. Naturally, cortisol concentrations are higher in the daytime [80], and changes occur throughout the day and in response to stressful stimuli. This is a physiological response commonly observed and activated via the hypothalamic/pituitary/adrenal axis, which mediates the secretion of adrenocorticotropic hormone and cortisol release by the adrenal cortex. This path is chronically activated in BD patients [75] and it is possible to establish an association between BDNF and cortisol levels and the concept of allostasis. Apparently, BDNF concentration is also increased mainly during daytime, along with cortisol levels following the circadian cycle [80]. This event can be explained as a co-regulation between these two variables in order to establish homeostasis. Increasing circulating levels of BDNF may provide a lower allostatic load and consequently a better regulation of existing cortisol.

Table 2. Cortical Changes in Depressive Bipolar Patients Compared to Healthy Subjects.

Author		Features			Results	
		Sample	Objective	Task	Outcomes	Conclusion
Almeida *et al*. [6]	A	15 (depressed)	Evaluate abnormal amygdala activity during positive and negative emotion processing	Perceive & label emotion	Amygdala ↑ (mild and neutral facial expressions)	Abnormally elevated (L) amygdala activity to mild sad and neutral faces might be a depression-specific marker in BD
		15 (healthy)			Amygdala ↔	
Lawrence *et al*. [64]	A	15 (depressed)	Compare responses within subcortical and prefrontal cortical regions to emotionally salient material	Perceive & label emotion	Ventral striatal ↑; thalamic ↑↑(fear); hippocampal ↑↑ (sad); VLPFC ↑↑ (happy)	BD patients demonstrated increased subcortical and ventral prefrontal cortical responses to both positive and negative emotional expressions
		15 (healthy)			Amygdala/hippocampus ↔; Thalamus ↑ (fear); parahippocampal gyrus ↑; VLPFC↔	
Vizueta *et al*. [53]	A	21 (depressed)	Examined neural activity in response to negative emotional faces during an emotion perception task	Perceive & label emotion	VLPFC (L/R) ↑; amygdala ↑; right orbitofrontal cortex ↑	BD depression is characterized by reduced regional orbitofrontal and limbic activation compared to healthy subjects
		21 (healthy)			VLPFC (L/R) ↑↑↑; amygdala ↑↑↑; right orbitofrontal cortex ↑↑↑	
Blumberg *et al*. [13]	A	10 (depressed)	Characterize state- and trait-related functional impairment in frontal systems in BD	Stroop Task	cVPFC ↑; rVPFC (L) ↓;	BD is associated with a trait abnormality in VPFC (L)
		20 (healthy)			cVPFC ↔; rVPFC (L) ↔;	
Diler *et al*. [65]	A	12 (depressed)	Identify differential patterns of neural activity in BD vs UD underlying response inhibition in adolescent	Go/ NoGo Task	Superior temporal (L) ↑; caudate (L) ↑; ACC (L) ↑	BD and UD shared similar neural responses in depression during response inhibition, but different to healthy control
		10 (healthy)			Superior temporal (L) ↔; caudate (L) ↔; ACC (L) ↔	
Perlman *et al.* [66]	A	21 (depressed)	Examine functional integration between the bilateral amygdala and PFC integrity of neural circuitry supporting abnormal emotion processing in depressed BD	Perceive & label emotion	Amygdala (R) ↑(fearful); VLPFC/VMPFC ↓	Differences in recruitment of amygdala–PFC circuitry support implicit emotion processing between remitted depressed BD and depressed-BD
		31 (remitted)			Amygdala (L/R) ↑ (all emotional conditions); VLPFC/ VMPFC ↓	
		25 (healthy)			Amygdala (L/R) ↔	
Marchand *et al*. [67]	A	14 (depressed)	Determine if the task activates structures of interest in depressed BD when euthymic	Paced motor; Stroop Task	Bilateral striatum ↑; ACC (R) ↑; medial frontal gyrus ↑	This finding provides evidence that the motor task may provide information about both state and trait functional abnormalities in BD
		14 (euthymic)			Bilateral striatum ↑↑↑; ACC (R) ↑↑↑; medial frontal gyrus ↑↑↑	
Marchand *et al*. [68]	A	14 (depressed)	Test the utility of a paced motor activation to evaluate FSC circuit function in BD depression	Paced motor; Stroop Task	Thalamus ↓; globus pallidus ↓; putamen ↓; DLCPF/Orbitofrontal ↓	This study supports the role of FSC circuit dysfunction in BD depression
		15 (healthy)			Thalamus ↑; globus pallidus ↑; putamen ↑; DLCPF/Orbitofrontal ↑(All in motor task)	

Subtitles: ↑- increased activation compared to control; ↓- reduced activation compared to control; ↑↑↑ - greater intensity compared to other groups; ↓↓↓ - lower intensity compared to other groups; ↔ - small percentage of activation; VLPFC - Ventral Lateral Prefrontal Cortex; DLCPF - Dorso Lateral Cortex Prefrontal; R - Right; L - Left; RL - Right Lateral; VMPFC - Ventromedial Prefrontal Cortex; ACC - Anterior Cingulate Cortex; cVPFC - Caudal Ventral Prefrontal Cortex; rVPFC - Rostral Ventral Prefrontal Cortex; FSC - Frontal-Subcortical. A - Acute Research; C - Chronic Research; All studies used functional magnetic resonance imaging (fMRI).

The use of mood stabilizing drugs such as lithium and valproate seem to increase the concentration of BDNF [81, 82], and positively affect BD symptoms by a second messenger mechanism, more specifically, inducing increased

intracellular signaling via G protein (Gs) expression, and increasing interaction with neurotransmitters linked to mood changes [83]. For example, it seems that the serotonin and neurotrophins, such as BDNF are also closely related, and signal in order to co-regulate the promotion of neuronal plasticity in several brain areas [84]. Increased expression of BDNF TrkB receptors is also caused by antidepressant drugs and mood stabilizers, which may favor BDNF/TrkB interaction and in turn, the cascade of physiological reactions.

Similar to effects produced by BDNF, GDNF seems to correlate negatively with BD symptoms (r = *-0.54*) [74], and a possible protector effect has been discussed, although there is no consensus so far [74, 85]. This neurotrophic factor is capable of promoting neuronal cell survival and differentiation of dopaminergic neurons, in addition to a high-affinity for dopamine capitation (?) [86]. Dopaminergic circuits are a direct participant of the mechanisms related to mood control. The reduction of dopamine is inversely related to depressive symptoms and its increase is directly associated to mania [87], and consequently GDNF is also an important piece of the puzzle to be investigated [86].

There is some evidence showing that circulating levels of GDNF are changed in BD, but not in the euthymic phase [74]. However, these findings have been debated [85]. Barbosa *et al*. [74] presented significant reduction in serum levels of GNDF in 35 manic patients (mean ± SD; 34.09 ± 48.80 pg/mL - $p \leq 0.05$) in comparison to 35 euthymic patients (mean ± SD; 76.74 ± 95.26 pg/mL - $p \leq 0.05$). In contrast, Rosa *et al*. [85] showed a significant increase of GNDF levels in depressive ($p=0.004$) and manic ($p=0.001$) patients, while euthymic patients matched the control group. Perhaps the difference between methods has generated these conflicting results [74, 85]. Another possibility is the use of pharmacological substances such as mood stabilizers (e.g., valproate and lithium), that possibly increase BDNF and GDNF concentrations.

Finally, it is known that the imbalance between pro- and anti-inflammatory cytokines is involved in the physiopathology of BD [42, 76]. Changes in the profile of certain cytokines, such as tumor necrosis factor alpha (TNF-α) and C-reactive protein, as well as interleukin 1 and interleukin 6, are commonly associated to mood disorders and others psychiatric disorders [76]. Evidence also supports a higher content of free pro-inflammatory cytokines in BD patients, compared to healthy subjects, thus demonstrating a severe inflammatory reaction in these subjects. According to Goldstein *et al*. [88], the chronic inflammatory process is directly related to expression of polymorphic genes and the increase of these pro-inflammatory substances. This sustained effect has an adverse impact in the neuroregenerative ability, or the resilience of important brain areas such as hippocampus, and can also contribute to the neuroprogression of the illness [40]. It is suggested that induction of the inflammatory process through excessive activation of brain microglia mediates the suppression of neurogenic effects in hippocampus, and similarly, blocking the microglial response by tetracycline restores cells in the subgranular region after 35 days [40]. Therefore, a higher concentration of circulating cytokines is implicated in an increase in neurotoxicity [89]. In this state of chronic inflammation, as noted in BD, macrophages remain in the brain to maintain a setting of continuous inflammatory signaling, and this mechanism may be responsible for demyelination, cell adhesion, as well as apoptosis of neurons and glial cells [89]. Thus, the continued use of drugs such as lithium (> than 3 months) seems to act as a braking mechanism for this deterioration process. These drugs appear to act by cross interaction signaling pathways such as adenylate cyclase, tyrosine phosphorylation, and phosphatoinositides, and therefore patients treated do not exhibit the same level of circulating pro-inflammatory cytokines compared to untreated patients [90, 91].

Certain cytokines can vary according to the cycles of the BD (e.g., manic, depressive or euthymic phase) [42]. In that sense there is a state-dependent concentration of different cytokines. The concentration of TNF-α, for example, does not differ across phases of the BD patient [92], although greater immune activation can be sustained during the exchange of depressive to mania cycle [93]. Independently, significantly higher levels of TNF-α are reported in bipolar patients, compared to control group ($p<0.05$) [42]. Similar results are reported by Usmani *et al*. [94], who observed a significant difference in the content of TNF-α in bipolar patients (99.86 ± 10.22 pg/ml), compared to healthy subjects (8.88 ± 2.84 pg/ml), independent of gender ($p>0.05$). On the other hand, interleukin-1 and interleukin-6 are significantly different between depressive bipolar patients (16.85 ± 3.17, e 3.67 ± 1.32pg/ml, respectively) and manic patients (9.54± 2.40 pg/ml, and not reported values, respectively), which in turn were different from the control group (17.65 ± 0.48, e 1.21 ± 0.22 pg/ml, respectively). Interleukin-2 seems to respond to the same pattern as TNF-α, differing only between bipolar and healthy controls.

CONCLUSION

The state of art demonstrates well-defined directions about the pathophysiology of BD. Different modifications are presented and some special traits resulting from the disease can be extracted, for example in cortical activity and on different neuropsychological and motor tasks, differing from patients with other psychiatric disorders. These changes are often associated with pre-existing changes, indicating the relationship between the cognitive decline mechanisms, functional and neuroanatomical changes, as well as abnormal neurotrophic and pro-inflammatory responses. It is, therefore suggested that physiological processes occur differently in bipolar subjects compared to healthy, affecting behavior and brain functions in such patients. Despite the progress, future directions are yet necessary to stablish the best way to neutralize or reverse these events.

LIST OF ABBREVIATIONS

BD = Bipolar Disorder

BDNF = Brain-Derived Neurotrophic Factor

ES = Effect Size

fMRI = Functional Magnetic Resonance Imaging

GDNF = Glial Cell Line-Derived Neurotrophic Factor

IGF-1 = Insulin-Like Frowth Factor 1

PFC = Prefrontal Cortex

TNF-α = Tumor Necrosis Factor Alpha

VEGF = Vascular Endothelial Growth Factor

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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