Neurosci. Bull. January, 2025, 41(1):181–185
https://doi.org/10.1007/s12264-024-01298-9

www.neurosci.cn
www.springer.com/12264

INSIGHT

Constructing A Theoretical Model to Bridge Neural Transition with a State Switch in Bipolar Disorder

Xiaonan Guo[1] · Lizichen Chen[2] · Jianbo Lai[1,4] · Shaohua Hu[1,3,4,5,6,7,8]

Received: 12 March 2024 / Accepted: 3 July 2024 / Published online: 12 September 2024

Reward or stress, which exists extensively, causes resilient emotional fluctuations under common situations. However, reward or stress is a typical trigger for manic or depressive episodes of bipolar disorder (BD), which is corroborated by psychological theory, biological findings, and psychosocial treatment approaches [1, 2]. During an episode of BD, the affective aberration can be persistent and switchable, accompanied by opposite constellations of cognitive and psychomotor symptoms. Characterized by uncontrollable mood ranging in severity, duration, and polarity, to disentangle the pathophysiology mechanism of BD is to delineate the mystery of affective fluctuations driven by reward or stress.

Biomarkers that pervade various diseases, however, even with the assistance of machine learning, are scarcely well-defined in psychiatric disorders [3]. Consequently, complicated models have been postulated to feature the mood longitudinally in individuals with BD, including Biological Rhythms Models, Discrete-Time Random Models, and Two-Dimensional Models [4]. However, the existing mathematical models are mainly focused on the mood of a pathological state, ignoring measurable neural substrates underlying the state switch.

Recent advances have illuminated the pathophysiology of BD with abnormality in the prefrontal-striatal circuit. Intriguingly, a model associating mood instability with striatum-mediated reward dysregulation has been proposed, incorporating biological indicators into a computational approach [5]. Mason *et al.* reconciled behavioral approach system theory (i.e., reward hypersensitivity) with the blunted reward sensitivity findings in some research. They argue that the elevated mood bias drives hypersensitivity to reward during manic episodes and hyposensitivity to reward during depressive episodes, which possibly explains the distinct behavioral phenotype of mania and depression in BD [5]. Empirical evidence suggested a propensity towards physiological changes in mood, which can be recognized as the degree to which mood induction biases reward valuation, as inferred from alterations of striatal responses and preference for options encountered during elevated moods [6]. Theoretically, when this propensity escalates to extremes, it resembles the phenotype of individuals with BD. During manic episodes, the metabolism increases in striatal regions [7]. In patients with acute mania, the ventral striatum exhibits hyperactivation in response to the omission of reward outcomes even with mood stabilizers, compared to healthy

Xiaonan Guo and Lizichen Chen contributed equally to this work.

✉ Jianbo Lai
laijianbo@zju.edu.cn

✉ Shaohua Hu
dorhushaohua@zju.edu.cn

1 Department of Psychiatry, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

2 Department of Engineering Mechanics, Zhejiang University, Hangzhou 310027, China

3 Nanhu Brain-computer Interface Institute, Hangzhou 311100, China

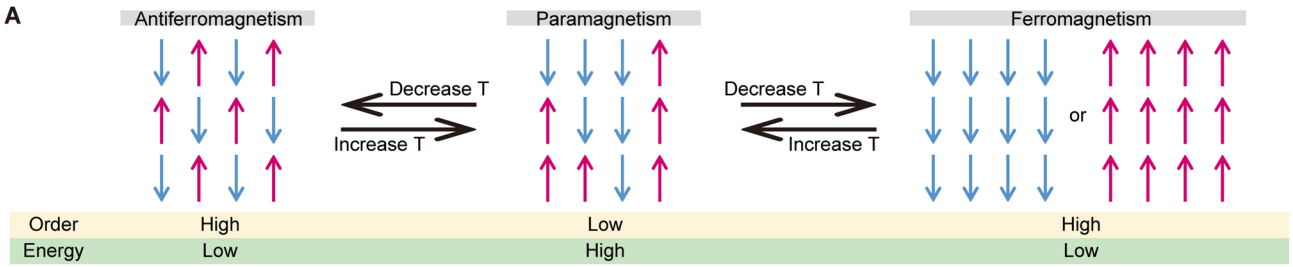
4 The Zhejiang Key Laboratory of Precision Psychiatry, Hangzhou 310003, China

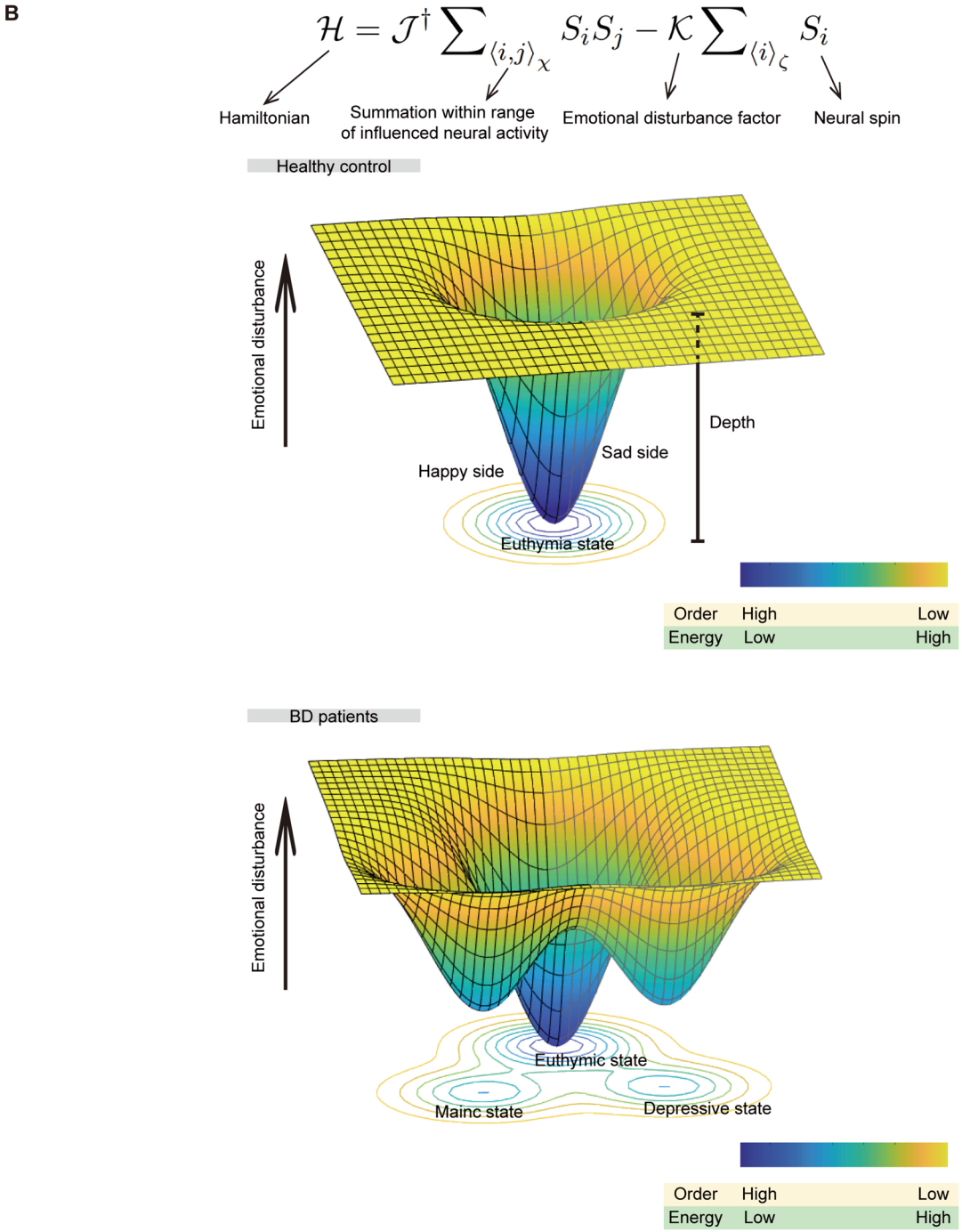
5 MOE Frontier Science Center for Brain Science and Brain-Machine Integration, Zhejiang University School of Medicine, Hangzhou 310003, China

6 Brain Research Institute of Zhejiang University, Hangzhou 310003, China

7 The State Key Lab of Brain-Machine Intelligence, Zhejiang University, Hangzhou, China

8 Zhejiang Engineering Center for Mathematical Mental Health, Hangzhou 310003, China


A
Antiferromagnetism
Paramagnetism
Ferromagnetism
Decrease T
Increase T
Decrease T
Increase T
or
Order High Low High
Energy Low High Low


B
$\mathcal{H} = \mathcal{J}^{\dagger} \sum_{\langle i,j \rangle_{\chi}} S_i S_j - \mathcal{K} \sum_{\langle i \rangle_{\zeta}} S_i$
Hamiltonian
Summation within range of influenced neural activity
Emotional disturbance factor
Neural spin
Healthy control
Emotional disturbance
Depth
Sad side
Happy side
Euthymia state
Order High Low
Energy Low High
BD patients
Emotional disturbance
Euthymic state
Mainc state
Depressive state
Order High Low
Energy Low High

◂**Fig. 1** A theoretical model to bridge neural transition with state switch in bipolar disorder. **A** Paradigm of magnetization indicated by spin under a certain temperature (T). **B** Emotion Valley as a framework for the symptom fluctuations in healthy control and BD patients. In the equation, $J^{\dagger}$ can be positive or negative (positive for the euthymic state, negative for the morbid emotion state). Under emotional disturbance, a healthy control can become happy (left side) or sad (right side) in the euthymic valley, while a BD patient tends to roll in the manic or depressive valley, allowing the state to switch.

controls [8]. In unmedicated hypomania-prone patients, striatal activation associated with reward value and prediction error is stronger in response to cues and outcomes, respectively [9]. In contrast, in medication-free patients with BD in depressive episodes, hypoactivation of the ventral striatum is detected both in 18F-fluoro-deoxyglucose positron emission tomography scans [10] and during loss anticipation in functional magnetic resonance imaging (fMRI) [11], compared to healthy controls. Of note, the severity of BD is significantly associated with reduced activation for wins compared with losses in the ventral striatum [12]. Thus, considering the crucial role of the ventral striatum in motivation control and affective value regulation, the aberrative state-specific activation of the ventral striatum is potentially implicated in fluctuations of emotions and behavioral styles. However, due to the confounding factors of medication as well as comorbid disease (e.g., substance abuse), and constricted trials examining the ventral striatum, interpretation of ventral striatum warrants caution.

Here, considering the state-specific activation in the ventral striatum, we advocate another novel theoretical model to bridge neural transition with the state switch in individuals with BD, which explains both the variability and the persistence of the mood state.

The Ising model, widely applied in exploring neural modeling, enables a formal description of neural transition. Originally, it was the mathematical representation of magnetism in statistical mechanics, featuring lattices of discrete variables representing "spins" in the state of up (+1, ↑) or down (-1, ↓) [13]. Of note, different phases can be identified through the orientations of spins (Fig. 1A). Paramagnetism is recognized with spins irregularly orientated, ferromagnetism with spins single-orientated (up or down), and antiferromagnetism with neighboring spins orientated oppositely in a regular pattern. The order can be reflected by spin orientations. Principally, paramagnetism with low order is of high energy (i.e., Hamiltonian), and ferromagnetism or antiferromagnetism with high order is of low energy. Based on the lowest energy principle, paramagnetism has a stable tendency toward ferromagnetism or antiferromagnetism. However, this stable tendency might be disrupted by temperature, which disturbs the order of spins. As temperature increases, the order decreases, thus allowing phase transition from ferromagnetism or antiferromagnetism of low energy toward paramagnetism of high energy. Altogether, temperature change drives phase transition. Otherwise, magnetization remains inertial. To date, the Ising model has been introduced into the neuroscience field to quantify the metabolic energy [14, 15] in the brain and model the sensorimotor cortex [16], and retina [17].

The mood of individuals with BD tends to vary among depression and euthymia as well as manic states, which resembles the magnetism phase transition. Thus, we hypothesized a state switch model for the neural transition of BD inspired by the Ising model (Fig. 1B).

Initially, the model was formulated that a neuron is like a spin, which takes the up- or down-orientation to represent neural excitation or inhibition. Here, a voxel in fMRI of the ventral striatum can be taken as an up or down-orientation spin to represent hyperactivation or hypoactivation. An emotional disturbance that influences mood on the positive or negative side (e.g., reward, stress), is treated as the temperature that mediates spin orientations [6]. We showed that, in individuals without mental disorders in the euthymic state, the neural ensembles are characterized by antiferromagnetism, with regular spin up and down of high order. When they are predisposed to an emotional disturbance that mimics a temperature increase, the neural spins are prone to direct irregularly and display unstable paramagnetism. However, when emotional disturbance is withdrawn that mimics a temperature decrease, individuals tend to return to the stable point of the euthymic valley as antiferromagnetism seeks the lowest energy. Respectively, the individuals become temporarily happy or sad, presenting resilience to mania and depression.

Contrarily, in individuals with BD, we propose that this model has three transparent emotion valleys (i.e., depression, euthymia, and mania). Depression or mania stands for ferromagnetism with opposite spin orientations, and the euthymic state stands for antiferromagnetism. Take an individual with BD in a euthymic state for example: under emotional disturbance (parallel with a temperature increase and order decrease), they tend to roll in the depression or mania valley, with a minor valley depth representing lower energy, compared to healthy controls. Once an individual with BD leaves the euthymic state and enters another emotion valley, he/she will have more orientated neural spins (depression state with more spins down, and mania state with more spins up), thus achieving the state switch. This individual will remain in the present state, except when extra energy is given for another phase transition.

As for episode frequency, bipolar II disorder has more depressive episodes than (hypo)manic episodes. Hence, the difference might be explained by the depression valley being shallower than the (hypo)mania valley. Specifically, in individuals with mixed symptoms of BD, we assume that rapid switches between depression and mania constitute the mixed

state. In this sense, we hypothesize that individuals with BD with mixed episodes have shallow both depression and mania emotion state valleys, in line with evidence that they are vulnerable to environmental stimuli [18]. Therefore, an emotional disturbance elicits rapid neural spin switches and then simulates the seemingly simultaneous states of both depression and mania.

Generally, we deduce that emotional disturbance transforms the orientations of neural spins and then leads to an emotion state switch, following dynamic system theory [19]. The susceptibility to emotional disturbance is negatively correlated with the depth of the euthymic state valley, raising the episode variety among heterogeneous BD situations. Meanwhile, emotional disturbance can sculpt the depth of the valley. In terms of the inertial trend in morbid state valleys, individuals with BD tend to be stable in their current state.

Regarding the treatment, we predicted that its efficacy depends on whether it can transform the depressive or manic state (ferromagnetism) to the euthymic state (antiferromagnetism or at least paramagnetism). The answer lies in two steps. The first is to drive the phase transition. Acute emotion intervention (e.g., mental crisis intervention) that encourages individuals with BD to get rid of the present morbid emotional state, is a requisite for the next state. The second is to augment the persistence in euthymic valleys. Decreasing the depth of morbid emotion valleys or increasing the depth of a euthymic valley (e.g., establish emotional disturbance-resilient neural plasticity through regular daily rhythms, psychotherapy, and psychotropic drugs such as mood stabilizers) is a trend for treating individuals with BD in the long term.

Promisingly, evidence has pointed out that the ventral striatum possibly displays state-specific activity. Further, the activity of the ventral striatum is the potential neural substrate that reflects the distinct behavioral styles under manic or depressive episodes and can be mediated by reward or stress. Therefore, the activation change in the ventral striatum can be modeled according to the mentioned approach as a result of an interplay of fast fluctuations with the valley depths shaped by long-term mechanisms. Meanwhile, the normalized variability in the slow-5 band, which is directly linked to the neuronal processes involved, is increased in the default-mode network and decreased in the sensorimotor network in depressed patients, whereas the opposite topographical pattern occurs in mania [20]. The contrasting patterns possibly explain the excessive concentration on internal thinking and psychomotor inhibition in depressive episodes and the excessive focus on external content and psychomotor overexcitement in manic episodes. Such opposite neural transition patterns can also be modeled in BD to bridge the biological findings with the cognitive and psychomotor fluctuations in BD. When the focus is on the sensorimotor network, a voxel is formulated as a spin, which can take the up or down orientation to represent activation or inactivation, respectively. However, in the default-mode network, a voxel takes the up- or down-orientation to represent inactivation or activation, respectively.

Since to date no accurate and non-invasive single-neuron recording for humans has been invented and applied, further biological validation in existing neural imaging techniques (e.g., fMRI) can be achieved using the self-consistent field to average the region of the brain as a neural domain (a set of ordered neighboring neural spins). Although the brain region contains both excitatory and inhibitory neurons and the actual neural activity is subtle and complicated, the state switch model here applies the simplified average activity within a certain range.

Taken together, the model integrates existing neural evidence of BD, links the magnetic transition with the neural activation switch of BD, and translates the basic physical parameters into the clinical situation of BD, which elucidates the fluctuating symptoms of BD. Thus, it leverages a state switch framework to capture the longitudinal changes in neural transitions. In the dynamic view, the Ising model is applied to achieve the mathematical analysis of the complicated, higher-dimension interactions of neurons or voxels, which provides a plausible candidate mechanism for the reorganization of the topologic region or network in explaining the state switch of BD. The model equation is shown in Fig. 1B. Apart from neighboring spins in the Ising model, we included the non-local influence of spins, which further models complicated neural interactions more than the neighboring spins. According to the selective activity of distinct brain subregions under certain emotional disturbances, we also divided the influence on certain ranges. Thus, this model establishes the neural transition representations for symptom switches in a manner closer to clinical scenarios.

Nowadays, biological findings suggest the cross-sectional profile of BD, and its collaboration with the promising power of the computational model will better elucidate the neural mechanism of BD from a dynamic perspective, and potentially pave the way for precise treatment of BD.

Acknowledgements This insight article was supported by the National Key Research and Development Program of China (2023YFC2506200), and the Leading Talent of Scientific and Technological Innovation - "Ten Thousand Talents Program" of Zhejiang Province (2021R52016). We sincerely thank Yalan Wen, Zhejiang University School of Medicine, for helpful comments and discussions of this paper. She was not compensated for her contribution.

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

References

1. Rantala MJ, Luoto S, Borráz-León JI, Krams I. Bipolar disorder: An evolutionary psychoneuroimmunological approach. Neurosci Biobehav Rev 2021, 122: 28–37.
2. Miklowitz DJ. Functional impairment, stress, and psychosocial intervention in bipolar disorder. Curr Psychiatry Rep 2011, 13: 504–512.
3. Meng X, Zhang S, Zhou S, Ma Y, Yu X, Guan L. Putative risk biomarkers of bipolar disorder in at-risk youth. Neurosci Bull 2024, https://doi.org/10.1007/s12264-024-01219-w.
4. Cochran AL, Schultz A, McInnis MG, Forger DB. A comparison of mathematical models of mood in bipolar disorder. Springer Series in Bio-/Neuroinformatics. Cham: Springer International Publishing, 2017: 315–341.
5. Mason L, Eldar E, Rutledge RB. Mood instability and reward dysregulation-a neurocomputational model of bipolar disorder. JAMA Psychiatry 2017, 74: 1275–1276.
6. Eldar E, Niv Y. Interaction between emotional state and learning underlies mood instability. Nat Commun 2015, 6: 6149.
7. Gonul AS, Coburn K, Kula M. Cerebral blood flow, metabolic, receptor, and transporter changes in bipolar disorder: The role of PET and SPECT studies. Int Rev Psychiatry 2009, 21: 323–335.
8. Abler B, Greenhouse I, Ongur D, Walter H, Heckers S. Abnormal reward system activation in mania. Neuropsychopharmacology 2008, 33: 2217–2227.
9. O'Sullivan N, Szczepanowski R, El-Deredy W, Mason L, Bentall RP. fMRI evidence of a relationship between hypomania and both increased goal-sensitivity and positive outcome-expectancy bias. Neuropsychologia 2011, 49: 2825–2835.
10. Brooks JO 3rd, Wang PW, Bonner JC, Rosen AC, Hoblyn JC, Hill SJ. Decreased prefrontal, anterior cingulate, insula, and ventral striatal metabolism in medication-free depressed outpatients with bipolar disorder. J Psychiatr Res 2009, 43: 181–188.
11. Yip SW, Worhunsky PD, Rogers RD, Goodwin GM. Hypoactivation of the ventral and dorsal striatum during reward and loss anticipation in antipsychotic and mood stabilizer-naive bipolar disorder. Neuropsychopharmacology 2015, 40: 658–666.
12. Satterthwaite TD, Kable JW, Vandekar L, Katchmar N, Bassett DS, Baldassano CF, *et al*. Common and dissociable dysfunction of the reward system in bipolar and unipolar depression. Neuropsychopharmacology 2015, 40: 2258–2268.
13. Ising E. Beitrag zur theorie des ferromagnetismus. Z Für Phys 1925, 31: 253–258.
14. Lynn CW, Cornblath EJ, Papadopoulos L, Bertolero MA, Bassett DS. Broken detailed balance and entropy production in the human brain. Proc Natl Acad Sci U S A 2021, 118: e2109889118.
15. Weistuch C, Mujica-Parodi LR, Razban RM, Antal B, van Nieuwenhuizen H, Amgalan A, *et al*. Metabolism modulates network synchrony in the aging brain. Proc Natl Acad Sci U S A 2021, 118: e2025727118.
16. Truccolo W, Hochberg LR, Donoghue JP. Collective dynamics in human and monkey sensorimotor cortex: Predicting single neuron spikes. Nat Neurosci 2010, 13: 105–111.
17. Schneidman E, Berry MJ 2nd, Segev R, Bialek W. Weak pairwise correlations imply strongly correlated network states in a neural population. Nature 2006, 440: 1007–1012.
18. Muneer A. Mixed states in bipolar disorder: Etiology, pathogenesis and treatment. Chonnam Med J 2017, 53: 1–13.
19. Scheffer M, Bockting CL, Borsboom D, Cools R, Delecroix C, Hartmann JA, *et al*. A dynamical systems view of psychiatric disorders-practical implications: A review. JAMA Psychiatry 2024, 81: 624–630.
20. Martino M, Magioncalda P, Huang Z, Conio B, Piaggio N, Duncan NW, *et al*. Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. Proc Natl Acad Sci U S A 2016, 113: 4824–4829.