A Psychophysiological Model of State Switching in Bipolar Disorder Based on the Salience Network

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Abstract

Bipolar disorder is a highly burdensome and refractory mental disorder, affecting individuals, families, and society. The challenge in bipolar disorder is that the treatment targeting the depressive state often carries the risk of inducing manic state, and vice versa, with the frequency of these alternating cycles often indicating the severity of the illness. Therefore, reducing the frequency of states switching in bipolar disorder patients and gradually achieving a stable state are crucial for effective treatment. The purpose of this study is to propose a dynamic process model of bipolar disorder states switching in order to further understand the treatment, patterns of occurrence and development, and pathophysiological mechanisms of bipolar disorder. Considering the remarkable potential of the salience network in brain switching, we have anchored the model on the functionality of the salience network and analyzed and demonstrated the pathways involved in bipolar disorder states switching within the framework of "physiological-psychological-neurological". By focusing on the salience network, this model provides valuable insights into the mechanisms underlying bipolar disorder states switching.

Full Text

Preamble

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Abstract

Bipolar disorder represents a highly burdensome and treatment-resistant mental illness that profoundly affects individuals, families, and society. A central challenge in managing bipolar disorder lies in the therapeutic paradox: interventions targeting depressive symptoms risk precipitating manic episodes, while treatments for mania may trigger depressive states, with the frequency of these alternating cycles often serving as an indicator of illness severity. Consequently, reducing the frequency of state transitions and gradually achieving mood stabilization constitute crucial therapeutic goals. This study proposes a psychophysiological model of state switching in bipolar disorder, anchored in the functionality of the salience network—a brain system with remarkable potential for mediating neural state transitions. By focusing on the salience network, this model analyzes and demonstrates the pathways involved in bipolar disorder state switching within a psychophysiological framework, offering valuable insights into treatment strategies, illness trajectories, and pathophysiological mechanisms.

Introduction

Bipolar disorder (BD) is a severe mental illness that imposes substantial burdens on individuals, families, and society [1-4]. Despite extensive research, the underlying mechanisms remain incompletely understood, and the clinical presentation is highly complex. Rather than manifesting as static conditions, BD symptoms involve cyclical alternations between distinct depressive and manic symptom clusters [5, 6]. Our previous work has demonstrated that manic and depressive states in BD may be associated with different pathological mechanisms [7-9], suggesting that distinct treatment and intervention strategies should be employed for different illness phases. However, the fundamental therapeutic challenge lies in the propensity of patients to transition between depressive and manic states [10]. Treatments targeting depression frequently carry the risk of inducing mania, and vice versa [10-15]. Moreover, the frequency of these alternating cycles often correlates with disease severity [16, 17].

Despite its importance as a key feature of BD, the processes and mechanisms

underlying symptom switching remain poorly understood—a knowledge gap considered the "holy grail of BD research" [12]. While numerous factors influencing state changes have been identified over recent decades [18, 19], the relationships among these factors and their collective role in driving BD state transitions remain unclear. Therefore, this work reviews the most consistent findings on BD state switching, including results from our own research, and attempts to unify them into a comprehensive psychophysiological model. This model may provide a common neurological basis applicable across different BD subtypes.

Potential Mechanisms of State Switching in Bipolar Disorder

Genes Investigations of BD pathophysiology must constantly acknowledge its strong genetic foundation. The genetics of BD have been extensively reviewed previously [20, 21], and numerous genome-wide association studies (GWAS) have identified many risk genes [22-27]. Our genetic imaging research has confirmed risk genes such as ANK3 and revealed that clock genes like RORB begin influencing circadian rhythms during childhood and adolescence [28]. This study reviews several risk genes specifically associated with state switching in BD and elucidates their impact on illness cycling.

Research has found that ANK3, one of the most prominent BD risk genes, provides insights into the emotional transitions characteristic of the disorder. For example, mice with heterozygous or homozygous ANK3 deletions exhibit manic-like behaviors at baseline, such as hyperactivity, while displaying depression-related behaviors under chronic stressors like repeated social defeat [29, 30]. Another risk gene contributing to mood transitions is Synaptotagmin-7 (Syt7). Shen et al. demonstrated that Syt7 deficiency produces behavioral fluctuations in mice, characterized by prolonged immobility under light conditions and reduced immobility under dark conditions across various behavioral tests [31], mimicking the circadian rhythm disturbances observed in BD patients. Notably, Syt7 knockout mice also show disrupted circadian rhythms [31], which are particularly relevant clinically as they often precede mood transitions. Single nucleotide polymorphisms (SNPs) in circadian rhythm genes (Period3 and ARNTL) and circadian output rhythm control genes (CLOCK and GSK3β) have been associated with BD-related symptoms [32, 33]. Additionally, the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene, while not specifically linked to circadian rhythms, has been particularly associated with rapid cycling in BD [34, 35]. These genes collectively enhance our understanding of state switching mechanisms.

In BD, genetic factors may influence emotional switching through two primary pathways. First, genes regulate the perception of internal and external stimuli in patients, broadly influencing emotional, cognitive, motivational, and physical manifestations [36-38]. Second, genes mediate neurotransmitter function. Aberrant gene expression affects the production, release, transmission, binding, and reuptake of specific neurotransmitters, thereby influencing brain development, behavior, and psychopathology [39-42]. Exploring these processes deepens our

understanding of BD pathophysiology.

Psychological Events The etiology and clinical course of BD are believed to be determined by interactions between genetic factors and diverse environmental events [43], including infections, climate changes, childhood trauma, and social support [44-47]. We emphasize the impact of psychological events—such as unemployment, examinations, and interpersonal relationship changes, along with any acute stressors that may induce emotional responses. Studies have found that positive psychological events and goal achievement often precede manic episodes, while negative events frequently associate with depression [48, 43]. Our research has also revealed that BD patients in different states exhibit distinct neural responses to identical emotional stimuli [8].

Psychological events can directly trigger emotional changes and, more importantly, may disrupt neurotransmitter systems [49], leading to mood cycling patterns that align with psychiatric disorder manifestations such as BD [50]. A report in *Science* confirmed that neurotransmitter transitions in the adult brain can be achieved through natural sensory stimuli, further regulating behavior [51]. The kindling hypothesis of mood disorders suggests this process may become increasingly spontaneous over time [52]. Furthermore, stress-induced alterations in the immune system can impact neurotransmitter systems and functional brain networks through immune dysregulation and subsequent inflammation [49]. Consequently, unexpected psychological events in the lives of individuals with BD serve as strong predictive factors for state transitions and carry significant treatment implications.

Neurotransmitters The neurotransmitter hypothesis of BD state switching is well-established. We have summarized several key neurotransmitters highly relevant to BD mood states and categorized them as predictive factors for mood transitions. Neurotransmitters such as dopamine (DA), serotonin (5-HT), and norepinephrine (NE), which are involved in antidepressant mechanisms, can significantly induce manic emotions. For instance, clinical studies have demonstrated that tricyclic antidepressants, ketamine, and levodopa effectively alleviate depressive symptoms by increasing 5-HT, NE, or DA levels [53-55]. However, when used in BD treatment, these medications can induce transitions to manic states to varying degrees [12]. Another key neurotransmitter that can induce transitions from mania to depression is acetylcholine. Van Enkhuizen et al. simulated depressive states in BD mice by elevating acetylcholine levels [15]. In addition to medication effects, the aforementioned risk genes and life events can also induce neurotransmitter changes, thereby mediating state transitions.

Further investigation is needed to explore how neurotransmitter dysregulation mediates BD state changes. We posit that neurotransmitter dysregulation leads to abnormalities in large-scale functional brain networks, including both within-network dysregulation and between-network disconnectivity. These network abnormalities further characterize the diverse symptoms observed in BD patients.

Large-Scale Functional Brain Networks

Since B. T. Thomas Yeo's discovery of functional networks inherent in the human cerebral cortex through intrinsic functional connectivity [56], growing evidence has demonstrated that emotional and cognitive functions are closely related to these intrinsic networks [57-60]. Rather than being limited to specific cortical or subcortical regions, Luiz Pessoa suggested that emotions should be understood through the interaction of large-scale networks [61].

Several researchers have characterized different BD states through functional coupling between networks. A recent review of BD mechanism studies found that combinations of different brain network activity states may produce distinct symptom sets corresponding to refined BD subtype classifications [62]. Specifically, when default mode network (DMN), sensorimotor network (SMN), and salience network (SN) activities are consistently enhanced, a manic state emerges, while consistent diminution of all three activities leads to depression. Furthermore, reduced DMN activation combined with increased SMN and SN activation produces manic symptoms with negative thinking, whereas the opposite pattern yields depressive symptoms with euphoric thinking. These results suggest that changes in large-scale brain networks may be responsible for symptom recurrence in BD.

While limited validation exists for these hypotheses, BD patients unquestionably exhibit impairments in large-scale brain networks. Our previous studies have demonstrated extensive structural and functional abnormalities in networks including the DMN, SMN, SN, central executive network (CEN), and language network (LaN) [63-65]. Notably, SN abnormalities profoundly affect the balance between brain networks [65]. The distribution of these networks is visualized in Figure 1 [Figure 1: see original paper].

We conducted a comprehensive review of potential mechanisms influencing state transitions in BD across physiological, psychological, and neural levels. We integrated these multifaceted factors and established their relationships in BD state switching (Fig. 2) [Figure 2: see original paper]. We argue that BD state switching results from a combination of multiple factors mediated by anomalous coupling between different functional networks. To further reveal the dynamics and processes of BD state switching, we propose a model based on the SN.

Modeling of State Switching in Bipolar Disorder

SN: The Core Network in BD

Abnormal SN function is frequently observed in BD patients [64], and a causal analysis across multiple disorders found that increased self-inhibitory connectivity of the SN represents a disorder-specific pattern for BD [67]. A study on functional segregation, integration, and balance in BD networks also identified the SN as a network that effectively predicts BD mood symptoms [68].

More importantly, the SN demonstrates exceptional potential for "brain switch-

ing." Since Vinod Menon proposed the triple network (TPN) model [69], it has been validated and widely applied in mental disorder research [70-73]. The TPN model primarily describes relationships between the SN, CEN, and DMN, proposing that the SN facilitates switching between the DMN and CEN through key nodes such as the anterior insula (AI) and anterior cingulate cortex (ACC) [69]. Researchers have also identified unique von Economo neurons present only in the SN, located in the AI, which facilitate network switching [74-77]. Due to the AI's prominence, studies often focus on cortical nodes when examining SN function. However, since its discovery as an important functional network in humans, the SN has been recognized as comprising both cortical and subcortical interactions [78]. A comprehensive consideration of interactions among various SN brain regions and their roles in information input and output enhances our understanding of how SN abnormalities impact mental disorders.

The SN includes key cortical and subcortical regions such as the AI, dorsal anterior cingulate cortex (dACC), thalamus, amygdala, substantia nigra (SuN), and ventral tegmental area (VTA), which are involved in perceiving and responding to homeostatic demands [78, 76, 69, 75]. The insular cortex plays a central role in detecting behaviorally relevant stimuli and coordinating neural resources, with atypical involvement of specific insular subregions representing a characteristic feature of many neuropsychiatric disorders [76]. For example, the AI receives incoming signals from both internal bodily sensations and external stimuli, performing relative salience detection to determine brain resource allocation [76, 79]. In BD patients, AI abnormalities can disturb salience detection, altering functional coupling across the entire brain. The ACC connects to motor systems and receives signals from the AI to output responses related to visceral, autonomic, behavioral, and cognitive processes, constituting the behavioral phenomenology of BD [62, 73, 75].

According to the TPN model, weakened insula-cingulate connectivity can lead to aberrant involvement of the frontoparietal CEN, impairing adaptive cognitive and goal-directed behaviors. Significant events affecting the DMN can alter self-referential mental activity. Furthermore, the SN significantly influences the LaN [73, 80]. Researchers have found that disrupted excitatory-inhibitory balance in the cingulate-insular, lateral prefrontal cortex, and superior/middle temporal regions at the synaptic level can cause structural and functional changes locally and across networks, impacting the dynamic representation of linguistic elements [80]. According to DSM-5, language disturbance is also a prominent diagnostic feature in BD. The representation of BD symptoms by SN subcortical nodes is more closely related to neurotransmitters. The VTA, rich in DA and 5-HT neurons, serves as a significant source region within the dopaminergic pathway, as does the SuN. Studies have shown that enhanced dopamine signaling strengthens thalamus-SMN coupling and increases SMN activity [81, 82]. In addition to DA regulation, the thalamus can directly receive sensory inputs from the external environment and send outputs to bodily motor systems [83, 84]. Threat salience stimuli in the external environment are detected by the amygdala, producing corresponding emotional and behavioral responses

[85, 86]. Similar to the VTA, the amygdala is also a site of 5-HT production, with studies indicating a close relationship between depression severity and decreased amygdala 5-HT [87]. Increased 5-HT levels can inhibit DMN activation [88]. Additionally, the amygdala, VTA, and ACC are all components of the reward circuitry. Strong signals from the amygdala and VTA can be transmitted to the SMN via the ACC, and excessive SMN activation can lead to highly motivated impulsive behavior [89]. The VTA and SuN project to the frontal cortex via the mesocortical pathway and substantia nigra reticularis, respectively, where inhibitory or excitatory dopaminergic modulation of prefrontal regions can influence higher cognitive functions [90].

In summary, we hypothesize that the SN is the core network mediating state switching in BD. Functional abnormalities in the SN lead to distorted perception of external and internal information in BD patients, accelerating symptom cycling and disruption. Accompanying neurotransmitter imbalances further contribute to this process, with medication often used to counteract these imbalances. Notably, these processes are influenced by genetic factors, as susceptibility genes modulate neurotransmitter systems and brain sensitivity to internal and external stimuli. This model is described in detail below.

Psychophysiological Model of State Switching in Bipolar Disorder Based on SN

The schematic diagram of the model is shown in Figure 3 [Figure 3: see original paper].

Under genetic regulation, the SN receives stimuli and neurotransmitter modulation from internal and external sources, affecting major brain functional networks and facilitating BD state switching. Positive internal and external stimuli prompt the SN to cause hyperactivation of the CEN, SMN, LaN, DA-related frontal regions, and suppression of DMN activity, leading BD patients into a manic state. Conversely, negative stimuli induce a depressive state. Stimuli of varying potency can cause disorganization of BD states (mixed or rapid cycling). Medications can provide direct modulation of these pathological processes.

Specifically, abnormal SN functioning leads to impaired significance detection in BD patients, making them more likely to detect negative or positive events in daily life and perceive them as highly salient information. Risk genes regulate physiological processes such as susceptibility to stimuli and neurotransmitter synthesis. When BD patients experience positive internal and external stimuli, the AI-ACC pathway promotes excessive SMN activation and shifts the DMN-CEN balance from a neutral state to low DMN activity and overactive CEN. Simultaneously, disrupted balance between the AI-ACC and superior/middle temporal areas and lateral prefrontal cortex leads to language network dysfunction. The thalamic pathway and VTA-SuN-thalamic pathway together contribute to SMN hyperactivation. The VTA-SuN pathway causes excessive prefrontal cortex activation involved in cognitive functions. These regions are not

an intrinsic brain network but rather specific frontal lobe areas associated with DA. Amygdala-VTA influence on the ACC also facilitates SN-mediated shifting of brain networks into a state of excessive activation, resulting in transition to mania (Fig. 4A [Figure 4: see original paper] right). Conversely, when BD patients experience negative internal or external events, these pathways inhibit corresponding brain activity, leading to transition to depression (Fig. 4A left). When conflicts exist between internal and external information (e.g., positive external events with negative internal experiences, or vice versa), BD patients may enter a mixed state or experience rapid cycling between mood states.

Additionally, pharmacotherapy regulates physiological processes such as neurotransmitter synthesis, exerting direct and wide-ranging effects on BD patients, though often accompanied by the risk of inducing state switching.

According to this model, BD state transitions are dynamic processes requiring continuous accumulation of internal and external inputs. When cumulative stimuli reach a critical threshold, they trigger a significant shift in SN salience detection (from negative to positive salience or vice versa), precipitating BD state transitions. This suggests that depressive and manic phases are not discrete states, but rather represent a continuous process (Fig. 4B). We therefore speculate that a sensitive period may exist for state transitions between stable depressive and manic states in BD patients, accompanied by greater risk of accelerated switching (Fig. 3B). This sensitive period may manifest as a mixed-symptom phase or a symptomatic remission period, depending on SN functional status. Previous studies have indicated that despite abnormal functional connectivity in motor areas, DMN, and CEN in euthymic BD patients, normal SN function may mediate entry into a remission state [91].

Clinical Implications and Future Directions

The strengths of this model lie in its comprehensive integration of physiological, psychological, and neural perspectives, elucidating the pathological processes underlying BD state transitions and their correspondence with major clinical manifestations. Located centrally in the brain and comprising key cortical and subcortical structures, the SN serves as a natural bridge connecting various functional regions (Fig. 1) [Figure 1: see original paper]. Without anchoring the model to the SN, providing a comprehensive description of BD state transition pathophysiology would be challenging.

Reducing BD state transition frequency and achieving gradual stability has long been a therapeutic challenge. This model reveals that external events influence BD state changes through multiple pathways. We therefore consider external events to be important triggering factors in BD state transitions. The atypical perception of external stimuli by the SN, regulated by genetic factors, serves as the catalyst for these transitions. Consequently, treating BD patients requires special attention to life events. Creating different types of events could serve as an adjunctive approach to counteract BD episodes and help patients

gradually achieve stable relief. For instance, recent research has shown that sleep deprivation enhances amygdala-ACC connectivity, leading to improved mood in individuals with depression [92]. Furthermore, pharmacological treatment for BD patients should consider practical life aspects and be adjusted flexibly.

Our model also deduces a sensitive period of state switching during BD development, which could benefit clinical management. Due to increased transition risk during this sensitive period, treatment approaches should be cautious, conservative, individualized, and promptly adjusted. For euthymic BD patients, treatment focus can shift toward stabilizing and maintaining SN function rather than continuing medication solely targeting depressive or manic symptoms. In ethically approved cases, non-pharmacological treatments such as psychotherapy or transcranial magnetic stimulation (TMS) could be utilized to indirectly improve SN function.

In the future, this model may be expanded to other psychiatric disorders. Any psychiatric condition can be described as a transition from normal to pathological states, and this model may provide valuable insights for developing pathological transition models for other disorders.

However, we currently lack a precise description of the timing of BD patient state transitions. The exact moment when SN salience prediction changes and subsequently mediates state transitions remains unclear. While we have identified a sensitive period, this is still insufficient for fully understanding BD mechanisms. Further research is needed to achieve a more comprehensive understanding of BD and its dynamics. Future studies should focus on identifying the sensitive period in BD, applying methods such as machine learning to individualize classification and identify sensitive periods in patients, which could have positive treatment implications.

Finally, our model focuses specifically on the processes and mechanisms of state switching in BD patients, which limits its ability to provide a comprehensive description of all BD pathophysiological mechanisms. In the future, various BD development models should be constructed and synthesized to achieve a better understanding of the disorder.

Conclusions

We have proposed a psychophysiological model of BD state switching based on SN functionality. This model provides a detailed description of the pathways involved in transitions between depressive and manic states and infers a sensitive period for state switching. We emphasize the significant role of psychological events as triggering factors. Our model contributes to a better understanding of the underlying mechanisms, diagnosis, treatment, and prediction of BD.

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Author Contributions

Conception and design of the study: G.Z. and Y.Z. Drafting the manuscript or figures: G.Z. Reviewing and commenting the manuscript: Y.Z. Critical revision of the manuscript: all authors. Funding acquisition: Y.Z.

Competing Interests

The authors declare no conflicts of interest.

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Figure Legends

Fig.1 Distribution of major networks in the brain. Abbreviation: SN salience network, DMN default mode network, CEN central executive network, SMN sensorimotor network, LaN language network. And the brain maps were built by Surf Ice (https://www.nitrc.org/projects/surfice).

Fig.2 The relationship between factors affecting state switching in BD.

Fig.3 The psychophysiological model of state switching in BD based on the SN. Under genetic regulation, SN receives stimuli and neurotransmitter modulation from internal and external sources, affecting major brain functional networks and functional areas and facilitating BD states switching. Positive internal and external stimuli prompted the SN to cause hyperactivation of the CEN, SMN, LaN, DA-related frontal lobes and suppression of DMN activity, and patients with BD entered a manic state. Conversely, BD patients enter a depressive state. Stimuli of different potency cause disorganization of the BD states (mixed or rapid cycling). Medicines can provide direct modulation of these pathologies. Abbreviation: SN salience network, AI anterior insula, ACC anterior cingulate cortex, Tha thalamus, SuN substantia nigra, VTA ventral tegmental area, DA dopamine, 5-HT serotonin, DMN default mode network, CEN central executive network, SMN sensorimotor network, LaN language network, DA-Frontal frontal brain regions associated with dopamine, + positive, - negative.

Fig.4 Switching between depression and mania in BD is a continuous process. (A) SN regulates the activity of major brain networks. Depressive state on the left, manic state on the right. (B) There is a switch-sensitive period during the switch between depression and mania in BD patients. This period is accompanied by a greater risk of switching. Abbreviation: SN salience network, DMN default mode network, CEN central executive network, SMN sensorimotor network, LaN language network, DA-Frontal frontal brain regions associated with dopamine.

Note: Figure translations are in progress. See original paper for figures.