

Circadian Clocks in the Regulation of Neurotransmitter Systems

Authors

Jana-Thabea Kiehn¹, Frank Faltraco², Denise Palm², Johannes Thome², Henrik Oster¹

Affiliations

- 1 Institute of Neurobiology, University of Lübeck, Lübeck, Germany
- 2 Department of Psychiatry and Psychotherapy, University of Rostock, Rostock, Germany

Key words

circadian clocks, clock genes, neurotransmitter, psychiatric disorders, attention-deficit hyperactivity disorder (ADHS)

received 21.12.2018
 revised 28.08.2019
 accepted 08.10.2019
 published online 30.10.2019

Bibliography

Pharmacopsychiatry 2023; 56: 108–117
 DOI 10.1055/a-1027-7055
 ISSN 0176-3679
 © 2019, Thieme. All rights reserved.
 Georg Thieme Verlag KG, Rüdigerstraße 14,
 70469 Stuttgart, Germany

Correspondence

Henrik Oster
 Institute of Neurobiology, Center of Brain, Behavior & Metabolism
 University of Lübeck
 Marie Curie Street
 23562 Lübeck
 Germany
 henrik.oster@uni-luebeck.de

ABSTRACT

To anticipate and adapt to daily recurring events defined by the earth's rotation such as light-dark and temperature cycles, most species have developed internal, so-called circadian clocks. These clocks are involved in the regulation of behaviors such as the sleep-wake cycle and the secretion of hormones and neurotransmitters. Disruptions of the circadian system affect cognitive functions and are associated with various diseases that are characterized by altered neurotransmitter signaling. In this review, we summarize the current knowledge about the interplay of the circadian clock and the regulation of psychiatric health and disease.

The Circadian Clock System

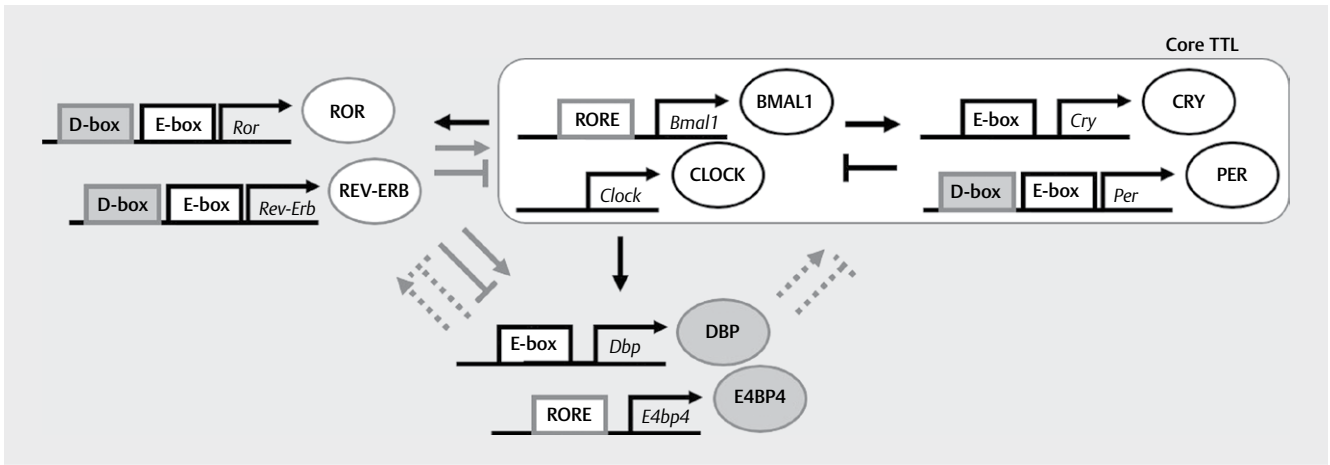
In mammals, the circadian clockwork is comprised of interlocked transcriptional-translational feedback loops (TTLs; ► **Fig. 1**). In the circadian core TTL, the transcription factors brain and muscle Arntl-like protein 1 (BMAL1/ARNTL) and circadian locomotor output cycles kaput (CLOCK), the latter of which can in some tissues be replaced by neuronal PAS domain protein 2 (NPAS2), bind as heterodimers to *E-boxes* in the promoters of *period1–3* (*Per1–3*) and *cryptochrome1/2* (*Cry1/2*) to activate their transcription during the day. In the following hours, PER and CRY proteins, in contrast, repress BMAL1:CLOCK-mediated transactivation, which is reinitiated in the following morning after degradation of PER and CRY [1]. This core TTL is stabilized by auxiliary interlocking TTLs (► **Fig. 1**). *E-boxes* can be found in the promoters of many other clock-controlled genes, which are subsequently expressed in a circadian rhythm. It was estimated that over 40% and 80% of all murine and primate protein-encoding genes, respectively, display circadian rhythmic expression in at least 1 tissue [2, 3].

Light entrainment of the circadian system

Molecular circadian clocks are expressed in every mammalian nucleated cell. For coherent physiological output, these different circadian clocks need to be synchronized with each other and with external time environmental conditions. Therefore, the circadian system is organized in a hierarchical order with a master pacemaker residing in the hypothalamic suprachiasmatic nucleus (SCN) [4]. Intrinsically photosensitive retinal ganglion cells expressing the photopigment melanopsin project via the retino-hypothalamic tract (RHT) to the SCN [5] and by affecting the expression of *Per* in the SCN synchronize the SCN clock with the external light-dark cycle [6]. Subsequently, the SCN resets central extra-SCN and peripheral clocks through neuronal and humoral signals [7].

Sleep is clock-controlled

The most prominent circadian behavioral function is the sleep-wake cycle. Confinement of sleep to the night or day in diurnal and nocturnal species, respectively, is controlled directly by the SCN clock. The SCN projects, via the sub-paraventricular zone and the



► **Fig. 1** Molecular circadian clock In the core TTL, BMAL1 and CLOCK (black arrows) induce transcription of *Cry* and *Per* by binding to E-boxes in their promoters. CRY and PER inhibit CLOCK:BMAL1-mediated transcription. In an auxiliary TTL, ROR (grey arrows) and REV-ERB (grey bar-headed lines), whose transcription is activated by CLOCK:BMAL1, activate and inhibit transcription of genes, respectively, e.g. *Bmal1*, by competing for binding to ROREs in their promoters. Furthermore, transcription of *Dbp* and *E4bp4* are controlled by CLOCK:BMAL1 and ROR/REV-ERB, respectively. Subsequently, DBP (dashed arrows) and E4BP4 (dashed bar-headed lines) build another auxiliary TTL by activating and inhibiting transcription of genes containing D-boxes in their promoters, respectively.

dorsomedial hypothalamus (DMH), to sleep-regulating brain regions such as the ventrolateral preoptic nucleus, the lateral hypothalamus, and the locus coeruleus (LC) [8]. The circadian clock, subsequently, regulates sleep timing, leading to early (larks) and late (owls) chronotypes. Furthermore, clock gene polymorphisms are associated with sleep disorders (e.g., delayed sleep phase disorder) [9–11]. Besides sleep timing, the SCN clock also affects sleep architecture as, for example, REM sleep predominantly occurs during the nadir of the SCN-controlled core body temperature rhythm [12, 13].

Sleep is an important regulator of synaptic plasticity [14]. According to the “synaptic homeostasis” hypothesis, synaptic strength is downregulated during sleep that facilitates energy saving and refinement of synaptic plasticity, thereby improving cognitive functions [15]. Additionally, genes encoding numerous synaptic components are expressed in a circadian pattern [16]. Long-term potentiation (LTP), a major correlate of synaptic plasticity, displays diurnal alterations and, during the dark period, the clock protein REV-ERB α seems to be critical for NMDAR-dependent synaptic potentiation in the hippocampus [17, 18]. Interestingly, in the hippocampus, the phosphorylation of GSK3 β displays a circadian pattern and alterations of GSK3 activity affect both the molecular circadian clock and LTP [19]. Day-night differences in hippocampal LTP vanish in mice carrying a deletion of the receptor of the pineal hormone melatonin, which is accompanied with worse and arrhythmic spatial learning capabilities [20].

Through multi-synaptic control, the SCN clock regulates the expression of the pineal hormone melatonin, which is often referred to as the “sleep hormone” due to its role in timing sleep onset and latency [21]. Melatonin is synthesized and secreted during the night and acts as *zeitgeber* (i.e., synchronizer) for many peripheral clocks but also provides feedback to the SCN itself [22]. Subsequently, disruptions of the circadian system and sleep disturbances are often interconnected. Sleep and circadian disruptions are often ob-

served in mental disorders, which are associated with altered expression of neurotransmitters. Therefore, circadian regulation of neurotransmitters might play a role in the development and treatment of these disorders.

Neurotransmitters and the Circadian Clock

Neurotransmitters are endogenous chemicals that are released by neurons, including, for example, glutamate, gamma-aminobutyric acid (GABA), glycine, acetylcholine, dopamine (DA), (nor-)epinephrine, histamine, and serotonin. Circadian regulation of major neurotransmitters of the mammalian central nervous system is discussed below.

DA

Probably the best studied neurotransmitter with regard to circadian regulation is DA, which plays a major role in reward-motivated behavior (reviewed in [23]). In the brain, DA is mainly produced in neurons of the mesolimbic system arising in the ventral tegmental area (VTA) and the *substantia nigra* (SN) and projecting to the ventral striatum including the *nucleus accumbens* (NAc), the amygdala, and the prefrontal cortex. Baseline striatal DA of mice and rats displays circadian rhythmicity with higher DA levels during the night [24, 25]. Furthermore, DA biosynthesis, transport, and degradation are controlled by the circadian clock. *E-boxes* have been identified in the promoters of tyrosine hydroxylase (TH, the rate-limiting enzyme of DA synthesis), DA transporter (DAT), and monoamine oxidase-A (MAO-A, a DA-degrading enzyme), which subsequently display circadian rhythmicity in their expression [26–29]. Interestingly, also DA signaling itself seems to be under circadian control. Expression of the DA receptors *Drd1*, *Drd2*, and *Drd3* has been shown to display diurnal rhythmicity in the NAc that is abolished by *Npas2* knockdown, whereby *Drd3* expression is directly controlled by the clock proteins ROR and REV-ERB [30–32].

The existence of an endogenous rhythmic clock in the VTA is controversially discussed, but endogenous rhythmic clock gene expression has been shown in the NAc [33–35]. Still, circadian rhythmicity in the VTA could be induced by indirect projections from the SCN via the lateral hypothalamus, the lateral habenula, the paraventricular thalamic nuclei, or the medial preoptic nucleus (► **Fig. 2**; reviewed in [23]).

Therefore, it is not surprising that several clock gene mutant mice display dopaminergic alterations. *Per2* mutant mice show higher basal DA release, lower MAO-A and D1R, and higher D2R expression, which has been associated with a depression-resistant phenotype of these mice [26]. *Rev-Erba*^{-/-} mice show mania-like behavior that is induced by missing inhibition of REV-ERB α onto *TH* gene expression, thereby leading to a hyperdopaminergic state [36]. *Clock- Δ 19* mice show increased dopaminergic activity, TH expression and altered striatal D1R and D2R expression. This may explain their bipolar mania-like phenotype that is characterized by disrupted circadian sleep, hyperactivity, lower anxiety, and decreased depression-related behavior [37, 38].

On the contrary, DA affects the circadian system. In primary murine striatal neurons, the expression of *Clock* and *Per1* can be inhibited by D2-class receptor agonists, whereas *Per1*, *Clock*, *Npas2*, and *Bmal1* expression can be stimulated by D1-class receptor agonists [39]. DA depletion dampens striatal PER2 expression in vivo, which can be rescued by rhythmic activation of D2R [25]. Interestingly, DA is an important entrainment factor of the pre-natal SCN [40].

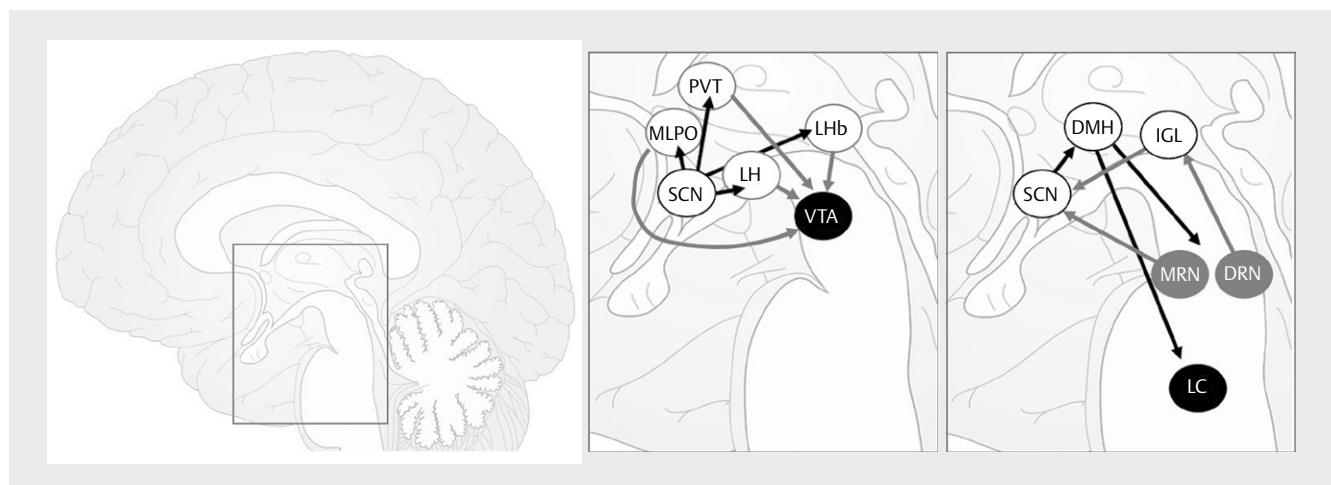
Serotonin

Another monoamine interacting with the circadian system is serotonin (5-hydroxytryptamine, 5-HT), which is also a precursor of melatonin and is involved in the regulation of emotions and mental well-being. The major production sites of 5-HT in the brain are the Raphé nuclei of the brainstem. There, the mRNA of the rate-limiting enzyme of 5-HT synthesis, tryptophan hydroxylase, is rhythmically

expressed and, thus, 5-HT is rhythmically secreted. However, this rather seems to be remotely regulated by the SCN via corticoids than by a circadian clock in the Raphé nuclei (reviewed in [41]). Interestingly, 5-HT plays an important role in photic entrainment of the SCN. The 5-HT reuptake transporter and different 5-HT receptors (5-HT_{1B}, 5-HT₇, 5-HT_{2C}) are expressed in the SCN and 5-HT is rhythmically released in the SCN by Raphé terminals. This release is highest during the active phase (i. e., during the night and day in nocturnal and diurnal species, respectively) [42]. 5-HT modulates light-induced phase shifts in locomotor activity and 5-HT depletion disrupts circadian rhythmicity in sleep [42, 43]. Selective serotonin reuptake inhibitors (SSRIs), which are commonly used in the treatment of major depression, change circadian rhythmicity. The SSRI fluoxetine induces behavioral phase-advances and alters clock gene expression in the SCN of rats [44]. This may, at least in part, be mediated by the direct projection of the median Raphé nucleus or the indirect projection of the dorsal Raphé nucleus via the intergeniculate leaflet to the SCN. In turn, the SCN projects primarily via the DMH to the Raphé nuclei (► **Fig. 2**) (reviewed in [41]). In conclusion, the serotonergic and the circadian system are strongly interconnected.

Glutamate

Glutamate is the major stimulating neurotransmitter and ubiquitously expressed throughout the brain. The RHT uses glutamate, which is subsequently involved in the relay of light information to the SCN. Several subunits of different glutamate receptors are expressed in the SCN and glutamate antagonists can block light-induced behavioral phase shifts (reviewed in [45]). Interestingly, glutamate is also involved in the endogenous activity of SCN neurons since astrocytes inhibit SCN neurons during the day by regulating extracellular glutamate [46]. Glutamate uptake and the activity of glutamine synthetase, which degrades synaptic glutamate, in the SCN are higher during the day than during the night, whereby this



► **Fig. 2** Interconnection of the SCN with the dopaminergic, serotonergic, and noradrenergic system. The SCN does not project directly to the VTA, where dopaminergic neurons arise. But it possibly projects indirectly via the medial preoptic nucleus (MLPO), paraventricular thalamic nuclei (PVT), lateral hypothalamus (LH), and/or lateral habenula (LHb). The SCN projects (black arrows) indirectly via the DMH to the LC and the medial (MRN) and dorsal raphe nuclei (DRN), which are the major central production sites of norepinephrine and serotonin, respectively. The raphe nuclei project (grey arrows) either directly (MRN) or indirectly (DRN) via the intergeniculate leaflet (IGL) back to the SCN.

diurnal rhythmicity of glutamate uptake does not persist under constant environmental conditions [47]. Expression of the glutamate transporter *Eaat3* in the SCN of rats is elevated around the dark-light transition [48]. Alterations in the expression of glutamate-associated genes have also been observed in clock gene mutant mice. *Clock-Δ19* mice show altered expression of glutamate receptors in the NAc and the VTA [37, 49]. *Per2^{Brdm1}* mutant mice express lower levels of glutamate transporter *Eaat1* mRNA and protein leading to reduced glutamate uptake by astrocytes. The resulting increase in glutamate levels in the extracellular space has been associated with alcohol dependence in mice and humans [50].

GABA

Comparable to its precursor glutamate, the major inhibitory neurotransmitter GABA is ubiquitously expressed in the brain. In the SCN, 95% of all neurons are GABAergic [51]. Although GABA-A receptor subunit b1 is downregulated in the VTA of *Clock-Δ19* mice and the GABA-synthesizing glutamate decarboxylase *GAD67* shows diurnal oscillations in some brain regions, rather little is known about how GABA itself or its signaling are regulated by the circadian clock [37, 52].

Norepinephrine

The neurotransmitter norepinephrine (NE; noradrenaline) is involved in the modulation of attention, arousal, and cognition. It is synthesized from DA mainly in the LC of the brainstem, which belongs to the ascending arousal system regulating the sleep-wake cycle. In the lower brainstem and SCN of rats, NE is highest during the early morning [53, 54]. In the rat pineal gland, NE release is high during the night [55]. Interestingly, NE increases melatonin synthesis and induces rhythmic clock gene expression in the pineal gland *in vitro*, indicating an important role of NE in the rhythmicity of melatonin signaling [56]. In the LC of rats, activity of the NE-synthesizing DA-beta-hydroxylase and of the NE-degrading enzymes MAO-A and MAO-B are higher during the night, whereby expression of MAO-A is probably directly clock-controlled, as previously mentioned [26, 57, 58]. Elevated *Per1* expression in TH-positive cells in the LC around the day/night transition as compared to the early subjective day indicates the existence of an endogenous circadian clock in this brain region. Rhythmicity in the LC may result from SCN projections via the DMH (► **Fig. 2**), since lesions of the latter eliminate circadian changes in LC impulse activity [59] and loss of LC neurons in *Nr2f6* mutant mice affects clock gene expression in LC target regions such as the somatosensory cortex [60].

Psychiatric Disorders and the Circadian Clock

Psychiatric disorders are heritable to a high degree and associated with various clock gene single nucleotide polymorphisms (SNPs; ► **Table 1**).

Attention-deficit hyperactivity disorder

Behavioral states like sleep disturbances and traits like late chronotype have a genetic background, as well as inattentiveness, hyperactivity, and impulsivity—the core symptoms of attention-deficit hyperactivity disorder (ADHD) [61, 62]. ADHD patients perform worse in neurocognitive tests, especially in reaction time variabil-

ity, intelligence/achievement, vigilance, working memory, and response inhibition. This might be due to problems in switching from resting to an active cognitive state [63, 64]. Concerning the involvement of neurotransmitter systems in ADHD, research has so far largely focused on DA. Many studies show increased DAT binding in ADHD patients [65, 66]. Furthermore, ADHD has been associated with variants in DA receptors, 5-HT transporters and receptor subunits, and glutamate receptors [67–69]. A high percentage of adults suffering from ADHD report sleep problems and have a later chronotype, which might arise from the disorder itself or, in turn, aggravate it [70, 71]. For pharmacological treatment of ADHD, stimulant and nonstimulant medications are used [72] and influence clock gene expression [60]. The stimulant methylphenidate and the nonstimulant atomoxetine increase synaptic catecholamine concentrations, particularly DA and NE via inhibiting their presynaptic reuptake [73, 74]. Both drugs alter clock gene expression in the murine brain (e. g., *Per2* expression in the SCN and the paraventricular nucleus) [75, 76]. Thus, medical treatment of ADHD might lead to further disruption of circadian rhythms, underlining the chrono-pharmacological importance of identifying the right time of treatment. Interestingly, 1 study demonstrated a general loss of rhythmicity in the expression of *PER2* and *BMAL1* in the oral mucosa of ADHD patients [77]. Furthermore, ADHD is found to be associated with a SNP in the 3' untranslated region of the human *Clock* gene (rs1801260 T/C) in some, but not all, studies [11, 78–80].

Schizophrenia and bipolar disorder

Schizophrenic patients show, besides the more “popular” psychotic symptoms like delusions and hallucinations, often also a lack of motivation, poor expression of emotions, and cognitive impairments (i. e., speed of processing, attention, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition) [81–83]. For a long time, schizophrenia has been described as a disease of DA dysfunction. Schizophrenic patients, especially the ones with a high risk for psychosis, show higher dopaminergic activity and antipsychotics often antagonize D2 and D3 receptors [84–86]. However, not all symptoms of schizophrenia (e. g., cognitive impairments) can be explained by DA. Therefore, the contribution of other neurotransmitters has been discussed including glutamate, 5-HT, acetylcholine, and GABA [87].

Schizophrenia is often associated with sleep and circadian impairments, including insomnia, irregular and fragmented sleep-wake cycles, and altered free-running rhythms [88–91]. A recent study showed a circadian variation in the occurrence of auditory hallucinations in schizophrenia patients with the most frequently and longest lasting ones at 18:00–21:00 [92]. Furthermore, recent studies show dampened expression of clock genes in skin fibroblast and blood cells of schizophrenic patients [93, 94]. The C allele of the same *Clock* SNP rs1801260 (T/C) as described above for ADHD is also associated with schizophrenia in Japanese and Han Chinese [95, 96]. Additionally, the *Clock* SNPs rs3736544, rs1193815, rs11133385, and rs3749474 are associated with schizophrenia in Japanese females. However, these associations are statistically significant only before correction for multiple testing [97]. Additionally, SNPs in *Arntl* (rs2290036) and *Per2* (rs934945, rs10462023) and other clock genes are associated with schizophrenia and bipo-

► **Table 1** Association of clock gene SNPs with psychiatric disorders (ADHD: attention deficit hyperactivity disorder, AUD: alcohol use disorder, BD: bipolar disorder, MDD: major depressive disorder, MD: mood disorder, SCZ: schizophrenia).

| Gene | Strongest association | Clinical association | Reference | |
|-----------------|------------------------------|----------------------|-------------|------|
| Clock | rs1801260 | ADHD | [62, 84–85] | |
| | | BD | [86] | |
| | | MDD | [64] | |
| | | SCZ | [65] | |
| | rs3805148 | ADHD (inattention) | [84] | |
| | | MD | [87] | |
| | rs12504300 | ADHD (inattention) | [84] | |
| | rs4864542 | | | |
| | rs12649507 | | | |
| | rs534654 | | | |
| | rs6850524 | BD | [68] | |
| | rs4340844 | | | |
| | rs3805148 | | | |
| | rs3736544 | BD | [87] | |
| | rs12504300 | BD | SCZ | [66] |
| | | | | [87] |
| | rs12648271 | BD | [87] | |
| | rs6850524 | | | |
| | rs10462028 | | | |
| | rs2412648 | BD | [76] | |
| rs11240 | AUD | [80] | | |
| rs1193815 | AUD combined with depression | [81] | | |
| | SCZ | [66] | | |
| Per1 | rs11133385 | SCZ | [66] | |
| | rs3749474 | SCZ | [64] | |
| | | MD | | |
| rs3027172 | AUD | [83] | | |
| | AUD | [88] | | |
| Per2 | rs934945 | Winter depression | [89] | |
| | rs934945 | SCZ | [67] | |
| | Rs10462023 | | | |
| Per3 | rs707467 | BD | [74] | |
| | rs10462020 | | | |
| | rs228697 | Anxiety | [78] | |
| | VNTR rs57875989 | | | |
| | rs12137927 | | | |
| | rs228644 | Depression symptoms | [77] | |
| | rs226482 | | | |
| VNTR rs57875989 | SCZ | [65] | | |
| Cry1 | rs2287161 | MD | [76] | |
| | rs10861688 | BD | [75] | |
| Cry2 | rs10838524 | Winter depression | [79] | |
| | rs10838527 | | | |
| | rs3824872 | | | |

lar disorder [98, 99]. Interestingly, late chronotype and longer sleep duration have been associated with a higher risk for schizophrenia in genome-wide association studies of self-reported chronotype

and sleep based on the UK biobank [100, 101]. Data from constitutive studies suggested that chronotype and schizophrenia share similar genetic pathways [100].

Bipolar patients display cognitive heterogeneity and dependent on study design and included subjects worse cognitive performance has been shown for verbal learning, visual learning and memory, processing speed, working memory, attention, and global intelligence [102]. Interestingly, stronger cognitive impairment seems to be associated with earlier disease onset and more episodes of mania and depression. Hereby, manic episodes are associated with enhanced activity of the noradrenergic system, shown by increased NE concentrations in urine and cerebrospinal fluid, whereas the opposite occurs during depressive episodes [103]. The enhanced activity of the noradrenergic system might furthermore trigger increased melatonin release in manic episodes. Additionally, it has been speculated that a dysbalance of DA receptors and transporters occurs in bipolar disorder with increased striatal D2/3 receptor availability during manic and increased DAT levels during depressive episodes [104].

Opposite effects during the different episodes are also observed for sleep. During the manic episodes, the need to sleep is decreased in 69–99%, and during the depressive episodes, insomnia and hypersomnia occur in up to 100% and 24–78% of the bipolar patients, respectively [105]. Interestingly, melatonin levels of these patients are decreased in both episodes as well as in euthymic states [106]. Some studies show a higher light sensitivity by a stronger depression of melatonin, which is reduced by treatment with lithium carbonate or sodium valproate [107–110]. Disturbed circadian rhythms have been reported for locomotor activity, body temperature, cortisol, and different hormones [106]. Clock SNPs (rs1801260, rs534654, rs6850524, rs4340844, rs3805148, rs3736544, rs12504300, rs12648271, rs6850524, rsrs10462028) also are associated with bipolar disorder, particularly with higher life time recurrence rates, increased occurrence of insomnia, worse response to treatment of sleep disturbances, relapse of manic episodes, and evening preference [111–113]. Furthermore, the Clock SNPs rs534654, rs6850524, and rs4340844, the Per3 SNPs rs707467, and rs10462020), and the Cry1 SNPs rs2287161, and rs10861688 have been associated with bipolar disorder [99, 114–116].

Other psychiatric disorders

Patients with major depressive disorder (MDD) display anhedonia, feelings of worthlessness or guilt, loss of energy, and reduced concentration [117]. Brains of these patients have a lower DA, 5-HT, and NE content/action and altered binding of these neurotransmitters to their respective receptors [118]. However, the variability of MDD and the long onset until antidepressants work suggest additional causes for this disease [117]. Along this line, MDD has also been associated with altered connectivity of GABA and glutamatergic neurons [119].

In MDD many physiological rhythms are changed, including melatonin, NE, thyroid stimulating hormone, cortisol, and 5-HT, and transcript rhythmicity is weaker in different brain regions of MDD patients [120–123]. MDD patients display rhythmic mood changes over the course of the day, often with severe depression in the early morning and mood brightening until the early evening [122]. For clinical symptoms of depression, an association with 3 Per3 SNPs

(rs12137927, rs228644, rs228682) has been found in a cross-sectional genetic association study [124]. Two other *Per3* SNPs (rs228697, rs57875989-VNTR) have been associated with anxiety disorder, suggesting a role of *Per3* in mood regulation [125]. Furthermore, winter depression could be associated with 3 SNPs in the *Cry2* gene (rs10838524, rs10838527, rs3824872) [126]. *Clock* SNPs (rs2412648, rs11240) have also been associated with alcohol use disorder. Hereby, the T allele of rs2412648 (T/G) is a risk factor for alcohol dependence [127]. The G allele of rs11240 (G/C) and the haplotype TTGC of the *Clock* SNPs rs3805151, rs2412648, rs11240, and rs2412646 was shown to be associated with comorbid depression and alcohol use disorder [128]. For extensive review of *Clock* gene association with psychiatric disorders see Schuch et al. (2018) [129]. Additionally, a *Per1* SNP (rs3027172 C/T) was associated with the use of alcohol. The C allele is a risk factor for problematic drinking and an increased risk for adult alcohol use disorder. It was demonstrated that C allele carriers exposed to elevated early life stress have a higher risk for problematic drinking [130].

Conclusion

Accumulating evidence suggests that circadian clock and different neurotransmitter systems interact at multiple levels. Genetic alterations in the clock gene machinery—just like external perturbation of the clock system (e. g., in shift workers)—may predispose individuals for the development of psychiatric disorders. At the same time, neurofunctional changes may feedback on circadian rhythm regulation. Since many psychiatric disorders are associated with sleep disturbances, stabilization of the circadian system by fixed sleep-wake cycles and light therapy has been shown to be a promising therapeutic tool [131–134]. Additionally, behavioral rhythm therapies (e. g., interpersonal and social rhythm therapy [IPSRT]) can stabilize daily activities of patients and have been shown to be as successful as other established intensive psychotherapies in bipolar disorder [103]. Unfortunately, especially in schizophrenia research, only few studies have been conducted to test if stabilizing circadian behavior improves disorder severity [135].

Furthermore, pharmacological treatment has to be carefully timed according to the chronotype of the patient to prevent further disruption and induce stabilization of the circadian system. Several psychopharmacological drugs affect circadian rhythmicity, including methylphenidate, atomoxetine, lithium, valproic acid, quetiapine, agomelatine, and SSRIs [71, 75, 106, 121, 136–139]. Interestingly, whereas melatonin treatment of ADHD patients improves only sleep latency, but not ADHD scores, treatment with agomelatine, a melatonin agonist, affects both [71, 140, 141]. Unfortunately, circadian effects of pharmacological drugs and how circadian rhythms of neurotransmitters are affected in patients of psychiatric disorders are often not or poorly investigated. From a clinical perspective, this interaction may open new roads for the prevention, diagnosis, and treatment of psychiatric disorders through stabilization, observation, or manipulation, respectively of circadian rhythms and clocks in patients and subjects at risk.

Conflict of Interest

Johannes Thome has received financial support from pharmaceutical companies (Actelion, Astra Zeneca, Bristol-Myers Squibb, EVER Neuro Pharma GmbH, Janssen-Cilag, Lilly, Lundbeck, MEDICE, Merz, Novartis, Pfizer, Roche, Servier, Shire, Trommsdorff) some of which manufacture medication used in the treatment of ADHD patients. Jana-Thabea Kiehn, Denise Palm, Frank Faltraco, and Henrik Oster have no potential conflicts of interest to disclose.

References

- [1] Buhr ED, Takahashi JS. Molecular components of the mammalian circadian clock. *Handb Exp Pharmacol* 2013; 3–27
- [2] Zhang R, Lahens NF, Ballance HI et al. A circadian gene expression atlas in mammals: Implications for biology and medicine. *Proc Natl Acad Sci* 2014; 111: 16219–16224
- [3] Mure LS, Le HD, Benegiamo G et al. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. *Science* 2018; 359: eaao0318
- [4] Ralph MR, Foster RG, Davis FC et al. Transplanted suprachiasmatic nucleus determines circadian period. *Science* 1990; 247: 975–978
- [5] Gooley JJ, Lu J, Chou TC et al. Melanopsin in cells of origin of the retinohypothalamic tract. *Nat Neurosci* 2001; 4: 1165
- [6] Travnickova-Bendova Z, Cermakian N, Reppert SM et al. Bimodal regulation of mPeriod promoters by CREB-dependent signaling and CLOCK/BMAL1 activity. *Proc Natl Acad Sci USA* 2002; 99: 7728–7733
- [7] Buijs RM, van Eden C, Goncharuk VD et al. The biological clock tunes the organs of the body: Timing by hormones and the autonomic nervous system. *J Endocrinol* 2003; 177: 17–26
- [8] Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005; 437: 1257–1263
- [9] Archer SN, Carpen JD, Gibson M et al. Polymorphism in the PER3 promoter associates with diurnal preference and delayed sleep phase disorder. *Sleep* 2010; 33: 695–701
- [10] Kalmbach DA, Schneider LD, Cheung J et al. Genetic basis of chronotype in humans: insights from three landmark GWAS. *Sleep* 2017; 40: 2
- [11] von Schantz M. Phenotypic effects of genetic variability in human clock genes on circadian and sleep parameters. *J Genet* 2008; 87: 513–519
- [12] Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995; 15: 3526–3538
- [13] Mouret J, Coindet J, Debilly G et al. Suprachiasmatic nuclei lesions in the rat: alterations in sleep circadian rhythms. *Electroencephalogr Clin Neurophysiol* 1978; 45: 402–408
- [14] Raven F, Van der Zee EA, Meerlo P et al. The role of sleep in regulating structural plasticity and synaptic strength: Implications for memory and cognitive function. *Sleep Med Rev* 2018; 39: 3–11
- [15] Tononi G, Cirelli C. Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* 2014; 81: 12–34
- [16] Hannou L, Roy PG, Roig MNB et al. Transcriptional control of synaptic components by the clock machinery. *Eur J Neurosci* 2018 Dec 2 [Epub ahead of print]

- [17] Chaudhury D, Wang LM, Colwell CS. Circadian regulation of hippocampal long-term potentiation. *J Biol Rhythms* 2005; 20: 225–236
- [18] Choi JE, Kim S, Lee J et al. Circadian regulation by REV-ERB α mediates hippocampal E-LTP in a time-dependent manner. *Exp Neurobiol* 2018; 27: 344–349
- [19] Besing RC, Rogers CO, Paul JR et al. GSK3 activity regulates rhythms in hippocampal clock gene expression and synaptic plasticity. *Hippocampus* 2017; 27: 890–898
- [20] Jilg A, Bechstein P, Saade A et al. Melatonin modulates daytime-dependent synaptic plasticity and learning efficiency. *J Pineal Res* 2019; 66: e12553
- [21] Perreau-Lenz S, Kalsbeek A, Garidou ML et al. Suprachiasmatic control of melatonin synthesis in rats: Inhibitory and stimulatory mechanisms. *Eur J Neurosci* 2003; 17: 221–228
- [22] Pevet P, Challet E. Melatonin: both master clock output and internal time-giver in the circadian clocks network. *J Physiol Paris* 2011; 105: 170–182
- [23] Mendoza J, Challet E. Circadian insights into dopamine mechanisms. *Neuroscience* 2014; 282: 230–242
- [24] Ferris MJ, España RA, Locke JL et al. Dopamine transporters govern diurnal variation in extracellular dopamine tone. *Proc Natl Acad Sci* 2014; 111: E2751–E2759
- [25] Hood S, Cassidy P, Cossette MP et al. Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via daily activation of D2 dopamine receptors. *J Neurosci Off J Soc Neurosci* 2010; 30: 14046–14058
- [26] Hampp G, Ripperger JA, Houben T et al. Regulation of monoamine oxidase A by circadian-clock components implies clock influence on mood. *Curr Biol* 2008; 18: 678–683
- [27] Kawarai T, Kawakami H, Yamamura Y et al. Structure and organization of the gene encoding human dopamine transporter. *Gene* 1997; 195: 11–18
- [28] Yoon SO, Chikaraishi DM. Tissue-specific transcription of the rat tyrosine hydroxylase gene requires synergy between an AP-1 motif and an overlapping E box-containing dyad. *Neuron* 1992; 9: 55–67
- [29] Sleipness EP, Sorg BA, Jansen HT. Diurnal differences in dopamine transporter and tyrosine hydroxylase levels in rat brain: Dependence on the suprachiasmatic nucleus. *Brain Res* 2007; 1129: 34–42
- [30] Akhisaroglu M, Kurtuncu M, Manev H et al. Diurnal rhythms in quinpirole-induced locomotor behaviors and striatal D2/D3 receptor levels in mice. *Pharmacol Biochem Behav* 2005; 80: 371–377
- [31] Ozburn AR, Falcon E, Twaddle A et al. Direct regulation of diurnal *Drd3* expression and cocaine reward by NPAS2. *Biol Psychiatry* 2015; 77: 425–433
- [32] Ikeda E, Matsunaga N, Kakimoto K et al. Molecular mechanism regulating 24-hour rhythm of dopamine D3 receptor expression in mouse ventral striatum. *Mol Pharmacol* 2013; 83: 959–967
- [33] Webb IC, Baltazar RM, Wang X et al. Diurnal variations in natural and drug reward, mesolimbic tyrosine hydroxylase, and clock gene expression in the male rat. *J Biol Rhythms* 2009; 24: 465–476
- [34] Abe M, Herzog ED, Yamazaki S et al. Circadian rhythms in isolated brain regions. *J Neurosci* 2002; 22: 350–356
- [35] Landgraf D, Long JE, Welsh DK. Depression-like behaviour in mice is associated with disrupted circadian rhythms in nucleus accumbens and periaqueductal grey. *Eur J Neurosci* 2016; 43: 1309–1320
- [36] Chung S, Lee EJ, Yun S et al. Impact of circadian nuclear receptor REV-ERB α on midbrain dopamine production and mood regulation. *Cell* 2014; 157: 858–868
- [37] McClung CA, Sidiropoulou K, Vitaterna M et al. Regulation of dopaminergic transmission and cocaine reward by the clock gene. *Proc Natl Acad Sci* 2005; 102: 9377–9381
- [38] Spencer S, Torres-Altora MI, Falcon E et al. A mutation in CLOCK leads to altered dopamine receptor function. *J Neurochem* 2012; 123: 124–134
- [39] Imbesi M, Yildiz S, Dirim Arslan A et al. Dopamine receptor-mediated regulation of neuronal “clock” gene expression. *Neuroscience* 2009; 158: 537–544
- [40] Ferguson SA, Rowe SA, Krupa M et al. Prenatal exposure to the dopamine agonist SKF-38393 disrupts the timing of the initial response of the suprachiasmatic nucleus to light. *Brain Res* 2000; 858: 284–289
- [41] Ciarleglio CM, Resuehr HES, McMahon DG. Interactions of the serotonin and circadian systems: Nature and nurture in rhythms and blues. *Neuroscience* 2011; 197: 8–16
- [42] Cuesta M, Mendoza J, Clesse D et al. Serotonergic activation potentiates light resetting of the main circadian clock and alters clock gene expression in a diurnal rodent. *Exp Neurol* 2008; 210: 501–513
- [43] Nakamaru-Ogiso E, Miyamoto H, Hamada K et al. Novel biochemical manipulation of brain serotonin reveals a role of serotonin in the circadian rhythm of sleep-wake cycles. *Eur J Neurosci* 2012; 35: 1762–1770
- [44] Cuesta M, Clesse D, Pévet P et al. New light on the serotonergic paradox in the rat circadian system. *J Neurochem* 2009; 110: 231–243
- [45] Ebling FJ. The role of glutamate in the photic regulation of the suprachiasmatic nucleus. *Prog Neurobiol* 1996; 50: 109–132
- [46] Brancaccio M, Patton AP, Chesham JE et al. Astrocytes control circadian timekeeping in the suprachiasmatic nucleus via glutamatergic signaling. *Neuron* 2017; 93: 1420–1435.e5
- [47] Leone MJ, Beaulieu C, Marpegan L et al. Glial and light-dependent glutamate metabolism in the suprachiasmatic nuclei. *Chronobiol Int* 2015; 32: 573–578
- [48] Cagampang FRA, Rattray M, Powell JF et al. Circadian variation of EAAC1 glutamate transporter messenger RNA in the rat suprachiasmatic nuclei. *Mol Brain Res* 1996; 35: 190–196
- [49] Dzirasa K, Coque L, Sidor MM et al. Lithium ameliorates nucleus accumbens phase-signaling dysfunction in a genetic mouse model of mania. *J Neurosci* 2010; 30: 16314–16323
- [50] Spanagel R, Pendyala G, Abarca C et al. The clock gene *Per2* influences the glutamatergic system and modulates alcohol consumption. *Nat Med* 2005; 11: 35–42
- [51] Abrahamson EE, Moore RY. Suprachiasmatic nucleus in the mouse: Retinal innervation, intrinsic organization and efferent projections. *Brain Res* 2001; 916: 172–191
- [52] Weber M, Lauterburg T, Tobler I et al. Circadian patterns of neurotransmitter related gene expression in motor regions of the rat brain. *Neurosci Lett* 2004; 358: 17–20
- [53] Lew GM. Circadian rhythms in blood pressure and norepinephrine in genetically hypertensive and normotensive rats. *Gen Pharmacol Vasc Syst* 1976; 7: 35–40
- [54] Semba J, Toru M, Mataga N. Twenty-four hour rhythms of norepinephrine and serotonin in nucleus suprachiasmaticus, raphe nuclei, and locus coeruleus in the rat. *Sleep* 1984; 7: 211–218
- [55] Driifhout WJ, van der Linde AG, Kooi SE et al. Norepinephrine release in the rat pineal gland: The input from the biological clock measured by in vivo microdialysis. *J Neurochem* 1996; 66: 748–755

- [56] Andrade-Silva J, Cipolla-Neto J, Peliciari-Garcia RA. The in vitro maintenance of clock genes expression within the rat pineal gland under standard and norepinephrine-synchronized stimulation. *Neurosci Res* 2014; 81–82: 1–10
- [57] Daiguji M, Mikuni M, Okada F et al. The diurnal variations of dopamine- β -hydroxylase activity in the hypothalamus and locus coeruleus of the rat. *Brain Res* 1978; 155: 409–412
- [58] Chevillard C, Barden N, Saavedra JM. Twenty-four hour rhythm in monoamine oxidase activity in specific areas of the rat brain stem. *Brain Res* 1981; 223: 205–209
- [59] Aston-Jones G, Chen S, Zhu Y et al. A neural circuit for circadian regulation of arousal. *Nat Neurosci* 2001; 4: 732–738
- [60] Warnecke M, Oster H, Revelli JP et al. Abnormal development of the locus coeruleus in Ear2(Nr2f6)-deficient mice impairs the functionality of the forebrain clock and affects nociception. *Genes Dev* 2005; 19: 614–625
- [61] Voinescu BI, Szentagotai A, David D. Sleep disturbance, circadian preference and symptoms of adult attention deficit hyperactivity disorder (ADHD). *J Neural Transm* 2012; 119: 1195–1204
- [62] Bae SM, Park JE, Lee YJ et al. Gender difference in the association between adult attention deficit hyperactivity disorder symptoms and morningness-eveningness. *Psychiatry Clin Neurosci* 2010; 64: 649–651
- [63] Claesdotter E, Cervin M, Åkerlund S et al. The effects of ADHD on cognitive performance. *Nord J Psychiatry* 2018; 72: 158–163
- [64] Pievsky MA, McGrath RE. The neurocognitive profile of attention-deficit/hyperactivity disorder: A review of meta-analyses. *Arch Clin Neuropsychol* 2018; 33: 143–157
- [65] Spencer TJ, Biederman J, Madras BK et al. In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: A focus on the dopamine transporter. *Biol Psychiatry* 2005; 57: 1293–1300
- [66] Madras BK, Miller GM, Fischman AJ. The dopamine transporter and attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005; 57: 1397–1409
- [67] Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: A meta-analytic review. *Hum Genet* 2009; 126: 51–90
- [68] Faraone SV, Perlis RH, Doyle AE et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005; 57: 1313–1323
- [69] Huang X, Wang M, Zhang Q et al. The role of glutamate receptors in attention-deficit/hyperactivity disorder: from physiology to disease. *Am J Med Genet B Neuropsychiatr Genet* 2019; 180: 272–286
- [70] Philipsen A. Differential diagnosis and comorbidity of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) in adults. *Eur Arch Psychiatry Clin Neurosci* 2006; 256: i42–i46
- [71] Coogan AN, McGowan NM. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Atten Deficit Hyperact Disord* 2017; 9: 129–147
- [72] Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: A systematic review. *JAMA* 2016; 315: 1997–2008
- [73] Wilens TE. Effects of methylphenidate on the catecholaminergic system in attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol* 2008; 28: S46–S53
- [74] Bymaster FP, Katner JS, Nelson DL et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology* 2002; 27: 699–711
- [75] Baird AL, Coogan AN, Kauffling J et al. Daily methylphenidate and atomoxetine treatment impacts on clock gene protein expression in the mouse brain. *Brain Res* 2013; 1513: 61–71
- [76] O'Keefe SM, Thome J, Coogan AN. The noradrenaline reuptake inhibitor atomoxetine phase-shifts the circadian clock in mice. *Neuroscience* 2012; 201: 219–230
- [77] Baird AL, Coogan AN, Siddiqui A et al. Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. *Mol Psychiatry* 2012; 17: 988–995
- [78] Xu X, Breen G, Chen CK et al. Association study between a polymorphism at the 3'-untranslated region of CLOCK gene and attention deficit hyperactivity disorder. *Behav Brain Funct* 2010; 6: 48
- [79] Kissling C, Retz W, Wiemann S et al. A polymorphism at the 3'-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* 2008; 147B: 333–338
- [80] Allebrandt KV, Roenneberg T. The search for circadian clock components in humans: New perspectives for association studies. *Braz J Med Biol Res* 2008; 41: 716–721
- [81] Elvevåg B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol* 2000; 14: 1–21
- [82] Nuechterlein KH, Barch DM, Gold JM et al. Identification of separable cognitive factors in schizophrenia. *Schizophr Res* 2004; 72: 29–39
- [83] MacKenzie NE, Kowalchuk C, Agarwal SM et al. Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. *Front Psychiatry* 2018; 9: 622
- [84] Laruelle M, Abi-Dargham A, van Dyck CH et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci* 1996; 93: 9235–9240
- [85] Howes OD, Williams M, Ibrahim K et al. Midbrain dopamine function in schizophrenia and depression: A post-mortem and positron emission tomographic imaging study. *Brain* 2013; 136: 3242–3251
- [86] Egerton A, Chaddock CA, Winton-Brown TT et al. Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: Findings in a second cohort. *Biol Psychiatry* 2013; 74: 106–112
- [87] Yang AC, Tsai SJ. New targets for schizophrenia treatment beyond the dopamine hypothesis. *Int J Mol Sci* 2017; 18: 1689
- [88] Wulff K, Dijk DJ, Middleton B et al. Sleep and circadian rhythm disruption in schizophrenia. *Br J Psychiatry* 2012; 200: 308–316
- [89] Mills JN, Morgan R, Minors DS et al. The free-running circadian rhythms of two schizophrenics. *Chronobiologia* 1977; 4: 353–360
- [90] Nofzinger EA, van Kammen DP, Gilbertson MW et al. Electroencephalographic sleep in clinically stable schizophrenic patients: Two-weeks versus six-weeks neuroleptic-free. *Biol Psychiatry* 1993; 33: 829–835
- [91] Chouinard S, Poulin J, Stip E et al. Sleep in untreated patients with schizophrenia: a meta-analysis. *Schizophr Bull* 2004; 30: 957–967
- [92] Koizumi T, Suzuki T, Pillai NS et al. Circadian patterns of hallucinatory experiences in patients with schizophrenia: potentials for chronopharmacology. *J Psychiatr Res* 2019; 117: 1–6
- [93] Johansson AS, Owe-Larsson B, Hetta J et al. Altered circadian clock gene expression in patients with schizophrenia. *Schizophr Res* 2016; 174: 17–23
- [94] Sun HQ, Li SX, Chen FB et al. Diurnal neurobiological alterations after exposure to clozapine in first-episode schizophrenia patients. *Psychoneuroendocrinology* 2016; 64: 108–116
- [95] Takao T, Tachikawa H, Kawanishi Y et al. CLOCK gene T311C polymorphism is associated with Japanese schizophrenics: A preliminary study. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2007; 17: 273–276

- [96] Zhang J, Liao G, Liu C et al. The association of CLOCK gene T3111C polymorphism and hPER3 gene 54-nucleotide repeat polymorphism with Chinese Han people schizophrenics. *Mol Biol Rep* 2011; 38: 349–354
- [97] Kishi T, Kitajima T, Ikeda M et al. Association study of clock gene (CLOCK) and schizophrenia and mood disorders in the Japanese population. *Eur Arch Psychiatry Clin Neurosci* 2009; 259: 293–297
- [98] Liu JJ, Hukic DS, Forsell Y et al. Depression-associated ARNTL and PER2 genetic variants in psychotic disorders. *Chronobiol Int* 2015; 32: 579–584
- [99] Shi J, Wittke-Thompson JK, Badner JA et al. Clock genes may influence bipolar disorder susceptibility and dysfunctional circadian rhythm. *Am J Med Genet B Neuropsychiatr Genet* 2008; 147B: 1047–1055
- [100] Lane JM, Vlasac I, Anderson SG et al. Genome-wide association analysis identifies novel loci for chronotype in 100 420 individuals from the UK Biobank. *Nat Commun* 2016; 7: 10889
- [101] Lane JM, Liang J, Vlasac I et al. Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. *Nat Genet* 2017; 49: 274–281
- [102] Van Rheeën TE, Lewandowski KE, Bauer IE et al. Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. *Bipolar Disord* 2019 Aug 13 [Epub ahead of print]
- [103] Gold AK, Kinrys G. Treating circadian rhythm disruption in bipolar disorder. *Curr Psychiatry Rep* 2019; 21: 14
- [104] Ashok AH, Marques TR, Jauhar S et al. The dopamine hypothesis of bipolar affective disorder: The state of the art and implications for treatment. *Mol Psychiatry* 2017; 22: 666–679
- [105] Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry* 2008; 165: 820–829
- [106] Abreu T, Bragança M. The bipolarity of light and dark: a review on bipolar disorder and circadian cycles. *J Affect Disord* 2015; 185: 219–229
- [107] Hallam KT, Olver JS, Norman TR. Melatonin sensitivity to light in monozygotic twins discordant for bipolar I disorder. *Aust NZ J Psychiatry* 2005; 39: 947
- [108] Hallam KT, Olver JS, Horgan JE et al. Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers. *Int J Neuropsychopharmacol* 2005; 8: 255–259
- [109] Hallam KT, Olver JS, Norman TR. Effect of sodium valproate on nocturnal melatonin sensitivity to light in healthy volunteers. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 2005; 30: 1400–1404
- [110] Lewy AJ, Nurnberger Jr, Wehr TA et al. Supersensitivity to light: Possible trait marker for manic-depressive illness. *Am J Psychiatry* 1985; 142: 725–727
- [111] Benedetti F, Dall'aspezia S, Fulgosi MC et al. Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet* 2007; 144B: 631–635
- [112] Benedetti F, Serretti A, Colombo C et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet* 2003; 123B: 23–26
- [113] Lee KY, Song JY, Kim SH et al. Association between CLOCK 3111T/C and preferred circadian phase in Korean patients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; 34: 1196–1201
- [114] Brasil Rocha PM, Campos SB, Neves FS et al. Genetic association of the PERIOD3 (Per3) clock gene with bipolar disorder. *Psychiatry Investig* 2017; 14: 674–680
- [115] Drago A, Monti B, De Ronchi D et al. CRY1 Variations impacts on the depressive relapse rate in a sample of bipolar patients. *Psychiatry Investig* 2015; 12: 118–124
- [116] Soria V, Martínez-Amorós E, Escaramís G et al. Differential association of circadian genes with mood disorders: CRY1 and NPAS2 are associated with unipolar major depression and CLOCK and VIP with bipolar disorder. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 2010; 35: 1279–1289
- [117] Malhi GS, Mann JJ. Depression. *Lancet Lond Engl* 2018; 392: 2299–2312
- [118] Liu Y, Zhao J, Guo W. Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. *Front Psychol* 2018; 9: 2201
- [119] Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron* 2019; 102: 75–90
- [120] Li JZ, Bunney BG, Meng F et al. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc Natl Acad Sci* 2013; 110: 9950–9955
- [121] Daut RA, Fonken LK. Circadian regulation of depression: a role for serotonin. *Front Neuroendocrinol* 2019; 100746
- [122] Bunney JN, Potkin SG. Circadian abnormalities, molecular clock genes and chronobiological treatments in depression. *Br Med Bull* 2008; 86: 23–32
- [123] Souètre E, Salvati E, Belugou JL et al. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res* 1989; 28: 263–278
- [124] Maglione JE, Nievergelt CM, Parimi N et al. Associations of PER3 and RORA circadian gene polymorphisms and depressive symptoms in older adults. *Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry* 2015; 23: 1075–1087
- [125] Liberman AR, Kwon SB, Vu HT et al. Circadian clock model supports molecular link between PER3 and human anxiety. *Sci Rep* 2017; 7: 9893
- [126] Lavebratt C, Sjöholm LK, Soronen P et al. CRY2 is associated with depression. *PLoS One* 2010; 5: e9407
- [127] Kovanen L, Saarikoski ST, Haukka J et al. Circadian clock gene polymorphisms in alcohol use disorders and alcohol consumption. *Alcohol Alcohol* 2010; 45: 303–311
- [128] Sjöholm LK, Kovanen L, Saarikoski ST et al. CLOCK is suggested to associate with comorbid alcohol use and depressive disorders. *J Circadian Rhythms* 2010; 8: 1
- [129] Schuch JB, Genro JP, Bastos CR et al. The role of CLOCK gene in psychiatric disorders: Evidence from human and animal research. *Am J Med Genet B Neuropsychiatr Genet* 177: 181–198
- [130] Baranger DAA, Ifrah C, Prather AA et al. PER1 rs3027172 genotype interacts with early life stress to predict problematic alcohol use, but not reward-related ventral striatum activity. *Front Psychol* 2016; 7: 464
- [131] Wulff K, Gatti S, Wettstein JG et al. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci* 2010; 11: 589–599
- [132] Wirz-Justice A, Benedetti F. Perspectives in affective disorders: Clocks and sleep. *Eur J Neurosci* 2019 Jan 31 [Epub ahead of print]
- [133] Gruber R, Grizenko N, Joobar R. Delayed sleep phase syndrome, ADHD, and bright light therapy. *J Clin Psychiatry* 2007; 68: 337–338
- [134] Rybak YE, McNeely HE, Mackenzie BE et al. An open trial of light therapy in adult attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 2006; 67: 1527–1535

- [135] Cosgrave J, Wulff K, Gehrman P. Sleep, circadian rhythms, and schizophrenia: Where we are and where we need to go. *Curr Opin Psychiatry* 2018; 31: 176–182
- [136] Geoffroy PA, Curis E, Courtin C et al. Lithium response in bipolar disorders and core clock genes expression. *World J Biol Psychiatry* 2018; 19: 619–632
- [137] Moreira J, Geoffroy PA. Lithium and bipolar disorder: Impacts from molecular to behavioural circadian rhythms. *Chronobiol Int* 2016; 33: 351–373
- [138] Landgraf D, Joiner WJ, McCarthy MJ et al. The mood stabilizer valproic acid opposes the effects of dopamine on circadian rhythms. *Neuropharmacology* 2016; 107: 262–270
- [139] Coogan AN, Schenk M, Palm D et al. Impact of adult attention deficit hyperactivity disorder and medication status on sleep/wake behavior and molecular circadian rhythms. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 2019; 44: 1198–1206
- [140] Niederhofer H. Treating ADHD with agomelatine. *J Atten Disord* 2012; 16: 346–348
- [141] Mohammadi MR, Mostafavi SA, Keshavarz SA et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: A randomized double blind clinical trial. *Iran J Psychiatry* 2012; 7: 87–92