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## The role of the circadian system in the etiology of depression

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### ABSTRACT

Circadian rhythms have evolved in almost all organisms enabling them to anticipate alternating changes in the environment. As a consequence, the circadian clock controls a broad range of bodily functions including appetite, sleep, activity and cortisol levels. The circadian clock synchronizes itself to the external world mainly by environmental light cues and can be disturbed by a variety of factors, including shift-work, jet-lag, stress, ageing and artificial light at night.

Interestingly, mood has also been shown to follow a diurnal rhythm. Moreover, circadian disruption has been associated with various mood disorders and patients suffering from depression have irregular biological rhythms in sleep, appetite, activity and cortisol levels suggesting that circadian rhythmicity is crucially involved in the etiology and pathophysiology of depression.

The aim of the present review is to give an overview and discuss recent findings in both humans and rodents linking a disturbed circadian rhythm to depression. Understanding the relation between a disturbed circadian rhythm and the etiology of depression may lead to novel therapeutic and preventative strategies.

### 1. Introduction

Multiple lines of evidence suggest a relationship between the circadian system and depressive disorder (Spulber et al., 2022). First, in many depressed patients the severity of symptoms follows a diurnal rhythm with an improvement in the evening hours (Wirz-Justice, 2008). Second, sleep disturbances are by far the most common complaints in mood disordered patients: difficulties falling and staying asleep, as well as early morning awakenings (Laskemoen et al., 2019; Steardo et al., 2019). Moreover, sleep problems may predict the recurrence of depressive symptoms in patients with prior depression (Fang et al., 2019; Kumagai et al., 2019). Third, associations with depressed mood have been found for disturbed biological rhythms in body temperature, cortisol, and melatonin (Bauduin et al., 2018; Pariante and Lightman, 2008; Srinivasan et al., 2006). Fourth, disruption of circadian patterns, which are defined as all processes in living beings that follow a 24-h cycle under the influence of light and dark may cause mood disorders, as for example in shift workers (Walker et al., 2020). Fifth, a transcriptome-wide analysis suggested that the amplitude in expression of several circadian genes is attenuated in different brain regions of

depressed patients, however, in a more recent study none of these circadian genes were associated with major depressive disorder (MDD) (Li et al., 2013; Melhuish Beaupre et al., 2020). Finally, treatment targeting the circadian system has been shown to be effective in depressive disorder (Hühne et al., 2018; Monteleone et al., 2011). Although the link between the circadian system and mood has been firmly established, the underlying mechanism by which circadian disruption contributes to depression is unknown. Here, after outlining the neurobiology of the circadian system, components which are known to influence circadian rhythm and whose alterations may contribute to the development of depression in both humans and rodents will be reviewed. Finally, the treatment of circadian rhythm disruptions in depression will be discussed.

### 2. The neurobiology of the circadian system

The circadian timing system is a hierarchal and complex system (Dibner et al., 2010). The rotation of the earth generates an alternate of day and night in 24 h. Living organisms have adapted to this rhythm in order to be able to synchronize their behavior and bodily functions such

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as sleep-wake cycles, metabolic processes, and hormone secretion. At the top of the system resides the master pacemaker in the brain, which is the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. Downstream there are peripheral clocks in nearly every body cell (Hastings et al., 2018). At a molecular level, all circadian elements are endogenously regulated in the same way. Molecular core clock components, which are defined as genes whose protein products are necessary for the generation and regulation of circadian rhythms, act via autoregulatory transcriptional and translational feedback loops to generate a rhythm of approximately 24 h. The primary transcriptional feedback loop includes the genes *CLOCK* (circadian locomotor output cycles kaput) and *BMAL1* (brain-muscle-*arnt*-like protein 1), which both generate protein heterodimers that translocate to the nucleus of every cell, and bind to the promoter region of the clock genes *Period* (*Per1*, *Per2* and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*). This binding results in transcription of the proteins *PER* and *CRY*. Subsequently, *PER* and *CRY* form heterodimers that in turn inhibit the activity of *CLOCK*/*BMAL1* complexes, thereby shutting down their own transcription. As *PER* and *CRY* proteins are degraded, repression on *CLOCK*/*BMAL1* is relieved and the ~24 h cycle begins again. A secondary transcription/translation feedback loop is formed by the nuclear receptors *ROR* (retinoid-related orphan receptors) *a*, *b* and *c* and *REV-ERB $\alpha$* /*REV-ERB $\beta$*  (also known as *NR1D1* and *NR1D2*, respectively), that compete for binding sites on the *BMAL1* gene. Together, these proteins stabilize *BMAL1* transcription, thereby ensuring proper circadian timing and adding robustness to the core clock (Mendoza-Viveros et al., 2017).

All clocks need to be synchronized internally and externally in order to follow the daily solar cycle (Wahl et al., 2019). Synchronization to the external world is performed mainly by light cues. This light information, detected by retinal ganglion cells in the retina of the eyes, is transmitted via the retinohypothalamic tract to the SCN (Blume et al., 2019). The light information synchronizes the SCN neuronal cells, which in turn provides rhythmic output (Dibner et al., 2010). The rhythmic signals from the SCN are subsequently passed to neuronal, hormonal and other local outputs, resulting in the synchronization of the peripheral clocks and the coordination of daily sleep wake rhythms, feeding behavior, metabolic processes, hormonal release, and body temperature (Silver and Kriegsfeld, 2014).

The normal day-night rhythm can become disrupted as a result of artificial light at night, shift-work, reduction of sleep duration and/or quality and transmeridian travel resulting in jetlags (Drake and Wright, 2011). Aging, dementia and neurodegenerative diseases such as Huntington's disease and Parkinson's disease may also cause a deterioration in circadian rhythm (Farajnia et al., 2012; Kudo et al., 2011a; Kudo et al., 2011b; Nakamura et al., 2011). As many physiological events function with a 24 h cycle, it is not surprising that circadian disruption is associated with a wide array of diseases, such as metabolic disorders, cancers, and psychological disorders, including cognitive impairment and, of particular interest to the current review, depression (Coomans et al., 2013a; Hadadi et al., 2020; Walker et al., 2020).

### 3. Circadian system disruptions and depression

#### 3.1. Light and the SCN

Emerging evidence suggests that exposure to aberrant light disrupts the circadian system as well as negatively influences mood, regularly accompanied by suppressed neuroimmune pathways, possibly via glucocorticoids (Bedrosian and Nelson, 2013). Indeed, the expression of immune associated brain-derived neurotrophic factor (BDNF) and pro-inflammatory cytokine interleukin-1 beta were both suppressed in the hippocampus in rodents with depressive-like symptoms due to circadian disruptions, while plasma corticosterone concentrations were elevated (Chen et al., 2021).

Studies with animal models exposed to light at night indicate

detrimental effects on molecular mechanisms of the clock, behavior, and physiology (Coomans et al., 2013a; Grone et al., 2011; Ohta et al., 2005; Shuboni and Yan, 2010). Both the C3H and Swiss-Webster mouse strain exposed to constant light demonstrate increased depressive-like behavioral responses as evaluated by the forced swim test (FST) and sucrose preference test (Becker et al., 2010; Fonken et al., 2009). Similar in rats, after exposure to constant light for eight weeks, anhedonia was observed in a sucrose consumption test, and increased grooming in the open-field test, which is thought to reflect depressive- and anxiety-like behavior respectively (Tapia-Osorio et al., 2013).

A complete lack of light cues in the environment may also elicit behavioral features similar to those observed in depressed patients. For example, rats exposed to constant darkness showed a dysregulation of the sleep-wake cycle as well as impairment of the noradrenergic system which has been associated with stress-induced depression (Gonzalez and Aston-Jones, 2006). Even though circadian behavioral and hormonal patterns were conserved, mild depressive-like indicators were observed using the anhedonia test, while mild anxiety-like behaviors were observed using the open field test and the FST (Gonzalez and Aston-Jones, 2008).

In addition to total light deprivation, evidence from animal models suggest a role for day length in mood (Workman and Nelson, 2011). Siberian hamsters, which are nocturnal in a laboratory setting, exposed to short, winter-like, day lengths develop depressive-like responses in the FST and anxiety-like responses in the elevated plus maze (Workman and Nelson, 2011). Research from Prendergast and colleagues showed that Wistar rats exposed to short day lengths, show behavioral despair in the FST as well as anhedonia (Prendergast and Kay, 2008). Studies performed in the diurnal fat sand rats (*Psammomys obesus*) and Nile grass rats (*Arvicanthus Neoliticus*) show depression-like behavior in the FST when maintained under short photoperiod (Einat et al., 2006; Krivisky et al., 2011). The antidepressant bupropion reversed the effects of short photoperiod conditions in the FST in these animals (Krivisky et al., 2011).

Mimicking chronic jetlag also affects mood in rodents. Exposing C57BL/6J mice to 6-h light phase advances every three light/dark cycles results in higher behavioral despair as measured in a forced swim test, but not in anhedonia as measured by sucrose preferences tests (Chen et al., 2021).

As the master regulator, the SCN is responsible for all day-night rhythms in behavioral and physiological processes. SCN ablation in rodents disrupts the circadian rhythm in amongst others, activity, sleep structure and metabolism (Coomans et al., 2013b; Liu et al., 2012). Bilateral ablation of the SCN has been shown to result in depressive-like symptoms in rats (Tataroglu et al., 2004). In a recent study, dampening of the SCN amplitude by optogenetics stimulation, increased anxiety-like behavior (Vadnie et al., 2021). Surprisingly, even a single SCN stimulation in the active phase of the mouse, when SCN neuronal firing is low, was sufficient to increase anxiety-like behavior.

Together, these studies show that circadian disruption in rodents, either by ablating the master clock, or exposure to aberrant light cycles, result in depressive-like symptoms. These findings are in line with case-report studies in humans, finding that damage of the SCN due to trauma or surgery, modulates circadian systems resulting in irregular sleep-wake rhythm, which may induce depressive symptoms (DeRosso et al., 2014).

#### 3.2. The HPA axis

Both the circadian and stress systems are fundamental for survival. Moreover, communication between both systems is crucial for rapid adjustment to physiological activities. In addition to circadian system disturbances, chronic or severe acute stress is one of the most prevalent factors contributing to the multifactorial and complex etiology of depression. Activation of the HPA axis by a stressor stimulates neurons of the hypothalamic paraventricular nucleus (PVN) to secrete

corticotrophin releasing hormone (CRH) and vasopressin (AVP) into the portal vessel system leading to the anterior pituitary (Herman et al., 2016). The pituitary in turn secretes adrenocorticotrophic hormone (ACTH), which causes the adrenal cortex to release glucocorticoids (GC). Elevated levels of circulating GCs form a negative feedback loop by suppressing the PVN and pituitary, thereby resetting the activated HPA axis (Evans et al., 2013). Glucocorticoid actions enhance the survival chance by providing the body with an appropriate physiological and cognitive response after a challenge (McEwen et al., 2015). The tissue-specific response to GCs depends on the expression of its receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR).

In post-mortem brain tissue from patients suffering from mood disorders, side-specific reductions in GR mRNA levels were observed (Webster et al., 2002). Chronic or severe acute stress leads to hyperactivity of the HPA axis which is associated with MDD in (vulnerable) people (Muscatell et al., 2009). A failure to properly terminate the stress response after a stressful situation can add to the development of depression (Muscatell et al., 2009). Impaired regulation of the HPA axis is often detected in people suffering from depression, showing both a dampening of the circadian cortisol level as well as hypercortisolemia (Keen-Rhinehart et al., 2009). However, the exact role of hyper- and hypocortisolemia is not exactly clear as these endocrine aberrations are only observed in a subset of depressed patients (Gudmand-Hoeyer et al., 2014; Wolkowitz et al., 2009).

The relation between stress and the circadian system is reflected by the mechanism whereby the SCN controls the diurnal variations in GC levels via two systems (Nader et al., 2010). First, the SCN stimulates the secretion of GCs in a diurnal rhythm via efferent connections to the PVN. Second, the SCN alters the sensitivity of the adrenal cortex to ACTH via autonomic nerve projections, thereby modulating glucocorticoid release in an HPA-axis independent manner (Kalsbeek et al., 2012). Moreover, high levels of GC, as observed in stressful situations, can phase shift peripheral clocks. The SCN itself however does not express GR, suggesting that effects of chronic stress on the SCN are mediated by connected GR-containing brain regions (Pezük et al., 2012).

Several studies reported that bilateral destruction of the SCN disrupts the secretion of HPA axis hormones, resulting in reduced depressive-like behavior in rats (Mistlberger, 2005; Tataroglu et al., 2004). Regarding the influence of clock genes on the HPA axis, the clock gene *Cry2* knock-out mice show alterations in the HPA axis with increased levels of corticosterone together with anhedonic behavior (Lamia et al., 2011; Savalli et al., 2015). Interestingly, GCs also synchronize *Per1* gene expression via glucocorticoid response elements (GREs), which are found on the DNA of the gene (Yamamoto et al., 2005). The GR-impaired mouse, which has impaired expression of GRs in its brain, also has altered expression of the clock gene *Per1* (Paizanis et al., 2010). Phenotypically this mouse exhibits hyperactivity of the HPA axis and shows depression and anxiety related behavioral responses (Massart et al., 2012). Thus, although GCs have no direct effect on the SCN, disturbances in GC levels do affect transcriptional levels of *Per1* in peripheral tissue as well as in the SCN and other brain regions (Balsalobre et al., 2000; Gilhooley et al., 2011).

### 3.3. Neurogenesis

Neurogenesis is defined as a process of generating functional neurons from precursors and is therefore involved in neural plasticity (Ming and Song, 2011). Neurogenesis occurs throughout life in several regions of the brain and is essential for normal functioning (Varea et al., 2012; Wainwright and Galea, 2013). The development of neurons during the life span, the so-called "adult neurogenesis", occurs in mammals only in specific parts of the brain including the hippocampus. Neurogenesis is subjected to several extrinsic factors including the circadian rhythm

(Ming and Song, 2011). For example, exposure to light and light intensity increases the active p21-activated kinase 1 (PAK1), which directly affects neurogenesis as this effector protein is involved in axon and dendrite development (Shan et al., 2015).

Chronic circadian disruption inhibits neurogenesis in the hippocampus as shown in rats exposed to jetlag protocols (Kott et al., 2012), which is associated with depressive behaviors (Horsey et al., 2019). This decrease in neurogenesis was larger in rats exposed to a 6-h phase advance (comparable to an East-bound flight from New York to Paris) compared to a 6-h phase delay. Interestingly, alongside to circadian abnormalities, depression is associated with reduced neurogenesis in the hippocampus (Varea et al., 2012; Wainwright and Galea, 2013), as shown both in animal and human post-mortem studies (Eisch and Petrik, 2012; Samuels and Hen, 2011). It has been shown that the hippocampus has a high expression of GRs and therefore might be vulnerable to the effects of stress and depression (Wang et al., 2012). Also, depending on the number of episodes and duration, patients suffering from depression display reduced hippocampal volume (Cobb et al., 2013; Sheline et al., 2003). Whether ablation of hippocampal neurogenesis is sufficient to induce depressive-like symptoms is not clear as animal studies show contradictory results (Jayatissa et al., 2010; Wang et al., 2015). This inconsistency in findings could be well explained by the fact that in addition to impaired neurogenesis in the hippocampus, other significant factors may also play a role in the development of depressive symptoms in certain rodents such as genetic predisposition or environmental insults.

In addition to the hippocampus, neurogenic activity in the dentate gyrus (DG) also follows a diurnal rhythm with enhanced rates of neurogenesis during the night (Holmes et al., 2004; Tamai et al., 2008). Antidepressants, such as fluoxetine as well as agomelatine, stimulate neurogenesis in the DG, but this effect on neurogenesis is dependent on the presence of a diurnal rhythm in corticosterone as has been shown in several animal studies (Huang and Herbert, 2006). Furthermore, a flattened GC rhythm reduces neurogenesis in the DG (AlAhmed and Herbert, 2010; Pinnock and Herbert, 2008). The core clock proteins, *PER2* and *BMAL1*, have been shown critical for hippocampal neurogenesis (Borgs et al., 2009; Bouchard-Cannon et al., 2013). Additional studies are required to elucidate the role of the clock on neurogenesis in the context of depression in humans.

### 3.4. Melatonin

Nearly 80 % of the patients suffering from depression report disturbances in sleep architecture (Armitage, 2007). Physiological sleep regulatory mechanisms include the active role of the SCN and the modulatory effects of melatonin on the electrical activity of the SCN. Melatonin production occurs at night in humans and diurnal animals. The rhythm in melatonin secretion from the epiphysis is driven by the SCN (Coomans et al., 2015). Light information, via the SCN, represses the enzymatic activity of N-acetyltransferase, the enzyme that converts serotonin into melatonin (Coomans et al., 2015), resulting in low to absent levels of melatonin during the day. Melatonin in turn controls the circadian rhythm and regulates sleep by transmitting information about the occurrence and duration of darkness (Kunz, 2004; Monteleone et al., 2011). Exposure to artificial light at night, when melatonin levels are high, suppresses pineal melatonin synthesis, which can interfere with normal sleep (Arendt, 2006; Chang et al., 2015).

A particular feature of MDD is the abnormality in the timing and distribution of rapid eye movement (REM) and non-REM (NREM) sleep stages (Armitage, 2007). Reduced nocturnal melatonin levels could account for these symptomatic disturbances in sleep and is associated with depression in humans (Srinivasan et al., 2006). Melatonin offset might also be delayed as shown in depressed patients (Parry et al., 2008). In contrast to nocturnal levels, melatonin appears to be relatively elevated

**Table 1**  
Circadian system disruptions and depression.

Author (s)	Humans/rodents	Circadian rhythm disruption	Effect on depressive symptomatology
<i>Light and the SCN</i>			
Becker et al. (2010);Fonken et al. (2009)	Rodents (C3H and Swiss-Webster mouse)	Constant light	Increased depressive-like behavior (forced swim test and sucrose preference test)
Tapia-Osorio et al. (2013)	Rodents (rats)	Constant light (eight weeks)	Increased depressive-like behavior (sucrose preference test)
Gonzalez and Aston-Jones (2006, 2008)	Rodents (rats)	Constant darkness	Dysregulation of the sleep-wake cycle, impairment of the noradrenergic system, mild depressive-like behavior (anhedonia test)
Workman and Nelson (2011)	Rodents (Siberian hamsters)	Short day lengths	Increased depressive-like behavior (forced swim test)
Prendergast and Kay (2008)	Rodents (Wistar rats)	Short day lengths	Behavioral despair, anhedonia (forced swim test)
Einat et al. (2006);Krivisky et al. (2011)	Rodents (diurnal fat sand rats and Nile grass rats)	Short photoperiod	Increased depressive-like behavior (forced swim test)
Chen et al. (2021)	Rodents (C57BL/6J mice)	Jetlag (6-h light phase advance)	Behavioral despair (forced swim test and sucrose preference test)
Tataroglu et al. (2004)	Rodents (rats)	SCN ablation (bilateral)	Depressive-like symptoms
DelRosso et al. (2014)	Humans	SCN damage (trauma or surgery)	Irregular sleep-wake rhythm
<i>The HPA axis</i>			
Keen-Rhinehart et al. (2009)	Humans	Dampening of the circadian cortisol level	Often in people suffering from depression
Mistlberger (2005); Tataroglu et al. (2004)	Rodents (rats)	HPA axis hormones disruption (via SCN destruction)	Increased depressive-like behavior
Lamia et al. (2011);Savalli et al. (2015)	Rodents (Cry2 knock-out mice)	HPA axis hormones disruption (via clock genes)	Anhedonic behavior
Massart et al. (2012)	Rodents (glucocorticoid receptor impaired mouse)	HPA axis hyperactivity (via impaired brain glucocorticoid receptor)	Increased depressive-like behavior
<i>Neurogenesis</i>			
Horsley et al. (2019)	Rodents (rats)	Hippocampal neurogenesis inhibition (jetlag)	Increased depressive-like behavior
Wang et al. (2015)	Rodents (Norbin-deficient mice)	Hippocampal neurogenesis ablation	Increased depressive-like behavior
<i>Melatonin</i>			
Srinivasan et al. (2006)	Humans	Reduced nocturnal melatonin levels	Demonstrated in people suffering from depression
Parry et al. (2008)	Humans	Delayed melatonin offset	Demonstrated in people suffering from depression
Crasson et al. (2004)	Humans	Increased daytime melatonin levels	Demonstrated in people suffering from depression
<i>Monoamine signaling</i>			
Sleipness et al. (2007)	Rodents (rats)	Disrupted dopamine transporter rhythm (via SCN lesioning)	Contributing to the etiology of depression
Spencer et al. (2013)	Rodents (mPer1 and mPer-2 deficient mice)	Altered striatal transcription of monoamine oxidase A	Increased anxiety-like behavior
Olejniczak et al. (2021)	Rodents (mice)	Altered signaling in the mesolimbic dopaminergic system (via Per1 deletion)	Increased depressive-like behavior

during daytime in these patients, corroborating circadian disruptions (Crasson et al., 2004). Aberrations in the mRNA of the enzyme responsible for the conversion of serotonin to melatonin, acetylserotonin O-methyltransferase (ASMT), have been shown in patients with depressive disorders (Talarowska et al., 2014).

### 3.5. Monoamine signaling

One of the hypotheses of the underlying pathophysiologic basis of depression postulates abnormalities in monoamine neurotransmitter systems. Monoamine signaling is involved in arousal, motivation, and reward systems. Various monoamines are involved in the circadian system and might contribute differently to corresponding features of depression. Norepinephrine, secreted by the locus coeruleus, is related to energy levels, anxiety, and interest in life. Dopamine, secreted by the ventral tegmental area (VTA), is related to motivation, attention, reward, pleasure, and interest in life. Serotonin, secreted by the raphe nuclei, is related to compulsions and anxiety (Verheij et al., 2018). For serotonin it has been shown that disrupting or ablating portions of the serotonergic system is not sufficient to induce a depressive phenotype in rats (Lieben et al., 2006).

The SCN projects, through local expression of clock genes and through indirect connections, to monoaminergic brain regions that synthesize serotonin, dopamine and norepinephrine. SCN rhythmic output causes circadian rhythms in neurotransmitter synthesis and release. The VTA receives temporal information from the SCN via the medial preoptic nucleus and via orexin neurons in the hypothalamus (Coomans et al., 2015). Lesioning of the SCN disrupts the circadian

rhythm in dopamine transporter and tyrosine hydroxylase expression in rats, which can potentially alter dopaminergic transmission, thereby contributing to the etiology of depression (Sleipness et al., 2007). Circadian-clock components have been linked to the monoamine metabolism. Transcription of the enzyme monoamine oxidase A (MAO-A), which oxidizes monoamines, is regulated by the clock components BMAL1, NPAS2 and PER2. In accordance, PER2 mutant mice have increased dopamine levels (Hampp et al., 2008). Spencer and colleagues showed that anxious mice had reduced mPer1 and mPer2 expression in the nucleus accumbens and, similarly, that mice deficient for both mPer1 and mPer2 displayed increased anxiety-like behavior (Spencer et al., 2013). Recently, it has also been shown that complete deletion of only Per1 in mice results in depressive-like behavior (Olejniczak et al., 2021). These rodent studies show that dopamine rhythms in the striatum may be causally linked to components of the circadian clock, and that disturbances in this system can initiate anxiety or depression-like behavior.

For serotonin, it has been shown that this neurotransmitter is not only under SCN rhythmic output but also vice versa: serotonin neurons from brain areas associated with mood project back to the (ventromedial) SCN thereby interfering with the clock function (Lowry et al., 2008). Indeed, PET1 knockout mice, i.e. rodents with deficient serotonergic phenotype of the raphe neurons, show a difference in amplitude of SCN activity (Ciarleglio et al., 2014). The physiology of this bilateral SCN-serotonin interaction is in line with findings of studies showing that abnormalities of serotonergic genes have been associated with both depressive symptoms and pronounced circadian rhythm disturbances, which are the case in patients with seasonal affective disorder (SAD)



(Ciarleglio et al., 2011). SAD is characterized by recurrent episodes of depressive symptoms together with augmented appetite, weight gain, and hypersomnia during winter with a spontaneous remission during summer (Akram et al., 2020).

#### 4. Treatment of circadian disruptions in depression

##### 4.1. Antidepressants

Antidepressants have been shown to modify monoaminergic (i.e. serotonin, dopamine and norepinephrine) function, but it is not known how antidepressants exactly exert their therapeutic effects. Even though antidepressant drugs have been shown to directly influence monoamine levels, there is a delayed effect on mood. Interestingly, normalization of the HPA axis after chronic exposure to antidepressants precedes recovery from depression (Ising et al., 2007). Antidepressants show a positive effect on circadian rhythm of serotonin metabolites in cerebrospinal fluid, suggesting an association between the treatment of depression and the recovery of the circadian rhythm (Salomon et al., 2005). Moreover, some antidepressant drugs restore the normal sleeping patterns even before they produce an improvement in mood (Schmid et al., 2006). Exogenous melatonin administration has also been shown to help normalize sleep in MDD patients (Kunz, 2004).

In addition to treatment in humans, administration in rodents of antidepressants counteracted the depressive-like features caused by light deprivation. The antidepressant agomelatine, however, had no effect in SCN lesioned rats, suggesting that this antidepressant requires an intact circadian system in order to exert its anxiolytic effects (Tuma et al., 2005). In a mouse model of anxiety/depressive-like behavior, melatonin treatment significantly ameliorated the depressive-like state caused by chronic corticosterone treatment (Crupi et al., 2010). Collectively, melatonin as well as its rhythm, might play an important role in the prevention or treatment of depression. Treatment with anti-depressants significantly increases neurogenesis as shown in both human and animal studies (Gupta et al., 2017; Lino de Oliveira et al., 2020). Moreover, the efficacy of antidepressants may be dependent on the upregulation of neurogenesis in the hippocampus (Samuels and Hen, 2011; Wainwright and Galea, 2013). Although animal studies are inconclusive about the role of neurogenesis in the development of depression, it is likely to play a role in the therapeutic effects of antidepressants.

##### 4.2. Non-pharmacological interventions

Various non-pharmacological interventions for depression are known to target circadian rhythm recovery, including bright light therapy, sleep deprivation and sleep phase advance therapy

(Cunningham et al., 2019). Bright light therapy is known to be an effective, non-invasive and well-tolerated treatment, in particular for patients with SAD. Lack of sufficient daytime light is thought to cause a phase shift in the rhythm of melatonin secretion leading to desynchronization between internal timekeeping processes and the external environment (Bedrosian and Nelson, 2013). Light therapy is hypothesized to normalize the rhythm of melatonin levels in these SAD patients. In addition to SAD, there is increasing evidence that bright light therapy might also be beneficial for patients with non-seasonal depression (Benedetti et al., 2007; Germain and Kupfer, 2008; Lam et al., 2016). In rodents, a recent study suggests that light-mediated induction of the clock gene *Per1* in the lateral habenula is involved in the anti-depressant effects of light therapy (Olejniczak et al., 2021). Additional studies are needed to determine the neurobiological mechanisms involved in the effects of light therapy on mood.

Sleep deprivation, which includes depriving at least one night of sleep, has been shown to be effective in around 50 % of depressed patients (Ioannou et al., 2021). These patients experience an increasing mood only during one day after sleep deprivation. Similar to light therapy, the underlying mechanism is unclear (Riemann et al., 2020). Finally, sleep phase advance therapy is an intervention in which depressed patients are instructed to wake up and go to bed earlier, in order to shift their circadian rhythm. This form of behavioral therapy should normalize circadian rhythm disturbances in depressed patients and thus may result in alleviating mood symptoms. However, sleep phase advance therapy has not been shown to be clinically effective for depression, although little research has been done into this type of therapy (Cunningham et al., 2019).

#### 5. Conclusions

The many and varied studies reviewed here strongly suggest a critical role for the circadian system as a modifier of mood-related behavior (Table 1). The circadian system is internally controlled, but strongly influenced by the environment. In particular exposure to light at unnatural times of the day and exposure to stress have their impact on the circadian rhythm, and can lead to depression. The circadian system has a major influence on depressive-like symptoms, which has been demonstrated in both rodent and human studies. Taking these studies together and from a broader, conceptual perspective, it can be postulated that the architecture of the SCN as well as the influence of light exposure on the SCN are both of great importance in the etiology of depressive symptoms, via direct or indirect pathways (Fig. 1). Anatomical SCN abnormalities may cause circadian disruptions directly as light information may not adequately result in rhythmic output, but also can structural abnormalities in the SCN provoke disruptions of rhythm in the release of HPA axis hormones or activity of monoaminergic neurotransmitters.

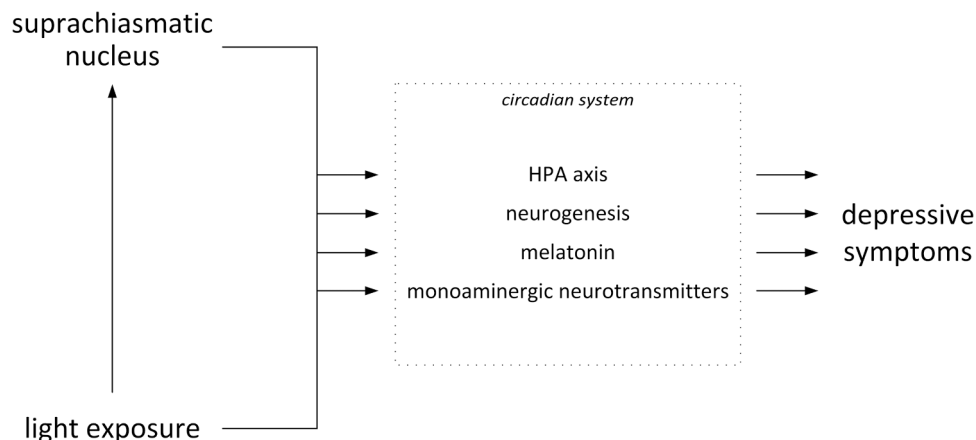


Fig. 1. Schematic diagram of system-level circadian rhythm disturbances contributing to depressive symptoms. HPA = hypothalamic-pituitary-adrenal.

These disturbed processes may play a critical role in the development of depressive symptoms. In addition to the SCN morphology, changes in light exposure by itself, with the SCN as the primary target, may be of great importance in the etiology of depression. For instance, jetlags are associated with mood symptoms directly through a decreased release of melatonin, but also reduced neurogenesis in the hippocampus as well as disruption of striatal dopamine rhythms, both due to light phase disturbances, seem to be important pathways for depression. While a lot of research has been done, many questions regarding the exact role of the circadian system in the etiology of depression remain unanswered. Future studies, including appropriate animal models, will have to determine how specific changes in rhythms within and between mood-related brain circuits can alter mood-related behavior. For example optogenetic studies in rodents, as well as digital phenotyping (Onnela and Rauch, 2016) combined with brain imaging in humans, will provide crucial information about the role of the circadian system in mood disorders. Further understanding the relation between the circadian system and the etiology of depression will be important to develop novel strategies aimed at prevention and treatment of depression-like behavior, both with pharmacological and with non-pharmacological interventions.

### Conflict of interest

None.

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