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Review

Astrocytes in the Circadian System: A Promising Target for Mood Disorder Interventions

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Abstract

Circadian rhythms and emotional health are fundamentally interconnected. Circadian rhythms are characterized by self-sustaining oscillations within biological systems that synchronize sleep-wake cycles and related physiological and biochemical processes with periodic environmental changes. Clinical observations have demonstrated the significant role of the biological clock in the regulation of mood and anxiety, indicating that disruptions in circadian pacemaker control may contribute to the development of mood disorders and psychopathology. Conversely, therapeutic interventions aimed at correcting circadian misalignment have been shown to alleviate symptoms of mood disorders. The mechanistic involvement of astrocytes in mood disorders has been well-established. Recent research indicates that astrocytes possess the ability to autonomously regulate circadian rhythms, independent of pacemaker neurons. In addition to modulating rhythmicity in the central pacemaker, the suprachiasmatic nucleus (SCN), astrocytes are involved in circadian regulation within emotion-related brain regions, such as the nucleus accumbens (NAc) and amygdala. Nonetheless, the precise mechanisms by which astrocytes influence mood through circadian pathways, and the potential for their rhythmic alterations to serve as therapeutic targets for mood disorders, remain incompletely understood. In this review we synthesizes contemporary evidence regarding the role of astrocytes as pivotal regulators of circadian rhythms, focusing on how their intrinsic transcriptional–translational feedback loop (TTFL) oscillations influence mood disorders. Additionally, we investigate the role of astrocytic neurotransmitters, such as glutamate, γ-aminobutyric acid (GABA), and purinergic signaling, in the circadian-mediated amelioration of mood pathologies. These insights offer novel perspectives for identifying chronotherapeutic intervention targets for mood disorders.

Keywords: astrocytes; circadian rhythms; mood disorders; glutamate; chronotherapeutic

1. Introduction

Mood disorders, characterized by significant disruptions in emotional regulation, pose a global health challenge in modern society [1,2]. According to data from the World Health Organization (WHO), over 300 million individuals suffer from depression, which is the leading cause of non-fatal health loss worldwide [3]. These disorders impose considerable personal and societal burdens, yet our understanding of their etiology and therapeutic targets remains limited [4]. From this standpoint, we argue that a closer integration of psychiatry with sleep and circadian science will enhance the understanding and treatment of mental illnesses [5]. Clinical research consistently indicates that disruptions in sleep-circadian rhythms are prevalent across all psychiatric disorder diagnostic categories [6]. Shift work, which poses challenges to the sleep-circadian system, is associated with an increased risk of developing depression and anxiety disorders [7]. Diurnal mood variations and sleep disturbances are commonly observed in major depressive disorder (MDD), while cyclical mood episodes and alterations in sleep patterns are fundamental clinical features of bipolar disorder (BD) [8]. Importantly, this relationship is bidirectional: both acute and chronic stress can disrupt circadian rhythms, and such disruptions can, in turn, influence emotional states. For example, exposure to light or manipulations of sleep that affect the circadian clock have a direct impact on mood [9]. Pharmacological treatments for MDD and BD, such as paroxetine and lithium, also have effects on the biological clock [10,11]. Furthermore, even in healthy individuals, the circadian clock plays a role in regulating emotions, as evidenced by distinct circadian rhythms in affective states and reward motivation under controlled conditions [12,13].

Astrocytes, which comprise approximately 30% of brain cells, are distributed throughout the central nervous system and engage in close interactions with neurons to maintain neuronal homeostasis. These glial cells support neurons through various mechanisms, including neurotransmitter uptake, ion buffering, metabolic support, and the secretion of neurotrophic factors [14–16]. Dysfunction in astrocytes impairs synaptic activity, and accumulating evidence suggests that astrocytes modulate neuronal cir-

cuits and influence behavior [17,18]. Recent research indicates that astrocytes play a role in modulating a range of behavioral domains, including sleep, circadian rhythms, perception, memory, and emotional states such as anxiety [19–21]. Postmortem histopathological studies of individuals with depression consistently report reduced glial cell densities, suggesting that aberrant astrocyte function may contribute to the pathophysiology of mood disorders [22–24]. Structural and functional deficits in astrocytes are correlated with maladaptive behaviors, positioning these cells as promising therapeutic targets for psychiatric and mood disorders. Traditionally, neurons were considered the sole timekeepers in the suprachiasmatic nucleus (SCN), with glial cells playing only supportive roles [25,26]. Recent discoveries indicate that astrocytes play an active role in the timing of the SCN network [25,27–31]. These glial cells possess cell-autonomous clocks that regulate extracellular concentrations of glutamate and γ-aminobutyric acid (GABA), thereby orchestrating the circadian rhythms of SCN neuronal activity [29,32,33]. In addition to their role in modulating rhythmicity within the central pacemaker SCN, astrocytes are also involved in emotion-related brain regions such as nucleus accumbens (NAc) [34–36], the medial prefrontal cortex (mPFC) [37–40] and ventral tegmental area (VTA) [41]. They further influence the rhythmic expression of core clock genes, including *Bmal1* and *Per2* [34,42].

This review synthesizes current evidence on the bidirectional relationship between circadian rhythms and mood disorders, with a particular focus on the involvement of astrocytes. Our aim is to consolidate diverse perspectives on astrocyte-mediated circadian modulation of mood pathology, identify existing research gaps, and propose mechanistic investigations for future astrocyte-targeted interventions in mood disorders.

2. Circadian Disruption in Mood Disorder

2.1 Molecular Sustenance of Circadian Oscillations

Circadian rhythms encompass the rhythmic physiological, biochemical, and behavioral changes that organisms undergo to adapt to approximately 24-hour light-dark cycles [25]. In mammals, circadian rhythms represent a hierarchical system that includes a central clock located within the SCN of the hypothalamus, as well as peripheral clocks distributed across various tissues throughout the body [43,44]. The SCN is anatomically and functionally divided into two subregions: the ventrolateral “core” and the dorsomedial “shell”, which are distinguished by their neuropeptide content. The core subregion contains neurons that express vasoactive intestinal polypeptide (VIP) and gastrin-releasing peptide (GRP), whereas the shell subregion contains neurons that express arginine vasopressin (AVP) [45]. These neuronal populations work synergistically to facilitate photic entrainment. The core subregion of the SCN receives photic input via the retinohypothalamic tract (RHT), which is mediated by glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) [46,47]. This photic information is then relayed to the shell subregion through neurotransmitters such as GABA, VIP, and GRP [48]. The mammalian circadian clock is primarily composed of a core feedback loop and a stabilizing loop. Within the core circadian loop, the heterodimer composed of circadian locomotor output cycles kaput (*CLOCK*) and brain and muscle ARNT-like 1 (*Bmal1*) facilitates the transcription of Period (*Per*) and Cryptochrome (Cry) genes through E-box enhancer sequences located in their promoters. The subsequent accumulation of the Period-Cryptochrome (PER-CRY) protein complex in the nucleus exerts negative feedback, thereby inhibiting the activity of the CLOCK-*BMAL1* heterodimer. As the PER-CRY complex undergoes degradation, a new cycle is initiated approximately every 24 hours. In the stabilizing loop, the CLOCK-*BMAL1* heterodimer regulates the nuclear receptors retinoic-acid-related orphan receptors alpha (Rorα) and nuclear receptor subfamily-group D member 1 (REV-ERB) via E-box sequences, with retinoic-acid-related orphan receptors (ROR) and REV-ERB subsequently activating and inhibiting *Bmal1* expression through the REV response element (RRE), respectively [25,49] (Fig. 1).

2.2 Circadian Disruption and Mood Disorders

The central circadian pacemaker regulates the organism’s circadian rhythms through these mechanisms. Under typical conditions, both central and peripheral rhythms are synchronized, thereby preparing the body for expected daily behavioral and environmental change [50]. However, circadian disruption occurs when there is a misalignment between the phase of entrainment and the external environment, potentially resulting in mood and behavioral disorders [51]. Mood disorders, in addition, can also affect circadian rhythms, and possibly accompanied by structural and functional brain alterations [52,53]. Neuroimaging studies have revealed volumetric changes in multiple brain regions in individuals with mood disorders, including the amygdala [54,55] and hippocampus [56,57]. Localized atrophy in the anterior-middle region of the right hippocampus has been found to correlate with later chronotypes in patients experiencing acute depression [58]. Supporting evidence from animal study indicates that unpredictable chronic mild stress (UCMS) induces anxiety- and depression-like behaviors in mice, significantly diminishes the amplitude of circadian locomotor activity (paralleling observations in patients with major depressive disorder), and simultaneously reduces molecular rhythm amplitude in the SCN while increasing rhythm amplitude in the NAc [59]. Chronotype refers to an individual’s preference for, or actual timing of, behavioral activities, and is influenced by genetic factors, age, sex, timing of light exposure, and social factors such as work and family schedules [50]. Chronotype also has significant implications for mood disorders, with late

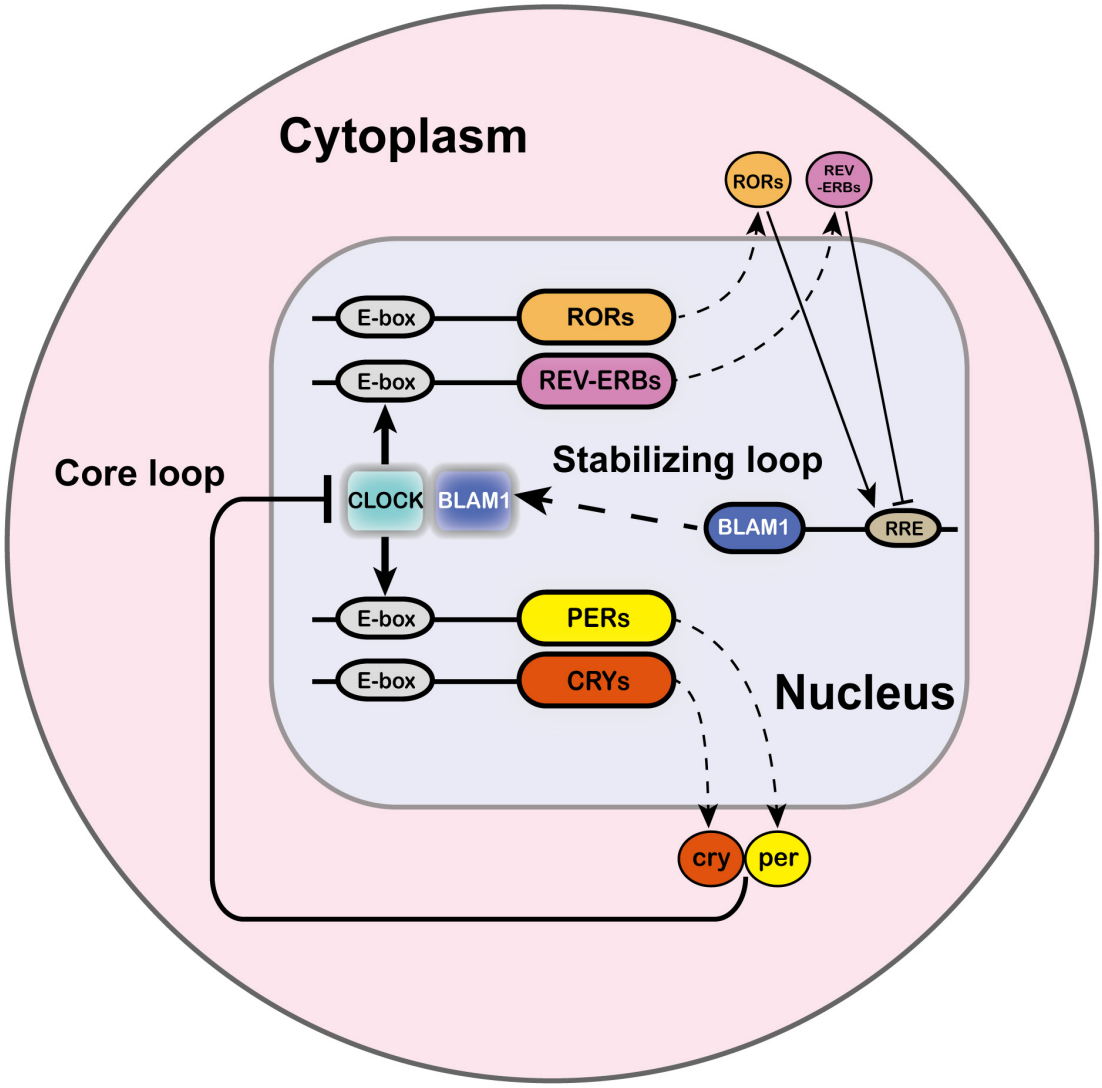

Fig. 1. The mechanism of TTFLs in circadian rhythms. The TTFL is intricate and involves multiple regulatory components. In mammals, the circadian rhythm primarily consists of the core loop and the stabilizing loop. Within the core loop, the heterodimer formed by CLOCK and *BMAL1* proteins initiates the expression of *Per* and *Cry* genes through enhancer box (E-box) regulatory sequences located in their promoters. The PER-CRY protein complexes subsequently accumulate in the nucleus, where they exert a negative feedback effect by inhibiting the activity of the CLOCK-*BMAL1* heterodimer. As the PER-CRY complexes degrade, a new cycle is permitted to commence approximately every 24 hours. In the stabilizing loop, the CLOCK-*BMAL1* heterodimer drives the expression of the nuclear receptors *Ror*α and REV-ERB via E-box elements. In turn, *Ror*α and REV-ERB modulate the expression of *Bmal1* by activating and repressing it through the REV response element (RRE), respectively. Black solid lines represent direct molecular interactions. Black dashed lines indicate indirect regulatory processes or spatial transitions. TTFL, transcriptional–translational feedback loop; *BMAL1*, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; *Ror*α, retinoic-acid-related orphan receptors alpha; Per, Period; PER-CRY, Period-Cryptochrome; REV-ERBs, nuclear receptor subfamily-group D member 1.

chronotypes and individuals experiencing social jet lag being at an increased risk for psychiatric disorders [60,61]. Notably, a late chronotype is well-recognized to be associated with a higher prevalence of depressive symptoms in both individuals with major depressive disorder and healthy controls [60,62,63]. A diffusion tensor imaging study has revealed differences in white matter integrity within the frontal and temporal lobes, cingulate gyrus, and corpus callosum among individuals with an evening chronotype, as compared to those with morning and intermediate chronotypes [64]. Furthermore, the evening chronotype is associated with increased bilateral amygdala sensitivity to negative emotional facial expressions and reduced functional connectivity between the dorsal anterior cingulate cortex (dACC) and amygdala, suggesting potential disruptions in emotion regulation circuitry [65]. Notably, Sex differences

play a crucial role in the regulation of circadian rhythms and the manifestation of mood disorders. During adolescence, boys exhibit a more significant shift towards a later chronotype relative to girls [66]. Additionally, adult males typically demonstrate a later chronotype than their female counterparts [67]. Moreover, factors such as sex hormones [68] and variations in brain structure and function [69] contribute to the increased vulnerability of women to mood disorders, such as anxiety, compared to men. Consequently, incorporating sex as a biological variable is essential for the development of more personalized, rhythm-based intervention strategies for individuals with mood disorders.

Additionally, clock gene polymorphisms have been associated with mood disorders, such as major depressive disorder and anxiety [70–73]. Research involving BD patients has identified that the *CLOCK* rs1801260 polymorphism, linked to the evening chronotype, correlates with discrepancies between subjective and objective assessments of depressive symptom severity. Similarly, the efficacy of antidepressants in MDD patients may have been influenced by variations in the Clock gene [73]. In addition to its association with depression and anxiety, human *CRY1*Δ*11* variant rescued the rhythm in the bioluminescence reporter *mPer2-Luc*, and the circadian rhythm lengthened for *CRY1*Δ*11* compared with that for WT *CRY1* [72, 74]. Animal models offer mechanistic validation for these clinical findings. shRNA knockdown of *Per2* and cAMP response element-binding protein (CREB) in the hippocampal Cornu Ammonis 1 (CA1) region led to mania-like behavior, whereas increasing the expression of these factors caused depression-like The inter-regulatory crosstalk between *Per2* and CREB might mediates transitions between mania-like and depression-like behaviors [75]. In a mouse model of depression, the mPFC demonstrates increased amplitude of negative loop genes *Per2* and *Cry2*, decreased amplitude of *Ror*α, downregulated expression of retinoic acid receptor-related orphan receptor beta (Rorβ), and shifted acrophases of *Per2*, *Cry2*, *Bmal1*, and *Ror*α. The silencing of the *Per2* gene in the mPFC results in effects analogous to those of antidepressants, whereas the activation of REV-ERB receptors exacerbates depression-like behaviors and counteracts the effects of ketamine [76]. Mice lacking the *Cry2* gene demonstrate anhedonia and exhibit altered diurnal patterns of gene expression in the amygdala, including abnormal rhythmic expression of the clock gene Basic helix-loop-helix family member e40 (Bhlhe40) during the dark phase [77]. Collectively, these findings suggest that clock genes, which are integral components of the circadian oscillator, are strongly associated with psychiatric disorders; however, altering or removing a clock gene will affect the other clock genes in that region, thereby changing their phase relationship with the SCN. The specific molecular and physiological mechanisms underlying these associations remain to be elucidated.

SCN receive numerous synaptic inputs, most notably from the RHT, which transmits light-responsive signals directly from the retina to synchronize biological rhythms via this zeitgeber [78,79]. Remarkably, astrocytes within the SCN exhibit an increase in cellular FBJ osteosarcoma oncogene (cFOS) expression in response to photic stimulation, indicating their potential role in light response and possibly in circadian entrainment [80,81]. Emerging evidence suggests the existence of an SCN-independent pathway, mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs), which provide excitatory synaptic input to neurons in the perihabenular nucleus (PHb) of the dorsal thalamus and play a role in mood regulation [82]. Research has confirmed that abnormal exposure to nighttime light significantly influences mood and may substantially elevate the risk of developing mood disorders, such as depression [83]. Mice exposed to constant light or light during the night has been shown to significantly exacerbate depression-like behaviors, such as decreased sucrose preference and increased immobility time, while also diminishing the amplitude of circadian rest-activity rhythms and reducing nighttime activity levels [84,85]. Additionally, dim light at night interferes with *Per1* gene expression in the hippocampus of postpartum mice, with a potential link to depression through the TGF-β signaling pathway [86]. However, the study has also indicated that nighttime light can induce depression-like behaviors through the ipRGC$\rightarrow$dpHb$\rightarrow$NAc neural circuit without disrupting circadian rhythms [87]. Consequently, the mechanisms by which nighttime light exposure contributes to mood disorders remain incompletely understood. Although environmental light can contribute to the development of mood disorders, specific light exposure can conversely serve as a therapeutic intervention. Light therapy, or phototherapy, has been shown to be effective in treating perinatal depression [88], unipolar depression [89], and bipolar depression [90]. Furthermore, the efficacy of light therapy for mood disorders is contingent upon the specific mood disorder and the timing of light exposure, which is crucial to its effectiveness. For instance, adjunctive midday bright light therapy (BLT) [91] and morning BLT [92] have been found to benefit bipolar depression, whereas early morning bright light therapy is recommended for depression [93,94]. This conclusion has also been corroborated by animal experiments, which demonstrated that morning BLT exhibits greater antidepressant efficacy compared to evening BLT [95]. Although research indicates that one hour of high-intensity light exposure during the active phase enhances the expression of SCN clock genes, including *Per1*, *Per2*, and *Cry1* [96], suggesting that circadian genes may play a role in this process, the underlying mechanisms of light therapy's efficacy for mood disorders remain unclear. Beyond phototherapy, the timing of drug administration in relation to the circadian phase can be optimized to enhance efficacy, minimize adverse effects, or modulate circadian rhythms.

For example, the administration of the antipsychotic aripiprazole in the morning was found to significantly enhance lipid and cholesterol profiles compared to its evening administration [97]. Conversely, administering risperidone in the evening led to greater weight gain and increased levels of glycated hemoglobin relative to morning administration [98]. Evening administration of melatonin promotes phase advances in patients with delayed sleep-wake phase disorder and may positively influence the psychopathology of other disorders suspected to involve comorbid sleep-circadian disruption [99].

Although extensive clinical evidence and foundational research substantiate the therapeutic efficacy and underlying mechanisms of circadian rhythm interventions for mood disorders, current intervention strategies predominantly target neurons. Astrocytes, which engage in bidirectional interactions with neurons to dynamically modulate cellular functions, are pivotal glial cells in the context of mood disorder interventions [100]. The role of astrocytes in circadian regulation is gaining recognition, necessitating further investigation into their potential as key therapeutic targets for modulating circadian-related mood disorders.

3. Astrocyte-Mediated Circadian Control of Mood Disorder

3.1 Astrocytes in SCN Circadian Rhythm Regulation

The SCN is predominantly comprised of neurons and astrocytes. Neurons within the SCN are essential for sustaining circadian rhythms, as they autonomously regulate clock gene expression to initiate rhythmic patterns and synchronize molecular clocks in peripheral tissues [25,26]. Increasing evidence suggests that astrocytes, which are neuronally active and possess cell-autonomous TTFL clocks, are vital components of the SCN's timekeeping system [27,28]. Astrocytes display pronounced intrinsic rhythmicity, as evidenced by the 24-hour oscillations of glial fibrillary acidic protein (GFAP), a specific marker for astrocytes, under both light-dark (LD) cycles and constant darkness (DD) conditions [101]. The $[Ca^{2+}]_i$ in astrocytes, crucial for neuroglial interactions, exhibits rhythmic fluctuations, peaking at night and reaching troughs during the day [29]. Notably, these astrocytic $[Ca^{2+}]_i$ oscillations are antiphasic to those observed in neurons [27,29]. The observed phase difference between SCN astrocytes and neurons indicates a mutually antagonistic coupling mechanism. In this model, daytime signals emitted by electrically active neurons inhibit astrocytic functions, whereas the nocturnal suppression of circadian neurons and their associated neuropeptidergic networks permits astrocytic activation, which may in turn suppress neuronal activity [29].

Astrocytes have been demonstrated to participate in the modulation of circadian rhythms in the SCN. The conditional knockout of *Bmal1* in SCN astrocytes, identified by the Aldehyde dehydrogenase 1 family member L1 (Aldh1l1) promoter, exhibit an extension of the circadian period of the SCN and alterations in locomotor activity rhythms in mice [30]. Similarly, targeting astrocytes via the Glutamate aspartate transporter (GLAST) promoter in *Bmal1* conditional knockout mice, exhibit a delayed onset of the active phase of locomotor activity [102]. These findings collectively underscore the correlation of clock genes within astrocytes in regulating the organism's circadian rhythms. Additionally, the circadian period is extended in Csnk1ε (CK1ε) tau mutation mice, whereas the circadian period of behavior and SCN firing rates *in vitro* is reduced in CK1$\varepsilon^{Tau/Tau}$ mice [103]. Similarly, deleting the short-period CK1ε^{tau} mutation specifically from SCN astrocytes caused prolonged rhythms in the SCN and behavior [104]. Moreover, the specific expression of *Cry1* in astrocytes within Cry-null SCN slices or Cry-null mice restores normal molecular clock function and circadian behavior, mirroring the effects observed when *Cry1* is expressed exclusively in SCN neurons [31]. This evidence further confirmed the effects of astrocytes in regulating SCN molecular rhythms. In summary, SCN astrocytes exhibit rhythmic expression patterns that are distinct from SCN neurons and possess the capacity to autonomously drive and encode the SCN circadian timekeeping.

3.2 Clinical Evaluation of Circadian Astrocytic Biomarkers in Mood Disorders

Research has established the critical role of astrocytes in circadian regulation. Furthermore, astrocytic dysfunction may disrupt normal brain function and potentially contribute to the development of mood disorders [105]. Research on astrocyte morphology and astrocyte-specific biomarkers has identified hypertrophy of astrocyte cell bodies and processes in the anterior cingulate cortex (ACC) of individuals who have died by suicide with depression [106]. Additionally, studies have reported a reduction in astrocyte density and decreased expression of the classical astrocyte marker GFAP in various brain regions, such as the amygdala and ACC, in patients with MDD [106,107]. In contrast, in depressed suicide victims, a downregulation of GFAP mRNA and protein expression has been observed in the dorsomedial thalamus and caudate nucleus, despite the presence of enlarged astrocyte cell bodies and processes [108]. Moreover, increased serum levels of the calcium-binding protein S100β in MDD patients have been associated with the severity of symptoms. Neuroimaging and histopathological investigations have consistently demonstrated a robust correlation between BD and cortical thinning in both gray matter (GM) and white matter (WM). This cortical thinning can be ameliorated through lithium treatment [109–112] and is associated with localized neuronal and astrocytic loss [113,114]. This clinical evidence suggests that reduced astrocyte density and/or impaired astrocyte function may play a role in the pathogenesis of MDD [115].

Furthermore, studies on astrocyte rhythm-regulating proteins have demonstrated downregulated expression of astrocyte-associated proteins, including glutamine synthetase (GS), glutamate transporters, and connexins, in patients with mood disorders [116,117]. Glutamate serves as a critical gliotransmitter through which astrocytes modulate circadian rhythms to sustain the TTFL in the SCN. Inhibition of astrocytic glutamate transport has been shown to disrupt the TTFL in the SCN [29]. Empirical evidence indicates that the mRNA expression of GS, indicative of astrocytic glutamate handling capacity, is diminished in the dorsolateral prefrontal cortex (dlPFC), premotor cortex, and amygdala of individuals with depression [116]. Similarly, analyses of specific cortical regions in patients with MDD reveal downregulation of genes encoding the high-affinity astrocytic glutamate transporters solute carrier family 1 member 2 (SLC1A2) and solute carrier family 1 member 3 (SLC1A3) [118]. Connexin 30 (Cx30) and connexin 43 (Cx43) are essential proteins that facilitate calcium wave propagation and inter-astrocytic communication. Targeted inhibition of glutamate release via Cx43 hemichannels can influence the expression of circadian clock genes in SCN neurons [31]. Research has demonstrated reduced expression of Cx30 and Cx43 in the dlPFC of individuals with MDD who have died by suicide [119]. Similar findings have been reported for aquaporin-4 (AQP4), with decreased expression levels observed in MDD patients [105]. Glutamate transporters serve as a principal mechanism through which astrocytes regulate glutamate concentrations. Additionally, in astrocytes and hippocampal slices, glutamate release is predominantly facilitated by Cx43 hemichannels [120]. This observation implies that the downregulation of glutamate transporters and connexins in patients with mood disorders corresponds with the observed trend of diminished rhythmic expression in the SCN and may constitute a mechanism contributing to circadian disruption. Nonetheless, research concerning the regulation of astrocytic glutamate rhythms has predominantly concentrated on the SCN. It remains uncertain whether the circadian disruption symptoms associated with mood disorders originate from intrinsic rhythm alterations within mood-related brain regions or are contingent upon glutamate projections from the SCN. Human-based studies, particularly those involving post-mortem analyses, possess substantial limitations that obscure the generalizability of these findings. Consequently, further mechanistic studies employing animal models are necessary for validation.

3.3 Circadian Rhythms in Astrocytes Underlies Mood Disorder Pathogenesis

3.3.1 Cell-Autonomous Circadian Rhythms in Astrocytes Underlie Mood Disorder

A review of genetic evidence from various animal models suggests that astrocytic networks within the brain modulate behavioral changes, including those related to sleep, circadian rhythms, and depression-like behaviors [20]. Moreover, exposure to acute or chronic stress stimuli induces both functional and structural alterations in astrocytes, potentially resulting in deficits in emotion-related behaviors [121]. The SCN functions as the central circadian pacemaker of the brain. The rhythmic expression of TTFL genes and circadian behaviors are directly modulated by chemogenetic or optogenetic activation of SCN neurons [78,79]. Additionally, the amplitude of molecular rhythms within the SCN diminishes following stress intervention with UCMS [59]. Recent studies have revealed that astrocytes also exhibit cell-autonomous TTFL rhythms, a finding corroborated by *ex vivo* SCN slices expressing astrocyte-specific TTFL genes [31,104].

In addition to its established role in modulating reward-related rhythms, the NAc may also serve as a circadian oscillator, integrating sensory and circadian inputs to temporally regulate motivated behaviors [122]. Electrophysiological study has demonstrated that medium spiny neurons (MSNs) within the NAc exhibit circadian fluctuations in glutamatergic synaptic transmission, peaking during the excitatory phase that aligns with the active/dark period in mice [123]. Moreover, dopamine levels and its metabolites in the NAc display pronounced circadian rhythms [124–126], and the transcription of genes such as tyrosine hydroxylase, dopamine transporter, monoamine oxidase A, and dopamine receptor D1 (Drd1), D2 (Drd2), D3 (Drd3) is directly influenced by the molecular circadian clock [127–132]. Research indicates that UCMS not only reduces the amplitude of circadian locomotor activity and molecular rhythms in the SCN of depressed mice but also increases the amplitude of molecular rhythms in the NAc brain region. Furthermore, there is a negative correlation between the time spent swimming in the forced swim test (FST) and the time spent in the open arms of the elevated plus maze (EPM) with the *Per2*::luc rhythm amplitude in the NAc [59]. Recent research has demonstrated that NAc astrocytes not only express robust rhythms in all canonical clock genes, but approximately 43% of the entire NAc astrocyte transcriptome exhibits a significant diurnal rhythm [34]. In contrast, only 6% of the entire NAc (encompassing all cell types) was found to be rhythmic [133], the astrocyte-specific rhythm highlights the complexity of circadian regulation within the NAc. Disruption of the molecular clock specifically within NAc astrocytes showed alterations in exploratory and emotional behaviors during the daytime, but not at night, suggesting significant circadian variation [34] (Table 1, Ref. [32,34,35,89,134–138]). The NAc is a critical brain region involved in emotion regulation, receiving projections from PFC neurons and modulating mood and stress responses [139]. Collectively, these studies suggest the presence of an intrinsic, functional circadian clock system within the NAc that orchestrates its functions across different times of the day. Furthermore, these rhythms may be entrained by rewarding stimuli and/or indirectly influ-

Table 1. Effects of circadian manipulations on astrocyte phenotype and emotional behavior.

Affected region	Manipulation	Astrocyte phenotype	Emotional behavior	References
NAc	*Bmal1* deletion	GFAP expression ↑ AMPA (Gria1/2/3/4) expression ↑ NMDA (Grin2a/2d/3a) expression ↑ mGluRs (Grm2) expression ↑ GLT-1 expression ↑ AMPA/NMDA EPSC ratio during the day ↓	Circadian day: locomotor response to novelty ↑ Circadian day: the number of center entries (OFT) ↑ Circadian day: time in the lighted (dark/light box) ↑	[34]
	GCre+ *Per2*fl/fl	GAT-2/Slc6a13 and Drd3 expression ↓ Glutamate levels ↓ *Per2* expression ↓	Immobile time (FST) ↓ Time in the open section (O-maze) ↑	[35]
	Per1/2 deletion	N/A	Time in the lighted (dark/light box) ↓ Locomotor activity in the light (dark/light box) ↓ Time in the open arms (EPM) ↓	[134]
	Per2 deletion	Glutamate levels ↓ GAT-2/Slc6a13 and Drd3 expression ↓	Despair and anxiety ↓	[135,136]
SCN	*Bmal1* deletion	N/A	Escape latencies and number ↑	[89]
	Cry1-null slices	Circadian day: GAT-3 ↑ [GABA]e ↓ Circadian night: GAT-3 ↓ [GABA]e ↑	N/A	[32]
VTA	Clock-Δ19	N/A	Anxiety-related behavior ↑	[137,138]

PM, Elevated plus maze; EPSC, excitatory postsynaptic currents; FST, forced swim test; GABA, γ-aminobutyric acid; GAT, GABA transporter; GFAP, glial fibrillary acidic protein; GLT-1, glutamate transporter 1; Gria, glutamate ionotropic receptor AMPA type; NAc, nucleus accumbens; OFT, open field test; SCN, suprachiasmatic nucleus; VTA, ventral tegmental area; N/A, not determined; ↑, increase; ↓, decrease.

enced by innervation from the SCN [122,140–143]. Although a direct neural pathway from the SCN to the NAc has yet to be identified, it is plausible that the NAc receives circadian information indirectly from the SCN via the paraventricular nucleus of the thalamus (PVT) [122]. However, the detailed mechanisms underlying these processes remain to be elucidated. Furthermore, the neuronal composition of the SCN and NAc is notably similar, as both regions are predominantly composed of GABAergic neurons [144–146]. Importantly, the use of UCMS models selectively altered rhythm amplitudes specifically in the SCN and NAc, while rhythms in other regions typically associated with anxiety and depression remained relatively unaffected [59]. Consequently, astrocyte rhythms within the NAc might play a pivotal role in the regulation of mood disorders.

Neurons in the mPFC receive inputs from the cortex, thalamus, and limbic system, and project to multiple brain regions, including the amygdala, NAc, dorsal raphe nucleus (DRN), and lateral habenula (LHb), to regulate emotion and stress responses, establishing the mPFC as a vital region for emotional control [139]. Clinical investigations into the mPFC and the striatum—brain regions associated with positive affect—indicate that individuals with an evening chronotype exhibit diurnal patterns of positive affect characterized by a phase delay and reduced amplitude, alongside diminished overall metabolic activity in these regions during both morning and evening wakefulness. Collectively, these preliminary findings may represent a potential mechanism underlying the heightened risk of mood disorders among late chronotype [42]. This suggests a possible link between the emotional regulatory functions of the mPFC and the circadian clock. Previous studies have demonstrated that the ablation of mPFC astrocytes via L-α-aminoadipic acid showed behaviors indicative of depression and anxiety, such as reduced sucrose preference, increased immobility time, and a higher incidence of escape failures in learned helplessness paradigms [37,38] (Table 2, Ref. [37,40,147–155]). The pharmacological inhibition of astrocyte function, which induces depressive-like effects, further corroborates this hypothesis. For example, the central blockade of astrocytic glutamate in the prefrontal cortex has been shown to influence depressive-like effects [147].

The amygdala, a downstream target of mPFC neuronal regulation, plays a crucial role in the modulation of emotions, including fear and anxiety [156]. The basolateral amygdala (BLA) functions as the primary input structure of the amygdala, receiving a wide array of sensory information from the thalamus and cortex [157]. Previous research has demonstrated that chronic unpredictable mild stress intervention leads to a reduction in reactive astrocyte activity within the BLA. In contrast, chronic (21-day) optogenetic stimulation of Channelrhodopsin-2 (ChR2) in BLA astrocytes help to mitigate anxiety-like behaviors in mice exposed to UCMS [109]. Notably, investigations into neuronal involvement have revealed that activation of BLA

Table 2. Effects of astrocyte-specific manipulation on circadian and behavioral consequences.

Affected region	Manipulation	Change in astrocytes	Rhythmic molecular phenotype	Emotional behavior	Reference
SCN	GFAP-Cre mice; WIN 55,212-2 treatment	CB1/2Rs ↑	*Per2*::Luc rhythms ↑ ADO ↑	N/A	[153]
	Vgat-Cre; ChR2 mice	N/A	The homecage activity period or tau ↓ The amplitude of homecage activity rhythms ↓	Time in the center (OFT) ↓ Open arm entries and open arm time (EPM) ↓	[150]
mPFC	Cx43-shRNA mice	Cx43 ↓	ATP levels ↓	Sucrose preference (SPT) ↓ Immobility (FST) ↑ Time in the central area (OFT) ↓ Time in the open arms (EPM) ↓ Probability of entering the open arms (EPM) ↓	[40]
	WT mice; AAV2/5-GfaABC1D-Cx43-mCherry treatment	Cx43 ↑	ATP levels ↑	Sucrose preference (SPT) ↑ Immobility (FST) ↓ Time in the central area (OFT) ↑ Time in the open arms (EPM) ↑ Probability of entering the open arms (EPM) ↑	[40]
	WT mice; DHK treatment	EAAT2 ↓	Typical waking EEG	Latency to begin drinking sucrose ↑ Intracranial self-stimulation thresholds ↑	[147]
	WT mice; L-AAA treatment	Astracyte ↓	N/A	Sucrose preference (SPT) ↓ Latency to feed in novelty suppressed feeding test ↑ Immobility duration (FST) ↑ Escape latency (AAT) ↑	[37]
	WT mice; ATP or ATP-γ-S treatment	N/A	N/A	CSDS-induced social avoidance (SIT) ↓ CSDS-induced immobility (FST) ↓ CMS-induced fur condition ↓ Post-CMS sucrose preference (SPT) ↑	[152]
ZI	WT mice; hPMCA2w/b treatment	Ca^{2+} ↓	GABAergic neuronesactivation ↑ GAT-3 expression ↑	Anxiety-like behaviour ↓	[151]
BLA	LDN-212320 treatment	EAAT2 ↓	N/A	Entries and time spent in the center (OFT) ↓ Exploration of the open arms (EPM) ↓	[149]

Table 2. Continued.

Affected region	Manipulation	Change in astrocytes	Rhythmic molecular phenotype	Emotional behavior	Reference
LHb	WT mice; DHK treatment	EAAT2 ↓	N/A	Entries and time spent in the center (OFT) ↑ Exploration of the open arms (EPM) ↑	[149]
	GLT-1flox/flox mice; DHK treatment	EAAT2 ↓	LHb neurons ↑ REM sleep ↑ Latency to the onset of REM ↓ Unimodal distributions for all three sleep stages	Immobility duration (TST) ↑ Latency to the first immobility episode ↓	[148]
CeM	WT mice; AAV8-GFAP-hM3D-mCherry treatment	Ca^{2+} ↑	N/A	Freezing response ↓ Fear response ↓ No anxiety behavior	[149]
N/A	*Per2*::Luc transgenic mice; IB-MECA treatment	N/A	*Per1* and *Per2* expression ↑ *Per1* and *Per2* rhythms period length ↑	N/A	[154]
	THP-1 (TIB-202) cells; CGS21680 treatment	N/A	Clock and Bmal mRNA ↑ *Per2* mRNA ↓ *Rev-erbα* mRNA ↑	N/A	[155]

AAT, active avoidance test; ATP-γ-S, adenosine 5-(3-thiotriphosphate) tetralithium salt; BLA, basolateral amygdala; CB, cerebellum; CeM, medial central amygdala; ChR2, channelrhodopsin; Cx, connexin; DHK, dihydrokainic acid; EEG, Electroencephalogram; EPM, Elevated plus maze; FST, forced swim test; Gria, glutamate ionotropic receptor AMPA type; L-AAA, L-α-aminoadipate; LHb, lateral habenula; NAc, nucleus accumbens; OFT, open field test; mPFC, medial prefrontal cortex; REM, rapid eye movement; SCN, suprachiasmatic nucleus; SPT, sucrose preference test; TST, tail suspension test; WT, wildtype; N/A, not determined; EAAT, excitatory amino acid transporter; ↑, increase; ↓, decrease.

astrocytes contribute to alleviates anxiety, whereas activation of BLA glutamatergic neurons does not reduce anxiety-like behaviors in stressed mice [158]. Furthermore, clinical studies indicate that the observed reduction in amygdala volume in patients with mood disorders may primarily result from a decrease in astrocyte density rather than neuronal loss [159,160]. Collectively, these findings suggest that the function of amygdala astrocytes may operate independently of neuronal activity. Recent clinical research suggests a potential association between the emotional regulatory function of the amygdala and the circadian clock, as evidenced by increased bilateral amygdala sensitivity to negative emotional facial expressions in patients with an evening chronotype [65]. This finding may elucidate, from a neuroregulatory perspective, the frequent comorbidity of mood disorders and circadian rhythm disruptions. Conversely, animal study has demonstrated that while UCMS diminishes the amplitude of circadian locomotor activity and molecular rhythms in the SCN of depressed mice, the rhythmicity of *Per2* expression in the frontal cortex and amygdala remains largely unaffected [59]. It is hypothesized that astrocytes within the amygdala may play a pivotal role in rhythm regulation. However, further research is needed to elucidate how these astrocytes modulate rhythmic changes in the amygdala under conditions of mood disorders.

Integrating the aforementioned evidence, astrocytes appear to be integral components of the anxiety regulatory circuitry, extending from the mPFC to downstream regions such as the amygdala and NAc. In light of the increased sensitivity to negative emotional expression observed in individuals with an evening chronotype, the regulation by the mPFC, amygdala, and NAc demonstrates a distinct temporal bias. Research indicates that astrocytic $[Ca^{2+}]_i$ undergoes rhythmic fluctuations, characterized by a peak during the night and a trough during the day [29]. Neuronal signals released during the daytime suppress astrocytic function, whereas the nocturnal silencing of neuronal networks permits astrocytic activation [29,130], a phenomenon consistent with chronotype trends identified in clinical studies. Nonetheless, these studies predominantly focus on specific brain regions and primarily describe effects. Therefore, the precise mechanistic role of astrocytic rhythmic alterations in mood disorders necessitates further investigation.

3.3.2 Astrocytic Clock Genes and Mood Disorder Pathogenesis

Rhythmic neuronal activity and neurotransmitter expression within the SCN are regulated by the Clock gene. Consequently, alterations in circadian clock gene expression may lead to disruptions in neuronal physiology, ultimately impacting peripheral biological systems governed by the SCN [25,43,44]. Remarkably, astrocytes in other brain regions beyond the SCN were also found to have significant rhythmicity [122].

Studies have demonstrated significant rhythmicity in the circadian molecular clock function of the NAc. Sustained bioluminescent rhythms have been observed in the NAc *ex vivo* using the *PER2:LUC* mouse model [59,161], corroborating gene expression analyses in mice that reveal significant diurnal variation in molecular clock mRNA levels within the NAc [59,133,142,162–164]. This phenomenon is corroborated by RNA-sequencing analyses of human post-mortem NAc tissue, which reveal pronounced rhythmic expression of canonical clock genes, such as *Bmal1*, *Npas2*, *Period*, *Cryptochrome*, and *Rev-erbα*. Furthermore, pathway analyses identify *Circadian Rhythm Signaling* as a significantly enriched pathway among the top rhythmic genes [165,166]. Mice deficient in both *Per1* and *Per2*, in the NAc, exhibit markedly heightened anxiety and depression phenotypes [134]. Similarly, both the genetic deletion of *Per2* in glial cells and adeno-associated virus (AAV)-mediated deletion of *Per2* specifically in the glial cells of adult mice might be associated with behaviors resistant to depression and anxiety (include increased time spent in the open section of the elevated zero maze (O-maze) and decreased immobility time in the FST). However, astrocyte-specific *Per2* knockout mice maintain normal circadian parameters [35], although the deletion of *Per2* from SCN astrocytes extends the overall TTFL period and circadian behavior [29,104]. Therefore, while the rhythmic expression of the *Per2* gene in SCN astrocytes may contribute to mood regulation, in the NAc, astrocytic *Per2* may influence emotional function solely as a nuclear receptor co-regulator, independent of circadian regulation [36].

It has been demonstrated that the knockdown of *Bmal1* specifically within the SCN leads to reduced circadian rhythmicity, desynchronized single-cell rhythms, and exhibit an increase in behaviors indicative of despair, anxiety, and helplessness [135,136]. In contrast, the functional disruption of the *Bmal1* molecular clock in NAc astrocytes is associated with improvements in reward- and emotion-related behaviors, such as increased time spent in the open arms of the EPM and a higher number of center entries in the open field test (OFT) during the day, but not at night [34]. However, another study reported that the deletion of *Bmal1* in NAc astrocytes does not influence emotional behaviors such as despair or anxiety [35]. Notably, the effects of disrupting the *Bmal1* molecular clock in SCN versus NAc astrocytes on mood regulation appear to be diametrically opposed. The attenuation of activity within the SCN, which serves as the central circadian pacemaker, results in the disruption of rhythmic patterns in downstream brain regions that are directly implicated in emotion regulation [136,167]. This suggests that disturbances in the SCN's central rhythmic pacemaker may directly induce alterations in brain regions responsible for emotion regulation, thereby impacting emotional behavior. In contrast, the rhythmic regulation within the NAc is generated locally within this downstream brain region and does not influence the central

rhythmic control exerted by the SCN. Similar to the SCN, the NAc is primarily composed of GABAergic neurons, and astrocytes within the NAc play a pivotal role in maintaining glutamate homeostasis [144,145]. The regulation of glutamate by astrocytes in the NAc is believed to contribute to reward modulation and susceptibility to drug addiction [130,168,169]. Moreover, the functional disruption of the *Bmal1* molecular clock in NAc astrocytes has been shown to significantly upregulate the expression of genes related to glutamate [34]. Moreover, the astrocyte-specific deletion of *Bmal1* across the brain results in astrocyte activation and the expression of inflammatory genes, thereby promoting neuronal death *in vitro* [36]. The neuroinflammation resulting from *Bmal1* deletion may be linked to the onset of mood disorders. Thus, while astrocytic *Bmal1* in both the NAc and SCN plays a role in emotion regulation, the underlying pathways differ, with the regulation of glutamate transport likely serving as a key mechanism for astrocytic *Bmal1* in the NAc (Fig. 2).

The ventral tegmental area (VTA), a critical region involved in the regulation of reward and emotion, demonstrates a distinct rhythmic organization, including Clock gene rhythms [122,170]. Diurnal transcriptional regulation of key enzymes responsible for dopamine (DA) synthesis and degradation within the VTA has been documented [13,128], alongside circadian variations in the activity of VTA DA neurons [171]. Research indicates that Clock-Δ19 mutant mice display altered expression of several pivotal dopamine-related genes within the VTA, which correlates with enhanced DA neuron functionality, such as increased mean firing rates and bursting activity [137,138]. Additionally, changes in astrocytic Ca^{2+} levels can influence adenosine A1 receptor (A_1R) activity on GABAergic neurons, leading to the disinhibition of DA neurons and resulting in anxiolytic and antidepressant effects [41]. Consequently, the mechanism by which VTA astrocytes contribute to the regulation of mood disorders, akin to the regulation by Clock, involves the modulation of DA neuron activity, although direct evidence substantiating this mechanism is presently insufficient.

The evidence for direct neuronal projections from the SCN to downstream regions involved in emotion regulation, such as the NAc and VTA, remains limited. Consequently, it is not possible to definitively ascertain whether the observed astrocytic rhythmic changes in the NAc and VTA are directly regulated by the SCN or if they arise from indirect effects of mutations affecting various unrelated processes in other brain regions. Current evidence supports the presence of a neural connection from the SCN to the striatum, which influences anxiety- and depression-like behaviors in mice. Additionally, SCN lesions or *Bmal1* knockout result in altered amplitudes of circadian gene oscillations and total mRNA levels in the striatum, alongside activation of the brain-derived neurotrophic factor (BDNF)-tropomyosin receptor kinase B (TrkB) pathway [172]. Nevertheless, the specific regulatory mechanisms within the NAc and VTA require further investigation.

4. Circadian Gating of Emotional Circuits via Astrocyte-Derived Neurotransmission

4.1 Glutamate

Astrocytes, a predominant type of glial cell, play a crucial role in modulating glutamate levels through mechanisms of uptake, release, and maintaining neuro-metabolic homeostasis [173]. Investigations utilizing real-time imaging of extracellular glutamate concentrations within the SCN have demonstrated distinct circadian oscillations. Notably, the extracellular glutamate rhythm aligns with the $[Ca^{2+}]_i$ rhythm observed in astrocytes [29]. Prolongation of the Ca^{2+} rhythm period correspondingly extends the period of the glutamate rhythm [31]. In the context of arrhythmic Cry-null SCN, astrocyte-mediated glutamate regulation has been shown to influence neuronal rhythmic recovery, thereby affecting the overall circadian rhythm of the SCN [31]. As the central circadian pacemaker of the brain, the SCN displays disrupted Clock gene expression rhythms in response to various light intervention stimuli [85,174], which are associated with behavioral changes such as heightened depression-like behaviors and diminished anxiety-like responses [175,176]. Furthermore, dysregulation of glutamatergic signaling has been observed in preclinical models of depression and in patients with MDD [177,178]. Neuroimaging and postmortem analyses have consistently shown alterations in glutamatergic signaling in individuals with BD. The NMDAR antagonist ketamine has been validated as an effective antidepressant and anti-suicidal intervention for BD [179–181]. Therefore, The circadian regulation of extracellular glutamate concentration serves as a crucial mechanism through which astrocytes contribute to mood regulation. This process involves the transmission of temporal information, generated by astrocytes' cell-autonomous clocks, to the neurons of the SCN, thereby influencing affective states [25,31,104]. The question arises as to how the rhythmic fluctuations in astrocytic glutamate are communicated to SCN neurons.

Primarily, astrocytes mediate the removal and recycling of glutamate from the synaptic cleft. Cx43 is the predominant gap junction protein in astrocytes [182], playing a significant role in astrocyte-neuron interactions and capable of modulating circadian clock gene expression in SCN neurons [31]. At night, astrocytes release glutamate through Cx43 hemichannels, which activates NR2C-containing N-methyl-D-aspartate receptors (NR2C-NMDARs) on neuronal presynaptic membranes. This activation results in an increased $[Ca^{2+}]_i$ concentration, promoting the release of gamma-aminobutyric acid (GABA), which subsequently inhibits postsynaptic neuronal electrical activity. Conversely, during the day, the release of glutamate from astrocytes diminishes. Concurrently, the efficiency of excitatory amino acid transporters (EAATs) in clearing glutamate

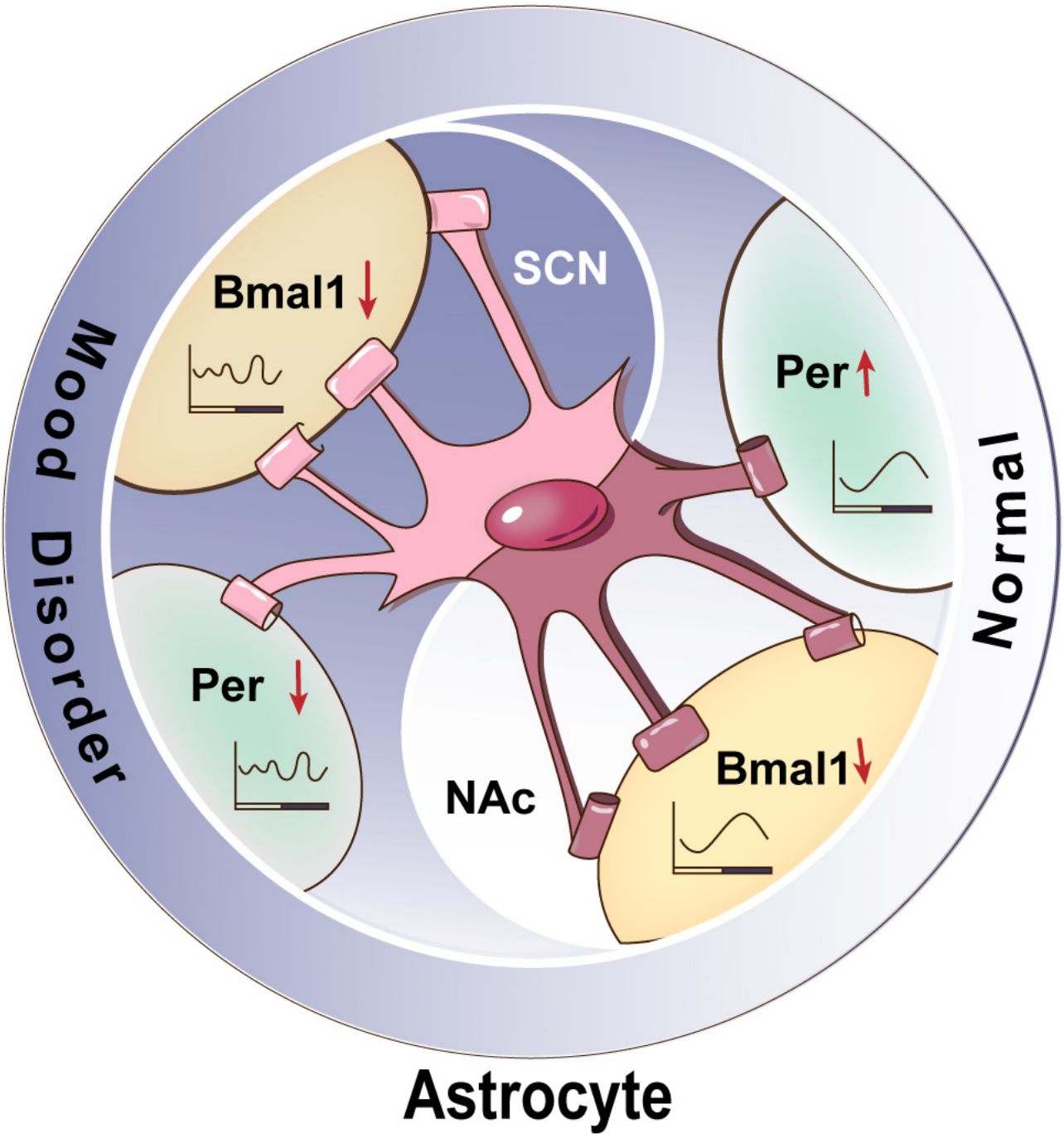

Fig. 2. Illustrates the regulation of astrocytic clock genes in the SCN and the NAc in the context of mood disorders. In the SCN, the astrocyte-specific deletion of *Bmal1* or Per disrupts circadian rhythms and is associated with the manifestation of mood disorder phenotypes. In the NAc, the astrocyte-specific deletion of *Bmal1* alleviates depressive-like behaviors without affecting circadian rhythmicity, while the deletion of Per results in mood disorder phenotypes while maintaining rhythmicity. SCN, suprachiasmatic nucleus; NAc, nucleus accumbens; ↑, increase; ↓, decrease.

is enhanced, leading to a decrease in extracellular glutamate concentration and a reduction in the inhibition of postsynaptic neurons, thereby facilitating peak neuronal electrical activity [29,33]. Furthermore, rhythmic changes in glutamate levels have also been observed in the hippocampus, a critical region for emotion regulation. Research indicates that the magnitude of long-term potentiation (LTP) in the hippocampus exhibits diurnal variation [183]. Specifically, during the dark phase, astrocytes retract their processes and reduce glutamate uptake, accompanied by a decrease in the rhythmic amplitude of NMDA EPSCs [184]. Circadian regulation influences the rhythmic capacity of astro-

cytes for glutamate release and recycling. Aberrant expression of astrocyte glutamate-associated proteins may result in an excitation-inhibition imbalance, potentially precipitating mood disorders such as anxiety and depression. Clinical studies have reported diminished expression and content of the glia-specific enzyme glutamine synthetase (GS) and the glutamate transporter 1 (GLT-1) in individuals with depression [118], along with the downregulation of SLC1A2 and SLC1A3 [118], and reduced expression of connexins Cx30 and Cx43 [119]. Furthermore, microinjection of a GLT-1 inhibitor into the rat PFC might induces depression-like behavior [147], suggesting compromised glutamate clearance and metabolism in specific brain regions.

The epithalamic habenula (Hb), a critical component of the brain's reward circuitry, contains an autonomous circadian clock that is functionally coupled to the SCN [185]. Moreover, the region-specific inhibition or deletion of GLT-1 in the lateral habenula (LHb) induces depression-like phenotypes, as evidenced by the tail suspension test (TST) and the novelty-suppressed feeding test (NSFT). The frequency of neuronal spikes in the LHb increases following pharmacological inhibition or virus-mediated deletion of GLT-1, correlating with depressive symptoms [148]. During daylight hours, the uptake capacity of GLT-1 is enhanced, facilitating the recycling of excess synaptic glutamate and maintaining glutamate homeostasis [29,30]. Inhibition of GLT-1 can result in glutamate accumulation and subsequent neurotoxicity [186], aligning with the observed effects of region-specific GLT-1 inhibition on emotional behavior. Therefore, it is plausible that GLT-1 inhibition exerts its effects predominantly during the daytime. Conversely, the targeted knockdown of EAAT2 within BLA astrocytes contribute to ameliorated anxiety-like behavior in stressed mice, whereas overexpression of EAAT2 in the BLA might induced anxiety-like behavior [149]. These findings suggest that the regulation of glutamate uptake and emotional behavior is specific to particular brain regions. In conclusion, rhythmic alterations in astrocytic glutamate levels may disrupt the balance between excitatory and inhibitory neurotransmission, potentially contributing to mood disorders. Nevertheless, the pathways vary across different brain regions, and glutamate homeostasis may offer temporal insights into the mechanisms underlying mood disorders.

In addition to inadequate glial glutamate reuptake, mood disorders are also linked to glutamate receptors, such as NMDA receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). Retinal recipient core neurons of the SCN express ionotropic NMDA receptors [48], with the core region containing GluN2A and GluN2B subunits, while the shell region predominantly contains GluN2C subunits. Previous research has suggested that the dorsal SCN is a vital component of the mammalian circadian pacemaker, with astrocytic Ca^{2+} exhibiting more pronounced oscillations in this region [29]. Inhibition of glutamatergic gliotransmission through a GluN2C-NMDAR antagonist disrupts rhythmic Ca^{2+} oscillations and *Per* gene expression in neurons, resulting in the desynchronization of SCN rhythms [29]. Mice deficient in *Per1* and *Per2* genes exhibit significantly heightened anxiety and depression phenotypes [134,187]. Astrocytes in the NAc are essential for maintaining glutamate homeostasis. Disruption of the circadian function of NAc astrocytes modifies AMPA receptor signaling in adjacent MSNs by decelerating decay kinetics and diminishing their responsiveness relative to NMDA receptors. This is accompanied by an upregulation of mRNA levels for AMPA subunits, specific NMDA receptors, metabotropic glutamate receptors (mGluRs), and glutamate transporters, ultimately influencing emotion-related behaviors [34]. These findings indicate that the rhythmic activity of astrocytes in the NAc during the regulation of mood disorders may be mediated through alterations in glutamate homeostasis.

In models of depression, enhanced burst activity of Hb neurons has been observed. Activation of Hb neurons induces burst activity via NMDA receptors, which exerts an inhibitory effect on the brain's reward circuitry, thereby contributing to symptoms of despair, anhedonia, and anxiety [188]. The mechanism of action for rapid-acting antidepressants, such as ketamine, involves modulation of this process. Ketamine primarily targets NMDA receptors, reducing the burst activity of Hb neuron-dependent NMDA receptors, thereby alleviating the inhibition of the reward circuit and rapidly ameliorating mood [189]. Clinical investigations have demonstrated that treatment with the NMDA receptor antagonist ketamine ameliorates depressive symptoms in patients with MDD and enhances the glutamine-glutamate complex to water ratio (Glx/W) as well as the gamma-aminobutyric acid to water ratio (GABA/W) in the mPFC [190,191]. Corresponding findings have been observed in animal models, where chronic mild stress (CMS) induces depressive-like behaviors and elevates NMDAR expression levels [192]. In contrast, ketamine administration reduces NMDAR expression and significantly increases extracellular glutamate concentrations [193]. Notably, selective inhibition of the GluN2A subunit by the NMDAR antagonist PEAQX markedly attenuates ketamine's antidepressant effects, whereas activation of the GluN2A subunit does not influence ketamine's efficacy [189]. These findings suggest that NMDAR inhibition constitutes a potential mechanism for alleviating mood disorders, although the roles of different NMDAR subunits may be divergent. For example, CMS has been shown to upregulate GluN1 receptor levels in the hippocampal synaptic membrane fraction without affecting GluN2A, while significantly increasing GluN2B levels [192]. However, recent study indicates that extensive activation of the GluN2A subunit might elicit antidepressant effects [189]. The effects of GluN2A intervention may vary depending on the specific brain region. Ionotropic NMDARs are emerging as a po-

tential target for the regulation of astrocyte-mediated glutamate rhythms in mood disorders. While ketamine research has predominantly focused on neuronal mechanisms, especially glutamatergic signaling [191,194], astrocytes also play a crucial role in modulating NMDAR activity by regulating extracellular glutamate rhythms [29,30,184], thereby influencing mood disorders. Investigating astrocyte regulation of specific NMDAR subtypes could represent a promising new research avenue.

4.2 GABA

Neurons within the SCN are primarily GABAergic, with nearly all SCN neurons expressing GABA [45]. Studies suggest that GABA-mediated neurotransmission can be either excitatory or inhibitory, depending on the circadian phase or subregion within the SCN [195,196], and has the capacity to synchronize or desynchronize the circadian rhythms of SCN cells [197]. Astrocytes are involved in the synthesis, transport, and release of GABA. During synthesis, GABA can be absorbed by astrocytes, converted into glutamine (Gln) via the tricarboxylic acid (TCA) cycle, and subsequently transported back to GABAergic neurons for GABA resynthesis [198]. GABA serves as a critical molecule in astrocyte-mediated circadian regulation. Astrocytes in the SCN facilitate coherent spatiotemporal circadian patterns of neuronal activity by rhythmically regulating glutamate uptake and release, as well as modulating GABAergic tone and receptor signal transduction [199,200]. Extracellular GABA levels within the SCN display pronounced rhythmicity, oscillating in phase with glutamate, with both reaching their peak during the night. These rhythms are antiphase to neuronal activity. In genetically arrhythmic SCN, GABA rhythms are absent but can be reinstated by activating the TTFL in astrocytes [32]. Furthermore, inhibiting synaptic GABA release disrupts neuronal circadian rhythms in the SCN, and suppressing astrocytic GABA synthesis eliminates the extracellular GABA rhythm and desynchronizes neuronal circadian activity. This indicates that astrocytic GABA synthesis is a vital pathway for intrinsic circadian regulation within the SCN circuitry [201]. Research indicates that a 3-hour exposure to light at the onset of the subjective night suppresses changes in glutamate and GABAergic activity, specifically in the frequency of miniature excitatory postsynaptic currents (mEPSC) and miniature inhibitory postsynaptic currents (mIPSC). In contrast, exposure to a skeleton photoperiod does not influence mEPSC or mIPSC frequency between the subjective day and night [202]. Additionally, the suppression of rhythms in SCN GABA neurons has been shown to increase anxiety-like behavior in mice [150]. These findings suggest that circadian disruptions may predispose individuals to mood and anxiety disorders, with an imbalance between excitation and inhibition potentially affecting emotional states. While there is growing evidence of reduced GABA levels in the PFC of patients with (MDD [203], the mechanisms by which astrocytic GABA release is altered in mood disorders remain poorly understood.

The astrocytic clock can modulate emotional behavior and regulate changes in GABA expression, although this occurs with clock specificity. For example, the targeted deletion of *Per2* in astrocytes contribute to alleviate anxiety, increase the mRNA expression of the GABA transporter 2 (GAT-2), and reduce glutamate levels in the NAc. In contrast, the knockout of *Per2* in neurons might decreases despair behavior without affecting anxiety, underscoring the specific role of astrocytes [35]. Additionally, research indicates that the deletion of *Bmal1* does not influence anxiety-like behavior or alter GAT-2/Slc6a13 expression in the NAc, but it does result in the downregulation of Drd3 expression. These findings suggest that *Per2* in astrocytes is the primary gene involved in regulating anxiety within the NAc [35]. Regarding GABA transport, GAT-1 and GAT-3 are expressed in the SCN, with GAT-3 predominantly localized to astrocytes. GATs facilitate the uptake of GABA into astrocytes to maintain normal circadian rhythms [201]. Study demonstrates that astrocytes encode the extracellular GABA rhythm by enhancing GAT-3-mediated GABA uptake during the day to clear synaptically released GABA, with the gene encoding GAT-3, Solute Carrier Family 6 Member 11 (Slc6a11), reaching peak expression in SCN astrocytes at circadian time 6 (CT6) [32]. During nighttime, astrocytes enhance the synthesis of GABA, thereby replenishing extracellular GABA levels and exerting inhibitory effects on neurons within the SCN. Disruption in GABA production or uptake results in the dysregulation of extracellular GABA rhythms, effectively abolishing its circadian cycling [201]. Research indicates that reactive astrocytes influence GABA homeostasis by downregulating GAT-3 expression, which leads to reduced GABA uptake, neuronal disinhibition, and the emergence of anxiety-like behaviors. Conversely, upregulation of GAT-3 has been shown to mitigate these anxiety-like behaviors [151]. Clinical study further suggests that individuals with an evening chronotype demonstrate increased sensitivity to negative emotions and a higher susceptibility to mood disorders [65]. Consequently, the regulation of GABA homeostasis by astrocytic GAT-3 may constitute a pathway contributing to the development of mood disorders during nighttime (Fig. 3).

4.3 Adenosine Triphosphate (ATP)

Additionally, ATP functions as a signaling molecule, facilitating astrocyte-neuron communication and purinergic signaling [204], and plays a role in regulating circadian variations [205]. Astrocytes within the SCN have the capacity to influence rhythmic oscillations via the release of ATP. In the SCN of rats, ATP concentrations exhibit rhythmic fluctuations, reaching their zenith during the dark phase and their nadir during the light phase [206]. Additionally, ATP demonstrates rhythmic oscillations in

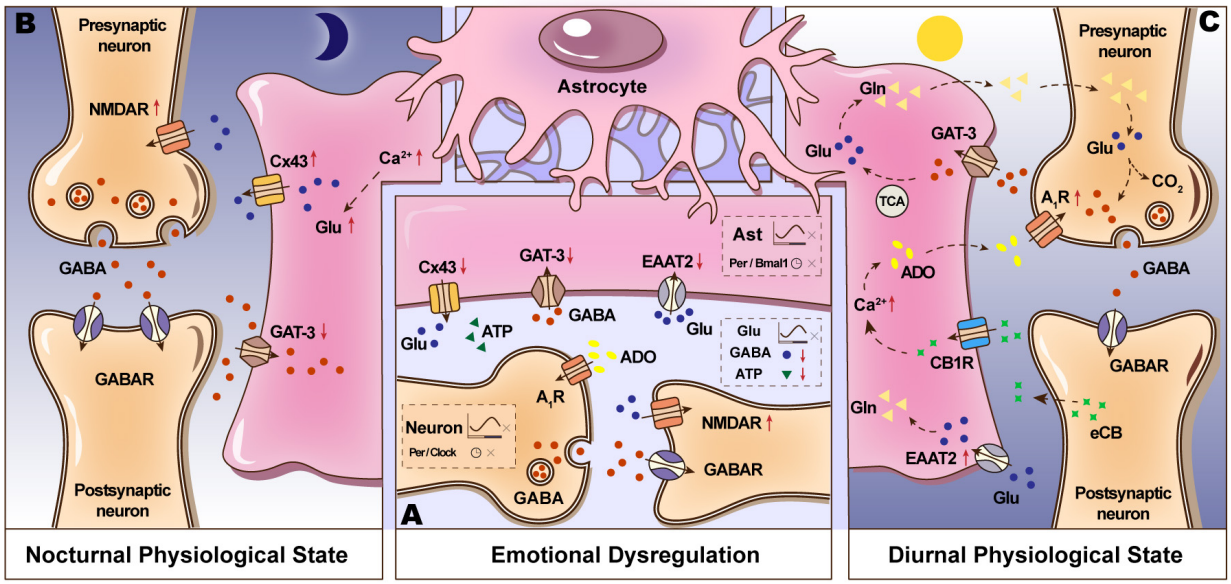

Fig. 3. The communication between astrocytes and neurons in both normal and mood disorder states in SCN. (A) In models of mood disorders, astrocytes exhibit a diminished expression of the glutamate transporter EAAT2, Cx43, and GAT-3. Conversely, neurons display an increased expression of NMDA receptor subunits GluN1 and GluN2B. Mood disturbances lead to the desynchronization of neuronal *Per* and *Clock* gene rhythms, while also disrupting the rhythms of glutamate in astrocytes. The specific ablation of core clock genes, such as *Bmal1* or Per, in astrocytes results in circadian fragmentation and exacerbates anxiety- and depressive-like behaviors. The disruptions in the rhythms of GABAergic interneurons can also lead to mood disorder. (B) During nocturnal periods (the active phase of an organism), astrocytes release glutamate via Cx43 hemichannels, which subsequently activates NR2C subunit-containing NMDA-type glutamate receptors (NR2C-NMDARs) in presynaptic neurons. This activation facilitates the release of GABA, thereby inhibiting the electrical activity of postsynaptic neurons. Astrocytic GAT-3 exhibits a diminished capacity for GABA uptake. (C) During diurnal periods, neurons in the SCN are active. GABA uptake by astrocytes via GAT-3 can lead to its conversion into glutamine through the TCA cycle, followed by its transport back into GABAergic neurons for GABA re-synthesis. Endocannabinoids released from postsynaptic neurons can interact with CB1 receptors on astrocytes, activating $[Ca^{2+}]_i$ signaling pathways. This activation may result in the release of adenosine, which acts on A_1Rs on neurons, thereby reducing GABA release. Furthermore, astrocytic EAAT2 proteins enhance the capacity for glutamate uptake. EAAT2, excitatory amino acid transporter 2; Cx43, connexin 43; GAT-3, GABA transporter 3; TCA, tricarboxylic acid; A_1R, adenosine A_1 receptor; GluN1, Glutamate Ionotropic Receptor NMDA Type Subunit 1; GluN2B, Glutamate Ionotropic Receptor NMDA Type Subunit 2B; ↑, increase; ↓, decrease.

both cortical astrocytes and astrocyte cultures, which are synchronized with the rhythmic fluctuations of mitochondrial calcium ion concentration $[Ca^{2+}]_i$ within astrocytes [207]. Among various neurotransmitters, extracellular ATP has been extensively investigated in relation to depression-like behaviors [208,209]. For example, mice that are susceptible to chronic stress display reduced levels of extracellular ATP [152], and diminished ATP levels in the hippocampus and mPFC are correlated with depression-like behaviors [152,210]. The astrocyte-specific expression of a dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE), which inhibits vesicular ATP release from astrocytes [211], help to increased immobility time in male mice during the FST [152]. In contrast, the deletion of glucocorticoid receptors (GR) in the mPFC decreases astrocytic calcium signaling and ATP release, thereby inducing depression-like behavior [39]. The administration of ATP has been shown to mitigate depression-like behaviors [152,210,212,213]. This evidence implies a potential association between low extracellular ATP levels and depression-like behaviors, which may also impact the rhythmic oscillations of the SCN [214]. However, research indicates that disrupting the vesicular release mechanism does not affect the circadian rhythm of ATP release in cultured cortical astrocytes [206,215], highlighting an apparent contradiction. Given that ATP release occurs through various pathways, including lysosomal release, connexin/pannexin hemichannels, volume-regulated anion channels, and calcium homeostasis modulators [216–218], and considering the rapid degradation of extracellular ATP by ectonucleotidases such as cluster of differentiation 39 (CD39), it may be necessary to analyze these alternative pathways [219].

Recent study has demonstrated that reduced expression of Cx43 in mPFC astrocytes results in decreased ATP release, which in turn induces depression- and anxiety-like

behaviors, whereas overexpression of Cx43 reverses these phenotypes [40]. Furthermore, ATP release from SCN astrocytes can also be modulated through P2X7 and P2Y receptors [220]. Research has demonstrated that P2 purinergic receptors display diurnal variations in response to ATP stimulation, reflecting the rhythmicity of ATP. Notably, P2X receptors are more prevalent during the circadian dark phase [204,221]. In parallel, mice vulnerable to chronic stress exhibit reduced extracellular ATP levels, and the activation of P2X2 receptors in GABAergic interneurons of the mPFC modulates depression-like behaviors in male mice [152,222]. Additionally, extracellular ATP can mitigate depression-like phenotypes through P2Y1 receptors in both neurons and glial cells [223,224]. Electroacupuncture has been shown to enhance the expression of P2Y1 receptors in the PFC, significantly ameliorating social avoidance and anxiety-like behaviors in socially isolated male mice [224]. Intriguingly, P2Y receptors exhibit higher expression during the circadian light phase, which is antiphase to ATP rhythmicity [221]. Thus, while P2 receptor activation enhances mood and increases ATP release, ATP rhythmic oscillation reaches its nadir during the light phase. It is established that P2X receptors are more abundant during the dark phase, aligning with the peak levels of their primary agonist, ATP. In contrast, P2Y receptors demonstrate increased abundance during the light phase, positioning them in antiphase relative to the ATP peak [214]. Consequently, further research incorporating additional intervention time points is warranted to elucidate the rhythmic mechanisms through which P2 receptors modulate ATP release in models of mood disorders.

4.4 Adenosine

Astrocytes undergo dynamic changes throughout the sleep-wake cycle, releasing sleep-inducing molecules that regulate brain activity and sleep architecture [225]. Adenosine is a pivotal sleep-regulating factor. Recent study indicates that, in addition to the conventional sleep homeostasis pathways in the basal forebrain (BF) and cortex, activation of astrocytes in the parafacial zone (PZ) specifically leads to increased extracellular adenosine via the ATP hydrolysis pathway, which subsequently activates A_1Rs to promote wakefulness [226]. Beyond its role in sleep regulation, adenosine and its metabolic enzymes, such as cytosolic 5′-nucleotidase (cN-II) and adenosine kinase (ADK), exhibit circadian oscillations [227]. Research indicates that adenosine mediates sustained synaptic inhibition by attenuating neuronal activity through A_1Rs [211] and influences the transmission of circadian photic signals [228]. The SCN neurons receive input from the RHT, thereby synchronizing cellular activity and the TTFL with external environmental rhythms [78,79]. Activation of adenosine A_1Rs located on RHT axon terminals has been demonstrated to inhibit the release of glutamate and mitigate light-induced phase shifts within the SCN [229]. Additionally, the activity of adenosine and Adenosine A_{2A} receptor (A_{2A}Rs) is regulated by the retinal clock, with peak levels occurring during nighttime. This clock-controlled activation of endogenous retinal cone A_{2A}Rs enhances nocturnal cone gap junction coupling and increases rod input to cones and horizontal cells (cHCs) [230]. Exposure to light during nighttime disrupts circadian rhythms and is associated with negative health outcomes [231]. The study using animal models suggests the existence of an SCN-independent pathway, mediated by ipRGCs that provide excitatory synaptic input to neurons in the posterior habenula (PHb) of the dorsal thalamus, which plays a role in mood regulation [82]. Conversely, although astrocytes do not directly receive input from the RHT, the reciprocal interaction between astrocytes and neurons can induce phase advances through neuron-astrocyte activation of cannabinoid receptors (CBRs), which subsequently feedback to activate neuronal adenosine receptors [153]. Thus, A_1Rs may play a crucial role in mood regulation through the transmission of photic signals within the central pacemaker.

Research indicates that the expression of adenosine A_1Rs and A_{2A}Rs in the SCN follows a rhythmic pattern, with elevated levels observed at circadian time 5 (CT5) and diminished levels at CT17. Activation of adenosine receptors by agonists stimulates the classical cAMP-CREB signaling pathway, resulting in increased expression of the clock genes *Per1* and *Per2* and an extension of the rhythm period. This pathway is similarly activated in SCN neurons in response to light stimuli [154,232]. *In vitro* study has further demonstrated that activation of A_{2A}Rs significantly enhances the expression of the clock genes *Clock* and *Bmal1* [155]. Additionally, targeted knockdown of *Bmal1* within the SCN contribute to diminished circadian rhythmicity, desynchronized single-cell rhythms, and heightened behavioral despair, anxiety-like behaviors, and helplessness [135,136]. Consequently, adenosine receptors in the SCN may modulate mood disorders through their regulatory effects on circadian clock mechanisms. Beyond the SCN, distinct subregions of the amygdala exhibit daily variations in Clock gene expression [233]. For example, *Per2* mRNA levels in the BLA exhibit significant circadian fluctuations over a 24-hour period and are associated with affective changes [234]. The targeted activation of astrocytes within the centromedial amygdala (CeM) leads to a reduction in the expression of learned fear responses. Synaptic modulation of CeL-evoked IPSCs and BLA-evoked EPSCs is inhibited by antagonists of A_{2A}Rs and A_1Rs, respectively [235]. Additionally, research conducted in the lateral septum (LS) demonstrates that the application of an adenosine A_1Rs antagonist can reverse the reduction in sEPSC frequency in LS neurons, whereas activation of A_1Rs further diminishes sEPSC frequency. Conversely, blocking adenosine A_{2A}Rs reverses the increase in sIPSC frequency in LS inhibitory (LSi) neurons, while activation of these receptors further elevates sIPSC frequency. This modulation of

LS neural circuitry plays a role in regulating social avoidance and anxiety-like behaviors in mice [236]. Collectively, these studies suggest that ATP/adenosine functions as a critical gliotransmitter in the regulation of emotions. By modulating presynaptic mechanisms, astrocytes can selectively regulate synaptic activity and exert inhibitory effects on neurons, thereby influencing emotional behavior. The mechanisms underlying the action of A_1R may vary between the CeM and the LS.

Furthermore, the expression of the hippocampal clock demonstrates circadian rhythmicity, and the factors that regulate this clock in the hippocampus have a significant impact on behaviors related to depression. For instance, the phosphorylation of the Clock protein in the hippocampus is involved in the regulation of the circadian clock [237]. Elevated levels of extracellular ATP and adenosine in the ventral hippocampal CA1 (vCA1) subregion predominantly originate from activated astrocytes. Inhibition of astrocyte function or blockade of the gap junction protein Cx43, which is widely distributed on astrocytes, substantially reduces extracellular ATP and adenosine levels in vCA1 and effectively mitigates anxiety and depression-like behaviors. Similarly, local administration of an $A_{2A}R$ antagonist in vCA1 produces comparable effects [238]. Recent study proofed that VTA astrocytes activated by stressors reduced the inhibition of DA neurons via presynaptic A_1Rs on GABAergic interneurons, which helped alleviate anxiety- and depression-like behaviors [41].

In conclusion, there exists a complex interplay between astrocytic ATP/adenosine rhythms and mood states within the SCN and other emotion-related brain regions. Despite this, circadian research in this specific domain remains sparse. Further investigation into these mechanisms could yield valuable insights into the connection between circadian rhythms and mood regulation.

5. Conclusions

A bidirectional regulatory relationship is evident between disruptions in circadian rhythms and psychoaffective disorders, with circadian phenotypes exhibiting variability across different mood disorder types, wherein astrocytes play a pivotal role. Bipolar disorder is a prevalent and severe mood disorder, characterized by recurrent major depressive episodes interspersed with hypomanic or manic episodes [239]. BD is also linked to significant disruptions in metabolic processes [240] and circadian rhythms [241]. Clinical investigations have found that individuals with BD experience elevated daytime melatonin levels and a delayed nocturnal melatonin peak during manic episodes [242]. Furthermore, melatonin secretion is delayed in bipolar depression compared to unipolar depression [242]. Genetic research on circadian clock genes indicates that *PER3* and *Rev-erbα* may be associated with an earlier onset of BD [243,244], whereas *Cry2*, *Clock*, and *ARNTL2* rhythm genes may correlate with higher relapse rates in BD [245–247]. Specifically, bipolar depression is associated with circadian alterations, including an late chronotype [248–250], phase delay [251–254], dampened amplitude, and low-amplitude rhythms [255]. Lithium, known for its well-established neuroprotective properties, is an effective therapeutic agent for BD [256]. Glycogen synthase kinase 3 beta (GSK3β) is identified as a pivotal therapeutic target of lithium in BD [257] and serves as a significant regulator of circadian rhythms [258]. Lithium's inhibition of GSK3β and activation of Akt occur in the frontal cortex, striatum, and hippocampus—regions of the brain associated with BD [259]. Increasing evidence suggests that astrocytes play a role in the pathophysiology of BD and are targets for lithium and other primary and adjunctive BD treatments [114,260–262]. Furthermore, both genetic and lithium-induced inhibition of astrocytic GSK3β have been demonstrated to enhance astrocyte populations, aligning with lithium's positive effects in counteracting GM and WM thinning in BD [263,264]. Although the neuropathological mechanisms underlying BD are not yet fully understood, GSK3β may serve as a crucial node through which astrocytic rhythms influence BD modulation.

In patients with MDD, abnormalities in mood and circadian parameters are evident. Notably, depressive symptoms tend to be more pronounced in the morning [265,266], and there is a marked advancement in the rhythm of melatonin secretion [267]. Additionally, there is a disruption in the expression of clock genes such as *BMAL1*, *PER1-3*, and *Rev-erbα*, along with a reduction in rhythm amplitude [35]. In conclusion, individuals with major depressive disorder predominantly exhibit circadian rhythm disruptions, characterized by phase delays or advances [268], reduced amplitude [255], altered sleep duration (either prolonged or shortened), and decreased daytime activity and energy expenditure [269–271]. Moreover, in patients with suicidal tendencies, hypertrophy of astrocytic cell bodies and processes has been observed in brain regions such as the ACC, amygdala, dorsomedial thalamus, and caudate nucleus [106], which is accompanied by a decrease in astrocyte density and reduced expression of GFAP [106–108]. Furthermore, expression levels of GS [116], Cx30, and Cx43 [119] are diminished in the dorsolateral prefrontal cortex (dlPFC), premotor cortex, and amygdala of depressed individuals, along with down-regulation of *SLC1A2* and *SLC1A3* gene expression in cortical regions [118]. This pattern is consistent with the overall decline in astrocyte expression. These proteins are known to play a role in regulating astrocytic rhythms [29,120], and their altered expression is in line with the reduced rhythmicity observed in the SCN, potentially contributing to the underlying mechanisms of circadian rhythm disturbances. However, the degree to which rhythmic regulation in these regions is directly governed by the SCN pacemaker remains uncertain. Therefore, it is imperative to investigate how extra-SCN regions, such as the amygdala, integrate with the output of the central pacemaker. Previous studies uti-

lizing techniques such as trans-synaptic tracing have confirmed the presence of neural connections between the SCN and the striatum. This study has demonstrated that dysfunction of the SCN may contribute to the pathogenesis of anxiety and depression by upregulating the BDNF-TrkB pathway in the striatum [172]. Additionally, single-cell transcriptomics can elucidate subtype-specific roles of astrocytes across various brain regions [272]. Although existing evidence partially supports the role of circadian rhythm disruption in mood disorders, substantial gaps persist in the evidence base concerning the association between circadian patterns and astrocytes. Investigating the relationship between the SCN and emotion-regulatory brain regions using these methodologies will enhance our understanding of the role of central-peripheral clock interactions in mood disorders. It should be noted that, while instrumental in investigating the neurobiological underpinnings of psychiatric disorders, existing animal models are insufficient in fully replicating human mood disorders [273]. This limitation is primarily due to the difficulty in validating these models, despite the presence of behavioral similarities to human depression or anxiety [274]. Consequently, mood disorder research requires more appropriate model to renovate the traditional methodologies.

Emotional disorders are frequently associated with comorbid disruptions in circadian rhythms, and the restoration of these rhythms can significantly influence the progression of such disorders. Astrocytes play an independent role in regulating the circadian rhythms of the SCN [25,27–31]. For example, extracellular levels of GABA and glutamate in the SCN exhibit pronounced rhythmicity, with both reaching their peak at night [32]. Similarly, ATP concentrations demonstrate rhythmic oscillations, peaking during the dark phase and reaching their lowest levels during the light phase [206]. In contrast, the rhythmic oscillations of receptor proteins exhibit an antiphase pattern: Slc6a11 (encoding GAT3) [32], P2Y receptors [221], and A1/A2A receptors [154,232] peak during the daytime. Comparable rhythmic alterations are observed in brain regions associated with emotion; for instance, the capacity for glutamate uptake by hippocampal astrocytes decreases during the dark phase [183,184], and disruptions in circadian function in NAc astrocytes impair glutamate homeostasis, subsequently affecting emotional behavior [34]. Furthermore, diminished nocturnal melatonin levels, phase delays [242], and dysregulated cortisol release [275,276] may contribute to emotional dysregulation. Empirical evidence indicates that activation of the NOD-like receptor family, pyrin domain containing protein 3 (NLRP3) inflammasome is associated with stress and lipopolysaccharide (LPS)-induced depression in animal models [277]. Exogenous administration of melatonin has been demonstrated to mitigate LPS-induced depression-like behaviors by downregulating NLRP3 activation in the brain [278]. The inhibitory effect of melatonin on the NLRP3 inflammasome is mediated through various proteins and pathways, including the NF-κB signaling pathway [279] and the TXNIP/NLRP3 axis [280]. Additionally, research has identified a connection between the NLRP3 inflammasome and phenotypic alterations in astrocytes. Specifically, activation of the NLRP3 inflammasome induces a shift in astrocytes toward the neurotoxic A1 state [281–283], whereas inhibition of this transformation may alleviate depression-like behaviors in chronic unpredictable mild stress (CUMS) models [284]. Nonetheless, current research predominantly focuses on microglia, leaving the regulatory mechanisms in astrocytes insufficiently elucidated. The glymphatic system, an intricately organized waste clearance network, is dependent on the polarization state of astrocytes and the expression of the AQP4 protein [285]. The polarization of AQP4 in astrocytes, governed by circadian rhythms, aids glymphatic function, and genetic deletion of AQP4 disrupts the circadian regulation of cerebrospinal fluid (CSF) distribution [286]. Prior research has suggested that dysregulated cortisol levels not only contribute to mood disorders but may also impair astrocytic polarization [287] and diminish AQP4 expression [288]. Preservation of the circadian rhythm of AQP4 polarization in astrocytes has been demonstrated to alleviate depressive symptoms in murine models of depression. Consequently, the regulation of nocturnal melatonin secretion and cortisol concentrations may constitute a viable strategy for achieving inflammatory control and mitigating mood disorders, wherein astrocytic AQP4 and A1/A2 phenotypic plasticity are likely to play pivotal roles.

Currently, rhythmic genes and the aforementioned targets are under investigation for their potential in therapeutic development for mood disorders. Notable examples include light therapy, which targets the RHT photic input [96], the NMDA receptor antagonist ketamine [289,290], and AMPA receptor modulators [291]. Research indicates that exposure to one hour of high-intensity light during the active phase leads to the upregulation of *Per1*, *Per2*, and *Cry1* expression in the SCN, thereby modulating pathophysiological processes [96]. Furthermore, evening administration of melatonin facilitates phase advances in the circadian clock of individuals with delayed sleep-wake phase disorder [99]. The NMDA receptor antagonist ketamine can modulate the upstream CREB signaling pathway of clock genes to improve depressive symptoms [289,292]. Additionally, ketamine also manifests distinct circadian motor activity patterns and temporal responses, such as the association between a low-amplitude 24-hour activity rhythm and rapid depressive relapse [293]. Notably, the clinical investigation of the timing effects in subanesthetic ketamine has yet to be addressed, but such as are being planned [290]. In individuals with bipolar disorder, skin fibroblasts transfected with *Per2* luciferase reporter constructs (*Per2::luc*) exhibited extended circadian periods compared to healthy controls, and lithium, a common therapeutic agent for bipolar disor-

der, was found to resynchronize and enhance the amplitude of the attenuated molecular rhythms in these cells [294]. The investigation of astrocyte-associated neurotransmitter rhythms provides a neurobiological basis for chronotherapeutic interventions in mood disorders. Consequently, examining the "astrocyte-circadian rhythm-emotional circuit" axis through the perspective of astrocytic rhythmic proteins holds significant promise for the advancement of astrocyte-targeted chronotherapeutics with precise timing. This research provides compelling evidence for expanding time-of-day therapies and exploring chronopharmacological treatments for mood disorders.

Abbreviations

A_1R, adenosine A_1 receptor; $A_{2A}R$, Adenosine A_{2A} receptor; ACC, anterior cingulate cortex; ADK, adenosine kinase; Aldh1l1, Aldehyde dehydrogenase 1 family member L1; AQP4, aquaporin-4; ATP, Adenosine triphosphate; AVP, arginine vasopressin; BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; BF, basal forebrain; Bhlhe40, Basic helix-loop-helix family member e40; BLA, basolateral amygdala; *BMAL1*, brain and muscle ARNT-like 1; CA1, Cornu Ammonis 1; CBR, cannabinoid receptors; CD39, cluster of differentiation 39; CeM, centromedial amygdala; cHCs, cones and horizontal cells; ChR2, Channelrhodopsin-2; CLOCK, circadian locomotor output cycles kaput; cN-II, cytosolic 5′-nucleotidase; CREB, cAMP response element-binding protein; *CRY1*, Cryptochrome 1; Cx30, Connexin 30; Cx43, connexin 43; DA, dopamine; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; Drd3, dopamine receptor D3; DRN, dorsal raphe nucleus; EAATs, excitatory amino acid transporters; EPM, elevated plus maze; FST, forced swim test; GABA, γ-aminobutyric acid; GAT-2, GABA transporter 2; GFAP, Glial fibrillary acidic protein; GLAST, Glutamate aspartate transporter; Glu, glutamine; GLT-1, glutamate transporter 1; GM, gray matter; GRP, gastrin-releasing peptide; GS, glutamine synthetase; Hb, habenula; ipRGCs, intrinsically photosensitive retinal ganglion cells; LHb, lateral habenula; LS, lateral septum; LSi, LS inhibitory; LTP, long-term potentiation; MDD, major depressive disorder; mEPSC, miniature excitatory postsynaptic current; mGluRs, metabotropic glutamate receptors; mIPSC, miniature inhibitory postsynaptic current; mPFC, medial prefrontal cortex; MSNs, medium spiny neurons; NAc, nucleus accumbens; NSFT, novelty-suppressed feeding test; OFT, open field test; PACAP, pituitary adenylate cyclase-activating polypeptide; Per, Period; PFC, prefrontal cortex; PHb, perihabenular nucleus; PZ, parafacial zone; RHT, retinohypothalamic tract; *Ror*α, retinoic-acid-related orphan receptors alpha; Rorβ, retinoic acid receptor-related orphan receptor beta; S100β, calcium-binding protein β; SCN, suprachiasmatic nucleus; SLC1A2, solute carrier family 1 member 2; SLC1A3, solute carrier family 1 member 3; Slc6a11, Solute Carrier Family 6 Member 11; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; TCA, tricarboxylic acid; TrkB, tropomyosin receptor kinase B; TST, tail suspension test; TTFLs, transcriptional–translational feedback loops; UCMS, unpredictable chronic mild stress; vCA1, ventral hippocampal CA1; VIP, vasoactive intestinal polypeptide; VTA, ventral tegmental area; WM, white matter.

Author Contributions

Conceptualization, LK, PL and YH; literature search and organization, HL and YZ; writing—original draft preparation, PL and SS; writing—review and editing, HL; visualization, SS; supervision, LK and YH; funding acquisition, YH. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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