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REVIEW ARTICLE

A unified model of the pathophysiology of bipolar disorder

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Abstract

This work provides an overview of the most consistent alterations in bipolar disorder (BD), attempting to unify them in an internally coherent working model of the pathophysiology of BD. Data on immune-inflammatory changes, structural brain abnormalities (in gray and white matter), and functional brain alterations (from neurotransmitter signaling to intrinsic brain activity) in BD were reviewed. Based on the reported data, (1) we hypothesized that the core pathological alteration in BD is a damage of the limbic network that results in alterations of neurotransmitter signaling. Although heterogeneous conditions can lead to such damage, we supposed that the main pathophysiological mechanism is traceable to an immune/inflammatory-mediated alteration of white matter involving the limbic network connections, which destabilizes the neurotransmitter signaling, such as dopamine and serotonin signaling. Then, (2) we suggested that changes in such neurotransmitter signaling (potentially triggered by heterogeneous stressors onto a structurally-damaged limbic network) lead to phasic (and often recurrent) reconfigurations of intrinsic brain activity, from abnormal subcortical–cortical coupling to changes in network activity. We suggested that the resulting dysbalance between networks, such as sensorimotor networks, salience network, and default-mode network, clinically manifest in combined alterations of psychomotricity, affectivity, and thought during the manic and depressive phases of BD. Finally, (3) we supposed that an additional contribution of gray matter alterations and related cognitive deterioration characterize a clinical–biological subgroup of BD. This model may provide a general framework for integrating the current data on BD and suggests novel specific hypotheses, prompting for a better understanding of the pathophysiology of BD.

Introduction

Bipolar disorder (BD) is defined by the occurrence of active episodes of mania and depression, which show opposite constellations of disturbances in psychomotricity, affectivity, and thought, along with asymptomatic periods of euthymia [1, 2]. BD is a prevalent, severe, and debilitating psychiatric disorder, and the understanding of its pathophysiology represents a major challenge for contemporary research in psychiatry and neuroscience [1, 3].

In the last decades, a number of robust and consistent alterations have been detected in BD across diverse areas of research, including immune-inflammatory changes, structural brain abnormalities (in gray and white matter), and functional brain alterations (from neurotransmitter signaling to intrinsic brain activity) [4–9]. However, the relationship between these core alterations in BD is complex and still unclear.

Therefore, in this work, we provide an overview of the most consistent findings on BD, along with the results from our work on this topic, attempting to unify them in an internally coherent working model of the pathophysiology of BD.

Data overview on bipolar disorder

Immunological alterations

Evidences of immune dysregulation and inflammation in psychiatric disorders including BD have been accumulated

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since the 1980s, as firstly described by Maes and other Authors, concerning both cytokines and immune cells, in the peripheral circulation and central nervous system [5, 10–15]. In particular, levels or activity of pro-inflammatory cytokines, e.g., interleukin (IL)-6, tumor necrosis factor (TNF)α, interferon (IFN)γ, and other soluble factors such as C-reactive protein (CRP), were found to be consistently elevated in the active phases of BD, mania and depression, with complete or partial normalization during euthymia [16, 17]. Notably, a longitudinal investigation showed that manic episodes were accompanied by state-dependent inflammatory activation (i.e., increased IL-6 and CRP levels) [18]. Moreover, activation of T cells with increased circulating levels of CD4+ T cells and decreased levels of CD8+ T cells, along with activation and increased peripheral levels of monocytes and activation of microglia, have been consistently detected in BD [13, 19–25]. In our previous work, we further specified the T cell alterations in BD, by showing in the peripheral circulation an increase in the early generated CD4+(CD28+) T cells along with a decrease in the differentiated effector CD8+(CD28−) T cells (effector memory, terminal effector memory, and IFNγ-producing CD8+ T cells) [26]. This pattern was strongly associated to BD patients recruited during mania, while less evident in patients recruited during depression or euthymia [26].

Together, these data may suggest that BD is associated to immune activation with a predominant pro-inflammatory profile.

Gray and white matter brain alterations

A large amount of structural neuroimaging data on psychiatric disorders has been accumulated since the 1990s and gray matter (GM) abnormalities were found in BD, although with heterogeneous results [27, 28]. No altered GM volumes were found in first episode and early stage of BD [29, 30]. However, evidence of widespread neuroprogressive loss of GM volume, especially in the frontal areas, has been demonstrated in longitudinal studies and associated with longer illness duration, and this has been related to progressive cognitive deterioration in BD [31, 32].

White matter (WM) abnormalities resulted to be a consistent finding in BD, as shown by several structural imaging studies since the 1990s and diffusion magnetic resonance imaging (dMRI) studies since the 2000s [33]. Increased rate of deep WM hyperintensities was consistently reported in BD [27]. Furthermore, reduced WM volumes were found in BD, even during first episodes [27, 29]. Importantly, widespread WM microstructure alterations (as mainly shown in dMRI data by decreased fractional anisotropy and increased radial diffusivity) were then robustly detected in BD [34–39]. The greater and most consistent WM changes in BD were found in the cingulum (especially anterior cingulum and regions close to the subgenual anterior cingulate cortex, and posterior cingulum) and corpus callosum (especially genu and body), as well as in frontal areas (especially orbitofrontal and subgenual regions), parahippocampal areas, and tracts such as the uncinate fasciculus and fornix, which mostly connect regions of the limbic system [34–39]. In our previous work, we found that widespread WM abnormalities were mainly detectable in patients recruited during the active phases of illness, while WM alterations localized in the anterior midline structures characterized all phases of BD [40]. Moreover, we observed the most consistent WM alterations, as well as deficits of structural connectivity in the anterior midline regions, in patients recruited during mania [26, 41]. Coherently with WM alterations shown in imaging studies, neuropathological data in BD revealed consistent reductions in number or density of oligodendrocytes, along with myelin abnormalities, in anterior brain regions especially [33, 42, 43].

Relationships between white matter and immunological alterations. In our prior work on BD, we firstly detected a specific correlation between WM alterations and the reduction in circulating terminal effector CD8+ T cells (especially in patients recruited during mania) [26]. Notably, such correlation was found only for terminal effector CD8+ T cells, which were reduced in the circulation and are effector cells prone to tissue migration, but not for other cells such as CD4+ T cells [26]. Moreover, WM alterations were also found to correlate with levels of cytokines such as TNFα and IFNγ in BD [44].

Considering all these data, some intriguing similarities as well as specific differences can be noted between BD and multiple sclerosis (MS), the prototype of immune-inflammatory demyelinating diseases of the central nervous system, with potential pathophysiological and psychopathological meanings [5, 26, 45, 46]. Beyond a robust epidemiological association [5, 15, 47–51], a similar immunological pattern can be observed between the two diseases, i.e., the increase in CD4+/CD8+ T cell ratio in the circulation, which is associated with accumulation of effector CD8+ T cells into brain's WM lesions in MS (suggesting that activated CD8+ T cells migrate into the brain where they recognize components of the myelin and contribute to WM damage as effector cells) [19, 26, 52–54]. Coherently, widespread damage in (normal appearing) WM has been reported in both disorders [38, 55, 56]. However, we observed that such WM alterations show a different spatial pattern, with a greater impairment in the anterior brain regions in BD and in the posterior brain regions in MS [57]. Coherently, we also showed that the occurrence of depressive symptomatology in MS was specifically

associated to WM alterations in a cluster mainly encompassing basal ganglia and thalamic areas (including the fornix) that are part of the limbic system, along with a related functional dysconnection of neurotransmitter-related brainstem nuclei [58]. These findings support the possibility of a partial mechanistic overlap in the immune-mediated WM damage between BD and MS, along with the potential role for a specific spatial pattern of WM alterations in the emergence of psychiatric symptomatology.

Collectively, these data may suggest that BD is associated with an immune response sustained by CD4+ T cells that lead to activation of CD8+ T cells and related inflammatory state, and such activated effector CD8+ T cells may migrate into brain tissue where their cytotoxic effects might contribute to widespread WM damage, which most consistently affects tracts connecting regions of the limbic system.

Limbic network alterations

The limbic network (LN) includes the subgenual anterior cingulate cortex and orbitofrontal cortex, along with their connections to the neurotransmitter-related brainstem nuclei, amygdala, hypothalamus, anterior thalamus, and hippocampus, and is involved in the stress-related modulation of homeostasis and neurotransmitter signaling [59–62]. Since the late 1990s, alterations in the LN have been investigated and consistently detected in depressive and bipolar disorders by Drevets, Ongur, Savitz, Mayberg, and other Authors [61, 63, 64]. Specifically, a localized decrement of GM volume was found in the subgenual anterior cingulate cortex and orbitofrontal cortex, which was associated with a reduction in glia without an equivalent loss in neurons, in BD [4, 65, 66]. Increased volume of the amygdala, along with volume reductions in the hippocampus, has been repeatedly detected in BD [4]. Moreover, structural network dysconnectivity (e.g., deficits in clustering and nodal efficiency) was consistently and specifically detected across such limbic regions (including orbitofrontal, cingulate, and hippocampal gyri) in BD [67, 68]. Finally, state-dependent changes in the metabolic activity of the subgenual anterior cingulate and orbitofrontal cortices, along with increased baseline metabolism in the amygdala and hyperactivity of the hypothalamus–pituitary–adrenal (HPA) axis (especially during mania), have been robustly associated with BD [4, 64, 69]. Importantly, the structural damage in the LN in BD seems to be related to metabolic overactivity [4]. Accordingly, inhibition of overactive limbic regions (e.g., inducing a metabolic decrease in the subgenual anterior cingulate cortex and related areas via chronic deep brain stimulation) was found to produce a clinical improvement of depressive symptomatology [64, 70].

Together, all these data might suggest that BD is characterized by an immune-mediated WM damage and its specific localization in the LN may play the core role in the pathophysiology of the disorder.

Stress response, inflammation, and changes in neurotransmitter signaling

Alterations of the LN in BD may have a complex role in the interplay between stress response, inflammation, and neurotransmitter dysregulation [5]. Stress-induced activity in the LN is associated with transient increases in dopamine (DA) and norepinephrine signaling, opioidergic signaling, and HPA axis activity, along with changes in serotonin (5HT) metabolism [71–73]. Moreover, stress response (both stress hormones, such as cortisol or norepinephrine, and sympathetic innervation) modulates immune cell activity, by acutely inducing a Th2 shift in the Th1/Th2 balance, while chronically causing low-grade inflammation characterized by increased pro-inflammatory factors such as IL-6, IFNγ, and TNF [5, 74, 75]. Interestingly, stress system activation can be associated with increased vulnerability to pathogens, especially viral diseases, e.g., a reactivation of latent herpesvirus can occur during stress responses [5]. Accordingly, an association between infection with cytomegalovirus (or also toxoplasma gondii) and depressive or bipolar disorders was reported [5]. Thus, viral reactivation, in presence of immune dysregulation, may contribute to inflammation and brain damage [76]. In turn, pro-inflammatory mediators are able to modulate neurotransmitter signaling [5, 77–79]. Specifically, pro-inflammatory cytokines, such as IFNγ, TNFα, and IL-6, enhance the activity of the indoleamine 2,3-dioxygenase (IDO) enzyme, which diverts tryptophan away from 5HT synthesis and favors the kynurenine pathway [5, 77–79]. This results in decreased availability of 5HT along with production (by activated microglia) of various metabolites, such as the quinolinic acid (able to activate NMDA receptors, potentially inducing excessive glutamate signaling and related excitotoxicity) and kynurenic acid (an NMDA receptor antagonist) [5, 77]. In turn, changes in frontal glutamatergic NMDA-mediated signaling may alter both DA and 5HT signaling (which are mainly reduced or increased by NMDA receptor agonists or antagonists, respectively) [80]. Furthermore, TNF and IL-1 induce the mitogen-activated protein kinases (MAPKs), which increase the expression and function of monoamine transporters, leading to decreased synaptic availability of neurotransmitters such as 5HT and DA [78]. Accordingly, inflammatory stimuli have been shown to induce a decrease in DA release in the basal ganglia, along with reduced activation of the ventral striatum and related emotional blunting, in both healthy and depressed individuals [78].

Coherently, increased levels of inflammatory markers, possibly along with related DA reductions, were associated with functional dysconnection between ventral striatum and ventromedial prefrontal cortex (correlating with anhedonia) and between dorsal striatum and supplementary motor area (correlating with psychomotor inhibition) in depressed patients [81]. However, it is worth noting that decreased availability of 5HT has been shown to induce a functional dysconnection of the 5HT-producing brainstem nuclei only in patients with affective disorders (and not in healthy subjects) [82].

Altogether, these data suggest that stress response and inflammation are physiologically able to induce changes in neurotransmitter availability, and this could pathologically affect the functional architecture of brain activity in BD, potentially in relation to structural alterations of the LN.

Intrinsic brain activity alterations

The functional architecture of intrinsic brain activity revealed various alterations in BD, as shown by resting-state functional MRI studies since the 2000s. Abnormalities in the subcortical–cortical functional connectivity (FC) have been associated with BD, as firstly reported by Anand et al. [83]. Moreover, increased FC between thalamus and sensorimotor cortical areas (along with decreased FC between thalamus and associative frontal cortices) was detected in BD by Anticevic et al. [84] and this finding has been consistently replicated [85–87]. At a network level, a functional dysconnectivity within the default-mode network (DMN) in BD was firstly detected by Ongur et al. in 2010 [88]. Subsequently, functional alterations were also reported in the other main networks, including sensorimotor network (SMN), salience network (SN), and central executive network (CEN), in BD (e.g., [89–93]). However, findings are heterogeneous, at times inconsistent, potentially also reflecting the clinical heterogeneity of BD. Accordingly, our group conducted a series of studies on BD investigating its different phases of illness separately (rather than considering BD overall), aiming to detect distinct brain alterations in mania and depression, which may reflect more closely the underlying pathophysiological features.

Neurotransmitter signaling alterations. In our prior work, we preliminary detected a functional dysconnection of neurotransmitter-related nuclei in BD, with distinct patterns in the different phases of illness [87]. The FC between 5HT-related raphe nuclei (RNi) and basal ganglia-thalamic regions was reduced in mania [87]. Additionally, the FC between DA-related substantia nigra (SNc) and basal ganglia-thalamic regions was reduced in depression (with psychomotor inhibition) [87]. These functional data complemented biochemical and behavioral findings on neurotransmitter signaling in mania and depression. Specifically, decreased 5HT transmission in BD, and in the manic phase especially, as well as decreased DA transmission in the depressive phase, have been reported as the most consistent neurotransmitter finding in BD [6, 94]. Coherently, deficits in 5HT activity have been associated with manic-like symptomatology (e.g., behavioral impulsivity), while deficits in DA activity with depressive-like symptomatology (e.g., motor inhibition) [95–99].

Subcortical–cortical loop alterations. In our previous work, we confirmed the thalamus-SMN hyperconnectivity in our BD sample and extended this finding by showing a distinct pattern of alterations in the active phases of illness [87]. Specifically, the thalamus-SMN FC increased by switching from mainly negative connectivity in healthy subjects to mainly positive connectivity in mania, reflecting an abnormal coupling between thalamus and SMN signals [87]. By contrast, the thalamus-SMN FC increased from mainly negative connectivity in healthy subjects to around-zero connectivity in depression (with inhibited psychomotricity), actually reflecting a decrease in the absolute strength of correlation (i.e., dissociation) between thalamus and SMN signals [87]. Moreover, the thalamus-SMN FC was unchanged in euthymia and, notably, was increased in agitated depression (similarly to mania rather than inhibited depression, suggesting a specific association between thalamus-SMN FC and psychomotor alterations) [87]. Additional subcortical–cortical FC alterations were found in the different BD phases by other Authors: increased FC between basal ganglia and thalamus, and between amygdala and SMN areas (along with decreased FC between amygdala and anterior cingulate cortex) was detected in mania, while increased FC between basal ganglia and SN areas was observed in depression [100–102].

Large-scale network alterations. In our prior work, we found altered topographical distribution in the neuronal variability (i.e., temporal variability of BOLD signal fluctuations, an indirect index of neuronal activity) across the cortex of BD patients, with opposite patterns in the active phases of illness [103]. Specifically, the ratio between neuronal variability in the SMN and DMN (in the ultra-low frequency band slow5 [104]) was increased in mania (i.e., the balance between SMN and DMN was tilted toward the SMN), and decreased in depression (i.e., the SMN/DMN balance was tilted toward the DMN), while no changes in this parameter were found in euthymia [103]. Moreover, we observed an abnormal global signal representation in BD, which was greater in SMN areas in mania while in DMN areas in depression [105]. We also showed reduced intra-network FC within the DMN in mania, while reduced FC within the SMN in depression [41, 90, 106]. Finally, we detected distinct alterations in regional homogeneity and degree of centrality (measures of local and global connectivity, respectively) in the BD phases: regional

homogeneity and degree of centrality (in the ultra-low frequency band slow4 [104]) were decreased in the DMN during mania (deficits of higher frequencies in the DMN were associated with their increase in SMN areas); conversely, regional homogeneity was decreased in the SMN during depression [106]. Notably, all these alterations in intrinsic brain activity coherently correlated with manic and depressive symptomatology in opposite way (interestingly, psychomotor hyperactivity positively correlated with SMN connectivity, while distractibility, which can be considered a deficit in internal thought, negatively correlated with DMN connectivity) [41, 90, 103, 105, 106]. Furthermore, network alterations were reported in the various BD phases by other Authors. Decreased FC within the DMN and increased FC within the dorsal attention network were detected during mania [88, 107]. Mania-inducing brain lesions were found to selectively disrupt functional connections of the associative areas, such as the dorsolateral prefrontal and temporal cortices, or the orbitofrontal cortex [108]. Network hyperconnectivity and greater clustering in the superior frontal gyrus (including the premotor cortex), amygdala, and midbrain (encompassing the DA-related SNc and ventral tegmental area, VTA) have been associated with manic symptomatology [109]. Conversely, decreased amplitude of low-frequency fluctuations in SMN areas (and increased in SN areas) were detected in depression [110]. Increased regional homogeneity was observed in DMN regions in depression [111]. Altered clustering and efficiency in the LN and DMN have been associated with depressive symptomatology [109, 112]. Finally, absence of network alterations was mainly reported during euthymia [113].

Together, these data show that mania might be associated with a functional dysconnection of the 5HT-related RNi, an increase in thalamus-SMN FC toward positive values, and a relative increase in SMN activity along with a decrease in DMN activity (coherently with the negative correlation of RNi-related FC with thalamus-SMN FC and SMN activity, as observed in healthy subjects) [87, 103, 114]. Conversely, depression might be associated with a functional dysconnection of the DA-related SNc, a decrease in thalamus-SMN FC toward around-zero values, and a relative decrease in SMN activity along with an increase in DMN activity (coherently with the positive correlation of SNc-related FC with the absolute value of thalamus-SMN FC and SMN activity, as observed in healthy subjects) [87, 103, 114]. Thus, such findings might suggest that the manic and depressive phases of BD are characterized by distinct functional reconfigurations of intrinsic brain activity, from changes in neurotransmitter signaling to abnormal subcortical–cortical coupling and alterations in network balancing.

Unified model of the pathophysiology of bipolar disorder

Based on the reported data, we propose a unified model of the pathophysiology of BD (Fig. 1).

Damage in the limbic network and alteration of neurotransmitter signaling

We hypothesize that the core pathological alteration in BD is an LN damage resulting in alterations of neurotransmitter signaling. Although heterogeneous conditions can lead to such damage, we suppose that the main pathophysiological mechanism is traceable to an immune-mediated WM damage involving the LN connections, which destabilizes the neurotransmitter signaling.

Immune dysregulation. A dysimmune response with a predominant pro-inflammatory profile occurs in BD [5]. According to the pathophysiological model of prototypical dysimmune diseases, environmental factors (e.g., microbial infections, physical or chemical agents) are supposed to trigger, on a susceptible polygenic background, a predominant and chronic pro-inflammatory activation (e.g., via molecular mimicry or bystander activation of pattern recognition receptors); it has been suggested that similar mechanisms also play a role in BD [5, 115].

White matter alterations. A widespread alteration of WM microstructure is associated with BD [37, 40]. The dysimmune response may lead to migration of immune effector cells, such as activated effector T cells, into brain tissue (along with activation of microglia and increase in pro-inflammatory mediators) and consequent cytotoxic activity on oligodendrocytes and myelin may result in widespread WM damage (similarly to what observed in MS) [5, 26, 54, 56, 57].

Immune-mediated white matter damage in the limbic network and destabilization of neurotransmitter signaling. A concomitant stress-related limbic overactivity is associated with BD [4, 5, 64]. This could play a role in the resulting spatial pattern of the immune-mediated WM damage, as characterized by greater involvement of the LN [37, 40, 41, 57]. Hypothetically, an LN hypermetabolism may divert the cerebral blood flow, along with the pro-inflammatory cells/mediators, onto its hyperactive regions. This may result in a (immune-mediated) structural alteration in such (stress-related) LN, mainly encompassing the subgenual anterior cingulate cortex, orbitofrontal cortex, and their reciprocal connections with the subcortical areas and neurotransmitter-related brainstem nuclei [4, 61, 62]. Thus, such structural alterations in the connections of LN may result in correspondent functional alterations of the neurotransmitter-related nuclei [58], destabilizing the neurotransmitter signaling

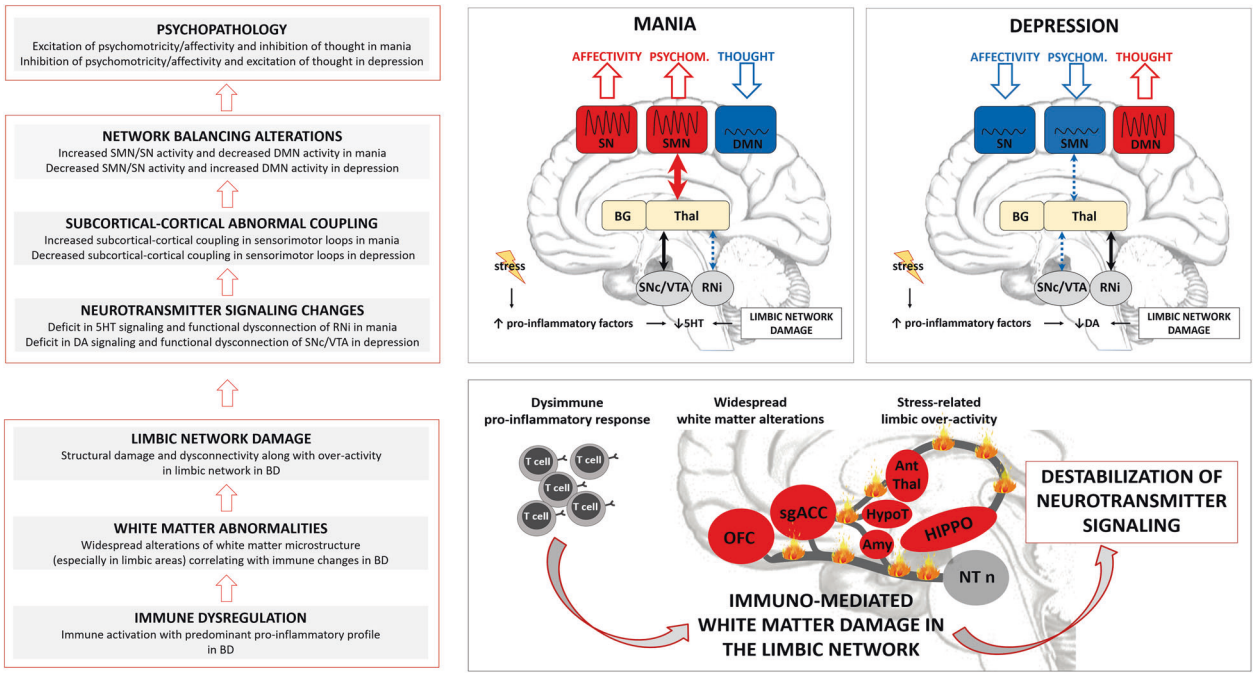

Fig. 1 Unified model of the pathophysiology of bipolar disorder. *Damage in the limbic network and alteration of neurotransmitter signaling (lower part).* According to the model, the core pathophysiological mechanism in BD could be traceable to an immune-mediated white matter alteration resulting in a limbic network damage, which destabilizes the neurotransmitter signaling increasing its susceptibility to perturbations. *Functional reconfiguration of intrinsic brain activity and psychopathology (upper part).* Changes in neurotransmitter signaling (triggered by heterogeneous stressors and inflammatory states onto a damaged limbic network) may then lead to phasic reconfigurations of intrinsic brain activity, from abnormal subcortical–cortical coupling to changes in network balancing. Finally, this may clinically manifest in the psychopathological alterations of mania and depression. *Abbreviations*: BD bipolar disorder, OFC orbitofrontal cortex, sgACC subgenual anterior cingulate cortex, Amy amygdala, HypoT hypothalamus, Ant Thal anterior nuclei of thalamus, HIPPO hippocampus, NT n neurotransmitter-related nuclei, DA dopamine, 5HT serotonin, SNc/VTA substantia nigra/ventral tegmental area, RNi raphe nuclei, BG basal ganglia, Thal thalamus, SN salience network, SMN sensorimotor network, DMN default-mode network.

and increasing its susceptibility to perturbations by various stressors from the external or internal environment.

Functional reconfiguration of intrinsic brain activity and psychopathology

In accordance with our recently proposed three-dimensional model of brain functioning and behavioral/phenomenological patterns [9], we then suggest that changes in neurotransmitter signaling (potentially triggered by heterogeneous environmental stressors onto a structurally-damaged LN) lead to phasic (and often recurrent) reconfigurations of intrinsic brain activity. This might represent a pathological re-setting of the pre-existing baseline in intrinsic brain functioning (and related temperamental features), resulting in distinct changes in network balancing that alter the basal pattern of input/output processing. Finally, this may clinically manifest in the complex psychopathology of manic and depressive states of BD. See Supplementary Material and our previous work [9].

Stress response, inflammation, and changes in neurotransmitter signaling. The occurrence of a stress response, which is facilitated by a hyper-(re)active stress system and able to trigger the active episodes of BD, can cause a prolonged increase in pro-inflammatory factors, such as IL-6, IFNγ, and TNF (e.g., a stress-related Th2 shift in the Th1/Th2 balance may favor a reactivation of latent infection of viruses, like herpesviruses, with related pro-inflammatory rebound) [5, 74]. This, in turn, can induce a reduction of 5HT availability (e.g., via IDO activity and kynurenine pathway enhancement) and/or DA availability (e.g., via MAPK activity enhancement) [5, 77, 78]. A decrease of neurotransmitter availability in a structurally-damaged LN may then lead to a functional dysconnection of the neurotransmitter-related nuclei, finally resulting in functional reconfigurations of intrinsic brain activity.

Changes in neurotransmitter signaling, functional reconfigurations of intrinsic brain activity, and psychopathological states. A reduction of 5HT availability may lead to RNi dysconnection (e.g., [87]). This may result in an abnormal neuronal coupling in the sensorimotor subcortical–cortical loops (e.g., [87]). In turn, this may lead to increased levels of intrinsic activity within the SMN and SN at the expense of the DMN (and related shift toward slow4) (e.g.,

[41, 88, 90, 103, 105–108]). This may over-tune the intrinsic brain activity onto the current environment and clinically manifest in a manic state with excited psychomotricity and affectivity as well as inhibited thought [9]. Conversely, a reduction of DA availability may lead to SNc/VTA dysconnection (e.g., [87]). This may result in a neuronal decoupling in the sensorimotor subcortical–cortical loops (e.g., [87]). In turn, this may lead to decreased levels of intrinsic activity within the SMN and SN with relative increase in the DMN (and related shift toward slow5) (e.g., [103, 105, 106, 110, 111]). This may de-tune the intrinsic brain activity from the current environment and clinically manifest in a depressive state with inhibited psychomotricity and affectivity as well as excited thought [9]. Furthermore, other combinations of changes in neurotransmitter signaling may also occur, resulting in other specific reconfigurations of intrinsic brain activity and related psychopathological states [9, 116]. See Supplementary Material.

Additional pathophysiological factors and clinical–biological subgroups of illness

Finally, we suppose that additional pathophysiological factors may result in clinical–biological subgroups of BD. According to our model, the typical form of BD is primarily characterized by immune-inflammatory factors and related WM damage mainly encompassing the LN. Consequent phasic reconfigurations of intrinsic brain activity might superimpose onto structurally-preserved GM, manifesting in the psychopathological alterations during the active episodes and remission during euthymia. The extent of LN damage could be related to episode recurrence (with lesser or greater LN damage in the occurrence of one/few or multiple episodes, respectively). This may result in the phasic-recurrent course of illness. On the other hand, we suggest that a subgroup of BD might be characterized by additional neurodevelopmental and/or neurodegenerative factors (e.g., alterations in synaptic plasticity) that result in GM loss [4, 31]. Thus, the reconfigurations of intrinsic brain activity might superimpose onto structurally-damaged GM, so that the psychopathological alterations during the active episodes might be associated with impoverished contents of thinking and behavior that persist even during euthymia. The extent of GM damage could be related to cognitive deterioration (with lesser or greater GM damage in the secondary presentation (after recurrent episodes) or primary presentation (since the first episode) of cognitive deterioration, respectively). This may result in a tendency to a progressive course of illness. Thus, such distinct clinical–biological subgroups of BD with predominant relapsing-remitting or progressive patterns (partially mirroring the subtypes of MS) [54, 117] might be related to a predominant contribution of immune-inflammatory or neurodevelopmental/neurodegenerative pathophysiological factors.

See Supplementary Material for a discussion of various critical issues (e.g., [118–120]) and future directions.

Conclusions

Our unified model might provide a framework for integrating the current data on BD and suggest novel specific hypotheses that can be tested in future investigations, prompting for a better understanding of the pathophysiology of BD. In turn, this could provide novel diagnostic markers and therapeutic targets, opening the door to potential new strategies of therapy.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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