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The Role of the Circadian Clock in Animal Models of Mood Disorders

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ABSTRACT

An association between circadian clock function and mood regulation is well established and has been proposed as a factor in the development of mood disorders. Patients with depression or mania suffer disturbed sleep/wake cycles and altered rhythms in daily activities. Environmentally disrupted circadian rhythms increase the risk of mood disorders in the general population. However, proof that a disturbance of circadian rhythms is causally involved in the development of psychiatric disorders remains elusive. Using clock gene mutants, manipulations of sleep/wake and light/dark cycles, and brain lesions affecting clock function, animal models have been developed to investigate whether circadian rhythm disruptions alter mood. In this review, selected animal models are examined to address the issue of causality between circadian rhythms and affective behavior.

KEYWORDS: circadian rhythms, mood disorders, depression, bipolar disorder, animal models, mice

INTRODUCTION

Major depressive disorder (MDD) and bipolar disorder (BD) are disabling neuropsychiatric conditions. MDD is characterized by episodes of depressed mood, whereas the less common BD is characterized by episodes of both depression and abnormal mood elevation (mania). Interestingly, many MDD and BD patients show diurnal variation in mood as well as abnormalities in rhythmic processes like sleep, appetite, and social interaction (Boyce & Barriball, 2010). While the idea of an

association between mood disorders and circadian rhythms is not new (Papousek, 1975), interest in the precise relationship between mood and the circadian clock has grown substantially with the development of mechanistic insights into the circadian system (McCarthy & Welsh, 2012). As a result, animal models have been developed to investigate the causal connection between circadian rhythms and mood. These models have employed various methods to manipulate the clock, including genetic (mutations in clock genes), behavioral or environmental (manipulations of sleep/wake and light/dark cycles), anatomical (brain lesions), and pharmacological methods (Kronfeld-Schor & Einat, 2012). However, it is still unclear whether these animal models establish proof of a causal relationship between circadian rhythms and mood dysregulation.

CIRCADIAN CLOCKS

Most organisms have evolved endogenous circadian (ca. 24 hr) clocks to anticipate the recurring environmental changes brought about by the Earth's rotation. These rhythms are synchronized ("entrained") to the 24h day by external timing cues, called *Zeitgebers* (German: *Zeit* = time, *Geber* = giver). Light is the main *Zeitgeber,* so the circadian system is primarily entrained by the day/night cycle (Daan & Pittendrigh, 1976). While the master circadian pacemaker is the suprachiasmatic nucleus (SCN) of the hypothalamus, most tissues harbor autonomous cellular clocks (Albrecht, 2012). The SCN receives light information via intrinsically photosensitive retinal ganglion cells (ipRGCs) and synchronizes peripheral clocks throughout the body by neuronal and humoral pathways (Dibner, Schibler, & Albrecht, 2010; Ecker et al., 2010). Besides the SCN, many other brain regions, including some implicated in mood regulation, receive direct input from ipRGCs (Hattar et al., 2006). Non-SCN clocks are important to stabilize the circadian system throughout the body and to regulate local rhythmic processes, and clocks in brain regions regulating mood are perhaps in the best position to cause mood disruption.

In mammalian cells, circadian rhythms emerge from autoregulatory transcriptional-translational feedback loops (TTLs) that regulate rhythmic expression of core clock genes. The core TTL comprises the transcriptional activators CLOCK, NPAS2, and BMAL1 (ARNTL), acting at E-box regulatory elements on DNA, and the transcriptional repressors CRY1/2 and PER1/2/3, which regulate their own rhythmic expression via delayed negative feedback on CLOCK/BMAL1. The TTL is regulated by auxiliary elements like casein kinase 1 δ/ε (CK1δ/ε), glycogen synthase kinase 3 (GSK3), and F-box/LRR-repeat protein 3 (FBXL3), which fine-tune the molecular circadian clock (Koike et al., 2012; Lowrey & Takahashi, 2011) **(Figure 1)**. One cycle of activation and repression of gene expression is completed in approximately 24

hours and then starts anew. Downstream genes rhythmically activated by core clock genes are known as clock-controlled genes.

One hallmark of circadian clocks is autonomy, or the ability to sustain rhythms in the absence of Z*eitgebers*. Even under constant ("free-running") conditions, the periods of circadian rhythms stay close to 24 hours (Jud, Schmutz, Hampp, Oster, & Albrecht, 2005; Pittendrigh, 1960). Organisms also start to free-run if the period of environmental rhythms is too short or too long for the circadian system to entrain (Jud et al., 2005).

THE CIRCADIAN CLOCK AND MOOD DISORDERS

The clinical characteristics of mood disorders like BD and MDD include a number of features that could reflect a disturbance in circadian rhythms (Boyce & Barriball, 2010; McCarthy & Welsh, 2012; McClung, 2007a). In addition, the length of the day (duration of light exposure) has a strong impact on both the circadian system and mood, as in the precipitation of mood episodes during the shorter days of winter in patients with seasonal affective disorder (SAD) (Lewy et al., 2007). Furthermore, mood disorders appear more often when rhythms are disrupted by changes in day/night schedules, as in shift workers (Rosenberg & Doghramji, 2011) and transmeridian travelers suffering from "jet lag" (Srinivasan et al., 2010). Accordingly, therapeutic treatments targeting the circadian clock have been developed for mood disorders, including light exposure, shifting of sleep/wake schedules (Lewy et al., 2007; Pail et al., 2011; Wu et al., 2009), and melatonergic drugs (Di Giannantonio & Martinotti, 2012; Fornaro et al., 2013). Supporting these clinical findings, certain polymorphisms in circadian clock genes are associated with mood disorders (Etain, Milhiet, Bellivier, & Leboyer, 2011; McCarthy, Nievergelt, Kelsoe, & Welsh, 2012). Finally, a recent human postmortem study showed that 24 hr rhythms of gene expression in mood-regulating brain regions of MDD patients were weaker than in control subjects, which could be due to lower rhythm amplitude in individual patients, poor synchronization with the light/dark cycle, and/or poor synchronization among rhythms within an individual (Li et al., 2013).

ARE MOOD DISORDERS CAUSED BY DISRUPTED RHYTHMS?

While such associations between mood and circadian rhythms are now widely accepted, the suggestion that circadian rhythm abnormalities *cause* these disorders remains controversial, and difficult to test in human patients. It remains possible that causality points in the opposite direction, i.e.

that mood dysregulation causes rhythm disturbances (Gorka, Moryl, & Papp, 1996; Takahashi et al., 2013; Ushijima, Morikawa, To, Higuchi, & Ohdo, 2006), or that both mood and rhythms are affected by a common pathological process, but have little to do with each other **(Figure 2)**. In this context, it is important to point out that while commonly called "clock genes", the molecular components of the circadian clock have pleiotropic functions, including many functions that have nothing to do with the clock: manipulating clock genes affects more than just circadian rhythms. Consequently, mood effects of clock gene mutations could be mediated by non-circadian effects. Similarly, anatomical lesions, drug treatments, and light manipulations targeting the circadian clock may alter processes not involved in circadian timekeeping. Nevertheless, with a newly detailed understanding of the clock, and good experimental tools now available, the question of whether circadian clock dysfunction causes mood disorders is within reach, and amenable to empirical testing.

CIRCADIAN RHYTHMS IN ANIMAL MODELS OF MOOD DISORDERS

GENETIC MANIPULATION:

Since the circadian clock TTL mechanism was described, numerous transgenic mice have been generated with mutations in one or more of the component clock genes. Among these, some have been characterized for motor activity, reward processing, anxiety-like behavior, or behavioral despair, phenotypes of interest in animal models of mood disorders **(Table 1)**.

CLOCK GENE:

The *Clock-d19* mutant mouse carries a deletion of exon 19 of the gene *Clock*, leading to the translation of a dominant negative CLOCK protein (King et al., 1997; Vitaterna et al., 1994). The mutated CLOCK protein is non-functional but competes with its paralog NPAS2 for DNA binding, thereby producing a more severe rhythm phenotype than in the *Clock* knockout mouse. *Clock-d19* mice have free running rhythms with a long period (~27 hours), followed by arrhythmia after a few days in constant darkness (Vitaterna et al., 1994). In addition, *Clock-d19* mice show mania-like behavior (Naylor et al., 2000; Ozburn, Larson, Self, & McClung, 2012; Roybal et al., 2007). Compared to wild-type (WT) mice, *Clock-d19* mice are hyperactive and need less sleep. Furthermore, they show increased reward seeking behavior: i.e., greater preference for self-administered sucrose, cocaine, or rewarding electrical self-stimulation to the medial forebrain bundle. In despair- and anxiety-based tests like the forced swim test, the learned helplessness paradigm, or the elevated plus maze, *Clock-d19* mice express lower

anxiety (higher impulsivity) and less immobility. Taken together, these features model many aspects of mania observed in BD patients.

Since *Clock* is an important component of the circadian TTL and its mutation leads to major disturbances of rhythmicity and mood, *Clock-d19* mice have been proposed as evidence of a causal link between circadian rhythms and mood regulation (McClung, 2007b). However, it is not clear whether mood-related phenotypes in *Clock-d19* mice are really caused by changes in circadian rhythmicity.

(i) In *Clock-d19* mice, restoration of WT *Clock* expression specifically in the ventral tegmental area (VTA) leads to a reduction of mania-like behaviors (Roybal et al., 2007), and in WT mice, VTA-specific knockdown of *Clock* transcription leads to aspects of mania-like behavior (Mukherjee et al., 2010). These data show that *Clock* gene function in the VTA is causally connected to mania-like behaviors. Subsequent work has revealed that *Clock-d19* animals have increased dopamine levels, higher bursting rates of VTA dopaminergic neurons, increased dopamine sensitivity, and more dopamine receptors in dorsal striatum (Coque et al., 2011; McClung et al., 2005; Spencer et al., 2012). Accordingly, *Clock-d19* mice show altered neurophysiology in dopaminergic projections from the VTA to the nucleus accumbens (NAc) (Dzirasa et al., 2011).

These results highlight the multiple effects of the *Clock-d19* mutation on the mesocortical and mesolimbic dopamine systems, but effects on rhythms in the VTA have not been as well characterized. The SCN projects to the VTA indirectly via the medial preoptic nucleus (Luo & Aston-Jones, 2009), but there is little evidence that the VTA can sustain rhythms autonomously without SCN input. A rhythmic subpopulation of VTA dopamine neurons was identified in gene expression and electrophysiological studies of intact animals (Baird, Coogan, Kaufling, Barrot, & Thome, 2013; Baltazar, Coolen, & Webb, 2013; Kerman et al., 2012; Luo, Georges, & Aston-Jones, 2008; Wei et al., 2011). However, *Per* expression is not rhythmic in isolated VTA slices (Abe et al., 2002), suggesting that *in vivo* VTA rhythms are driven by the SCN **(Figure 3)**. This implies that in *Clock-d19* mice with a global rhythm disturbance, VTA-specific restoration of *Clock* might not be sufficient to restore rhythms in the absence of rhythmic SCN input. A demonstration that dopamine rhythms are restored after tissue-specific rescue of *Clock* gene expression in the VTA would counter this prediction, establishing that disrupted rhythms in the VTA could mediate the mania-like behaviors of *Clock-d19* mice.

(ii) Cholecystokinin (CCK) has been proposed as a possible mediator of CLOCK's effects on midbrain dopamine systems (R. N. Arey et al., 2013; Schade et al., 1995). CCK is a rhythmic negative modulator of dopamine regulated at the transcriptional level by BMAL1/CLOCK, and is reduced in *Clock-d19* mice, possibly accounting for elevated dopamine and manic behavior in these mice. If CCK is indeed normally

rhythmic in the VTA, then loss of rhythmic activation by BMAL1/CLOCK should lead to reduced CCK, and therefore elevated dopamine and mania, preferentially at times of day when CCK is normally high. This could be tested by characterizing mood in *Clock-d19* animals at different times of day.

(iii) The mood stabilizer lithium reduces mania-like behavior in *Clock-d19* mice (Dzirasa et al., 2010; Kozikowski et al., 2011). The mechanism of the mood stabilizing effect of lithium is still unknown, but lithium inhibits GSK3β (Klein & Melton, 1996), and GSK3β phosphorylates and regulates multiple clock components, so it has been proposed that lithium acts on mood by affecting the clock. However, GSK3β increases degradation of CLOCK (J. R. Paul, Johnson, Jope, & Gamble, 2012; Spengler, Kuropatwinski, Schumer, & Antoch, 2009), so inhibition of GSK3β by lithium should lead to an increase of CLOCK protein (Gould & Manji, 2005; King et al., 1997; Spengler et al., 2009), and increased CLOCK-d19 protein in mutant mice would be predicted to further impair rhythms. This suggests the possibility that the positive mood-altering effects of lithium in *Clock-d19* mice are not mediated by effects on circadian rhythms.

(iv) Mania-like behavior in *Clock-d19* mice is also reduced by pharmacological inhibition of CK1δ/ε (R. Arey & McClung, 2012). CK1δ/ε kinases phosphorylate PER proteins, promoting their degradation (Meng et al., 2008). Hence, CK1 inhibition leads to increased accumulation of PER protein. Importantly, this was shown to re-instate rhythms in arrhythmic *Vipr2*$^{-/-}$ mice (Meng et al., 2010). Thus, increasing PER in *Clock-d19* mice, where *Per1* and *Per2* expression are reduced, may strengthen circadian rhythms and could thereby normalize mood (Vitaterna et al., 2006). On the other hand, inhibition of CK1δ also leads to period lengthening (Loudon et al., 2007), which would presumably further lengthen the already abnormally long period seen in *Clock-d19* mice, so the normalizing effect of CK1 on mood is unlikely to be mediated by this mechanism. Further studies are needed to confirm the circadian consequences of CK1 inhibition in *Clock-d19* mice or in other animal models of mania.

Considering the evidence to date, then, the *Clock-d19* mouse represents an interesting model of mania, but it would be premature to conclude that its mood phenotype arises from a circadian rhythm disturbance, rather than alteration of a pleiotropic, non-circadian function of CLOCK. The expression of CLOCK is constitutive (not rhythmic) in most brain regions (Ko & Takahashi, 2006), so the mania-like phenotype of *Clock-d19* could arise from elimination of a constitutive, rather than rhythmic, drive on expression of genes directly targeted by CLOCK. Characterization of affective behaviors in the *Clock*$^{-/-}$ mouse, where the CLOCK protein is completely absent but rhythms are intact (Debruyne et al., 2006) may discriminate between circadian and non-circadian roles of CLOCK in the regulation of mood. Double-knockouts of *Clock* and *Npas2* could also be informative (DeBruyne, Weaver, & Reppert, 2007). On the other hand, if the manic behavior of *Clock-d19* mice is mediated through effects of the mutation

on clock dynamics, similar phenotypes should be observable in other models where other clock genes are mutated to produce similar rhythm defects; this possibility will be examined in detail below.

***PERIOD GENES: PER1-2*:**

In *Per1*$^{ldc-/-}$ mice, there are no mood phenotypes under baseline conditions. However, there are differences in voluntary alcohol consumption, seen only after social defeat stress, suggesting altered reward processing pathways sensitive to stress (Dong et al., 2011; Zghoul et al., 2007).

Mouse studies have revealed a more prominent role for *Per2* in mood and reward processing. Chronic unpredictable stress causes depression-like behavior in mice and reduces the amplitude of *Per2* rhythms in the SCN, both of which can be reversed by the antidepressant desipramine (Jiang et al., 2011). Interestingly, *Per2* rhythms recover more quickly than depression-like behaviors, showing that these effects are dissociable. In a similar study of chronically stressed animals (Kinoshita, Miyazaki, & Ishida, 2012), *Per2* rhythm amplitudes were reduced in SCN, as were rhythms of GSK3β phosphorylation throughout the brain. With lithium given during the dark phase, both GSK3β phosphorylation and *Per2* rhythms could be restored, but whether this improved mood was not tested. In *Per2* mutant models, the mood phenotype depends on the nature of the mutation. Two distinct *Per2* mutants have been created: *Per2*$^{Brdm1-/-}$ mice lack 87 residues from the PAS dimerization domain whereas *Per2*$^{ldc-/-}$ mice lack exon 5 and portions of exon 6 (Bae et al., 2001; B. Zheng et al., 1999). While *Per2*$^{ldc-/-}$ and *Per2*$^{Brdm1-/-}$ show similar rhythm phenotypes in behavioral and gene expression assays, *Per2*$^{Brdm1-/-}$ mice have a mania-like phenotype whereas *Per2*$^{ldc-/-}$ mice do not (Hampp et al., 2008; Spencer et al., 2013). However, different measures of mood were used in these studies, which could explain the discordant results. *Per1*$^{ldc-/-}$; *Per2*$^{ldc-/-}$ double mutants, which are arrhythmic, have increased anxiety-like behavior; they have yet to be characterized with respect to other mood-related phenotypes.

How *Per* genes affect mood related behaviors is not well established, but *Per2* does impact dopamine metabolism. The gene monoamine oxidase A (*Maoa*) encodes an enzyme critical for termination of dopamine signaling. Its promoter contains an E-box (Hampp et al., 2008), such that *Maoa* expression is rhythmic and dependent on BMAL1, NPAS2, and PER2. In *Per2*$^{Brdm1-/-}$ mutant mice (B. Zheng et al., 1999), the rhythmic expression of *Maoa* is severely attenuated, and the constitutive activity of MAOA is lower at all times of the day. Despite the fact that MAOA is no longer rhythmic in *Per2*$^{Brdm1-/-}$ mice, dopamine release in the NAc is still rhythmic in a light/dark cycle, and dopamine levels are higher throughout the day. Consequently, *Per2*$^{Brdm1-/-}$ mice show less depression-like behavior in the forced swim test throughout the day. Thus, the behavioral changes in *Per2*$^{Brdm1-/-}$ mutants may depend on

constitutive differences in dopamine levels, and not differences in circadian rhythms resulting from the loss of PER2 **(Figure 4)**. Further studies of different mutant mice, e.g. non-rhythmic mice with constant high PER2 expression, could discriminate between circadian and non-circadian effects of PER2.

D-BOX BINDING PROTEIN (DBP):

Dbp$^{-/-}$ mice show shorter free-running periods (Lopez-Molina, Conquet, Dubois-Dauphin, & Schibler, 1997). Accordingly, when *Dbp* expression is suppressed in Rat-1 fibroblasts, circadian period is shortened by approximately 1 hour, and overexpression of *Dbp* leads to a period lengthening (Yamajuku et al., 2011). *Dbp* gene variants are associated with increased alcohol consumption in rats and BD patients (Niculescu et al., 2000; Rodd et al., 2007). At baseline, *Dbp*$^{-/-}$ mice are hypoactive, interpreted as depression-like behavior (Le-Niculescu et al., 2008). However, when exposed to chronic stress or sleep deprivation they become hyperactive, gain more weight, and consume more alcohol, which are signs of a mania-like mood state. The switch between depression-like and stress-triggered mania-like behavior makes the *Dbp*$^{-/-}$ mouse an interesting model for BD. Whether the mood-related phenotypes depend on circadian abnormalities of *Dbp*$^{-/-}$ mice, however, was not investigated.

F-BOX/LRR-REPEAT PROTEIN 3 (FBXL3):

The mutant *after hours* (*Afh*) is a mutation of *Fbxl3*, encoding FBXL3, a member of the F-Box protein family involved in degradation of CRY1 and CRY2 via ubiquitination (Busino et al., 2007). *Afh* mutants are characterized by a long free-running period of ~26.5 hours. In contrast to *Clock-d19* and *Per1/2* mutants, *Afh* mutants remain rhythmic in constant darkness (Godinho et al., 2007). Due to similarities with the circadian phenotype of *Clock-d19*, *Afh* mice were recently tested for mood disturbances. Indeed, the *Afh* mutation leads to reductions in anxiety- and depression-like behavior, similar to those observed in *Clock-d19* mutants (Keers et al., 2012).

In *Afh* mice, *Per1/2, Cry1, and Bmal1* expression rhythms have reduced amplitudes in SCN and liver (Godinho et al., 2007). Therefore, it is expected that non-SCN brain areas in *Afh* mice, including those which regulate mood, would also be affected, and perhaps even more so than SCN, as these regions lack the network properties of the SCN that confer robustness against genetic mutations (Liu et al., 2007). It would also be interesting to test mood phenotypes in another *Fbxl3* mutation called *overtime* (Siepka et al., 2007).

CASEIN KINASES

Mutations in post-translational clock modulators also affect mood phenotypes in mice. CK1δ and CK1ε phosphorylate core clock proteins and trigger their degradation (Etchegaray et al., 2009). Knockouts of CK1δ/ε lead to long periods, whereas a gain of function mutation of CK1ε (*tau*) leads to short periods (Etchegaray et al., 2009; Loudon et al., 2007; Ralph & Menaker, 1988). Genetic deletion of CK1ε leads to an increase in reward-seeking behavior (Bryant et al., 2012). Conversely, when overexpressed in the forebrain, CK1δ causes increased motor activity and decreased anxiety, but decreases in reward-seeking behavior (Zhou et al., 2010).

GLYCOGEN SYNTHASE KINASE 3 (GSK3)

GSK3α/β are well known targets of the mood stabilizer lithium, and inhibition of GSK3 by lithium has been proposed to mediate its therapeutic effects (O'Brien & Klein, 2009). These proteins also phosphorylate several circadian TTL components, regulating their degradation (J. R. Paul et al., 2012; Spengler et al., 2009). GSK3 mutants with decreased expression or brain specific overexpression both have long circadian periods (Lavoie, Hebert, & Beaulieu, 2013; J. R. Paul et al., 2012). Brain-specific overexpression of GSK3 (*Gsk3-OX*) results in phase-shifted temperature and behavior rhythms (Ahnaou & Drinkenburg, 2011). As GSK knockout is lethal in mice, mutants with haploinsufficiency ($Gsk3^{+/-}$) or resistance to inhibitory phosphorylation (*Gsk3-PX*) have been studied. $Gsk3^{+/-}$ phenocopies several aspects of lithium treatment, exhibiting long circadian period, as well as resistance to despair, and less impulsivity in the open field test (O'Brien et al., 2004). However, using a different background strain, another study applying multiple behavioral tests could not confirm these phenotypes of $Gsk3^{+/-}$ mice (Bersudsky et al., 2008).

Disinhibition of GSK3 using the *Gsk3-PX* mutant, or brain specific overexpression of GSK3 (*Gsk3-OX*), lead to mania-like phenotypes, with increases in motor activity, impulsivity, and (in *Gsk3-OX*) reward seeking behaviors. (O'Brien et al., 2004; Polter et al., 2010; Prickaerts et al., 2006). Curiously, although the *Gsk3-OX* mutant shows decreased despair in the forced swim test (T. F. Ackermann, Kempe, Lang, & Lang, 2010), it exhibits increased despair in the learned helplessness paradigm (Polter et al., 2010). In this study, however, learned helplessness training and testing were carried out in the same environment, which confounds despair with fear conditioning (Maier & Watkins, 2005).

SODIUM POTASSIUM ATPASE (ATP1A3)

Mice heterozygous for the *Myshkin* mutation of ATP1A3, a brain specific sodium-potassium ATPase (NKA), show a ~40% reduction of NKA activity in the brain, and display mania-like behavior (Mynett-Johnson et al., 1998; Tochigi et al., 2008). They also have a longer circadian period and longer activity phase. Lithium and valproic acid, mood stabilizers known to influence the circadian clock, attenuate the mood phenotypes of *Myshkin* mice (Kirshenbaum et al., 2011). On a molecular level, the mutation leads to increased levels of calcium and phosphorylated AKT (Berridge, 2012; Noguchi, Wang, Pan, & Welsh, 2012; O'Brien & Klein, 2009; X. Zheng & Sehgal, 2010).

It is worth pointing out, however, that changes in both circadian rhythms and mood in response to manipulations of *Dbp*, F-box proteins, kinases, or ATPases may well be unrelated parallel events, reflecting ubiquitous involvement of these enzymes in cellular physiology, and may not imply causality.

Table 1: Effects of clock gene mutations on circadian rhythms and mood in mouse models.

nes	Mutant	Circadian Period	Amplitude	Simplified Mood Phenotype	Activity	Reward	Despair	Anxiety	Drug Responitivity	References
ck	*Clock-d19*	Long/AR	↓	Mania-like	↑	↑	↓	↓	Lithium, GSK-3b inhibitor	Ozburn, 2012; Roybal, 2007; Vitaterna, 1994, Kozikowski,2011
	Per1$^{ldc-/-}$	Short/AR	↓	=	=	N.D.	N.D.	=	N.D.	Bae, 2001; Spencer, 2013
	Per1$^{Brdm-/-}$	Short	↓	Depression-like	=	↓	N.D.	N.D.	N.D.	Abarca, 2002; Zheng, 2001
	Per2$^{ldc-/-}$	Short/AR	↓	=	=	N.D.	N.D.	=	N.D.	Bae, 2001; Spencer, 2013
	Per2$^{Brdm1-/-}$	Short/AR	↓	Mania-like	=	↑	N.D.	N.D.	N.D.	Abarca, 2002; Zheng, 2001
	Per1$^{ldc-/-}$*; Per2*$^{ldc-/-}$	AR	↓	Anxiety-like	=	N.D.	N.D.	↑	N.D.	Bae, 2001; Spencer, 2013
xl3	*Fbxl3*$^{afh/afh}$	Long	↓	Mania-like	=	N.D.	↓	↓	N.D.	Godinho, 2007; Keers, 2012
p	*Dbp*$^{-/-}$	Short	=	Mixed	↓$^{\$}$ / ↑$^{\$\$}$	N.D	N.D.	N.D	VPA	Le-Niculescu, 2008; Lopez-Molina, 1997; Yamajuku, 2011
1	*Csnk1ε*$^{-/-}$	Long	=	Mania-like	=	↑	N.D.	N.D.	Methamphetamine	Bryant, 2012; Loudon, 2007
	*Csnk1δ OX**	N.D.	N.D.	Mania-like	↑	↓	N.D.	↓	D-amphetamine, methylphenidate	Zhou, 2010
	Csnk1δ$^{-/-}$	Long	↓	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	Etchegaray, 2009
k3	*Gsk3β*$^{+/-}$	Long	N.D.	Anxiety-like	=	N.D.	↓	↑	N.D.	Lavoie, 2013; O'Brien, 2004
	*Gsk3β OX***	Shifted	↓	Mania-like	↑	N.D.	↓	↓	N.D.	Ahnaou, 2011; Prickaerts, 2006
	Gsk3α/β-PX	Long	↓	Mania-like	↑	↑	↓$^{\#}$ / ↑$^{\#\#}$	↓	D-amphetamine	Ackermann, 2010; Paul, 2012; Polter, 2010
1a3	*Myk/*$^{+}$	Long	N.D.	Mania-like	↑	↑	↓	↓	Lithium, VPA	Kirshenbaum, 2011

N.D. = not determined; "=" = no change; ↕ = increased/decreased; AR = arrhythmic

* mood phenotypes with striatum-specific overexpression

** circadian phenotype with brain-specific overexpression

$ non-stressed animals

$$ stressed animals

forced swim test

learned helplessness

Summary of Mouse Mutant Studies

In summary, at least six gene families involved in the circadian TTL have been implicated in mood regulation by mouse mutant studies (Table 1), reminiscent of human genetic association studies which have also implicated a number of circadian clock genes in mood disorders (McCarthy et al., 2012). Of these, *Per2*, *Clock*, and *Gsk3*β are implicated in both animal models and human genetic studies. In patients with MDD and BD, there is considerable heterogeneity and co-morbidity with other psychiatric conditions, such as anxiety disorders, substance use disorders, and attention deficit hyperactivity disorder. Conversely, in mice, similar mood-related phenotypes can emerge from distinct genetic abnormalities. Hence, the circadian clock in humans may be vulnerable to genetic perturbation in several distinct ways, some of which impact shared features of multiple disorders, whereas others impact unique features of particular disorders.

But do existing mouse models provide definitive evidence that mood dysregulation can be caused by circadian clock dysfunction? Each mutant shows a distinct mood/rhythm combination phenotype. Mutants with similar changes of circadian period do not necessarily have the same mood phenotype, whereas similar mood characteristics sometimes occur with opposite changes of circadian period. Reduced rhythm amplitude, on the other hand, is a common feature of each of the animal models in which it was tested. However, in some cases mutations with similar amplitude decreases lead to opposite changes in mood behavior (e.g. compare *Clock-d19*, *Per2*$^{Brdm1-/-}$, and *Fbxl3*$^{afh/afh}$ to *Per1*$^{ldc-/-}$ and *Per2*$^{ldc-/-}$). Thus, while mouse models do suggest that circadian clock components are important for mood regulation, the discrepancies between circadian and mood phenotypes suggest that non-circadian roles of these proteins might account for at least some of their effects on mood.

Next steps in determining causality in genetic models

Further studies could help resolve the role of circadian timing per se in mood regulation:

(i) Rhythmic behavioral output is mainly regulated by the SCN, yet the SCN is especially resistant to clock gene mutations compared to other tissues (Liu et al., 2007). Hence, clock gene mutants with mood related phenotypes may show arrhythmicity in brain areas important for mood regulation, even if this is not manifest in locomotor behavior rhythms. Depending on the anatomical distribution of arrhythmicity, animals may show varying mood phenotypes, perhaps corresponding to the well-known clinical heterogeneity of mood disorders in human patients.

(ii) To investigate the role of circadian clock amplitude, clock gene expression rhythms could be examined in particular brain regions of mutant mice. Low amplitude in some brain areas might

correspond to specific phenotypes indicating mood dysregulation (e.g., inactivity, despair, reduced reward-seeking, anxiety), whereas other areas may be associated with generalized mood instability (i.e., greater deviations of mood, regardless of direction). Drugs that increase amplitude in mouse models would be predicted to improve depression- or mania-like phenotypes.

(iii) To investigate the role of circadian period, T-cycles (light/dark cycles with a total length different from 24 hours) could be used to manipulate the circadian misalignment resulting from mutant period. If period is important for a mood phenotype, T-cycles matching the intrinsic free-running period of mutant animals should normalize mood phenotypes by correcting abnormal phasing. On the other hand, WT control animals entrained to non-24hr T-cycles may show depression or mania-like behavior due to abnormal phasing, similar to mutant mice in a 24 hour day.

LIGHT/DARK MANIPULATIONS

ALTERATIONS IN PHOTOPERIOD:

Photoperiodism, the physiological response to seasonal changes in day length, depends on the circadian system (Hazlerigg & Wagner, 2006). As a result of seasonal adaption, the circadian system is reorganized on multiple levels, such that phase relations among cells within the SCN, among the SCN and peripheral organs, and between clock gene and output rhythms are altered (Carr et al., 2003; Inagaki, Honma, Ono, Tanahashi, & Honma, 2007; Tournier et al., 2007; VanderLeest et al., 2007). The duration of daily activity varies seasonally in rodents, and at the level of the SCN, this is encoded by the phase relationship among individual SCN neurons. In some species, there are dramatic seasonal changes in metabolism, coat color, and reproductive physiology and behavior, mediated through the SCN-controlled pineal hormone melatonin (Goldman, 2001). In human seasonal affective disorder (SAD) (Rosenthal et al., 1984), depressive episodes are more common in the winter, and this has led to photoperiodically responsive models of depression in rodents (Kronfeld-Schor & Einat, 2012; Workman & Nelson, 2011).

In many of these studies using photoperiod, nocturnal animals were used to investigate mood problems that occur in humans, a diurnal (day-active) species. However, biological timing mechanisms in diurnal and nocturnal organisms differ in many respects (Challet, 2007). In both groups, lengthening of the night extends the duration of nocturnal melatonin production (Hazlerigg & Wagner, 2006), but this has opposite physiological effects in diurnal and nocturnal animals. In diurnal animals, for instance, melatonin suppresses locomotor activity, whereas in nocturnal animals it stimulates activity (Huber,

Deboer, Schwierin, & Tobler, 1998). Importantly, melatonin administration ameliorates depression-like behaviors in nocturnal animals, but has the opposite effect in diurnal species (Ashkenazy, Einat, & Kronfeld-Schor, 2009; Haridas, Kumar, & Manda, 2013). Shortening the day length of diurnal animals leads to depression-like behavior (Einat, Kronfeld-Schor, & Eilam, 2006; Leach, Ramanathan, Langel, & Yan, 2013). Due to inconsistent results with nocturnal animals, and for better comparability with humans, the use of diurnal animals has been advocated in more recent publications (Flaisher-Grinberg, Gampetro, Kronfeld-Schor, & Einat, 2011; Kronfeld-Schor & Einat, 2012).

CONSTANT DARKNESS, CONSTANT LIGHT:

In the absence of *Zeitgebers*, the self-sustained circadian clock free-runs, reflecting intrinsic properties of the animal's clock. Kept in constant darkness (DD), mice show increases in depression-like behavior, based on increased immobility in the forced swim test (Gonzalez & Aston-Jones, 2008), although DD mice were not tested at a consistent circadian phase, a potentially serious confound. In DD, neurons in brain regions thought to be involved in depression undergo apoptosis, specifically noradrenergic (NA), serotonergic, and dopaminergic neurons in the locus coeruleus (LC), dorsal raphe, and VTA. NA-LC neurons exhibit circadian activity, and DD-induced apoptosis of these neurons decreases the amplitude of sleep-wake cycles in rats (Gonzalez & Aston-Jones, 2006). In the mouse hippocampus, DD decreases PER2 levels and increases NPAS2 levels. NF-κB inhibitors have effects similar to those of DD on both depression-like behavior and expression of PER2 and NPAS2, suggesting a common pathway governing mood regulation and the clock (Monje et al., 2011).

Electrical lighting disrupts natural daily cycles of environmental darkness, and this so called 'light pollution' has also been linked to circadian desynchrony and depression (Gorman, Evans, & Elliott, 2006; Navara & Nelson, 2007; Wyse, Selman, Page, Coogan, & Hazlerigg, 2011). Thus, constant light (LL) may also model some aspects of mood disorders. Dependent on the animal model, LL differs from DD in important ways, namely that rhythms typically persist in diurnal and nocturnal animals under DD, whereas nocturnal animals stay rhythmic in DD, but become arrhythmic in LL (Challet, Pitrosky, Sicard, Malan, & Pevet, 2002). In studies of nocturnal mice and rats kept in LL, anxiety- and depression-like behaviors are increased (Fonken et al., 2009; Tapia-Osorio, Salgado-Delgado, Angeles-Castellanos, & Escobar, 2013). Possible circadian mechanisms of depression-like behavior in LL include the loss of melatonin and corticosterone rhythms. Among nocturnal rats kept in LL, melatonin levels remain low, whereas corticosterone stays constantly high (Tapia-Osorio et al., 2013). Since these hormones rely on SCN clock output, loss of rhythms in melatonin and corticosterone could indicate a malfunction of the

SCN, and point to a mechanism by which rhythm disruption might cause depression-like behavior in nocturnal animals (Haridas et al., 2013; Herbert, 2013).

Although DD and LL animal models provide some rationale for a role of circadian clocks in mood disorders, they also have some weaknesses. *(i)* Nocturnal rodents are more sensitive than diurnal rodents to rhythm disruption by LL, and also have different responses to short photoperiod (Challet et al., 2002). Thus, humans may suffer less from light pollution or winter darkness than studies of nocturnal animals would suggest. *(ii)* DD or LL lighting conditions may not reflect the environmental conditions commonly faced by people.

Perhaps best reflecting the human situation, one recent study showed that dim light at night causes depressive behavior in the diurnal Nile grass rat (Fonken, Kitsmiller, Smale, & Nelson, 2012). Particularly in view of the fact that dim light at night modifies circadian entrainment (at least in nocturnal animals), this experimental design may prove useful (Bedrosian, Galan, Vaughn, Weil, & Nelson, 2013; Frank, Evans, & Gorman, 2010; Gorman et al., 2006). However, no circadian abnormalities were detected by Fonken et al. (2012), so it remains unclear if the depression-like behavior induced by dim light at night in diurnal rodents depended on alterations of the circadian clock. Moreover, one would expect reduced impact of dim light at night in diurnal animals and humans, since their closed eyelids during sleep at night greatly attenuate light exposure (Hatonen, Alila-Johansson, Mustanoja, & Laakso, 1999). Nevertheless, the move toward use of diurnal animals and environmentally valid light exposures in these studies has been a positive development, better reflecting the situation in humans.

Non-circadian basis of light effects on mood

Light could impact mood by non-circadian mechanisms, such as by altering overall alertness and sleep homeostasis (Stephenson, Schroder, Bertschy, & Bourgin, 2012), through multiple input pathways and brain regions (Hattar et al., 2006). One study using diurnal grass rats *(Arvichantis niloticus)* showed that the total amount of light per day (independent of day length) has an impact on forced swim test activity and saccharine solution preference (Leach, Adidharma, & Yan, 2013), arguing against a circadian-mediated photoperiodic response. In other cases, effects of light on mood might be explained by changes in overall levels of hormones like melatonin or corticosterone, independent of rhythm effects (Tapia-Osorio et al., 2013). In another study, increased depression-like behavior was found in mice exposed to light at abnormal times of the circadian cycle, but without any disturbance of sleep architecture or circadian rhythms (LeGates et al., 2012). In this study, mice were housed in a light cycle of 7 hrs light and 7 hrs dark (LD 7:7), to which mice cannot entrain (forced desynchrony), so that they

were repeatedly exposed to light at all phases of their free-running cycle. However, since only *Per2* expression was measured in SCN and liver, along with corticosterone and temperature rhythms, the circadian system could have been affected elsewhere in the brain or at the level of other clock genes. The most interesting aspect of this study is that mood effects were absent in mice lacking ipRGCs, raising the prospect that future studies selectively deleting subsets of ipRGCs (Schmidt, Chen, & Hattar, 2011) could pinpoint the target relevant for effects of light on mood. Another intriguing recent study showed that effects of photoperiod on depression-like behavior are associated with changes in the balance between dopamine and somatostatin expression in certain hypothalamic neurons of rats (Dulcis, Jamshidi, Leutgeb, & Spitzer, 2013). In this study, loss of dopamine neurons in long days led to depression-like behavior, assessed by elevated plus maze test and forced swim test. Finally, it is also possible that seasonal changes in mood could be mediated by endogenous circannual rhythms rather than responses to seasonal changes in photoperiod, as annual serotonin sensitivity levels of rats persist even under constant lighting conditions throughout the year (Nagayama & Lu, 1998; M. J. Paul, Zucker, & Schwartz, 2008).

Changing light input without affecting the circadian clock is difficult, making animal models based on photoperiod manipulation difficult to interpret with respect to determining the causal link between circadian rhythms and mood disorders. But overall, these studies suggest the possibility that the specific reorganization of the circadian system due to seasonal changes of day length may not be responsible for development of seasonal depression. Instead, the total amount of light or even the phase of a circannual cycle may be more important, and further research is needed to understand whether this, in turn, involves the circadian clock.

One possible way to distinguish circadian vs. non-circadian effects of light exposure would be to use an arrhythmic animal. If the animals develop new mood abnormalities under short days or dim light, the difference could be attributed to non-circadian effects of light exposure.

Since not all humans have SAD, it follows that some subjects are especially vulnerable to light changes, maybe due to genetic variation within their clocks. Thus, another approach would be to screen animals for their vulnerability to developing abnormal mood phenotypes under different lighting conditions. As done in other experimental setups like learned helplessness, chronic unpredictable stress, or drug studies, animals could be segregated into responders and non-responders (Christensen, Jensen, Bouzinova, & Wiborg, 2013; Strekalova, Spanagel, Bartsch, Henn, & Gass, 2004; Vollmayr & Henn, 2001). Then, the circadian clocks from susceptible and resistant animals could be characterized.

SLEEP/WAKE MANIPULATION:

Sleep, circadian rhythms, and clock genes are closely linked and overlap in regulating such diverse biological functions as memory, metabolism, and immunity (Landgraf, Shostak, & Oster, 2012). Thus, sleep deprivation is often considered to be chronotherapy, and cited as a theoretical basis for studying the relationship between the circadian clock and mood (Dallaspezia & Benedetti, 2011; McClung, 2007a). Total and partial sleep deprivation for one night effectively but transiently improves depressive symptoms in MDD and BD patients (Giedke & Schwarzler, 2002; Selvi, Gulec, Agargun, & Besiroglu, 2007). Consistent with this, sleep-deprived mice and rats show mania-like behavior such as hyperactivity, hypersexuality, aggressiveness, and stereotypic movements (Armani et al., 2012; Benedetti, Fresi, Maccioni, & Smeraldi, 2008; Gessa, Pani, Fadda, & Fratta, 1995), which were reduced by lithium, haloperidol, and tamoxifen. Although clock genes were not investigated in these studies, acute sleep deprivation is in principle sufficient to alter circadian clock gene expression in the cerebral cortex of mice, probably through altered binding of BMAL1, CLOCK, and NPAS2 to the promoters of other clock genes (Mongrain, La Spada, Curie, & Franken, 2011; Wisor et al., 2008). A few hours of sleep deprivation significantly advances the activity onset of hamsters (Antle & Mistlberger, 2000). In humans, BMAL1 is suppressed and melatonin increased in response to sleep deprivation (K. Ackermann et al., 2013; Goh, Tong, Lim, Low, & Lee, 2001). In human subjects, performance and temperature rhythms are altered after one night of total or partial sleep deprivation (Edwards & Waterhouse, 2009; Souissi et al., 2008).

Surprisingly, however, on the day after sleep deprivation therapy in depressed patients, even short naps of ~1 hr are enough to cause a relapse of depression (Riemann, Wiegand, Lauer, & Berger, 1993), even though such brief naps do not have major effects on the human circadian clock (Monk, Buysse, Carrier, Billy, & Rose, 2001). Although sleep is strongly modulated by the circadian clock and is the most clinically salient output rhythm, it is important to remember that sleep and circadian rhythms are different phenomena. Alternative explanations of how sleep deprivation may improve mood include sleep-associated changes in levels of cytokines, cortisol, or brain-derived neurotropic factor (BDNF) (Gorgulu & Caliyurt, 2009; Voderholzer et al., 2012; Voderholzer et al., 2004; Wu & Bunney, 1990; Yamaguchi, Maeda, & Kuromaru, 1978). Further studies are needed to determine whether the circadian clock is involved in the positive mood effects of sleep deprivation and the negative mood effects of subsequent naps.

BRAIN LESIONS:

SCN:

Complete lesions of the SCN circadian pacemaker (SCNx) lead to a general loss of endogenous rhythms at the tissue and whole animal levels, due to desynchrony of non-SCN oscillators. However, there is only limited evidence that SCNx animals suffer disturbed mood regulation. SCNx rats show less immobility in the forced swim test, but no impact on behavior in the social defeat paradigm (Arushanian & Popov, 1994; Tataroglu, Aksoy, Yilmaz, & Canbeyli, 2004; Tuma, Strubbe, Mocaer, & Koolhaas, 2005). However, reduced immobility in the forced swim test is in line with reduced depression-like behavior of *Clock-d19* and *Per1*$^{ldc-/-}$; *Per2*$^{ldc-/-}$ double knockout mice, which can also be arrhythmic.

SCNx is a harsh and imprecise method to cause arrhythmicity in animals, often affecting adjacent brain areas (Tataroglu et al., 2004). Since the optic nerves (including ipRGC axons) enter the brain very close to the SCN, it is possible that lesions aiming for the SCN also damage light input pathways to many brain regions, including those regulating mood (Hattar et al., 2006; Hattar, Liao, Takao, Berson, & Yau, 2002). As discussed, a lack of light input in itself is sufficient to change mood. Thus, SCNx does not only cause arrhythmicity, but could lead to numerous uncharacterized side-effects.

OLFACTORY BULB:

The olfactory bulb is one of very few tissues in which circadian rhythms have been shown to persist in the absence of SCN signals *in vivo* (Granados-Fuentes, Prolo, Abraham, & Herzog, 2004). Bilateral removal of olfactory bulbs of rats and mice results in depression-like behavior that can be reversed by antidepressant drugs (Cryan & Mombereau, 2004; Song & Leonard, 2005). Olfactory bulbectomy causes a range of neuroendocrine, immune, and neurotransmitter alterations, affecting the cortical-hippocampal-amygdala circuit, regions implicated in mood regulation. Studies in various animal species also show that olfactory bulbectomy has an impact on circadian rhythms, including period changes, cAMP level changes in the SCN, and damping of temperature and activity rhythms (Marcilhac et al., 1997; Meguid, Gleason, & Yang, 1993; Perret, Aujard, Seguy, & Schilling, 2003; Pieper & Lobocki, 1991; Vagell, McGinnis, Possidente, Narasimhan, & Lumia, 1991). Interestingly, some of these circadian effects can be reversed by antidepressants in hamsters and rats (Lumia, Teicher, Salchli, Ayers, & Possidente, 1992; Pieper & Lobocki, 1991). However, lesioning the olfactory bulb results in such extensive transformations throughout the brain that it is difficult to use this animal model to clarify the issue of causality between circadian oscillations and mood regulation.

CONCLUSION

Considerable evidence indicates that the circadian clock is associated with mood regulation. However, because of the many non-circadian effects of clock genes, this is not the same thing as saying that circadian clock dysfunction causes mood disorders. Indeed pleiotropy is widespread: During spermatogenesis, clock genes are constitutively expressed, so they presumably have a non-circadian function in these cells (Alvarez, Chen, Storer, & Sehgal, 2003). In the forebrain, *Per1/2* appear to play non-circadian roles in sleep homeostasis, since they increase during sleep deprivation but rebound immediately after sleep (Franken, Thomason, Heller, & O'Hara, 2007). Glutamate uptake by astrocytes is under the control of CLOCK, PER2, and NPAS2, but is not rhythmic, (Beaule, Swanstrom, Leone, & Herzog, 2009; Spanagel et al., 2005). In aging, hamsters carrying a mutation of *Ck1*ε live longer in free-running conditions than WT hamsters, and arrhythmic *Bmal1*$^{-/-}$ mice show drastic aging effects while other arrhythmic mutants do not (Kondratov, 2007). Thus, clock genes cannot be equated to the circadian clock as a functional unit. Certainly, manipulation of clock genes leads to modifications of rhythms, but this is just one consequence and might not be the reason for associated mood changes.

Distinguishing between circadian and non-circadian roles of a clock gene can be very difficult. Within the circadian TTL, manipulations of gene expression and rhythmicity of gene expression are tightly coupled. Mutation of a clock gene ordinarily results in diminished rhythms of other clock components and their outputs, but also loss of the clock protein itself. Furthermore, various non-rhythmic mutants may differ meaningfully in terms of clock function, as the clock can be stopped in a repressed or activated state, e.g. by *Bmal1*$^{-/-}$ vs. *Cry1*$^{-/-}$*;Cry2*$^{-/-}$ double mutants. As a consequence, it is not sufficient to investigate only one specific clock mutant model, and draw inferences about the role of *circadian rhythms* in a complex phenotype like mood disorders, because mutation of a clock gene may lead to effects that are independent of biological timing. The combination of genetic mutants and light/dark cycle manipulations might help to define a circadian contribution to mood regulation. If special lighting conditions affect mood in WT but not in arrhythmic clock mutant mice, this would indicate a rhythm-dependent effect of light.

Reduced circadian rhythm amplitude is a feature of many of the mouse models of mood disorders. This is in line with postmortem observations in brains of MDD patients (Li et al., 2013), but it does not explain why some animal models develop mania-like and others depression-like symptoms. Possibly, the combination of amplitude and phase changes in particular brain regions could lead to general mood instability or specify the direction of mood change. Some brain regions could be differentially affected by circadian disruptions, which might lead to a pathological mismatch in mood circuits, e.g. between

dopamine release and dopamine sensitivity. Furthermore, depending on which regions are most affected, different symptoms may appear. However, the use of different behavioral tests across animal studies complicates the interpretation of mood-related phenotypes, and makes it difficult to determine whether animal models show predominantly mania-like or depression-like behavior. More importantly, the limited number of behavioral tests performed to characterize most of the animal models limits confidence that they meaningfully resemble any human disorder. Convincing validation of animal models of mood disorders must include examination of a broad range of behaviors, as well as responses to therapeutic drugs. More generally, a central challenge in the study of psychiatric illness is the inherent difficulty of translating complex human behaviors to animal models. Whereas many animal models reproduce key aspects of behavior that are thought to be mechanistically related to mood symptoms in humans (Berton, Hahn, & Thase, 2012; Nestler & Hyman, 2010), none captures the full spectrum of illness phenotypes, making it impossible to say that dysregulation of the circadian clock fully explains a mood disorder. For example, increased activity of animals can be interpreted as a symptom of mania-like behavior, but can also be explained in non-affective terms. Moreover, it is not clear in any of the animal models whether circadian rhythm amplitude is reduced due to loss of single cell amplitude or dephasing of cells within a tissue. Further studies using consistent behavioral assays and examining single cell rhythm amplitude and phase in multiple brain regions may elucidate whether and how circadian rhythms contribute to mood regulation.

One promising approach is to manipulate gene expression in specific brain areas, like the rescue of *Clock* expression in the VTA of *Clock-d19* mice (Roybal et al., 2007). Currently, those experiments come, in our assessment, closest to evidence of rhythms being causal. However, without measuring rhythms in specific mood regulating brain areas before and after the manipulation, it is impossible to say whether the effect is mediated by circadian rhythmicity. Ultimately, in our view, the best way to prove that rhythmicity is important for mood regulation is to keep the clock intact but selectively manipulate rhythmicity (not mean level) of a single candidate rhythmic clock gene or output. That is, one would identify a rhythmic clock gene, signaling pathway, or physiological function in a defined group of neurons that is thought to be important for mood regulation, and show effects on mood of manipulating its rhythmicity without altering its mean level. Of course, this kind of “clamp” experiment is very difficult with current technology, but it has been approximated in some studies of the effect of Ca^{2+}/cAMP signaling on clock function (Harrisingh, Wu, Lnenicka, & Nitabach, 2007; O'Neill, Maywood, Chesham, Takahashi, & Hastings, 2008). Only in this way can effects of circadian rhythmicity be conclusively

distinguished from effects of presence, absence, or mean level of a clock component, signaling pathway, or physiological function.

Many behavioral studies show that manipulating the clock causes mood changes. But on the other hand, many studies provide evidence that manipulating mood modifies circadian rhythms. Moreover, manipulations of clock genes, sleep, or lighting conditions often affect both circadian rhythms and mood in parallel, but this does not prove that mood changes are caused by changes in the circadian clock, as these manipulations also have non-clock effects **(Figure 2).** Thus, a connection between circadian rhythms and mood is indisputable, but the direction of causality remains unclear. Despite the challenges associated with performing the required work, the requisite tools and understanding are now in place and considerable progress may be made in the coming years.

Figures

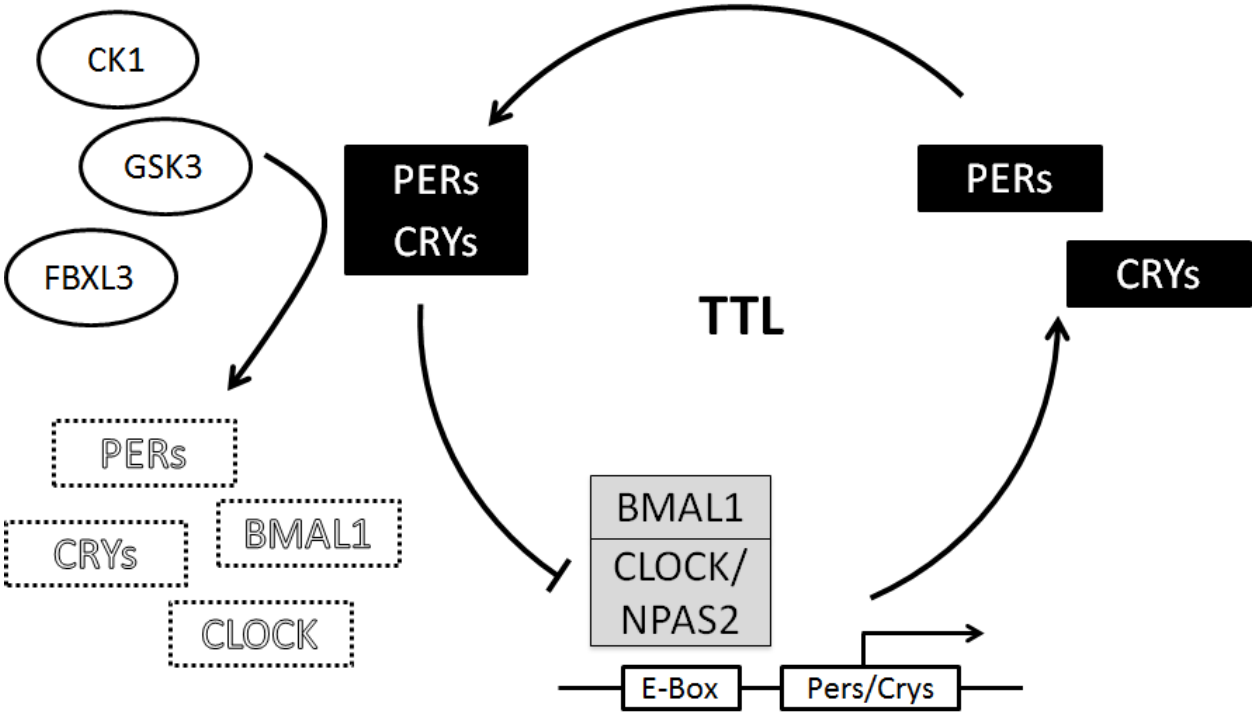

Fig. 1

Simplified scheme of the transcriptional-translational feedback loop (TTL). The BMAL1/CLOCK/NPAS2 complex binds to E-boxes of *Per/Cry* genes and activates their transcription. PER/CRY complexes inhibit BMAL1/CLOCK/NPAS2 and thereby their own transcription. Accessory modulators like CK1 and GSK3 regulate degradation of clock proteins to fine-tune their oscillations.

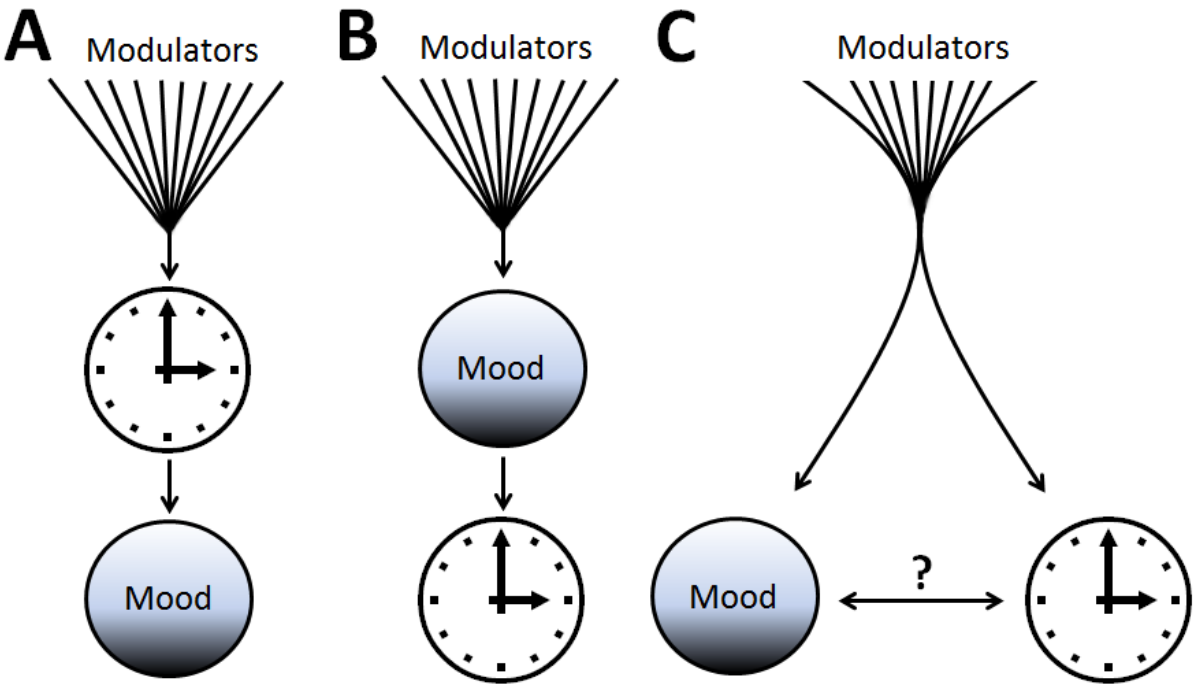

Fig. 2

Alternative explanations for how modulators may regulate circadian rhythms and mood. (A) Genetic modifications, light, drugs, and sleep scheduling affect the clock, which in turn regulates mood. (B) Changes in mood affect the circadian clock or output rhythms as symptoms of mood disorders. (C) Modulators independently regulate mood and the clock, which may also influence each other.

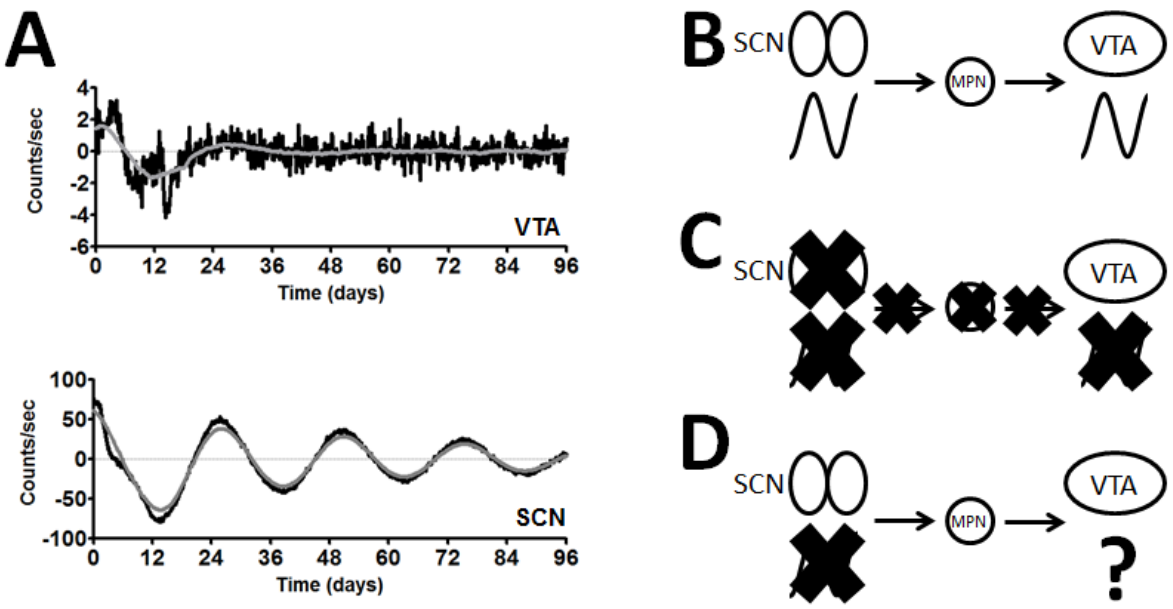

Fig. 3

VTA rhythms depend on rhythmic SCN input. (A) Organotypic cultured VTA slices of WT mice show no self-sustained PER2::LUC rhythms in the absence of the SCN (Landgraf & Welsh, unpublished data). In contrast, SCN slices show strong rhythms of PER2::LUC expression. (B) In intact WT animals the VTA indirectly receives rhythmic input from the SCN through the medial preoptic nucleus (MPN). (C) In the absence of rhythmic input, the VTA is predicted to be arrhythmic. (D) Does the rescue of WT *Clock* expression in the VTA of *Clock-d19* mice lead to VTA rhythms?

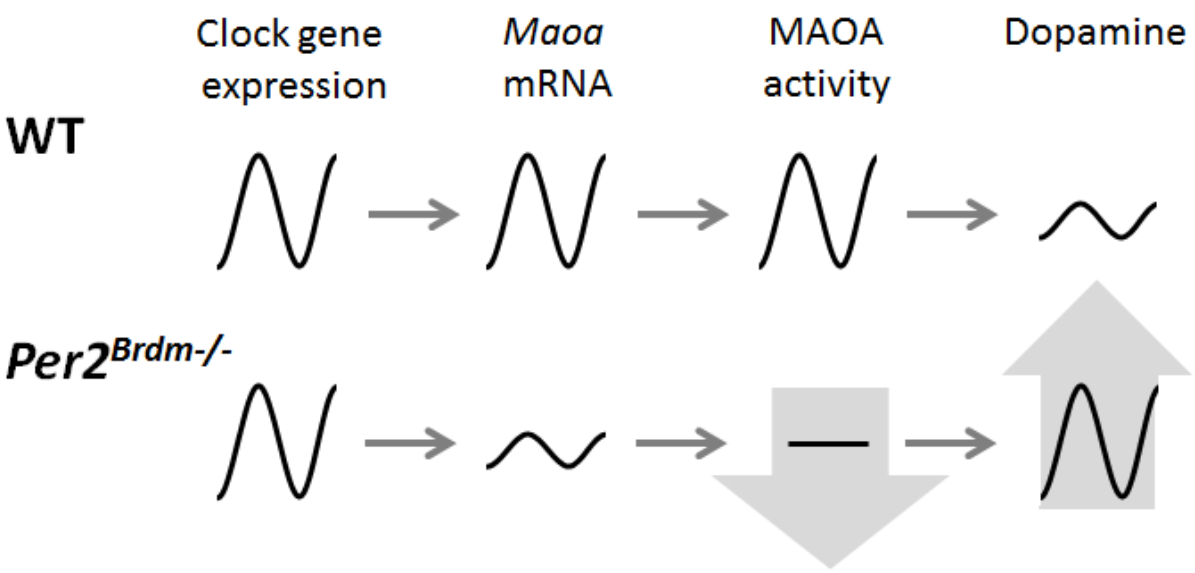

Fig. 4

Mutation of *Per2* leads to elevated dopamine levels. In WT mice, rhythmic clock gene expression leads to rhythmic Maoa expression, MAOA activity, and dopamine release in the NAc. In $Per2^{Brdm-/-}$ mice, clock gene expression rhythms are blunted, as are rhythms of Maoa expression and MAOA activity. However, rhythms of dopamine release appear even stronger, at least in a light/dark cycle. MAOA total activity is lower, leading to elevated dopamine levels, which in turn may explain mania-like behavior.

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