

## Review

# Pushing the Frontiers: Optogenetics for Illuminating the Neural Pathophysiology of Bipolar Disorder

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## Abstract

Bipolar disorder (BD), a disabling mental disorder, is featured by the oscillation between episodes of depression and mania, along with disturbance in the biological rhythms. It is on an urgent demand to identify the intricate mechanisms of BD pathophysiology. Based on the continuous progression of neural science techniques, the dysfunction of circuits in the central nervous system was currently thought to be tightly associated with BD development. Yet, challenge exists since it depends on techniques that can manipulate spatiotemporal dynamics of neuron activity. Notably, the emergence of optogenetics has empowered researchers with precise timing and local manipulation, providing a possible approach for deciphering the pathological underpinnings of mental disorders. Although the application of optogenetics in BD research remains preliminary due to the scarcity of valid animal models, this technique will advance the psychiatric research at neural circuit level. In this review, we summarized the crucial aberrant brain activity and function pertaining to emotion and rhythm abnormalities, thereby elucidating the underlying neural substrates of BD, and highlighted the importance of optogenetics in the pursuit of BD research.

Keywords: Bipolar disorder, optogenetics, pathophysiology, frontal-limbic system, biological rhythms, animal model

## Background

Bipolar disorder (BD), a crippling mental disorder characterized by mood cycling of manic (e.g., impulsivity, reduced need for sleep, increased energy and hyperactivity, reduced anxiety and depression) and depressive (e.g., helplessness, anhedonia, and reduced energy and activity) episodes, affects 1-4% of the population worldwide [1-3]. The risk of suicide in BD patients in terms of emotional extremes was 20-30 times higher compared with the non-BD population [4, 5], creating a giant burden for social healthcare and medical institutions [6].

It is imperative to understand the neural mechanisms of BD and identify potential targets for

therapeutic interventions. Therefore, animal models developed by drug, gene knockout, and chronic stress are applied as feasible research methods. Although BD patients usually show key features in emotional fluctuation and disrupted biological rhythms, the animal models to date cannot easily mimic the switching emotional phenotypes with high validity, which hinders the understanding of BD mechanism [7]. With the progression of optogenetics, exploring the possibilities of optogenetic control to promote research on BD mechanism represents a promising frontier.

Optogenetics, a combination of genetic and optical methods, has been utilized to regulate the activity of living cells in the real-time through ion flux under optical control [8, 9]. Channelrhodopsins [ChR], archaerhodopsin [Arch], and halorhodopsins [HR] are the most frequently employed opsins to modulate the neural activity [10-12]. After virally expressing the mentioned light-sensitive protein in certain brain regions through stereotactic injection, it allows the certain ion flux passing through the membrane when the specific light wavelength is given. This ion flux thus drives the alteration of neural excitability by changing the membrane potential. Under this circumstance, light, acting as the effector, achieves the manipulation of the activity in the desired neural ensembles both *in vitro* and *in vivo* with an experiment-tailored light pattern. Therefore, optogenetics shows advantages to operate with high spatial and temporal resolution [13, 14]. To date, this precise temporal and spatial light-control system has been integrated with other complimentary methods, such as electrophysiology, to further elucidate the psychiatric pathology [8].

Since dysfunction of the specific regions in the brain has been tremendously implicated in BD pathophysiology, it is necessary to mimic and rescue the dynamic emotional symptoms (namely, the emotion-related behaviors) of modelled animals that are consistent with clinical manifestations of BD. Therefore, in this review, we summarized the potential targets for optogenetic intervention from human evidence to back up the BD animal researches, and tried to shed light on the application of optogenetics in animal models on elucidating the possible mechanisms of BD.

## Neural basis of BD pathophysiology

As the brain is pivotal in mediating emotion and guiding behavior, it is supposed that some unique alterations in related brain regions sculpt the core symptoms in BD patients such as consistent emotional instability and disrupted biological rhythms. Growing evidence has demonstrated that the pathophysiology of BD probably lies in the structural and functional changes of frontal-limbic system (including the hippocampus, amygdala, septum, orbitofrontal gyrus, hypothalamus, dentate gyrus, and cingulate gyrus) [15], as well as the suprachiasmatic nucleus (SCN) (SCN belongs to the limbic system, but we separately discuss this peculiar nucleus in view of its specific rhythm-pacemaker role) [16]. The former frontal-limbic system is highly associated with affective regulation. It has also been demonstrated that dysregulated brain activity and the neurotransmitter pathways in this system might directly

delineate morbid emotions in BD patients. The latter SCN, acting as a circadian rhythm center, is manipulated by regulatory genes including *CLOCK*. Depending on this circadian gene expression, it in turn mediates the metabolic balance, which may also correlate with the emotional abnormalities in BD [16, 17]. In this review, we mainly focused on the frontal-limbic system and the SCN.

## Abnormalities in the frontal-limbic system

### Alterations in the brain activity

The first pathophysiological model of mood disorder in humans originated from the “limbic-cortical-striatal-pallidal-thalamic tract” model [18], which has now evolved into the “frontal-limbic” model. Anatomically, extensive dense reciprocal connections have been confirmed in the frontal-limbic system to predominantly participate in emotion mediation with top-down and bottom-up mechanisms [19, 20]. Morbidity of this system has been examined in the affective disorders, including BD. It seems that alterations in the brain activity (manifesting as changes in the functional connectivity via neuroimaging) within the frontal-limbic system, especially the compromised integrity in the frontal-subcortical and prefrontal-limbic areas, are overwhelmingly involved in the pathogenesis of BD [21-30]. Herein, we summarize the crucial alterations in the brain activity in the frontal-limbic system of diagnosed BD patients.

The frontal lobe is well known for its necessity in modifying the moods, and impairment of the frontal lobe negatively affects emotional cognition [31]. Studies have illustrated that the lingual gyrus, insula, putamen, bilateral superior frontal gyrus, and superior frontal gyrus have significantly altered low-frequency fluctuations in BD subjects compared with those in healthy controls [32, 33]. Notably, the hyperactivity of ventral cingulate cortex is more strongly associated with emotion state rather than medication results. Given the mood instability of BD, an earlier meta-analysis showed that the activation of the prefrontal cortex was attenuated in the manic state of BD, while the activation of the limbic system remained consistently enhanced across all the emotional states [34]. Specifically, decreased engagement of the medial orbitofrontal frontal cortex also plays a role during explicit regulation of the negative emotions of BD, leading to hopelessness that contributes to the risk of suicide [35]. Nevertheless, challenge remains since the frontal lobe is composed of heterogeneous functional components. Therefore, the role of specific subregions is still vague,

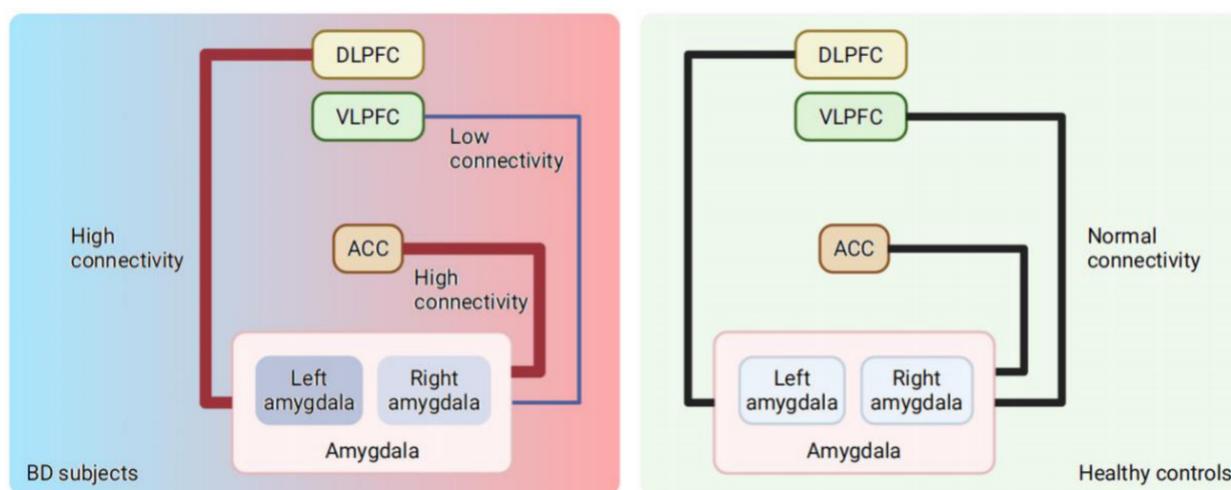
necessitating more precise voxel-based analysis or invasive research using optogenetics in animal models.

The amygdala, which is located in the limbic system, has long been illustrated in the emotional morbidity of BD. Evidence has shown that some regions in the prefrontal cortex, namely, the ventrolateral prefrontal cortex (VLPFC), the dorsolateral prefrontal cortex (DLPFC), and the anterior cingulate cortex (ACC), cooperate with the amygdala in the limbic system in processing emotion [36-38]. Therefore, the amygdala is able to extract emotional stimulus information from upstream brain regions and environmental stimuli, thus playing a central role in emotion processing and initiating arousal reactions to incoming information immediately. To achieve emotion regulation, the activation of the amygdala stimulates the fast-acting autonomic nervous system and the slow-acting hypothalamic-pituitary-adrenal axis through neuronal projections to the brainstem and hypothalamus, allowing adaptive modulation of stress responses [39]. Pathologically, different levels of amygdala activation can suitably reflect different mood states of BD [40, 41]. Specifically, heightened activation of the amygdala was illustrated in the manic state of BD, especially in the left amygdala while the patients were watching the fearful faces [41], indicating that the amygdala might regulate extreme emotions such as fear. It has also been reported that hyperactivation of the right amygdala while viewing fearful faces is correlated with a higher risk of developing BD [42-44]. A trend of left amygdala hyperactivation was observed in the depressive state of BD [45], but without statistical

significance. In addition, the activity of the PFC and amygdala was detected with less resilience in euthymic BD subjects than in healthy controls [46-49].

With regard to functional connectivity, BD patients exhibit higher connectivity of the amygdala with the ACC and DLPFC [50], as well as decreased connectivity between the VLPFC and amygdala [30, 51, 52], (**Figure 1**) which is possibly attributed to developmental failure [30] or neuroinflammation [53]. The ACC and DLPFC can regulate the negative emotional responses from the amygdala to resolve conflicts. At the same time, the activity of the ACC is directly attentionally modulated by the DLPFC. In fact, the left ACC and right hippocampus in BD patients showed decreased resting-state functional connectivity between the left ACC and the left orbitofrontal cortex compared with those of healthy controls [24]. For clinical practice, such connectivity changes revealed in subcortical, anterior temporal and ventral prefrontal regions responding to emotional events in BD patients have been considered biomarkers for the vulnerability and expression of BD [29].

Note that numerous studies have disclosed that the activity of brain regions in the frontal lobe and limbic system as well as the interplay between them are together presumed to contribute to the irregular emotion of BD patients. However, the causality between aberrant frontal-limbic systems and the pathology of BD remains elusive. All these discoveries in humans provide valuable target brain regions or circuits to promote the further dissection direction of neural mechanisms in animals.



**Figure 1. Changes in the amygdala activity and connectivity in BD subjects compared with healthy controls\*.** \*Both increased and decreased amygdala activation have been found in euthymic BD and healthy controls, which is not showed in this figure. Evidence showed increased activation of amygdala in BD subjects compared to healthy controls. The activity of left amygdala increased significantly during mania stage of BD, while the trend of increased activity of left amygdala has been observed in BD depression. Higher connectivity between the amygdala and the DLPFC, as well as lower connectivity between the amygdala and VLPFC was found in BD, and heightened connectivity was also detected between the amygdala and ACC. BD = bipolar disorder; VLPFC = ventrolateral prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex.

### **Dysregulated dopaminergic within the frontal-limbic system**

In parallel with altered activity and functional connectivity, dysregulated neurotransmitters have also been disentangled in BD. As the dysregulation of reward processing has been demonstrated in BD patients [60], dopamine, which has been demonstrated to be crucially involved in transforming emotional value or coding appetite, attracts the most attention [54].

Several functional magnetic resonance imaging studies employing reward tasks indicated the morbid neural activity in the frontal-limbic system of BD patients. In detail, during the hypomanic/manic period, the frontal-striatal neural circuit, which is highly involved in reward processing and approach-related effect, was elevated activated [55-58]. The metabolism rate decreased in the prefrontal cortex of bipolar mania patients, but increased in other frontal-limbic regions including dorsal cingulate cortex, striatal regions, nucleus accumbens (NAc), etc [59].

Beyond functional neuroimaging, molecular evidence was also gathered. In clinical practice, D2 blocker antipsychotics treatment is effective in many BD patients, which hints the potential pathology-involved targets. Experiments conducted with positron emission tomography in BD patients indicated the elevation of D2 receptor in several brain regions [60, 61]. Of note, different elevation in different region has a subtle effect. Remarkably, one research observed that psychosis was linked with higher D2 receptor density in the caudate nucleus [60], suggesting this local D2 receptor density represented for psychosis rather than mood state. Other studies based on postmortem BD patients revealed that the dopamine D2 receptor was upregulated in the DLPFC [62], and antidopaminergic treatment could increase the D2 receptor levels in animals [63]. Specifically, the activation of D2 receptors in the PFC was found to be connected to the activity and function of the hippocampus [64], while blockade of D2 receptors in the PFC led to dysfunction of the amygdala [65]. Taken together, these findings suggest that the dysregulation of dopamine and its receptors in the frontal-limbic system might be critical in BD pathogenesis. Hence, the shift release of dopamine or its available receptors in the functional regions might provide a reasonable explanation for BD pathophysiology.

Although the exact mechanism in BD remains enigmatic, based on anatomy and its functional evidence, it can be speculated that dopamine and its related receptors might be responsible for the mood

instability in BD through the interaction of the amygdala, hippocampus, and PFC. Among all these brain regions, the PFC likely serves as an upstream regulator. Primarily, it has been shown that dopaminergic projections into PFC have an indispensable role in reward processing [66], and its malfunction possibly explains the dysregulated "reward circuit". Optogenetic functional magnetic resonance imaging research has identified that stimulating dopamine neurons elicited the striatal activity, whereas locally enhanced medial PFC excitability hampered this striatal response and inhibited the behavioral drive for dopaminergic stimulation in rats. This chronic overactivity of the medial PFC further exerted a sustained suppression on natural reward-motivated behaviors, establishing an enduring state of anhedonia [67]. Of note, peculiar prefrontal-striatal activity is profoundly observed in the neuroimage evidence of BD, which might be explained by this mentioned optogenetic results. Specifically, dopamine has been shown to modulate the projection from the PFC into the amygdala. Photostimulation of medial PFC D1 terminals in the basolateral amygdala recapitulated the antidepressant effects in forced swim test and novelty suppressed feeding [68]. It has been demonstrated that the PFC can regulate the release of dopamine in the mesolimbic system [69-71], which in turn modulates the activity of the NAc that regulates emotion [72]. In particular, the PFC indirectly interacts with the amygdala by acting on dopamine neurons in other brain regions, including the ventral tegmental area (VTA) [73] and basal forebrain [74]. Of note, depending on dopamine neurons in the VTA, the PFC could also mediate the function of the hippocampus [75-77].

Generally, it was observed that the static aberrant activity and neurotransmitters/receptors are involved in the development of BD, but the dynamic mood switch was rarely explained. Therefore, more investigations are required to identify the cyclical changes in brain activity or neurotransmitter receptors. Considering the translation into neuroscience research, it is feasible to adopt the optogenetic tools to reproduce or reverse emotional abnormalities through manipulation of mentioned brain regions (e.g., PFC and amygdala) or neural transmitter (e.g., dopamine).

### **Dysfunction of the SCN and disrupted circadian rhythms**

Abnormal circadian rhythms are vital manifestations of BD [78]. However, the causal linkage between biological rhythms and emotions has yet to be clarified [79]. For quinpirole-induced animal

models of BD, one study clarified that individuals with decreased ability to recover from the disrupted circadian rhythm were more susceptible to BD [80]. Of note, disrupted circadian rhythms can also induce manic-like behaviors in mice [80, 81]. Moreover, lithium, a mood stabilizer widely prescribed in BD therapeutics, can stabilize and normalize the circadian rhythms and has been verified to be an effective therapy for ameliorating and preventing relapse into manic and depressive states of BD [82], which strongly suggests a bidirectional relationship between BD development and the disordered biological rhythm. In particular, a recent study demonstrated that central clock in the brain largely regulated peripheral metabolic rhythms [83]. Meanwhile, peripheral metabolism such as gut microbiota, was also found to interact with brain via epigenetic and genetic regulation [84], which deserves more attention in future research.

Considerable evidence has shown that circadian rhythms might be involved in the dysfunction of a region in the anterior hypothalamus named the SCN, which orchestrates daily behavioral and physiological oscillations [85-87]. The master circadian pacemaker in the SCN is largely sustained through the activity of cellular- and tissue-level "clocks" and stimuli from the surrounding environment [86, 88-90]. Specifically, the functions of central and peripheral biological clocks are mainly realized via regulatory genes located in SCN. These regulatory genes are synchronized by light signals and generate the body endogenous at a 24 hours rhythm [91]. Among various circadian pacemaker of the SCN, rhythmic *CLOCK* expression attracts the most attention. The oscillator *CLOCK* gene thus regulate circadian rhythms through a molecular feedback system including both their own transcription and other clock-controlled genes [86] [92] [93] without strong external influences [94]. Intriguingly, it appears that *CLOCK* gene expression is involved in mood regulation in response to SCN signals and environmental stimuli. However, whether this role relies on the SCN remains to be explored [16]. Studies have revealed that the dysregulation of *CLOCK* genes may promote the susceptibility to developing BD and influence circadian phenotypes, which accounts for relapse into episodes [95], indicating the causative role of the *CLOCK* gene. Furthermore, a clinical study proposed that circadian rhythms in the circadian clock gene expression and the cortisol alterations of the buccal cell might be utilized for predicting mania and depression episodes in BD patients [96].

Though direct evidence remains scarce, BD patients displayed enhanced functional connections in the SCN-paraventricular nucleus-dorsomedial

hypothalamus nucleus [82], suggesting that SCN dysfunction might disrupts the circadian rhythms in BD patients, and drives mood alterations through downstream interactions. In addition, components of the molecular biological clock are also found in extra-SCN regions, such as the hippocampus, amygdala, lateral habenula, NAc, and PFC [97-99], which should be taken into consideration when focusing on SCN clock.

In summary, abnormalities in the SCN and disrupted biological rhythms are probably involved in BD pathophysiology and thus may act as traits or state markers for BD emotional episodes. (Figure 2) In fact, resynchronization and normalization of circadian rhythms has proven effective in BD therapies [100, 101]. These findings provide inspiring evidence indicating disrupted rhythm as a contributor to BD, however, they further challenge us to determine which brain regions regulate mood through photic and nonphotic clock alterations. A rhythmic or unrhythmic neural manipulation depending on the light pattern is required to clarify this problem.

## Investigations of optogenetics in BD research

By means of its strong operability, optogenetics allows us to probe a defined brain region or neural circuit disorder in a spatiotemporal manner, thus straddling the field of psychiatry. However, in neuroscience, circuit mechanism discovery depends on the animal model that can be harnessed to utilize the invasive approaches. BD presents complex disorder behaviors including nuanced swing emotional states and disrupted circadian rhythm, making the construction of an animal model more challenging and obstructing the application of optogenetics. Although progression has been made, to date, no animal model has completely mimicked the featured manifestations of BD, including emotional fluctuation and dysregulated biological rhythms [102]. Artificially handled animals (stress/drug-induced or gene knocked-out) are often able to simulate only unipolar mania or depression [103, 104], impeding their reliability for the exploration of BD mechanisms. Nevertheless, it is still inspiring that neuroscience techniques are pushing the frontiers of psychiatry. Here, we mainly focus on the aberrant emotion and disrupted circadian rhythm that correlated to the frontal-limbic system and SCN, and suggest the investigations of optogenetics to facilitate the advance of BD research.

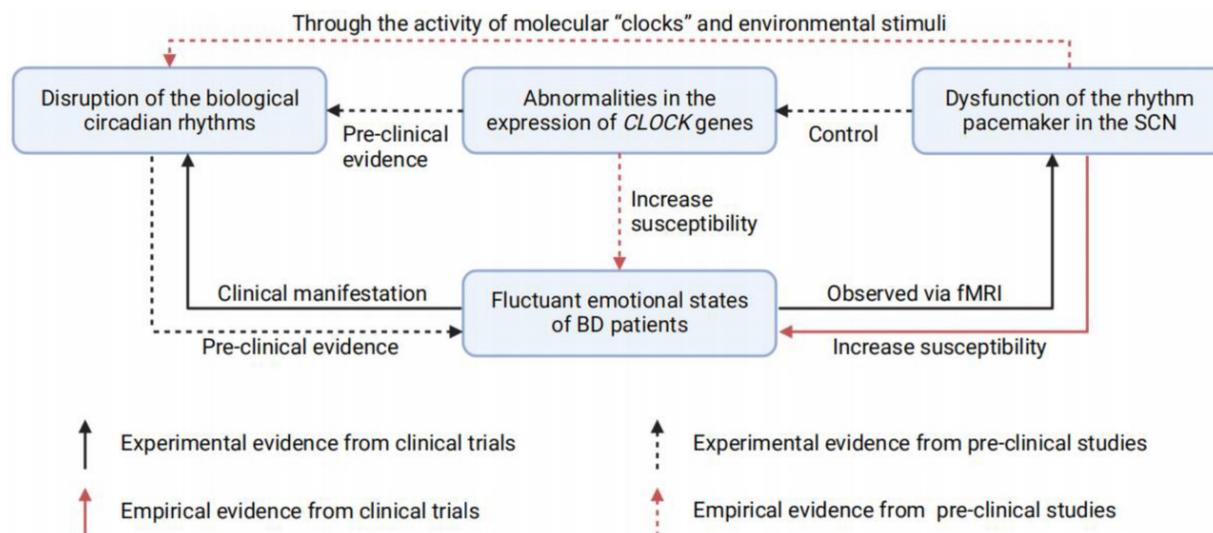
One of the known animal models of BD is established based on sleep deprivation, which perturbs the circadian rhythms and models mania episodes in rodents, as elucidated by McClung. Given

that sleep disruption stands as a hallmark feature of mania [105], and sleep deprivation has the capacity to incite manic episodes in individuals with bipolar disorder [106], this model shows significance of the validity in combining mood and circadian rhythm. Furthermore, sleep deprivation recapitulated various manic-like behaviors, encompassing insomnia, hyperlocomotion, aggressive interactions with conspecifics, increased sexual mounting behavior, and stereotyped behaviors such as sniffing and rearing [107]. Considering the SCN governs a sleep homeostatic process [108], it is undoubtedly an attainable behavioral model to examine their causal link.

Among all existing BD models, it is notably that the *CLOCK*Δ19 mice display a cycling mood profile of mania in the day and euthymia at night, and the elevation of mood coincides with increased excitation of VTA dopaminergic neurons [109]. When using RNA interference to specific knock down the *CLOCK* in VTA, mice exhibited hyperactivity and decreased anxiety behavior resembling the *CLOCK*Δ19 mice. However, it also displayed depression behavior in the forced swim and learned helplessness test, leading a mixed manic emotional state, and altered circadian rhythms [110], indicating the interaction between the emotion and the biological circadian rhythms. However, only one optogenetic experiment has been reported. Sidor et al. injected a double-floxed inverted open-reading-frame virus carrying the specific stable step-function opsin in the VTA of TH-Cre transgenic mice to allow direct persistent activation of

dopaminergic VTA neurons. After 7 day of optical activation for 1 h per day, mice exhibited mania-like behaviors with less anxiety, which was similar to the behavior of *CLOCK*Δ19 mice [111], suggesting that *CLOCK* may regulate emotion by acting on the activity of dopaminergic VTA neurons. Significantly, this work not only supported dopamine as an important bridge between cycling mood state and rhythm [112], but also established an operatable stimulation paradigm to reproduce the mania phase of BD. Moreover, optogenetic manipulation indicated that the activation of VTA GABAergic neurons (instead of dopaminergic neurons) alleviated dizocilpine induced hyperlocomotion [113], which might be harnessed to reduce the positive psychotic-like behaviors in BD patients. Further investigations should focus on the exact mechanisms that how chronic stimulation of dopaminergic VTA neurons drives the post-manipulation effect, with plasticity and metabolism alterations examined.

One different method to build the BD animal model used electrodes to stimulate the lateral hypothalamus (LHA) with 180 Hz frequency [114]. Activating the LHA, rats were successfully induced the mania behavior, including increased sexual self-stimulation, excessive rearing, feeding, and grooming during the kindling interval. Moreover, rats showed hyperlocomotion with decreased rest interval during the mania induction and post-mania days in both light and dark phases. Meanwhile, administration with lithium or valproic acid reversed manic-like behaviors in this model, which further



**Figure 2. The relationship between fluctuant emotions of BD, SCN dysfunction, *CLOCK* genes abnormalities, and disrupted circadian rhythms.** Disruption of the biological circadian rhythms is commonly found in BD patients, for its correlation with the emotional fluctuation. Pre-clinical studies also demonstrated the disrupted circadian rhythms could lead to depression- or mania-like behaviors in animals. Studies based on fMRI suggest that BD patients have dysfunctions in the SCN rhythm pacemaker, while observed SCN dysfunctions could increase the susceptibility of BD in health population. In addition, pre-clinical studies have also found that there are two ways for the dysfunctional SCN to cause circadian rhythms disruption: i) Through the activity of molecular "clocks" and environmental stimuli; ii) Through the expression of *CLOCK* genes. Of note, abnormalities in the *CLOCK* genes expression could also increase the susceptibility of BD, which has previously been proven pre-clinically. BD = bipolar disorder; SCN = suprachiasmatic nucleus; fMRI = functional magnetic resonance imaging.

confirmed its validity for BD animal model. Therefore, optogenetic manipulation targeting at the LHA can also be applied to establish a BD animal model. Meanwhile, specific LHA-related circuits can also be dissected to check out which circuit controls the corresponding behavior and how distinct circuits work together in BD development.

Although there is no ideal BD animal model currently, novel intervention measurements with optogenetics can be adopted in advance. In view of the above, we hypothesize a novel investigation for

building BD animal model, namely, applying short- or long-term optogenetic stimulation on the rhythm-related brain regions such as the SCN, and then observe the correlated behaviors.

Inspired by the innovative work of the McClung team, herein, we suggest the SCN as a potential optogenetic intervening target, to mimic the phenotype of bipolar disorder and unravel the potential BD mechanisms in modelled animals. Instructive studies applying optogenetics to elucidate the SCN functions are listed in **Table 1**.

**Table 1.** Studies using optogenetic methods to reveal the biological functions of SCN.

Time	Animals	Special treatments*	Other research technologies**	Results or conclusions	Ref.
2015	Male and female <i>Drd1a-ChR2 × PER2::LUC</i> mice	-	Immunohistochemistry protein culture and imaging locomotor activity monitoring	Optical manipulation of SCN firing rate resets the circadian rhythms <i>ex vivo</i> and <i>in vivo</i>	[142]
2016	Male and female Evans rats Male and female <i>C57BL/6J</i> , VP-Cre knock-in, ChETA, ArchT, and <i>V1aR<sup>-/-</sup></i> mice	Water restriction	Evans blue injection Retrograde fluorescent microspheres Immunofluorescence Single cell RT-PCR Immunofluorescence	Optogenetic inhibition SCN neurons to decrease the VP release suppresses the firing of OVLT neurons and prevents the corresponding increase in water intake during the anticipatory period.	[143]
2017	Male and female <i>Opn4<sup>flm1:lox2</sup></i> mice Male and female glutamate decarboxylase 2-IRES-Cre mice	Pharmacological manipulation: Ionotropic glutamate receptor blockers Visual stimuli	Immunofluorescence	Optogenetic activation of GHT neurons selectively inhibits the responses to retinal input of SCN and exhibits a day/night difference in a GABAergic manner	[144]
	Male and female <i>Grpr<sup>fl/y</sup></i> mice Male and female <i>Grprw<sup>fl/y</sup></i> mice	Selective neurons ablation Chemogenetic neurons silencing	Immunofluorescence Immunohistochemistry	Optogenetic activation of GRP or GRPR neurons located in the SCN promotes scratching behavior	[145]
2018	Male and female <i>C57BL/6J</i> mice Male and female <i>VIP-ires-Cre::Rosa-GCaMP5</i> mice	-	Immunohistochemistry	Optogenetic activation of VIP neuron in SCN with high frequency shifts gene expression rhythms <i>in vitro</i> and entrained circadian locomotor rhythms <i>in vivo</i>	[146]
	Male and female <i>C57BL/6J</i> mice Male and female <i>VIP-ires-Cre::Rosa-GCaMP5</i> mice	-	Wheel-running test	Glutamatergic and GABA input synapses in ventral SCN neurons exhibit light-dependent plasticity, which can regulate the responsiveness of SCN neurons to the wide range of light input.	[147]
2019	Male and female homozygous transgenic rats with an arginine vasopressin enhanced green fluorescent protein fusion gene expressed	Retina dissection	Immunohistochemistry	Optogenetic activation of VP-retinal ganglion cells axons projecting to SCN affects the activity of SCN cells through vasopressin.	[148]
2020	Male and female <i>C57BL/6J</i> mice Male and female AVP-Cre knock-in mice Male and female GAD-Cre mice	NanoTag recording implantation	Immunofluorescence	Optogenetic activation of the GAD-expressing OVLT neurons projecting to VP-expressing SCN neurons mimics the effect that hypertonic saline phase-advances the circadian locomotion	[149]
	Male and female <i>VIP-CRE</i> , <i>AVP-CRE</i> , <i>GRP-CRE</i> , <i>Syt10-CRE</i> , <i>CKIetau</i> , <i>Bmal1<sup>fl/fl</sup></i> , and <i>cFOS::GFP</i> mice	-	Immunofluorescence Immunocytochemistry	Optogenetic control shows that VIP+ SCN neurons increases nighttime instead of daytime sleep	[150]
	Male and female <i>VIP-IRES-Cre</i> mice	-	Wheel-running test Sleep-wake monitoring Immunohistochemistry Single-nuclei RNA-sequencing	Optogenetic manipulation clarifies VIP-expressing SCN neurons is required for the locomotor circadian rhythm	[151]
	Male and female <i>VIP-IRES-Cre</i> mice Male and female <i>ChR2-EYFP</i> mice Male and female <i>Archaeorhodopsin 3-EYFP</i> mice	Pharmacological manipulation: VIP receptor antagonist [D-p-Cl-Phe6,Leu17]-VIP, (+)-bicuculline, and ionotropic glutamate receptor blockers	-	Optogenetic manipulation helps reveal that VIP-expressing SCN neurons provided coordinated daily waves through GABAergic input to paraventricular hypothalamus and ventral thalamus, suppressing their activity during the mid to late day	[116]
	Male and female <i>CRF-Cre</i> , <i>GAD67-Cre</i> , <i>VGAT-IRES-Cre</i> , <i>Rosa26-LSL-tdTomato</i> , and <i>orexin-flp</i> mice	Chemogenetic inhibition of neurons	Sleep and wake recordings Locomotor activity measurement Calcium imaging Immunofluorescence	Optogenetic activation of the corticotropin-releasing factor neurons in the hypothalamic paraventricular nucleus, one of the output regions of SCN, promotes wakefulness relying orexin neurons in the LHA	[152]
2021	Male and female <i>Vip::Cre<sup>+/+</sup>Per2::Luciferase<sup>+/+</sup></i> , <i>Vip::Cre<sup>+/+</sup>floxed-ChR2<sup>+/+</sup></i> , <i>Vip::Cre<sup>±</sup>Per2::Luciferase<sup>+/+</sup></i> , and <i>Vip::Cre<sup>+/+</sup>floxed-ChR2<sup>+/+</sup>Per2::Luciferase<sup>+/+</sup></i> mice	-	-	Optogenetic activation of VIP-ergic SCN neurons simulating the long photic period induces related locomotor behavior	[117]

Time	Animals	Special treatments*	Other research technologies**	Results or conclusions	Ref.
2022	Male Vip::Cre <sup>+/+</sup> mouse				
	Male heterozygous Vgat-Cre and homozygous Vgat-Cre mice	-	Sleep and wake recordings Behavioral tests Immunofluorescence	Optogenetic manipulation influences the anxiety-like behavior	[153]
	Male and female Tg21-31Koba, Dat1-Ires-Cre, Drd1-GFP, and Drd2-GFP mice		Immunohistochemistry Laser-scanning microscopy Electron microscopy Light-sheet microscopy RNA-scope <i>in situ</i> hybridization Calcium imaging Behavioral tests	Optogenetics helps clarify that SCN send the neuropeptide to dopamine neurons in periventricular nucleus, which innervates lateral septum to control locomotion	[120]

\*The artificial intervention in the experimental group (animals or brain slices) except for gene knock-out (or knock-in), stereotactic injection (virus or other pharmacological intervention) or optogenetic stimulation.

\*\*The research technologies used in the study except for optogenetic methods, stereotactic injection (virus or other pharmacological intervention), neuronal electrophysiology, and statistical analysis.

SCN = suprachiasmatic nucleus; VIP = vasoactive intestinal peptide; VP = vasopressin; OVLT = organum vasculosum lamina terminalis; PCR = polymerase chain reaction; AVP = arginine-vasopressin (The full name of the gene will not be indicated here).

On account of the inability of other methods, such as chemical genetics, to simultaneously control spike frequency rhythms, it is important to manipulate the SCN by means of optogenetics in naive mice to simulate dysregulated biological rhythms and examine both timely and post manipulation mood states. Inspiringly, Jones et al. presented protocols for using both *in vitro* and *in vivo* optogenetics to regulate the activity of clock neurons in the SCN to investigate circadian physiology and behavior [115], and these protocols may act as a guide for the investigation of SCN in understanding the mechanism of BD in the future. A study used optogenetic stimulation of vasoactive intestinal peptidergic SCN neurons [116], which is required to transmit light information, *in vivo*. After that, PERIOD 2::LUCIFERASE (PER2::LUC) bioluminescent imaging was carried out to test the functional SCN network *ex vivo*. Long optogenetic activation reproduced the effect of a prolonged photic period in the subsequent longer SCN entrained phase and reduced the SCN free-running period *ex vivo*, and increased the analogous locomotion *in vivo* [117]. In addition, virally knocking down another circadian gene *Bmal1* in the SCN led to biological rhythms disruption as well as provoked learned helplessness, behavioral despair, and anxiety phenotypes in mice, which may be independent of light, hinting at the potential role of the SCN in indirect mood regulation [17, 83, 118, 119]. Of note, one optogenetic manipulation in the SCN influenced the anxiety phenotype in mice, which reminded us of the importance of the specific activating pattern applied [120].

Intriguingly, there is also one study using optogenetic approaches to enhance the understanding of abnormal attention and impulsion that might happen in BD related to the frontal-limbic system. It focused on the NAc, medial PFC, and their dopaminergic innervation from the VTA [121]. This study conducted the 5-choice serial reaction time task and illustrated that the optical activation of the somas

in VTA dopaminergic neurons that project to the NAc shell or medial PFC impaired attentive behavior immediately before the presence of cues. However, only the activation of the somas in VTA dopaminergic neurons that project to the NAc core provoked impulsive control behavior [122], hinting BD patients may have deficit in attention and impulse control [123]. Therefore, *in vivo* recording such as fiber photometry or electrophysiology within these projecting specific neural ensembles in BD model is needed to detect the function deficit at circuit level.

Notably, light can modulate behaviors both in rodents and humans, which is particularly evident in reward process. For example, greater reinforcing properties of cocaine are detected during the light than dark-phase of the light/dark cycle in rodents [124], which might be explained by the diurnal changes in dopaminergic activity within the frontal-limbic system [97]. Therefore, the intervention of optogenetics should not only consider how neural circuit activity impacts behavior but also how the timing of stimulation influences a given behavioral state [125]. In other words, given the overall network synchrony, it should be considered that which rhythm state that optogenetic stimulation is involved, and whether this artificial manipulation is in accordance with the natural biological rhythm of the animals.

Given that fluctuating mood states and disrupted circadian rhythms constitute two hallmark features of BD, it is on an urgent demand to create an ideal animal model, which presents both of these phenotypes. Future studies should focus on modeling more clinical symptoms of BD, which will hopefully provide an accessible approach to explore the neural mechanism. In addition, further investigation on existing animal model is also warranted. To parse the function of the complicated neural basis relevant to BD, proof-of-concept studies in virtue of optogenetics illuminating circuitry mechanisms in detail, thus helping to find potential targets to intervene through precise physical treatment such as deep brain

stimulation and repeated transcranial magnetic stimulation.

## Future Directions

### Distinguish the neural substates of BD from other psychiatric morbidities

Challenges remain in BD diagnosis since it is demanding to distinguish the bipolar depression from the unipolar depression or major depressive disorder (MDD). An encouraging finding is that some key reward circuit abnormalities remain consistent in different states of BD, which distinguish it from MDD. A study found that compared with MDD patients or healthy controls, BD patients in the depressive state showed elevated activation in the left VLPFC than MDD patients [126], which had been associated with increased arousal during the processing of the salient emotional stimuli [127]. For neurotransmitters, notably, glutamate levels in the frontal lobe were found to be elevated in BD patients but decreased in MDD patients [128, 129]. The glutamate pathways in the medial PFC are regulated by dopamine in nonhuman animals [130]. Therefore, these abnormalities in glutamate levels may also indirectly reflect the dysregulation of dopamine and reward processing. In particular, different levels of glutamate were observed in the distinct mood states of BD patients [131-133], which indicates a potential way to differentiate BD from MDD. Such findings also remain explorations at circuit level in BD condition.

Abnormalities in reward processing have been profoundly involved in BD [134], as well as other mental disorders, including MDD, schizophrenia and autism spectrum disorder [135-137], indicating that these morbidities possibly have structural or functional alteration in shared neural substrate. Despite the overlapping aberrant alternations in neural circuits, there are subtle differences among the segregated reward-related circuits. Fortunately, the application of optogenetic methods, which enable researchers to distinguish differences among reward processing neural circuits under different psychotic states, accelerates progress. For instance, seeking reward persistently regardless of the negative outcomes it brings is a character of mania, while depression is always anhedonia. While the anhedonia behavior has been well excavated, the strengthened reward seeking and attenuated punishment avoiding that can be rescued by BD treatment are far less explored. One study took advantage of optogenetic manipulation revealing that the rostro-medial tegmental nucleus regulated resistance to punishment [138]. However, whether this brain region participates in psychotic behavior of BD still remains to explore.

### Investigating the inherent neural abnormalities in different state of BD

The obstacle of BD research lies in the complexity that patients usually show more than two mood states (mania/hypomania, depression, and euthymia) and each state might have different neural substrates. Despite the limitations of the existing animal models, it is feasible to primarily dissect the dysfunctional circuits under mania or depression-like states. Due to the precise control of optogenetics, stimulation with low/moderate/high frequency can induce long-term depression/potential in specific synapses. As the latest studies have revealed that the altered synapse plasticity of the lateral habenula is implicated in the dynamic process of getting into depression [139, 140], it is worth considering which cohesive brain regions are rhythmically activated or inhibited to develop into persistent changes in plasticity and thus direct the corresponding behaviors. For instance, the synapse plasticity of SCN-paraventricular nucleus/dorsomedial hypothalamus nucleus can be examined after circadian disruption in some animal models, such as quinpirole-induced mania mice, to determine whether this connection encodes vulnerability to BD [80]. In spite of the obscure neural mechanism, the exciting/inhibiting balance [109, 141], the shift in dopamine release [69-71] and its functional receptor [62, 63] and the disrupted biological rhythms [16, 78] and other perspectives based on humans can all be tested in animal models to decipher the mystery of switching between states. Given the shortcomings of symptom-based diagnostics for mental disorders, optogenetic research will doubtlessly be one of the focuses in the future to design treatments tailored for its pathogenesis.

## Summary

To parse the complex neural pathophysiology of BD, proof-of-concept optogenetic explorations are expected to illuminate the obscure pathophysiology at the circuitry level in detail. Focusing on the fluctuating emotion and disrupted rhythms, we gathered previous evidence of the neural activity and neurotransmitter aspects within the frontal-limbic system and the SCN from clinical practice and animals. Then, based on this information, we suggested feasible optogenetic approaches to establish a valid animal model and offer further direction in the dissection of BD pathophysiology. Despite the scarcity of existing research, we provided novel views of the application of optogenetics in BD research, hoping to pave the way for preclinical treatment and identify potential targets for medical intervention.

## Abbreviations

BD: bipolar disorder; MDD: major depressive disorder; SCN: suprachiasmatic nucleus; PFC: prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; ACC: anterior cingulate cortex; NAc: nucleus accumbens; VTA: ventral tegmental area; LHA: lateral hypothalamic area; OVLT: organum vasculosum laminae terminalis; GABA:  $\gamma$ -aminobutyric acid; PER2::LUC: PERIOD 2::LUCIFERASE; VIP: vasoactive intestinal peptide; VP: vasopressin; PCR: polymerase chain reaction; AVP: arginine-vasopressin.

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### Authorship contributions

LZK, XNG carried out literature searches, prepared figures, and wrote the manuscript; YTS, LX, and HMH did visualization and literature searches; JL and SHH supervised the paper. All authors read and approved the final manuscript.

### Competing Interests

The authors have declared that no competing interest exists.

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