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# Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology

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**Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder:**

**A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology**

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## ABSTRACT

### **Aim**

Symptoms of bipolar disorder (BD) include changes in mood, activity, energy, sleep and appetite. Since many of these processes are regulated by circadian function, circadian rhythm disturbance has been examined as a biological feature underlying BD. The International Society for Bipolar Disorders (ISBD) Chronobiology Task Force (CTF) was commissioned to review evidence for neurobiological and behavioural mechanisms pertinent to BD.

### **Method**

Drawing upon expertise in animal models, biomarkers, physiology and behavior, CTF analyzed the relevant cross-disciplinary literature to precisely frame the discussion around circadian rhythm disruption in BD, highlight key findings, and for the first time integrate findings across levels of analysis to develop an internally consistent, coherent theoretical framework.

### **Results**

Evidence from multiple sources implicates the circadian system in mood regulation, with corresponding associations with BD diagnoses and mood-related traits reported across genetic, cellular, physiological, and behavioral domains. However, circadian disruption does not appear to be specific to BD and is present across a variety of high-risk, prodromal and syndromic psychiatric disorders. Substantial variability and ambiguity among the definitions, concepts and assumptions underlying the research has limited replication and the emergence of consensus findings.

### **Conclusions**

Future research in circadian rhythms and its role in BD is warranted. Well-powered studies that carefully define associations between BD-related and chronobiologically-related constructs, and integrate across levels of analysis will be most illuminating.

## **1. Introduction**

Involvement of disrupted circadian rhythms has been proposed across numerous dimensions of bipolar disorder (BD). This literature review from the International Society for Bipolar Disorders (ISBD) Chronobiology Task Force (CTF) is the final in a series [1, 2], and specifically aims to critically evaluate the evidence supporting involvement of circadian rhythms in the neurobiology of BD. There is considerable interest in circadian rhythms in BD, and the potential to develop diagnostic markers and treatments based on chronobiological principles [3]. Already, therapeutic interventions based on circadian principles are included in contemporary professional treatment guidelines for BD [4]. However, the ambiguous and incomplete chronobiology of BD literature limits utilization of these treatments, the development of standard protocols and the means to identify optimally responsive BD patients. Therefore, a more detailed characterization of the chronobiological underpinnings of BD is urgently required. The present review addresses this need by examining evidence across biobehavioral levels and outlining a program for future research. This project is innovative in its aim to review multidisciplinary research findings across animal models, human biomarkers, physiology, and behavior. Based upon this comprehensive and critical synthesis of evidence, the review provides novel commentary and agenda for future research.

## **2. Methods**

The circadian system is unusual, if not unique, as a biobehavioral system in that its functions can be investigated with high fidelity and mechanistic detail across multiple levels of analysis starting in the genome and into cells, organs, physiological systems, and behavior. Because of this, chronobiological research in BD requires multi-disciplinary integration. To achieve this integration as the basis for a rigorous critical review of relevant literature, MM and GM firstly developed a preliminary classification of the literature based on methods, namely, animal models, genetics, human biomarkers, and behavioral research. It was assumed that the findings from studies in these methodological domains would be largely incomparable due to differences in approach, outcome variables and conceptual assumptions. Given the disparate kinds of information collected across studies within

domains, it was not possible to conduct a structured literature review at the domain level, or at the level of synthesis across domains. CTF planning meetings discussed levels of evidence of the review, and based on expert consensus it was agreed that strict levels of evidence hierarchies used in other CTF projects (e.g. PRISMA [5]) were not feasible. Workgroups were instructed to attend to quality of evidence, and to identify gaps or lack of replication across studies. To manage ambiguity, we used an inclusive and broad definition of the BD phenotype, accepted all measures and proxies of circadian function, and considered all types of associations whether implicit or explicitly defined in the identified literature.

Members of the CTF self-selected to join one of four workgroups to address each of these methodological domains. Each workgroup elected a Chair and developed 3-4 falsifiable propositions to focus the review within a domain (Table 1). Individual workgroup members were allocated to review the literature and draft text for each proposition. In most cases, individual members of workgroups had specific topic expertise in relation to the propositions (including having recently generated systematic and/or critical review of the literature). Each workgroup convened on 3 - 4 occasions during 2020 to discuss progress on the individual tasks. Activities of the four workgroups were coordinated by MM and GM, who were in communication throughout. To harmonize communication across groups, MM and GM played the role of Chair (Human Biomarkers and Behavior, respectively) or liaison (Physiology, Animal Models, respectively) for each workgroup.

Draft reviews from each workgroup were received in late 2020 and integrated by MM and GM to highlight consistent/contradictory findings and areas where additional evidence was required. Additional input from the CTF was incorporated to ensure accuracy and completeness of the integrated reporting and critical synthesis. All members of the CTF reviewed and approved the final version.

**Table 1: Workgroups and propositions to methods-based reviews**

<b>Methods</b>	<b>Personnel</b>	<b>Propositions</b>
<b>Animal</b>	Colleen A. McClung*, Davide	1. SCN rhythms are essential for

<b>Methods</b>	<b>Personnel</b>	<b>Propositions</b>
<b>models</b>	Dulcis, Kyle D. Ketchesin, Alessandra Porcu Liaison: Greg Murray	affect regulation 2. Animal mutants are useful models for clock gene variation and effects on mood in humans 3. Experimental manipulation of light in animal models affects brain pathways for mood regulation 4. Mood stabilizing drugs engage the molecular clock as a therapeutic mechanism
<b>Physiology</b>	Robert Gonzalez*, Sean Cain, Benicio Frey, Corrado Garbazza, John Gottlieb, Philip Ritter Liaison: Michael McCarthy	1. Light exposure plays a causal role to initiate BD. 2. Light exposure plays a role in the phenotypic expression of BD. 3. Melatonin is fundamental to pathophysiology of BD 4. Melatonin plays a role in phenotypic expression of BD
<b>Human biomarkers</b>	Michael McCarthy*, Bruno Etain, Heon-Jeong Lee, Cynthia Marie-Claire, Daniel Smith	1. Variation in clock genes is essential to the pathophysiology of BD 2. Circadian abnormalities identify distinct BD subgroups 3. Circadian rhythm abnormalities are specific to BD 4. Mood episodes are associated with circadian misalignment.
<b>Behavior</b>	Greg Murray*, Lauren Alloy, Robert Gonzalez, John Gottlieb, Robin Nusslock, Richard Porter, Jan Scott, Holly Swartz	1. Circadian abnormalities are measurable pre-onset (vulnerability) 2. Circadian abnormalities are causal in symptoms and episodes

Methods	Personnel	Propositions
		3. Polarity of episodes are explained by phase delay/advance
	* Workgroup leader	

### 3. Results

The review addresses the pertinent neurobiology of circadian clocks (Section 3.1), then covers five multidisciplinary research themes that arose from the coordinated efforts of the CTF: Predisposing risk factors including vulnerability, heritability and genetic mechanisms (Section 3.2); Circadian disruption as a basis for defining sub-groups of BD (Section 3.3); Environmental risk factors, particularly light (Section 3.4); Specificity of circadian disruption in BD and across psychiatric disorders (Section 3.5); Circadian disruption across the illness course of BD (Section 3.6). Section 3.7 contains a tabular summary of key results from each of the subsections as a basis for the integrative critical Discussion (Section 4).

#### 3.1 Neurobiology of Circadian Clocks in Bipolar Disorder

In mammals, the suprachiasmatic nucleus (SCN) in the anterior hypothalamus is the master circadian pacemaker and is important for organizing daily 24 h rhythms in sleep/wake, activity, and other physiological processes and behaviors. Nearly all cells in the body express the circadian clock genes that support circadian rhythms, and many can sustain autonomous rhythms in isolated experimental preparations such as tissue slices and cell cultures

**Box 1 Definition of Clock Gene.** We define clock genes as those genes critically involved in the 24 h molecular timekeeping mechanism in mammalian cells. Clock genes are usually defined in rodents by loss of function mutations and subsequent effects on behavior observed under constant lighting conditions. With redundancy in the system, few clock gene mutants are fully arrhythmic under constant conditions, but many show irregular rhythm parameters and/or become arrhythmic with the loss of additional clock genes. There are ~20 established clock genes (Figure 1). The list is frequently growing to include new genes as candidates that may require additional description and validation.



(See Box 1). Included in these tissues are brain regions such as frontal cortex, limbic regions, ventral tegmentum (VTA) and ventral striatum that are implicated in reward pathways, affect and BD. In a study of baboons (a diurnal, non-human primate), gene expression was measured using RNA sequencing across the genome at 12 time points across 64 distinct tissues, including 22 brain regions [6]. Most brain regions examined showed rhythmic profiles, indicating the presence of cellular rhythms. However, each region was distinct both in the number and ensembles of rhythmic genes demonstrating context-dependence. Notably, rhythmic expression profiles were more likely to be found in genes serving essential processes in each tissue. These data indicate that while the SCN serves a critical role coordinating rhythms across the body, circadian rhythms are widespread across the nervous system, and interface with numerous processes that underlie healthy brain function and pathological processes that potentially contribute to neuropsychiatric disorders like BD. Therefore, loss of rhythm in a particular brain region and/or loss of coordination among brain regions is predicted to have detrimental effects on brain function that would be observable as changes in behavior, cognition and affect.

**Molecular clock network.** Clock genes form a transcriptional/translational feedback loop to maintain the essential functions underlying cellular circadian rhythms (Figure 1). At the center of this loop, the proteins CLOCK and BMAL1 (encoded from *ARNTL*) bind to form a heterodimeric transcriptional activator. The CLOCK/BMAL1 complex binds to E-box promoter elements in DNA, driving the expression of *PER1/2/3* and *CRY1/2*, transcriptional repressors that inhibit their own expression over ~24 h cycles to sustain a circadian oscillator. PER and CRY proteins coordinate to determine period length through negative feedback of CLOCK/BMAL1. In some instances, NPAS2 can substitute for CLOCK and may play an important role in cell types where NPAS2 expression is abundant, including medium spiny striatal neurons and other forebrain regions [7, 8]. Additional feedback loops have been described (e.g., *REV-ERB $\alpha/\beta$* , *RORA/B/C*, *DEC1* and *DBP*) that modulate rhythms in tissue-specific contexts. In the SCN, calcium and associated signal transduction pathways serve as clock inputs, linking the retinohypothalamic tract to the circadian clock through post-translational modification of clock proteins and modulation of transcription factors that regulate clock genes like *PER1/2* to entrain rhythms to light [9]. Post-translational modification of proteins by kinases (e.g., glycogen synthase 3 kinases [GSK3], and casein kinase 1 [CSNK1]), ubiquitin ligases (e.g., FBXL3) and other molecules

also regulate turnover of proteins to affect temporal kinetics of the feedback loop. The clock interfaces with stress pathways [10]. For instance, CHRONO (encoded from *CIART*) is upregulated by stress in the hypothalamus and is a transcriptional repressor of CLOCK/BMAL1 [11, 12].

[FIGURE 1 HERE]

**Role of the SCN in mood regulation.** Past research on the neurobiology of mood regulation in animal models of mood disorders has focused on the ventral striatum (nucleus accumbens), amygdala, hippocampus, cortical regions and monoaminergic inputs from the ventral tegmentum (VTA), raphe nucleus and locus coeruleus. The circadian rhythm hypothesis of BD has also drawn attention to the SCN. Several rodent studies have manipulated the SCN to determine its role in mood-related behavior. Counterintuitively, lesions of the SCN result in less depression-like behavior in the forced swim test [13, 14]. However, these unexpected findings are difficult to interpret since pathways traversing the SCN were likely destroyed and a lack of behavioral assessment over circadian time scales. To determine the role of the BMAL1 in mood regulation in a tissue restricted and neuroanatomically intact system, *Bmal1* short hairpin RNA (shRNA) was injected into the SCN of mice subsequently tested across a battery of behavioral assays [15]. *Bmal1* knockdown in the SCN resulted in increased depression-like and anxiety-like behaviors. Interestingly, SCN tissue explants were rendered arrhythmic but wheel-running rhythms remained intact. These results indicate that redundancies in the SCN may preserve circadian rhythms despite the disruption to overlapping affect-reward systems. Therefore, preliminary anatomical data support the idea that the SCN is linked to brain reward circuits and contributes to affect regulation.

**Photic inputs to the SCN.** Circadian clocks require external time signals (*zeitgebers*) to coordinate the internal biological activity of an individual with the environment. In humans, zeitgebers include temperature variation, and timing of meals, exercise, and social interaction. But in all mammals including humans, light is the most salient entrainment signal for the circadian clock. A class of melanopsin expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) are responsible for photic entrainment of clocks [16-18]. Unlike other retinal photoreceptors, ipRGCs are primarily non-

image-forming and have strong projections to the SCN, where they influence circadian rhythms [16]. IpRGCs also have direct projects to other subcortical structures in the amygdala, hypothalamus, and diencephalon. By communicating light information to these brain regions, ipRGCs play a role regulating mood, learning and memory [17, 19, 20]. In mice, it was shown that ipRGCs mediate light-induced mood changes through input to the perihabenular nucleus of the dorsal thalamus, and that ipRGCs were necessary and sufficient for effects of light on mood [19]. The study concluded that the mood-related pathway is SCN-independent. However, a 7 h light/dark (LD) cycle was used to force the SCN rhythm to “free run” independently of photic entrainment. The non-physiological nature of this method leaves open the question of SCN involvement. In humans, light can suppress functional magnetic resonance image (fMRI) activity in the habenula [21] and amygdala [22] and increase connectivity between the ventromedial prefrontal cortex and amygdala. In these studies, light simultaneously reduced negative affect, and suggesting it may regulate emotional control through this mechanism [22].

**Output mechanisms of the circadian clock.** BD presumably occurs from widespread dysfunction across neuronal systems, resulting in behavioral abnormalities manifesting primarily as mood and activity disturbances, with associated changes in arousal, cognition, and attention and brain structure. However, BD is also associated with endocrine abnormalities and changes in peripheral physiology. Clock-controlled genes (CCGs, Box 2) are rhythmically expressed in context-specific manner, often involved in the essential functions of a particular cell type and enriched in therapeutic drug targets [23]. By way of CCGs acting in separate organ systems, disrupted circadian rhythms might affect a variety of cellular and physiological processes, possibly explaining the wide range of effects

**Box 2 Clock Controlled Genes.** In genome-wide surveys, 50-80% of genes were found to be expressed rhythmically in at least one cell type. However, these rhythms are narrowly expressed and the majority of these genes show limited rhythmicity in other tissues. Moreover, they differ from clock genes as they are not critically involved in maintaining molecular oscillators in cells. Instead, clock-controlled genes (CCG) comprise output pathways of the circadian clock that exert circadian control over physiological processes for which daily timing is essential such as nutrient metabolism, cognition, goal directed activity and immune function.

of BD on various dimensions of health, [24-28]. Key CCG outputs are reviewed below. The list is not meant to be exhaustive, but rather highlights key BD-associated processes regulated by CCGs that may conceivably be affected by disrupted circadian rhythms.

**Melatonin.** Melatonin secretion is a key mechanism by which the central clock coordinates rhythms across the brain and peripheral organ systems. Twin studies reveal substantial heritability and variability in the levels of nocturnal melatonin secretion and its sensitivity to light [29]. Several studies have reported that individuals with BD demonstrate a hypersensitivity to nocturnal light [29-31] across a wide range of light intensities [32]. In one study comparing euthymic, medication-free BD participants and matched controls, a 2-fold increase in melatonin suppression was observed in the BD group [33]. Some studies suggest that the hypersensitivity to light, measured with melatonin suppression may be a trait marker of BD [33, 34]. Acetylserotonin O-methyltransferase (ASMT) is a key enzyme involved in the biosynthesis of melatonin. Both rare mutations and a common polymorphism in *ASMT* linked with lower expression have been associated with BD in candidate case-control studies [35]. Furthermore, in a study using actigraphy in 53 euthymic BD patients and 28 controls, subjects homozygous for a low activity *ASMT* allele showed association with longer sleep and interdaily stability [36]. However, not all findings support a trait association with melatonin-suppression [37-40]: One study conducted in euthymic, medication free BD subjects [39] and one conducted in BD subjects who were symptomatic and medicated [40] failed to demonstrate hypersensitivity to light compared to controls. Similarly, differences in melatonin suppression did not appear in an investigation of monochromatic blue or red light under dark conditions [38]. A recent study in major depressive disorder (MDD) supports the idea that melatonin suppression may change with state, showing that remitted MDD patients had nearly identical melatonin suppression responses to controls, whereas those currently depressed had reduced melatonin suppression [41]. During episodes of mania, patients with BD have been shown to display elevated daytime levels of melatonin compared to depressive patients or control subjects [34, 42]. Studies of BD have also examined the effects of mood state on melatonin secretion but have not measured light sensitivity. In depressed subjects, a comparison of 14 patients with BD and 18 patients with MDD revealed significantly lower melatonin levels and later onset of secretion in the BD subjects [43]. Further studies with clearly

defined light exposure protocols, larger cohorts and longitudinal mood assessments are required to clarify the role of melatonin in BD.

**Serotonin.** The human brain shows pronounced diurnal variation in serotonin (5-HT) levels, a neurotransmitter strongly linked with mood disorders [44]. Properties of the 5-HT system in mice including neuronal firing rate in the dorsal raphe nucleus, and brain neurotransmitter content are sensitive to light conditions and alteration of photoperiod [45]. The rate limiting step in 5-HT synthesis is under the control of tryptophan hydroxylase, an enzyme that shows diurnal variation in the raphe nuclei in response to signals from the SCN, endocrine and behavioral cues [46, 47].

**Dopamine.** Mania in BD is associated with increased dopamine activity [48, 49]. In the striatum, dopamine receptors, the dopamine transporter, and monoamine oxidase A (MAOA) all have strong diurnal rhythms in expression regulated by circadian proteins [50-52]. Tyrosine hydroxylase, the rate limiting enzyme in dopamine synthesis shows diurnal rhythms in expression controlled by CLOCK and REV-ERB $\alpha$  proteins [53, 54]. Loss of function mutations of either protein leads to a hyperdopaminergic state and mania-like behavior in mice [53, 55, 56].

**Calcium.** Genome wide association studies (GWAS) of BD strongly implicate calcium channel genes such as *CACNA1C* [57]. In neurons, rhythmic regulation of calcium signaling is important for neuronal activity and neuron/glia communication. In the SCN, intracellular Ca<sup>2+</sup> levels have distinct rhythms that are coordinated with ATP accumulation and *Per2* expression [58]. Following a light pulse, *Cacna1c* null mutant mice have a reduced ability to phase advance circadian rhythms [59]. In human fibroblasts, *CACNA1C* is rhythmically expressed, but BD patient cells carrying the *CACNA1C* risk allele have a reduction in this rhythm [60].

**Neuroinflammation.** Neuroimmune mechanisms may be involved in the pathophysiology of BD and can be connected to circadian rhythms in many ways [61-63]. Circadian rhythm disruption can increase levels of inflammatory cytokines [64-66]. CLOCK activation can increase NF $\kappa$ B mediated transcription [67, 68], whereas inflammation can alter *Per1* and *Per2* expression in the hypothalamus

and liver [69], and induce phase delays in the SCN [70, 71]. Inflammatory cytokines can disrupt spontaneous electrical activity rhythms in the SCN [72].

**Mitochondria.** The brain is vulnerable to oxidative stress and several studies have linked mitochondrial dysfunction to BD [73-75]. Several mitochondrial functions have circadian rhythms [76]. The molecular clock coordinates antioxidant response and mitochondrial functions through Sirtuin 1 (SIRT1) and nuclear factor erythroid-derived 2-like 2 (NRF2). SIRT1 becomes active in the presence of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and binds to CLOCK/BMAL1 to regulate transcription [77, 78]. In brain astrocytes, NRF2 is regulated by CLOCK. Arrhythmic *Clock* mutant mice show reduced levels of NRF2 and signs of oxidative damage [79, 80].

**Sleep and circadian rhythms.** Sleep problems are commonly used as evidence of circadian disruption. Sleep has multiple components, some of which are regulated by CCGs, but others controlled by non-circadian factors. Contemporary conceptualizations of sleep focus on the two-factor model in which the non-circadian homeostatic sleep system interacts with the circadian pacemaker to determine overall sleep characteristics [81]. In this way, sleep is strongly influenced by duration of wakefulness and an indirect marker of circadian rhythm. The sleep parameters most strongly influenced by circadian function include phase and amplitude (i.e., sleep and activity consolidation). Sleep latency, staging, and overall quality, are less related to circadian rhythms. While many aspects of sleep may have important roles in BD, sleep is considered primarily from the circadian perspective in the present literature review.

### 3.2 Circadian Disruption as a Predisposing Risk Factor in Bipolar Disorder

**Box 3. Circadian vs Diurnal Rhythms.** Biological rhythms entrain to environmental cues, especially light. Light effects may “mask” aberrant rhythms arising from intrinsic disorganization of the circadian clock to preserve (either fully or partially) rhythms aligned with the light/dark cycle, even in the context of a severely impaired circadian clock. For this reason, the chronobiological literature commonly refers to “circadian rhythms” as those measured in under constant light or dark conditions. In contrast, “diurnal rhythms” are measured under alternating light/dark conditions. Most human and clinical studies are performed under environmental conditions and not under controlled light/dark conditions in a laboratory. Therefore, while the term “circadian rhythm” is commonly used in the clinical literature, it is more accurate to consider in these studies of “diurnal rhythms.”

#### *A. Vulnerability for Bipolar Disorder*

High risk for BD can be defined in multiple different ways including familial risk, prodromal cases (sub-threshold symptoms of mania/hypomania), or temperamental features that may predispose an individual to a psychiatric disorder. Major findings from studies of these high risk groups and circadian rhythm abnormalities are discussed in detail in following sections and summarized in Figure 2.

**Individuals at familial high risk for BD.** Based on familial clustering of mental illnesses, the offspring of BD parents are often considered to be at high risk for developing BD. In a study of young adults at high risk for BD based on symptoms and/or family history compared to individuals with BD and controls, sleep/activity profiles differed between BD cases and controls. Profiles of high-risk individuals were similar to full threshold BD cases showing both insomnia and hypersomnia, sensitivity to shifts in rhythms, difficulty awakening and prolonged sleep latency [82]. In a study of 25 offspring of BD parents (OSBD) and 22 matched control offspring (OSC), group differences were noted in subjective sleep quality [83]. However, these were not significant after adjusting for mood and anxiety symptoms. Social rhythms and actigraphy measures (Figure 2) did not differ between

groups [83]. A second study found similar results with nominally significant changes in sleep and greater eveningness in OSBD (n=43) compared to OSC (n=42) interpreted as decreased need for sleep in the OSBD group, but no differences measures of actigraphy, sleep onset/offset or daytime functioning [84]. In 28 OSC, 13 OSBD, 23 OS of parents with MDD (OSMD), sleep duration was longest in OSMD. Sleep duration was significantly longer in OSBD vs OSC, but only over weekends and not during weekdays [85]. In a study of depressed adolescents, OSBD had a significantly longer sleep duration and greater daytime dysfunction compared to OSC [86] and were more likely to report hypersomnia, and increased appetite [87]. With respect to sleep mechanisms of mood regulation, shorter sleep duration in adolescent OSBD was selectively associated with increased activity in brain reward circuits [88]. Overall, family studies provide only limited evidence of circadian disruption in high-risk individuals. Quantitative rhythm measures using actigraphy or social rhythm metrics have failed to reveal BD-associated differences, whereas indirect links to circadian rhythms such as sleep abnormalities and greater eveningness have been observed in OSBD.

[FIGURE 2 ABOUT HERE]

**High-risk community samples and bipolar disorder spectrum cases.** Symptoms of hypomania in healthy individuals are considered risk factors for BD. Children at high-risk for BD based on hypomanic symptoms have been reported to have irregular timing of daytime activities and more variable sleep duration than controls, despite having similar average sleep duration [89]. A later study noted that, compared to a matched low risk group, actigraphy recordings in high-risk subjects showed significantly more delays and variability in sleep, more sleep fragmentation and lower relative amplitude [90]. In a study of 313 community adults, hypomanic symptoms were not associated with chronotype, but irritability and risk-taking were associated with greater eveningness and irregular sleep-wake times [91]. In contrast, depression was correlated with morningness in a study of 140 students [92]. In other studies of high and low risk young adults, significantly lower amplitude activity rhythms were observed in the high-risk group, especially in individuals with a history of depression and high scores on a mania scale, but no group differences were found in social rhythms [93-95]. Using the mood disorder questionnaire to stratify risk, lower amplitude activity rhythms were



again seen in the high-risk group, but with no difference in chronotype between the high and low risk groups [96]. In summary, low amplitude activity rhythms and delays are commonly reported across several actigraphy studies of high-risk groups defined by hypomanic symptoms. Other proxy measures of circadian rhythm such as chronotype, social rhythms have also been reported, but less consistently. Notably, the amplitude of activity rhythms may not reflect the amplitude of central circadian rhythms directed by the SCN and may be confounded by masking effects. Based on the identification of motor activity amplitude abnormalities in BD, further investigation into the relationship between motor activity and central rhythms is warranted.

BD exists on a spectrum that may include temperamental features, and hyperthymic temperament has been proposed as a risk factor for BD. In studies of healthy young adults, variability in sleep duration predicted scores of hyperthymia [97]. Hyperthymic temperament has been associated with morning chronotype, while depressive, cyclothymic, irritable and anxious temperaments were significantly associated with evening chronotype [98]. A large-scale internet-based survey of chronotype and temperament in 5,129 adults reported similar results: morningness was associated with hyperthymia, whereas eveningness was associated with cyclothymic, dysthymic, or disinhibited temperaments [99]. In 186 adolescents, eveningness was associated with affective problems, attention difficulties, and rule-breaking [100]. Overall, existing data indicate that hyperthymic temperament is associated with morning chronotype, while other affective temperaments and high-risk groups for BD show association with evening chronotype. This suggests hyperthymic temperament has distinct chronobiological characteristics compared to these other traits and the relationships among them relating to BD remain to be defined.

### *B. Heritability of Circadian Rhythm Phenotypes and Bipolar Disorder.*

**Genetic underpinnings of BD.** BD is heritable, with twin studies showing 60-90% concordance for BD I [101], and GWAS showing that 20-25% of variance is attributable to common genetic risk, with dozens of genetic risk factors identified for BD [57, 102]. Rare genetic variants have also been identified [103, 104]. Importantly, it is also clear from these studies that the genetic risk for BD

overlaps with that of other psychiatric disorders such as schizophrenia (SCHZ) and MDD, with BD I more similar to the former and BD II more similar to the latter [57, 102].

**Family and twin studies.** Studies of high-risk cohorts indicate that circadian disruption may be a heritable risk factor for BD. Indeed, most of the sleep/wake patterns and chronotype markers associated with BD are also found in healthy relatives of patients and individuals with elevated risk of BD [105]. Twin studies reveal that individual variation in daily activity is heritable [106]. For example, in a family study of BD patients covering 26 pedigrees, including 136 BD and 422 unaffected relatives, shared heritability of rhythmic activity traits and BD was examined [107]. Euthymic individuals with BD had longer sleep duration and later wake times compared to unaffected relatives. Moreover, the study identified >40 heritable phenotypes related to rest-activity timing in the BD pedigrees, with the strongest linkage for an actigraphy-derived measure of intradaily variability [108], but also evidence of fragmentation and lower overall daytime activity. Importantly, many of the activity-associated loci overlapped with BD-associated loci. Similar results were found in BD subjects and their healthy relatives using smart-phone based activity measures [109]. Compared to controls, BD subjects with mild-moderate depression had less activity and fewer social interactions, whereas euthymic unaffected relatives had decreased activity but typical social interactions suggesting activity is an intermediate phenotype.

### *C. Genetic Mechanisms in the Molecular Clock and Risk for Bipolar Disorder.*

**Candidate gene studies in animals and humans.** Genetic studies using inbred animals are commonly helpful for demonstrating the effects of a given gene compared to human studies where genetic variation is substantially higher and single gene effects may be harder to detect. Clock genes have been systematically mutated in mice to determine their role in affective behaviors [110]. Importantly, clock genes are conserved in humans. Accordingly, most have also been examined in candidate gene association studies in BD using single nucleotide polymorphisms (SNP). By modern standards, the candidate gene studies are considered underpowered. Nonetheless, some have yielded findings that were subsequently supported by GWAS [111]. Many of these studies have examined

multiple aspects of the BD phenotype, making replication of these studies particularly problematic and prone to false positive association.

**CLOCK.** One of the best characterized animal models of BD is the *Clock* $\Delta$ 19 mutant mouse. *Clock* $\Delta$ 19 mice encode a dominant-negative CLOCK protein, causing reduced amplitude, long period, delayed phase under a light/dark cycle and arrhythmic behavior under constant darkness [112]. *Clock* $\Delta$ 19 mice display a mania-like phenotype consisting of increased dopamine transmission, hyperactivity, increased reward-seeking and impulsivity-like behaviors, and decreases in depressive-like behavior, traits that are partly reversible by lithium [113-115]. In humans, common variants in *CLOCK* have been associated with BD and related phenotypes in candidate gene association studies [116-119], but have not been consistently replicated [120].

**ARNTL.** BMAL1 null mutant mice shows reduced lifespan and widespread physical abnormalities [121], limiting study of this mutant. Perhaps for this reason, it is also relatively understudied in human genetic studies. However, variants in *ARNTL* have been linked with BD [122, 123], and an epigenetic study suggests methylation of *ARNTL* was associated with BD [124]. BMAL1 null mutant macaque monkeys show irregular sleep/activity cycles, elevated stress hormones and increased psychosis, depression and anxiety-like behaviors [125].

**PER1/2/3.** *Per1* mutant mice show allele-specific phenotypes. *Per1*<sup>*Brdm*<sup>-/-</sup></sup> mutants display reduced response to psychostimulants and decreased reward-seeking, particularly after experimentally induced stress [126-128], whereas *Per1*<sup>*ldc*<sup>-/-</sup></sup> mutation does not cause an affective phenotype [129]. *Per2*<sup>*Brdm1*<sup>-/-</sup></sup> mutants display reduced immobility in the forced swim test, and increased sensitivity to cocaine and alcohol [126, 130]. Mutant mice lacking either *Per1* or *Per2* alone do show alterations in anxiety-like behaviors, but the loss of both *Per1* and *Per2* results in increased anxiety-like behavior [129]. In human imaging studies of healthy adolescents, *PER2* variants have been associated with reward processing in the prefrontal cortex [131]. Common variants in *PER3* have been associated with BD [123, 132] and multiple related phenotypes including age of onset, post-partum onset, brain white

matter integrity, and the rhythms in BD patient fibroblasts [133-137]. Functional *PER3* variants have also been linked with seasonal affective disorders [133].

**CRY1/2 and FBXL3.** CRY proteins in the nucleus accumbens are involved in depression-like helpless behaviors, and genetic knockdown of CRY1 in D1 dopamine receptor-containing neurons reduces susceptibility to stress-induced helplessness in mice [138]. Whole body *Cry1*<sup>-/-</sup> mice have increased depression-like behaviors, and *Cry1*<sup>-/-</sup>;*Cry2*<sup>-/-</sup> double knock-out mice have increased anxiety-like behavior [139-141]. CRY protein is regulated by FBXL3. The *Fbxl3* null mutant has increased stabilization of CRY, longer period and reduced anxiety- and depression-like behaviors [142-144].

**NR1D1 and RORA/B.** Stability of REV-ERB $\alpha$  was shown to be lithium-sensitive and SNPs in *NR1D1*, the gene encoding REV-ERB $\alpha$ , had been implicated in lithium responsiveness [145-147]. Accordingly, there has been considerable interest in the role of REV-ERB $\alpha$  in mood regulation. *Rev-erba* null mutant mice have a shorter free-running period, are more sensitive to photic phase advances, and exhibit mania-like behaviors with reduced immobility in the forced swim and tail suspension tests, increased exploratory behavior, hyperactivity, aggression, and motivation [53, 148, 149]. A BD-associated variant in *RORA* was linked with inflexible chronotype [150]. *RORB* was associated with pediatric BD in a candidate gene study of 153 family trios [151].

**DBP.** DBP has been associated with BD in human genetic studies [152-154]. *Dbp* null mutant mice are hypoactive and exhibit a shorter wheel-running period in constant conditions, and become hyperactive after exposure to stress or sleep deprivation [153, 155].

**CSNK1 and GSK3.** PER proteins are phosphorylated by casein kinases 1 $\delta$  and  $\epsilon$  (encoded from *CSNK1D/E*). *Csnk1e* overexpressing mice [156] and *Csnk1d* knockout mutants [157] both show mania-like phenotypes. In human subjects, evening chronotype in 107 patients with BD was associated with two intronic variants in *CSNK1E* [158]. Another family of protein kinases, GSK3 phosphorylates PER2 and other components of the molecular clock [145, 159, 160]. GSK3

overexpressing mice, and mice with mutations rendering GSK3 constitutively active are hyperactive, have a longer circadian period, and exhibit mania-like behaviors [161-163]. Conversely, pharmacological or genetic inhibition of GSK3 shortens period and phenocopies the mood-stabilizing effects of lithium [164, 165]. Human genetic studies have linked rare duplications of GSK3B to BD [166] and common genetic variants in GSK3B to lithium response [167, 168] and brain gray matter volume in neuroimaging studies of MDD [169].

**GWAS of clock genes, mood instability and bipolar disorder.** GWAS of BD have identified >60 gene loci associated with BD [57, 170]. GWAS typically involve very large cohorts and are unbiased with respect to underlying biological pathways, allowing them to identify novel genetic factors. In the most recent GWAS of >40,000 BD cases and 371,000 controls, genetic risk for BD was associated with decreased morningness and longer sleep duration. Using a novel technique to evaluate genetic dose effects (Mendelian randomization), the association between BD and chronotype was found to be unidirectional, implying a causal role for genetic liability for BD. In contrast, the association between BD and sleep duration was reciprocal implying bidirectional influence. These GWAS of BD did not reveal any single clock gene variant that was genome-wide significant. However, there was enrichment of BD-associated variants in *ARNTL*. Previous combined GWAS of BD-SCHZ revealed variants in *ARNTL* distinguished genetic risk for these disorders that is otherwise highly overlapping [170, 171]. A BD-associated risk locus on chromosome 1 is in proximity to *CIART* and has also been linked with chronotype in multiple GWAS [57, 172]. A disadvantage of GWAS is that in order to assemble large cohorts, there is often loss of phenotypic detail. However, more recent studies have improved upon this shortcoming (e.g., UK Biobank). In addition to being very large, these newer cohorts collect detailed clinical information, and sleep and activity phenotypes, making circadian rhythm analyses of psychiatric disorders possible [173].

**Polygenic risk analyses of bipolar disorder and mood instability.** Composite polygenic risk scores (PRS) can be derived from GWAS to estimate the aggregate risk from multiple SNPs. Using accelerometer data from the UK Biobank, Lyall and colleagues examined an objective measure of disrupted circadian rest-activity rhythms, relative amplitude and the relationship to mental health in

>91,000 individuals from a community sample [174]. PRS for low relative amplitude was significantly associated with BD, but also with mood instability, neuroticism, and MDD, indicating a non-specific relationship between circadian rhythm disruption and mood. In a related study, GWAS results from >70,000 subjects characterized by accelerometry were examined to identify a set of associated genetic markers in *NFASC*, *SLC25A17* and *MEIS1* that predict low relative amplitude [175]. PRS for low relative amplitude was also associated with mood and mental health-related phenotypes including mood instability (N=78,710), diagnosis of MDD (N=9,543), but not with BD (N=406). The relatively small BD sample may have been underpowered to show a specific association with BD diagnosis, but demonstrates the potential for identifying PRS associations between circadian dysfunction and symptom dimensions relevant to BD in very large samples with detailed assessment of sleep and activity.

Using PRS for chronotype, sleep duration, daytime sleepiness, and insomnia derived from GWAS of the UK Biobank cohort, differential genetic loading was examined in BD I and BD II [176]. The primary cohort included 4,672 BD cases and 5,714 controls, with a replication cohort of 4,366 BD cases and 6,091 controls. PRS for sleep duration was associated with BD I and PRS for insomnia was associated with BD II. PRS for morningness was negatively correlated only with BD I in the discovery cohort, but failed replication. These data confirmed that individuals with BD I have significantly greater genetic liability for longer sleep duration, and that BD II shows genetic liability for insomnia. The data regarding genetic liability for chronotype in BD I subjects were suggestive but inconclusive. Notably, sleep and circadian PRS may distinguish BD subtypes.

**Summary of vulnerability, heritability and genetic mechanisms of BD.** There is evidence that circadian disruption is common in individuals at risk for BD, including behavioral disturbances and increased genetic risk for chronotype and irregular sleep. However, there appears to be no unique association between circadian disruption and BD. Circadian disruption in sleep and behavior appear to be trans-diagnostic risk factors affecting not just BD, but also MDD and psychosis. Genetic risk for low amplitude, chronotype and sleep disruption generally indicate considerable overlap across MDD, SCHZ and personality traits such as neuroticism and overall well-being. Some findings suggest that

circadian rhythms are particularly disrupted in BD of recent onset, possibly increasing the vulnerability to stressful life events that may trigger episode recurrence and/or more severe episodes.

### **3.3 Circadian disruption as a basis for defining sub-groups of bipolar disorder.**

BD is heterogeneous and exists on a clinical spectrum with sub-types defined by various clinical features, some of which may share common aspects of circadian disruption [177]. These putative BD sub-groups could either include new and/or previously unrecognized groups, or overlap onto existing sub-groups defined by clinical presentation (e.g., age of onset, symptom clusters), clinical course (e.g., predominant polarity, patterns or recurrence/relapse, suicidality), and/or treatment response that differ across dimensions of circadian rhythm disruption. There may be particular value in identifying sub-types of BD patients with chronobiological disruption as some may have a more severe illness course [178], and/or respond preferentially to chronobiological interventions such as bright light therapy [1]. To date, only a few studies have explored the feasibility of classifying BD according to genetic variation in circadian systems, with a particular focus on lithium treatment response and more limited work on clinical features such as mood instability and seasonality.

**Lithium response.** Lithium responsive BD has been recognized as having distinct clinical features, and genetic underpinnings [179, 180]. The Pharmacogenomics of Bipolar Disorder study (PGBD) was a prospective maintenance trial of lithium monotherapy designed to identify genes associated with clinical response in BD I [180]. Chronotype at baseline was associated with response, with higher morningness scores predicting favorable outcomes [181]. In a subset of PGBD subjects, circadian rhythms were studied in cells grown from lithium responders (Li-R) and non-responders (Li-NR). The *Per2*-luc bioluminescent reporter was used to assess circadian rhythm parameters (amplitude, period and phase) in skin fibroblasts from 59 PGBD participants [181]. Compared to Li-NR, cells from Li-R had a shorter circadian period and/or were more likely to demonstrate period shortening upon lithium treatment *in vitro*. Li-NR fibroblasts had a longer period that did not change upon lithium treatment. Another study of BD using patient fibroblasts reported similar results, indicating that cells from BD donors had more variable rhythms compared to controls. In addition, in samples from BD patients the

number of mood stabilizing medications of the donor was correlated with period length in the cells. Cells with a long period were less responsive to pharmacological modulation of the circadian rhythms [182]. Circadian rhythms were also examined in a neurons using stem cell-derived neural progenitor cells (NPC) to grow neurons from controls, Li-R and Li-NR [183]. Compared to controls and Li-R, amplitude was reduced in the Li-NR samples. As in fibroblasts, shorter period was observed in NPCs from Li-R vs Li-NR. In single NPCs and neurons, Li-R and Li-NR both showed phase desynchronization compared to controls. These data suggest that trait-like differences in cellular rhythms negatively influence lithium treatment in BD patients, and that one of the mechanisms by which lithium may exert its therapeutic effects is by shifting period. In human studies, the high-risk offspring of BD parents determined to be Li-R or Li-NR have been evaluated longitudinally over two decades [184]. Compared to controls, the high-risk youth of BD parents had higher rates of sleep disorders, but there was no difference associated with parental history of lithium-response.

**Seasonality.** Seasonal changes in photoperiod affect day length and require adaptation by circadian rhythms. BD patients commonly show seasonal changes in mood, and seasonal affective disorder (SAD) occurs more frequently in BD compared to MDD or community controls. One recent study suggested that compared to MDD and BD I, subjects with BD II were the most likely to show seasonal mood variation and disability [185]. Previous studies of seasonal BD have found association with clock gene variants. In a genetic association study of 269 BD patients (26% with SAD), the authors studied 349 SNPs and after correction for multiple testing, identified significant associations with five variants in *NPAS2* [186]. A GWAS of SAD composed of both BD and MDD cases and healthy controls did not identify any genome-wide significant associations in clock genes variants, but reported associations with *NPAS2*, *CSNK1E* and *RORA* in gene set enrichment analyses [187]. Another study made use of PRS for BD, MDD and chronotype obtained from GWAS. In 256 MDD and 189 BD patients, there was a significant correlation between seasonal depression and the MDD-PRS, but not BD-PRS or morningness [188]. Therefore, there is preliminary evidence linking seasonal BD with clock genes, but the evidence is inconsistent.



**Other sub-phenotypes.** Other potential sub-phenotypes of BD and a relationship to circadian rhythms have been proposed including mixed features [189] and rapid cycling [190]. However, these phenotypes have not been fully studied with contemporary methods in large samples and are considered preliminary. Sub-phenotype studies rely upon detailed clinical characterization and large cohorts. As the GWAS increase in size and improve in clinical phenotyping, the ability to perform sub-group analyses of BD may increase.

### **3.4 Environmental Risk Factors for Bipolar Disorder**

Environmental factors' impact on circadian rhythm in BD. Light is the most important and best studied environmental cue for influencing circadian rhythms and mood. Meal timing and exercise are also relevant environmental factors but have not been studied in BD from a chronobiological perspective. Bright light therapy is an important feature of this discussion but has been reviewed in detail previously by the CTF and will not be addressed further [1].

Experimental manipulations of photoperiod. Animal studies permit investigations of light and photoperiod on circadian rhythms and mood, using controlled manipulation of light/dark cycles that would not be possible in humans, including constant darkness (DD) and constant light (LL).

**Animal models of variation in light.** In nocturnal mice, exposure to LL disrupts circadian rhythms of locomotor activity, body temperature, and sleep-wake and causes depressive-like behaviors and anhedonia in mice [65]. Exposure to dim light at night has also been shown to induce depressive-like behaviors in mice as well as induce inflammatory changes in gene expression, decreases in hippocampal neurotrophic factors and cause phase delays in circadian rhythms [66]. Using experimental photoperiod manipulation, long-day (19L:5D) and short-day (5L:19D) light exposures can model summer and winter photoperiods. Exposure to short- or long-day photoperiods has been found to induce neurotransmitter switching between dopamine and somatostatin in the paraventricular nucleus, affecting depression-like behaviors in adult rats [191]. Mice with reduced expression of the dopamine transporter (DAT) show mania-like behaviors. DAT mutants have also shown exaggerated

affective behaviors with experimental manipulation of photoperiod: more depression-like behaviors under 19L:5D conditions and more impulsivity-like behaviors under 5L:19D conditions [192]. Compared to control mice, mutants were unable to regulate DAT expression in response to photoperiod changes, suggesting that plasticity in the dopamine system is responsible for fine-tuning reward behaviors in response to changing light conditions. Because mice are a nocturnal species, the correspondence of these findings from mouse experiments to humans remains to be clarified.

**Human laboratory studies: Light sensitivity in BD.** Supersensitivity of melatonin suppression by light has been proposed as a biomarker for BD. Increased light sensitivity might reflect differences in the function of the eyes, in particular the melanopsin-containing ipRGCs or ipRGC-recipient regions of the retina. The post-illumination pupil response (PIPR) to light has been used as a marker of melanopsin sensitivity. In healthy individuals, PIPR has been found to positively correlate with manic traits [193]. In contrast, diminished PIPR to blue light was found in patients suffering from seasonal depression compared to healthy controls [194] and PIPR has been found to vary in winter vs summer in seasonally depressed patients, but not in healthy subjects [195]. In a study of patients newly diagnosed with BD (n=31), unaffected relatives (n=22) and controls (n=35), there were no group differences in PIPR, but remitted BD patients showed reduced responses compared to BD patients with active hypomanic/mixed symptoms, suggesting state-dependent differences in BD [196]. Taken together, the pattern of PIPR findings suggests a possible correlation of retinal light sensitivity with mood symptoms, particularly those for mania [34]. *In vitro* studies of human cells show a correlation between intracellular signaling pathways with the effects of light on melatonin secretion, with elevated activity in cells from BD patients compared to controls [197]. These findings are also supported by GWAS which suggest enrichment of genetic risk factors for BD in light-sensitive signaling pathways [198].

**Naturalistic studies of light exposure and BD.** Light exposure varies considerably across seasons and geography and could affect the development of photosensitive neural systems underlying mood. A large study of 5,536 patients at 50 sites across 32 countries showed that age of BD onset is earlier in places with greater increase in springtime light exposure [199], and that more hours of daylight at

the birth location during early life is associated with a later onset of BD [200]. This effect was most pronounced in individuals with BD I and a positive family history, suggesting the possible presence of a gene x environment interaction. In the same cohort, light exposure was associated with suicidal behaviors [201]. BD patients living at higher latitude with greater fluctuations in light across seasons were more likely to have experienced a suicide attempt compared to BD patients living in locations where seasonal light changes are less variable. Others have found that greater amount of light in spring/summer is associated with earlier age of BD onset, and higher rates of hospitalizations for mania [202]. In a cohort study of 181 BD patients, ambient light exposure was measured for seven consecutive days while measuring symptoms of depression [203]. After controlling for bedtime, activity, employment and manic symptoms, individuals in the top tercile of light exposure were significantly less likely to be depressed compared to the bottom tercile. Taken together, ambient light may have important effects on mood including onset of manic symptoms and current depressive symptoms.

**Visual impairment and retinal alterations in BD.** Investigations of individuals with a total absence of light perception or alterations in visual and non-visual pathways could help resolve the relationship between light and BD. Preliminary evidence indicates that congenital blindness may be protective against SCHZ [204], but no data are available for BD. One meta-analysis found patients with BD to have retinal thinning compared to healthy controls [205]. One study has described impaired color vision in BD [206].

**Summary of light exposure studies.** There is reasonable evidence suggesting that light exposure modulates brain circuits regulating mood in BD, and possibly age of onset and suicidality. The underlying mechanisms in humans have not yet been elucidated. There is no conclusive evidence that light exposure or individual differences in light processing play causal roles in BD.

### **3.5 Specificity of Circadian Disruption in Bipolar Disorder and Across Psychiatric Disorders**

BD commonly presents with psychiatric comorbidity and is often conceptualized to occur on an illness spectrum. In this way, BD may overlap with other mood and psychotic disorders. The existence of clinical disorders adjacent to BD at diagnostic transitions (e.g., MDD with mixed features, schizoaffective disorder) further underscores this notion and gains additional support from cross-disorder GWAS and neuroimaging studies [207, 208]. In genetic studies, BD is shown to have substantial overlap in the risk from common genetic variation with attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), MDD, and especially SCHZ [208]. Large structural MRI meta-analyses show substantial correlation in brain structure in BD across SCHZ, OCD and MDD [207]. The following section explores the degree to which circadian disruption is specific to BD and/or is shared across psychiatric disorders.

**Circadian disruption in high-risk populations.** Two studies reported polysomnography and sleep ratings for 20 help-seeking individuals who met high-risk criteria for psychosis or BD and healthy controls [209, 210]. Compared to controls, individuals in the high-risk group had less daytime activity, longer sleep duration, and lower amplitude motor activity rhythms with more irregular and fragmented rest-activity patterns. However, these results did not control for differences in mood symptoms and chronotypes were similar across groups. There were no differences that distinguished risk for BD vs. psychosis.

**Circadian disruption in clinical studies of prodromal psychiatric disorders.** In a study of 248 youth presenting with prodromal psychiatric symptoms, sleep-wake disturbance, social dysfunction and lack of energy predicted transition to full threshold mental disorders after 1 year, but the relationship was not specific to mood disorders [211]. A later study reported similar findings with poor sleep quality, longer sleep latency and greater daytime dysfunction among help-seeking, prodromal youth compared to controls, but no specific association with mood disorders or BD [212]. In a large, 5-year prospective study of >2,300 youth, sleep/wake disturbance predicted the transition from subthreshold to a syndromic mental disorder. Sleep/wake disturbance was lowest in individuals with non-specific symptoms (7%), higher in those with subthreshold syndromes (17%) and highest in those meeting full first-episode criteria for a disorder (32%) [213]. Regarding BD, mania-like

symptoms were one of several predictors of transition, but circadian sleep/wake disturbance showed no specific association with diagnosis. Further analysis identified predictors of transition to psychosis and BD [214]. Although rates of circadian disruption were nominally higher in individuals who developed BD compared with psychosis (42% vs. 8%), the difference was not significant after adjustment for covariates.

A large, longitudinal community cohort study examined associations of insomnia, hypersomnia, and daytime activity with BD onset among >1,800 youth [215]. Symptoms at age 15-19 years were compared with those after the onset of a mental disorder at age 19-25 years. Delayed sleep phase predicted onset of depression, but not mania/hypomania. Hypersomnia and anergia predicted the onset of BD. However, none of these associations were unique to BD and most showed similar associations with the onset of depressive or psychotic disorders. Similar conclusions were reached by a meta-analysis of 25 unique datasets (including >45,000 individuals) that reported sleep disturbance increased the odds for developing a mood or psychotic disorder in early adulthood, with similarly increased risk for BD, psychotic disorders or MDD [216].

**Chronotype and actigraphy as predictors of BD.** Among help-seeking youth with subthreshold, fully diagnosed disorders or mixed symptom patterns, individuals with emerging psychosis exhibited elevated morningness scores, while cases with emerging anxiety and depression had low morningness [217]. Individuals with emerging BD also reported lower morningness than controls, especially in depressed males. Among >1,400 students classified as being at high, medium, or low-risk of mental disorders, the high-risk group exhibited low morningness, but this was not uniquely associated with BD [218]. In 146 subjects with emerging psychiatric disorders assessed with actigraphy, medication use and manic symptoms were independently associated with lower amplitude and circadian disruption regardless of diagnosis [219]. The largest difference between individuals with emerging BD or MDD, was that relative amplitude was less robust in BD, and that weaker rhythms were associated with increased symptoms. Therefore, preliminary evidence from the cross-disorder studies of high-risk youth indicates that low rhythm amplitude is commonly observed across disorders. Chronotype may distinguish psychosis from BD.

**Do circadian biomarker studies distinguish BD from other psychiatric disorders?** The majority of biomarker studies in BD employ a single disorder, case-control design. However, studies of biomarkers comparing BD against additional clinical populations and controls have also examined genetic and molecular aspects of the circadian clock, primarily investigating SCHZ and MDD, but also ADHD, autism and alcoholism. Among these studies, instances of distinct circadian profiles are reported between BD and comparisons disorders. Candidate gene association studies have shown distinct sets of clock gene SNP associations between BD and MDD [116]. Among blood biomarkers, BD patients with evening chronotype were shown to have lower serum levels of IL6 and TNF $\alpha$  compared to MDD and controls who did not show any interactions between cytokines and chronotype in a community sample of 213 participants [220]. With respect to SCHZ, variants in the clock genes *ARNTL* and the *PER3* have been reported to help distinguish the genetic overlap with BD [132, 171]. However, most of these studies reporting BD-specific differences in circadian biomarkers were relatively small, and/or underpowered to distinguish clock associations versus both controls and a comparison group.

The majority of evidence from better powered human biomarker studies indicates that biological factors underlying circadian disruption in BD are shared across psychiatric disorders. In GWAS of chronotype, PRS for morningness are inversely correlated with risk for BD, but also MDD and SCHZ, and positively correlated with subjective well-being [176, 221-223], while PRS for low amplitude activity are associated with both MDD and BD as well as trait neuroticism [174, 175]. Although chronotype in these studies is not a perfect proxy for circadian clock function [2], this genetic evidence indicates that circadian disruption is associated with a variety of psychiatric phenotypes. In a study specifically designed to evaluate cross-disorder enrichment of PRS for chronotype, sleep duration and insomnia across BD, MDD, and SCHZ, there was widespread genetic overlap in all three disorders with each trait [224]. BD PRS overlap was for chronotype 64%, sleep-duration 76%, and insomnia 78%. While some unique sleep/circadian loci were found to overlap with each disorder, overall PRS overlap in BD, MDD and SCHZ was similar in magnitude. In cell lines and post-mortem brain, specific micro-RNAs (miRNAs-29a/c and 106b) have been linked to the circadian clock, and

have been independently linked to BD, MDD and SCHZ [225]. Using peripheral cell cultures and iPSC-derived neurons, circadian rhythm abnormalities have been described in BD, including anomalies in clock gene expression [226], period [137, 182], phase [183], and low amplitude [183, 227, 228]. Similar studies have revealed cellular rhythm abnormalities in SCHZ [229], alcoholism [230], Alzheimer's Disease [231], and ADHD [232]. However, none of these cell-based studies have compared two or more clinical samples directly, and some of the differences in rhythms parameters are distinct. For instance, in fibroblast studies, differences from controls in BD studies were seen in period, whereas in SCHZ differences were observed only in amplitude. In alcoholism, there was no difference between cases and controls, but period length was associated with illness severity. Therefore, it is difficult to make meaningful comparisons across diagnoses.

Methodological differences may further limit comparisons across disorders. For instance, gene expression rhythms measured with polymerase chain reaction (PCR) typically employ 4-6 h sampling intervals over 1-2 days and provide less precise estimates for rhythm parameters compared to those made using bioluminescent reporters that take frequent measurements in live cells over 5-7 days. Post-mortem studies of brain tissues have been developed as another means of assessing circadian biomarkers in humans with psychiatric disorders. In these studies, tissues are collected from individuals at different times of death. By doing so, it is proposed that rhythmically expressed genes can be examined across time at different phases, and the rhythms re-constructed for between-group analyses. These studies indicate widespread disruption of gene expression rhythms are present in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), hippocampus, amygdala, nucleus accumbens and cerebellum in MDD [233]; DLPFC in SCHZ [234]; and DLPFC in aged subjects [235], with adult sex differences in DLPFC and ACC [236]. In affected cases compared to controls, these studies generally show loss of rhythms in ensembles of functionally related genes. Notably, in SCHZ there are ensembles of genes that become rhythmic only in cases and not controls [234]. These data indicate that loss of rhythm may be pervasive across neuropsychiatric disorders, but that inappropriate gain of rhythm may be another source of circadian disruption. However, as with cell-based studies, comparisons across disorders have not been performed in the same study. Similarly, a detailed comparison of genes affected has not been completed, and only a small number

of brain regions have been examined. Therefore, there may be disease-specific signatures of rhythm disruption in the brain that remain undescribed. Interestingly, despite the importance of circadian disruption in BD, post-mortem gene expression studies of BD samples have not yet been published.

**Summary of comparative biomarker studies across disorders.** With respect to clock gene involvement, the overall conclusion is that circadian disruption shows considerable overlap across disorders, especially among BD, MDD and SCHZ. This lack of clear diagnostic boundaries is similar to other heterogeneous clinical features associated with BD, SCHZ and schizoaffective disorders such as psychosis, cognition, and brain morphology that have been proposed to constitute transdiagnostic “biotypes” [237]. From this perspective, it is possible that circadian disruption may also define a transdiagnostic biotype, but this remains conjecture and awaits experimental validation. Phenotypes differ importantly across psychiatric disorders, and the particular kind of circadian disruption and underlying molecular mechanisms may be important, meaning that psychiatric phenotypes may have both shared and unique features involving circadian rhythms. For instance, amplitude may be affected in one disorder and phase in another, with both negatively affecting sleep. Existing biomarker studies have so far failed to systematically compare molecular-genetic circadian profiles across disorders. Therefore, there may still be unrecognized molecular clock disruption that is specific to BD. Another area for study relates to state-dependent effects observed in BD that distinguish mania and depression [26, 27]. It is unknown how alterations in circadian biomarkers correlate with mood-dependent changes in gene expression and if similar states in other psychiatric disorders (e.g., depression in MDD) would show similar circadian profiles in BD. Preliminary work in this area has implicated rhythmically expressed genes in blood as a means of distinguishing MDD from BD [238]. Newer modalities such as epigenetics and microbiome analyses have been proposed, but remain to be examined.

### **3.6 Circadian Disruption Over the Illness Course of Bipolar Disorder**

#### *A. Circadian disruption in first episode BD.*



Accepted Article

It has been hypothesized that circadian disruption may trigger first manic or depressive episodes. Longitudinal studies of individuals at high-risk for BD commonly include first onset BD episodes. However, these studies differ in the threshold set for diagnosing BD. For instance, some classify BD cases that do not meet full diagnostic criteria (i.e. BD not otherwise specified, NOS) as fully syndromic BD, while others classify BD-NOS cases as ‘at-risk’ and consider only BD-I or II as fully syndromic. Moreover, cohorts may include individuals previously diagnosed with another psychiatric disorder. In a 6-year longitudinal study of 433 offspring of BD parents (OSBD) who participated in actigraphy and clinical assessment every two years, 11% developed a BD spectrum disorder [239]. When compared with 314 individuals who did not transition to BD, the new onset BD group was more likely to have an evening chronotype, inadequate sleep, prolonged sleep onset, and multiple awakenings. Importantly, both BD and control offspring commonly reported comorbid non-mood disorder diagnoses at baseline, confounding the interpretation. Opposite results were found in a longer, 10-year study of 107 adolescent OSBD, in which 12.8% of offspring without a mood disorder at baseline transitioned to BD [240]. Subthreshold manic symptoms proved the strongest predictor of transition while hypersomnia, anergia, and circadian reversal were not associated with transition to BD. Using the Social Rhythm Metric measure of stability of timing of daily activities [241], prospective studies of reward sensitivity have been performed on adolescents at high (n=138) or moderate-risk (n=95) for BD [242]. Over three years, irregular daily activities predicted first onset of a BD spectrum disorder in 10% of the cohort, with higher rates of conversion in the high-risk group (14% vs 4%) leading the authors to conclude that irregular social rhythms predicted BD onset only in high-risk individuals. In another study of social rhythms, 414 young adults with BD II or sub-threshold BD were followed for an average of 33 months [243]. In the sub-threshold BD group, irregular social rhythms significantly predicted subsequent mood episodes (usually depression) and conversion to BD. These findings are consistent with work reporting that life events that disrupt social rhythms often precede the onset of manic episodes in BD I and depressive episodes subthreshold BD and BD II participants [244, 245].

**Conversion from MDD to BD.** Some studies have specifically examined whether circadian disruption may help identify individuals with depression who later experience hypo/mania. In a

community sample of 3,021 youth followed for 10 years, baseline symptoms of depression were compared in individuals later diagnosed with MDD (n=659) or BD (n=35). Diurnal mood variation was associated with transition to BD, but no group differences were identified in hypersomnia, daytime activity or atypical symptoms [246]. In contrast, a 2-year longitudinal study of youth identified 50 participants who showed early transition to BD, then matched them with 50 individuals with MDD [247]. In this slightly larger, matched cohort, atypical symptoms of depression, especially hypersomnia and anergia were specifically associated with transition to BD.

**Circadian rhythm disorders and illness severity.** Circadian phase delay toward eveningness has been found in patients with BD and is associated with a more severe illness course [248-251]. Notably, up to one-third of BD patients have comorbid circadian rhythm disorders, most commonly delayed-sleep phase disorder [252]. BD patients with circadian rhythm disorders have a significantly worse illness course with earlier age of onset, more personal and family history of suicidal behaviors, higher recurrence rates and more antidepressant-related manic switches [178, 252, 253]. However, the direction of causality and specificity of these comorbidities with BD illness course are not clear. When considering actigraphy studies in exploring the course of BD over time, a systematic review of 27 studies identified rest/activity metrics including total activity, timing, and variability that were consistently associated with transition between different phases of BD that may be predictive of longitudinal course [254].

**Summary of illness course studies.** There is a weak signal for objectively measured longer duration of sleep and for lower amplitude activity in individuals at risk of BD. Limited evidence indicates later rise time, evening chronotype, irregular daytime activity and/or daytime dysfunction may also characterize those who will progress to BD and/or convert from MDD. However, many of these studies are limited by the participation of symptomatic subjects with subthreshold mood syndromes. Small samples, lack of correction for multiple comparisons and inconsistent application of diagnostic criteria confound interpretation. Studies in later stages of BD suggest circadian disruption is a risk factor for relapse, but do not control for depressive or manic symptoms that confound assessment of circadian disruption. Circadian sleep-wake disorders are associated with relapse, but the extent to

which this association is specific is unclear and may be similar to other conditions that undermine stability (e.g., anxiety, substance abuse or pain conditions).

### *B. Circadian Disruption in Mood States and Relapse*

**Do phase shifts cause mood episodes in BD?** Phase shifts have been associated with mood episodes in BD. The question of causality and state vs. trait issues have been addressed in variety of ways including the use of animal models, controlled and naturalistic human studies of BD patients, and as a biomarker of pharmacological interventions targeting mood symptoms.

**Phase shift studies in animal models.** Both diurnal and nocturnal animals exposed to altered light/dark cycles show circadian disruptions and adverse changes in mood-related behaviors. For example, rats exposed to phase advances, showed increased anhedonia and anxiety-like behavior [255]. Similarly, the light at night model in mice causes depression and anxiety-like behaviors and induces phase delays [66].

**Controlled human phase shift studies.** Both depressive and manic episodes have been studied. Supporting episodic state-associations, seven BD subjects were tracked longitudinally and spontaneous phase advances of activity and sleep were associated with resolution of depressive episodes [256]. More recent studies have incorporated gene expression biomarkers to study differences across mood episodes. In BD outpatients, 16 were recruited while manic, 22 while depressed and compared to 19 community controls. Circadian phase was estimated using buccal swabs to collect cells and measure *PER1* and *NR1D1* gene expression and salivary melatonin collected under dim light [42]. Compared to depressed BD patients and controls, manic BD patients showed a phase advance in melatonin onset and similar trends in gene expression. There were no significant differences in the depressed subjects. The study did not assess euthymic BD patients. Another biomarker study of circadian phase was conducted in hospitalized BD patients [257]. Circadian rhythms in 31 episodes of BD were evaluated at admission, at 2-week intervals during hospitalization, and at the time of discharge. Saliva and buccal swabs were obtained at regular time intervals for two days, and used to analyze cortisol and clock gene expression in epithelial cells.

Compared to controls, manic BD patients showed a ~7 h phase advance, whereas depressed BD patients showed 4–5 h phase delays. Interestingly, mixed episodes were associated with 6–7 h phase delays, intermediate between depression and mania. In these symptomatic BD patients, phase shifts tracked closely with mood symptoms and normalized prior to discharge. The authors point out that the ~7 h phase advance associated with mania could also be interpreted as an extreme ~17 h phase delay, indicating mood symptoms may shift on a continuum going from depression to mixed episodes and mania as phase delays increase. The model potentially offers an explanation as to why manic switches in/out of depression can occur suddenly and why mixed features are typically not sustained, as they exist as transition states. By proposing that individuals demonstrate differences in the potential range of phase shifts, this model was also used to explain differences across mood disorders, whereby BD I patients show the greatest phase shifts (up to 17 h), BD II are intermediate and unipolar depressed patients have the smallest phase shifts (only 4-5 h), suggesting both trait and state-like aspects of circadian phase shifting in BD. Additional evidence for phase delays in depression comes from studies of MDD. Three cross-sectional studies of MDD and healthy controls compared various phase angle differences between groups [258-260]. Each of these small studies found phase differences associated with depressive states that reflect the delay of one or more physiological, circadian rhythms. Another cross-sectional study of 18 depressed women examined the association between depressive symptoms and plasma DLMO and found the severity of depressive symptoms correlated with the degree of misalignment [261]. In an actigraphy study of the Dutch Bipolar Cohort (n= 107 BD, 74 unaffected siblings and 80 control), participants were assessed for symptoms and activity over 14 days [262]. All groups reported low levels of manic symptoms, but BD cases had significantly high levels of depression. The investigators found a longer sleep duration and later sleep offset in BD cases compared to unaffected siblings, but these differences were no longer significant after adjusting for depressive symptoms suggesting a state-like change. No other actigraphy parameter differentiated BD cases. Stable, trait-associations have also been reported. An early case-control study compared the urinary levels of 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine and motor activity in healthy controls and BD subjects transitioning through manic, depressive and euthymic states [263]; another study measured activity in manic and mixed states following subjects into

recovery [264]. These latter two studies both revealed phase advances spanning manic and depressive states and remission, suggesting a persistently stable circadian trait.

**Naturalistic human phase shift studies.** Studies have examined the clinical features of travelers admitted to psychiatric hospitals for mood or psychotic episodes. In a review, there was some indication of increased risk for mood relapse following long distance travel related to circadian misalignment, with depressive episodes possibly more likely with westward travel (requiring a phase delay to synchronize with local time) and manic episodes more likely travelling eastward (requiring a phase advance) [265]. However, the evidence is based on only three studies, none of which were conducted entirely with BD samples, randomization, or control participants who did not experience a mood episode. With seasonal time changes between daylight savings and standard time common in many areas, 1-h phase shifts have also been examined in a large registry study spanning 6 years. Among BD patients, there was no increased risk of hospitalization for mania in the 2 weeks following the time change compared to the 2 weeks before [266]. Shift work induces phase changes in susceptible people, and BD patients working at night may be at increased risk for relapse. Two case studies have examined shift work and BD [267, 268]. These reports provide preliminary support for phase disruptions causing mood disturbances in BD. Given the prevalence of shift work in modern society, its impact upon people with BD is in urgent need of more study.

**Summary of phase shift studies.** We provide tentative support for the hypothesis that circadian phase advances are related specifically to manic phases of BD and phase delays are related specifically to depression. It is unclear if depression in BD and MDD differ regarding phase delays. Further work is needed to determine whether phase changes are traits of BD reflecting stable vulnerabilities, or if they relate to manic and/or depressive states.

### *C. Rhythm-Modifying Effects of Mood Stabilizing Drugs*

**Animals and cellular models of mood stabilizers.** Mood stabilizing drugs commonly interact with the molecular components of the circadian clock and their therapeutic properties may relate in part to

these actions. In the *Clock* $\Delta$ 19 mouse model of mania, lithium administration normalized anxiety-like behaviors, and reduced hyperactivity effects that may occur through normalizing dopamine in the VTA and striatum [113-115, 269]. As described previously, the kinase GSK3 post-translationally regulates several clock proteins [145, 270-272]. Lithium inhibits GSK3 at therapeutically relevant concentrations and affects circadian rhythms in cells from BD patients [137, 182, 183]. Consistent with the notion that lithium engages clock proteins as part of the therapeutic mechanism, mutant mice lacking CRY1 and PER2 show distinct anti-depressant responses to lithium [273]. In *Clock* $\Delta$ 19 mice, selective inhibitors of GSK3 had lithium-like effects in reducing locomotor hyperactivity [274]. Similar effects were observed with inhibitors of casein kinase 1D, another post-translational regulator of PER2 [274]. Lithium and selective GSK-3 inhibitors increases circadian rhythm amplitude [275]. However, BD fibroblasts and neurons often lack this amplitude-increasing effect of lithium, speaking against rhythm amplification as a therapeutic drug mechanism [137, 183]. Instead, period change may be more critical. Lithium has been shown to generally lengthen period in cells, rodents, non-human primates and human subjects [137, 276-278]. However, this effect varies across individuals, is concentration dependent and not uniformly observed *in vitro* at therapeutically relevant concentrations. Unlike lithium, selective GSK3 inhibitors shorten, rather than lengthen, period, a difference that may be related to lithium's ability to also inhibit inositol monophosphatase [181, 275, 279, 280]. Suggesting an important role for period change in determining therapeutic outcomes, cells from lithium responsive BD patients are more likely to show period shortening effects from therapeutic levels of lithium *in vitro* whereas cells from lithium non-responders are more likely to show period lengthening [181]. In agreement with human laboratory studies, shorter period could be expressed as a phase advance under environmental light/dark conditions and would be predicted to have anti-depressant activity.

Valproic acid also has effects on circadian rhythms [281]. The dopamine transporter knockdown mouse (DAT-KD) exhibits hyperactivity, longer circadian period under constant conditions, and has been proposed as a model for mania [282]. In DAT-KD mice, valproic acid shortened period of wheel running behavior *in vivo* and PER2 expression in SCN slices *in vitro*, returning period length to control levels. Similar period shortening effects were observed in BD patient fibroblasts that had a

longer period prior to treatment [282]. Therefore, one common mechanism shared by GSK3 inhibitors and valproic acid is the association with shortening of circadian period and beneficial changes in mood-related behaviors. Similar to lithium, valproic acid also normalizes the manic-like behavior of the *Clock* $\Delta$ 19 mice via inhibition of histone deacetylase 2 (HDAC2) in the VTA [283]. It has yet to be determined if valproic acid impacts activity or molecular rhythms in these mice.

**Mood stabilizing drugs in BD patients and healthy individuals.** A small number of clinical studies have shown phase advances with antidepressant interventions in BD, MDD or mixed depressed samples. These include sleep phase advance, sleep deprivation, and tricyclic antidepressants [284-286]. Other “combination chronotherapeutic approaches” employ phase advance among other interventions such as lithium, phototherapy and sleep deprivation to show synergistic outcomes compared to a single intervention [287, 288]. There is also evidence that a common therapeutic mechanism underlies the fast-acting treatments short-term sleep deprivation, bright light therapy and ketamine. Ketamine and sleep deprivation were found to engage overlapping cortical pathways involved in circadian rhythms and mood [289]. In a clinical trial of 51 individuals with treatment refractory depression (N=21 with BD) and 38 controls, actigraphy was monitored over 3 days before and after ketamine administration [286]. Baseline circadian rhythm parameters predicted ketamine response. Rapid ketamine responders had advanced phase rhythms at baseline and on day 1 after treatment compared to ketamine non-responders or subjects who received placebo infusions. On day 3 the ketamine-responders also showed a higher amplitude activity rhythm and more activity overall compared to non-responders. Melatonin may also play a role in the therapeutic actions of mood stabilizers in BD. Both lithium and valproate reduce melatonin suppression in response to light in healthy volunteers [290, 291]. However, there was no effect of lithium on melatonin sensitivity reported in a sample of BD patients [37].

**Summary: Rhythm-modifying effects of mood stabilizing drugs.** Many mood stabilizing drugs have effects on circadian rhythms, and it remains plausible that interventions that advance phase (or shorten period) may have value in bipolar depression and that phase delaying (or period lengthening) effects may have anti-manic effects. However, these findings are largely from animal studies and

evidence supporting these mechanisms in humans is largely missing. Importantly, many mood stabilizers have both anti-manic and anti-depressant properties but can only affect rhythms in one direction at a time. Any explanation of circadian rhythm effects of drugs must account for this discrepancy. Overall, circadian rhythm modulation as a necessary component of mood stabilizer treatment for BD is weakly supported. Nonetheless, drug treatments that target the circadian clock in BD have a strong theoretical basis and should be studied further.

### 3.7 Summary of results

Sections 3.1 through 3.6 above highlight a significant body of research characterizing the chronobiological underpinnings of BD. Before critical integration of the evidence base in the Discussion below, we briefly note here key findings in each area.

**Table 2: Overview of key results**

Section	Summary of reviewed findings
<b>3.1 Neurobiology of circadian clocks in bipolar disorder</b>	<ul style="list-style-type: none"><li>• The molecular genetics and neuroanatomy of the circadian system are strongly conserved across mammals.</li><li>• Circadian clocks interface with biological pathways implicated in healthy and disordered mood regulation</li><li>• The role of the SCN in direct mood regulation is incompletely described.</li><li>• Rhythmic physiological, behavioral and cognitive processes are outputs of circadian clocks and regulated pathways implicated in BD: dopamine, melatonin, inflammation, sleep and metabolism.</li><li>• Extrapolation from nocturnal rodents to humans often required</li></ul>
<b>3.2 Circadian disruption as a - predisposing risk factor for bipolar disorder</b>	



Section	Summary of reviewed findings
A. Vulnerability for bipolar disorder	<ul style="list-style-type: none"><li>• Proxy markers of circadian rhythms have been examined as risk factors for BD vulnerability in subjects enriched in familial high-risk, affective temperament, and hypomanic symptoms.</li><li>• The circadian variables have been limited to sleep parameters, chronotype and motor activity rhythms</li><li>• BD risk phenotypes are generally associated with evening chronotype, poor sleep quality, and lower amplitude 24-hour sleep/activity rhythms.</li></ul>
B. Heritability of circadian phenotypes and bipolar disorder	<ul style="list-style-type: none"><li>• Large genetic studies indicate high heritability of BD, dozens of high-confidence genetic loci, only sparse evidence directly implicating clock genes in BD</li><li>• Considerable genetic overlap across BD, SCHZ, MDD, neuroticism and overall well-being</li><li>• Family and twin studies suggest that instability of 24-hour activity rhythms and long sleep duration are heritable and overlap with genetic risk for BD</li><li>• Heritability estimates of circadian rhythms rely upon indirect proxy measures, typically actigraphy-derived motor activity and sleep measures (objective or subjective)</li></ul>
C. Genetic mechanisms in the molecular clock and risk for bipolar disorder	<ul style="list-style-type: none"><li>• Polygenic genetic risk for chronotype, low amplitude activity rhythms and sleep duration identified as a trans-diagnostic risk factors for BD, MDD and SCHZ</li><li>• No unique association between circadian disruption and BD. Genetics underlying circadian disruption appears to be equally important as risk factors for MDD and SCHZ</li><li>• Suboptimal study designs: community samples, comparatively few clinical samples, incomplete psychiatric phenotyping, not powered for cross-disorder</li></ul>

Section	Summary of reviewed findings
<b>3.3 Circadian disruption as a basis for defining sub-groups of bipolar disorder</b>	<p data-bbox="706 226 803 254">analyses</p> <ul style="list-style-type: none"> <li data-bbox="657 279 1372 359">• Some BD subgroups may be more affected by circadian rhythm abnormalities</li> <li data-bbox="657 384 1372 514">• Lithium responsiveness is an established BD subtype with GWAS markers to identify lithium responders and non-responders</li> <li data-bbox="657 539 1372 619">• Low morningness associated with lithium-nonresponse in clinical trials</li> <li data-bbox="657 644 1372 774">• Lithium non-response is associated with longer circadian period, and lower amplitude in human cellular models using BD patient samples.</li> <li data-bbox="657 800 1372 919">• Inconsistent support in genetic association studies that parameters related to seasonal mood variation in BD involves clock gene variants</li> </ul>
<b>3.4 Environmental risk factors for bipolar disorder</b>	<ul style="list-style-type: none"> <li data-bbox="657 947 1372 1026">• Light exposure modulates brain circuits regulating affective behaviors</li> <li data-bbox="657 1052 1372 1182">• Early environmental light exposure associated with manic and depressive features of BD course, age of onset and suicidality</li> <li data-bbox="657 1207 1372 1287">• Underlying mechanisms of light on mood in humans have not been fully elucidated</li> <li data-bbox="657 1312 1372 1442">• No conclusive evidence that light exposure or individual differences in light processing play a causal role in the development of BD</li> <li data-bbox="657 1467 1372 1486">• No studies of other diurnal environmental factors</li> </ul>
<b>3.5 Specificity of circadian disruption in BD and across psychiatric disorders</b>	<ul style="list-style-type: none"> <li data-bbox="657 1514 1372 1593">• Circadian disruption is widely reported across disorders, especially in BD, MDD and SCHZ</li> <li data-bbox="657 1619 1372 1743">• Biomarker studies have so far failed to systematically compare molecular-genetic circadian profiles across disorders</li> </ul>

Section	Summary of reviewed findings
<b>3.6 Circadian disruption across the illness course of bipolar disorder</b>	<ul style="list-style-type: none"> <li>• State-dependent differences in BD are understudied: unknown if similar states in other psychiatric disorders (e.g., depression in MDD) are similar or distinct</li> </ul>
A. Circadian disruption in first episode BD.	<ul style="list-style-type: none"> <li>• Longer duration of sleep and lower amplitude reported in individuals at risk of BD</li> <li>• Later wake time, evening chronotype, irregular daytime activity and/or daytime impairment reported in first onset of BD and/conversion from MDD</li> <li>• Prodromal BD symptoms commonly include circadian disruptions, but these are not essential for conversion to syndromic BD</li> <li>• Studies are limited by the participation of symptomatic subjects with subthreshold mood syndromes</li> <li>• Small samples, statistical power and inconsistent application of diagnoses further limit quality of evidence in first episode studies</li> </ul>
B. Circadian disruption in mood states and relapse	<ul style="list-style-type: none"> <li>• Tentative support that circadian phase advances specifically associated with mania</li> <li>• Tentative support that circadian phase delays are specifically associated with depression</li> <li>• Unclear if BD and MDD differ regarding phase delays</li> <li>• Further work needed on state-trait characteristics of phase shifts and mood in BD</li> <li>• Circadian disruption is a risk factor for relapse, but most studies do not control for depressive or manic symptoms that confound assessment of circadian rhythms</li> <li>• Reports of circadian sleep-wake disorders associations</li> </ul>

Section	Summary of reviewed findings
C. Rhythm-Modifying Effects of Mood Stabilizing Drugs	<p data-bbox="704 226 1373 306">with relapse, but no demonstration of specificity compared to other co-morbid conditions</p> <ul data-bbox="659 331 1373 1024" style="list-style-type: none"> <li data-bbox="659 331 1373 411">• Mood stabilizing drugs have clear effects on circadian rhythms</li> <li data-bbox="659 436 1373 516">• Interventions that advance phase show anti-depressant properties may have value in the depressed phase of BD</li> <li data-bbox="659 541 1373 621">• In principle, phase delaying effects may have anti-manic effects, but evidence is weak</li> <li data-bbox="659 646 1373 726">• Lack of well controlled and adequately powered human studies</li> <li data-bbox="659 751 1373 873">• Lack of clear mechanism linking specific anti-manic and anti-depressant properties of a drug to circadian variables</li> <li data-bbox="659 898 1373 1024">• Only weak support that circadian rhythm modulation is a necessary component of mood stabilizer treatment in BD</li> </ul>

#### 4. Discussion

The preceding findings represent the summaries of the CTF, expertise-matched into four method-specific workgroups to conduct inclusive reviews of evidence for circadian associations with BD. Considered together, the findings of this review provide substantial evidence for a plurality of associations between circadian rhythm parameters and BD-related variables. Key results and conclusions are summarized above (Table 2). The following discussion provides a critical analysis of this evidence, and based upon these conclusions, aims to map an agenda for future research.

##### 4.1 Evidence for Associations Between Circadian Rhythms and Bipolar Disorder

Conclusions of the CTF align broadly with previous literature reviews, and do not undermine growing interest in circadian assessment and intervention for people with BD [1,2]. However, the present critical review more explicitly recognizes significant uncertainties in the evidence base (see Table 3). People at risk for BD commonly show sleep problems, low amplitude rhythms, and distinct chronotypes as early indicators. Circadian rhythms link multiple relevant neurobiological pathways with strong evidence for involvement in BD. Furthermore, photoreceptive inputs to the SCN and other brain structures play an important role in mood regulation, especially in animal models, while detailed mapping of photic input pathways have not been well-studied in humans. Strong evidence supports that genetic liability affecting chronotype, sleep and activity parameters intersect with genetic risk for psychiatric disorders, but not specifically for BD. Evidence is strong that changes in environmental light conditions affect mood. Preliminary and incomplete evidence indicates that light supports euthymia when optimally delivered but might provoke mood episodes when exposure is suboptimal and/or misaligned with circadian phase. The majority of evidence from biomarker and developmental studies of young people indicate that there is no particular enrichment of circadian rhythm disturbances in BD relative to mood or psychotic disorders. Nonetheless, several effective drug treatments for BD including lithium and valproic acid may have therapeutically relevant engagement with the circadian clock. The majority of evidence indicates there are stable trait-like differences in sleep and chronotype in BD but the evidence is often confounded by co-morbid psychiatric conditions and often derived from studies performed outside a controlled laboratory setting. Evidence supporting state-like abnormalities related to mood episodes and phase alignment has been provided, but is comparatively weaker, arising from fewer and smaller studies, with more variable and inconsistent outcomes. Importantly, the pattern of findings suggests that specificity to BD is unlikely, and consistent with a range of research outside BD, that measurable abnormalities in circadian function are associated with a range of psychiatric and medical disorders, developmental disorders, neurodegenerative disorders, metabolic disorders and cancers. In conceptualizing these findings into an integrated model of BD, we have considered the level of organization, disease specificity and relative importance of circadian function (Figure 3).

**Table 3: Associations between circadian function and bipolar disorder: Conclusions and methodological limitations across themes**

Theme	Key conclusions	Methodological limitations of conclusions
<b>Vulnerability, heritability and genetics</b>	<ul style="list-style-type: none"> <li>• Chronotype and behavioral measures of circadian function show associations with vulnerability to BD (strongest evidence is for amplitude)</li> <li>• BD- associated activity rhythm parameters (particularly amplitude) are associated with vulnerability/psychopathology</li> <li>• Large biobank studies show polygenic overlap across circadian and BD-related traits</li> <li>• Manipulation of core clock genes in mice confirm their involvement in circadian rhythms and mood related behaviors</li> </ul>	<ul style="list-style-type: none"> <li>• Chronotype, reward-sensitivity, social rhythms are non-specifically associated with BD risk</li> <li>• Actigraphy variables are at best proxies of circadian function, and different variables from different studies</li> <li>• Polygenic scores for circadian traits are non-specific including MDD and personality traits</li> <li>• Incomplete evidence that animal studies' gene-specific conclusions generalize to humans</li> </ul>
<b>Clinically distinct sub-groups of BD</b>	<ul style="list-style-type: none"> <li>• Morningness predicts lithium responsiveness, potentially</li> </ul>	<ul style="list-style-type: none"> <li>• Cellular rhythms in lithium responsiveness have only been</li> </ul>

Theme	Key conclusions	Methodological limitations of conclusions
<b>Environmental factors and biological mechanisms</b>	<p>underpinned by shorter period cellular rhythms</p> <ul style="list-style-type: none"> <li>• One large study links springtime availability of daylight to age of BD onset</li> <li>• Animal models of daily/seasonal light variations consistent with role in depression-related behaviors</li> </ul>	<p>investigated small samples</p> <ul style="list-style-type: none"> <li>• Sub-phenotypes not studied in large genetic samples</li> <li>• Meteorological sunlight levels are very remote proxies of light exposure at the eye</li> <li>• Problems comparing nocturnal rodents to diurnal humans</li> </ul>
<b>Specificity to BD</b>	<ul style="list-style-type: none"> <li>• Absence of specific circadian abnormalities to BD diagnosis is generally observed</li> </ul>	<ul style="list-style-type: none"> <li>• Piecemeal studies focusing on divergent circadian and sleep parameters</li> <li>• Biomarker studies have not directly compared disorders</li> </ul>
<b>Illness course</b>	<ul style="list-style-type: none"> <li>• Evening chronotype, poor sleep predicts onset of BD spectrum disorder in prospective studies</li> <li>• Evidence that mania is associated with circadian phase advance (including clock gene expression)</li> <li>• In one study, circadian correlates of BD became non-significant after adjusting for depressive symptoms</li> <li>• Animal studies suggest altered light/dark cycles</li> </ul>	<ul style="list-style-type: none"> <li>• Inconsistent findings across studies</li> <li>• Limited investigations of mood state changes with circadian phase shifts</li> <li>• Limited consensus in replications</li> <li>• Causality difficult to investigate in humans, particularly because of third variables (e.g., stress impacting mood and circadian rhythms)</li> <li>• Naturalistic studies have</li> </ul>

Theme	Key conclusions	Methodological limitations of conclusions
	<p>disrupt circadian function and mood</p> <ul style="list-style-type: none"> <li>• Animal and cellular models suggest lithium operates partly through cellular circadian mechanisms (shortening period)</li> <li>• Clinical studies suggest effective mood stabilizer interventions are associated with phase advances</li> </ul>	<p>been idiosyncratic with poor controls</p>

#### 4.2 Limitations of the literature

As a whole, the literature is diffusely organized, characterized by investigation of a large number of distinct questions, and assessed using different methods in samples selected on diverse criteria. Many of the proxies accepted as measures of circadian rhythms including actigraphy, sleep, and social rhythms are confounded by non-circadian factors (e.g., masking from light, homeostatic sleep pressure, effects of mood state) and/or incompletely understood in terms of underlying chronobiology. Overall, evidence for most conclusions was not robust, with even the stronger findings undermined by key weaknesses (see Table 2). Within studies, controls for alternative explanations are often missing. Cohorts are often small, and replication of specific findings is rare.

Overall, the findings can be best summarized as ‘a mosaic of evidence’ or ‘dappled evidence’ for non-specific involvement of the circadian system in BD [292, 293]. Whether this is deemed compelling or not depends on the robustness of individual pieces of evidence and whether a more theoretically integrated account is possible.



**Avoiding false positive inferences.** In the context of meta-scientific concern about failures to replicate [294], a major goal of the CTF was to attend to the risk of drawing false-positive associations (type I error) in the BD literature pertaining to circadian rhythms. We have identified four conceptual ambiguities that together increase the risk of type I error: definitions of circadian constructs, definitions of BD constructs and reliance on associative rather than causal study designs, and robustness of the findings.

**A plethora of ‘circadian’ variables.** Many variables can plausibly be the focus of chronobiological research. The elasticity of the concept may threaten construct validity across several dimensions. First, due to the masking effects of light, direct measurement of circadian parameters is often problematic in humans and the laboratory procedures available to unmask the endogenous component of 24-h circadian rhythms are complex, and rarely used at scale with clinical samples. Moreover, given the need for synchronization across multiple levels of organization throughout the body (Figure 3), circadian rhythms do not manifest as a single parameter that can be readily measured experimentally [295]. Similarly, circadian clocks are open systems, and the functions of input pathways (e.g., light) provide additional variables relevant to BD (Figure 3). Finally, common terms such as ‘circadian dysregulation’ and ‘circadian disruption’, are imprecise and lack consensus biological meanings [296]. Circadian disruption has been operationalized in various ways often implying that a particular BD-circadian association relates to dynamics that are state-like, transient and reversible (e.g. phase alignment), but also trait-like, stable and enduring (e.g. chronotype) [2]. This wide range of referents for ‘circadian abnormality’ gives chronobiologists too many degrees of freedom, and a critical assessment of the literature must be alert to false positive inferences within and across studies.

**[FIGURE 3 HERE]**

**A plethora of BD-related constructs.** Within the categorical clinical diagnoses, BD has numerous recognized facets and subtypes, many of which appear in circadian rhythm studies. Alternative

schemes including dimensional, prodromal, or illness-spectrum phenotypes are also widely studied (Figure 4). However, relationships among these categorical and dimensional variables are typically undefined and comparisons across schemes are often problematic. Therefore, evidence for association between a circadian parameter and symptom of BD (e.g., manic symptoms) may not be directly comparable to associations between the same circadian parameter and a phenotype measured on other dimensions (e.g., developmental course of BD in high-risk youth). The variety of BD constructs has implications for assessing the literature and associations with circadian rhythms. For example, if a categorical diagnosis of BD is the phenotype of interest, then evidence related to the specificity of circadian association are of the utmost importance. By contrast, if we adopt a transdiagnostic and dimensional view of BD-related phenotypes, then specificity is less relevant. Depending on the assumptions of the research, circadian disruption has been offered as a means to explain BD in contradicting terms, defined either broadly (e.g., BD spectrum [297]), or narrowly (e.g., subtypes of mood disorders [177, 298]).

**[FIGURE 4 HERE]**

**Distinct meanings of ‘association’.** The majority of circadian studies in BD-related literature assess association between variables and therefore suffer from the adage “correlation does not imply causality”. At least three types of ‘association’ between circadian function and BD appear in the literature: biomarkers, endophenotypes and mechanisms. *Biomarkers* are best understood as sensitive, specific and measurable indicators of a genetic, molecular, or chemical abnormality that reveals some feature of the disorder (e.g., severity, subtypes, response to treatment). Biomarkers often have prognostic value but are not necessarily causally related to a phenomenon. *Endophenotypes* (intermediate phenotypes) are stable, quantifiable, trait markers of disease susceptibility. *Endophenotypes* are often dimensional and can be identified either fully or in attenuated form in unaffected relatives of people with the disorder indicating elevated genetic risk. *Mechanisms* consist of interacting elements or components whose activities and interactions are organized so as to be responsible for a phenomenon [299]. Putative mechanisms for BD are genes, molecules, cells, brain systems or physiological/behavioral functions subserving mood symptoms. Circadian parameters are

frequently described as *biomarkers of BD*, for example in relation to predicting lithium response [181]; *endophenotypes of BD*, for example as a marker of reward sensitivity [131, 242] and as part of the *mechanism for BD*, overlapping with genetic risk for the disorder [175, 176]. These concepts are rarely defined in explicit terms in circadian studies of BD. Given the distinct implications underlying each kind of association, there may be considerable uncertainty when interpreting a significant finding, especially in the absence of consensus understanding of the theoretical framework. For reasons that differ across methodological approaches, studies demonstrating causality are less common or otherwise limited. When causality is demonstrated, it is commonly in the context of a simplified experimental system such as an animal or cell-culture model that is deficient in one or more key aspects of validity. For these reasons, even well-designed demonstrations of causality may not apply to patients with BD. In human studies, the randomized clinical trial (RCT) is commonly accepted as providing causal evidence. However, in most cases RCTs cannot provide the neurobiological mechanistic detail to prove irrefutably that a circadian mechanism is involved unless particular care is taken to study these features simultaneously. Few human circadian studies of BD employ the RCT design in any form. The commonly used cross-sectional, observations with case-control designs typically cannot determine causality. For these reasons, human studies in BD frequently overstate the certainty to which circadian mechanisms are responsible for explaining a particular finding.

### 4.3 Principles for a future research agenda

**Unresolved scientific issues.** The review has identified a number of central questions that remain unanswered. A selection of salient questions spanning various levels of scientific inquiry is outlined below (Table 4). Future experimentation to address these within each domain and across domains is high priority.

**Table 4: Questions for future research**

Domain	Question
Genetics	What is the role of pleiotropy for clock genes involved in mood regulation

Domain	Question
	(i.e., compared to other functions, is the circadian function of a risk gene essential to its role in BD)?
Genetics	How do we reconcile only modest agreement between human genetic studies of BD with mutant clock gene models in animals?
Neuroanatomy	How does rhythm translate into mood regulation and what brain systems serve this function?
Neuroanatomy	Are brain rhythms <i>per se</i> important for mood regulation or is stable mood mostly dependent on one or more rhythmic output functions (e.g., dopamine)?
Neuroanatomy	In which brain structures are rhythms essential for euthymia?
Light	Do the effects of light on mood in humans involve a circadian mechanism?
Behavior	What rhythm parameters best predict diagnosis, mood state, illness course?
Behavior	To what extent do sleep/activity rhythms relate to rhythmic changes in mood, affect and reward?
Behavior	What are the effects of shift work, jet lag, light at night, timing of social interactions on first episode, relapse, therapeutic outcomes in patients with BD?
Behavior	How do activity/sleep rhythm parameters (amplitude, phase, variability) relate to more direct measures of clock function (core body temperature) in humans?
Therapeutics	Do circadian biomarkers or behavioral phenotypes provide clinically actionable information?
Therapeutics	Are drugs that target molecular clock mechanisms therapeutic in BD?

**Methodological gaps in the literature.** Compared to other areas of neuroscience research in BD, chronobiology has relatively little research using MRI, PET and other human brain imaging methods, likely due to logistical hurdles associated with performing time course studies with these methods. Brain imaging has the potential to fill an important gap at the junction of neuroanatomy and behavior

in BD patient populations and should be encouraged. Other novel methods are beginning to be used in psychiatric populations such as epigenetics, microbiome analyses, and metabolomics but have not yet made an impact on circadian rhythm research in BD.

**Conceptual advances.** To advance the field, we propose that future research should be conducted in a more systematic and coordinated manner, premised on attention to empirical gaps, methods and theory. At the methodological level, replication must be a priority. Future empirical studies should adopt the three core open science principles of pre-registration, full disclosure of positive and negative findings, and replication as foundations for incremental progress. The definitional and measurement issues considered here (Figures 4-5) might be useful aids to specifying unambiguous hypotheses. Consensus among researchers on which methods and instruments are best suited for widespread use (e.g., via a formal Delphi study) may improve comparison across studies by harmonizing outcome variables. Structural changes in the systems of research funding, publication and career advancement may be required to fully implement some of these principles.

At the level of theory, we propose that future studies consider the design within a broad framework. Since different associations between circadian function and BD require different kinds of assessment (Figure 5), we also propose that studies be explicit about the type of association they are investigating (categorical, dimensional, biomarker, endophenotype, mechanism) and when possible, design studies to test causal relationships.

Finally, we note that the literature on circadian associations with BD phenotypes is almost completely silent on the question of integration across the various levels of experimentation. This is remarkable given that, relevant scientific data for the association between circadian rhythms and BD ranges from the very small (e.g., gene expression) through mid-level (e.g., brain circuits), to the whole organism (e.g., locomotor activity) and beyond (e.g., population studies). Without synthesis across these levels, it is difficult to draw conclusions explaining how the circadian system is involved in BD. Future research should consider ways by which different study designs may be coordinated, adopt scalable

measures, and close the gaps in theoretical frameworks. Open data access, resource sharing and promoting research across disciplines may advance these goals.

Explanatory integration is a long-standing aim of the neurobehavioral sciences and there is growing interest in theoretical work to achieve this through ‘new mechanistic’ and dynamic systems approaches [299, 300]. In this context, it is noteworthy that the circadian system has been presented as an example of the new approach to mechanistic explanation in biology potentially providing the robust theoretical grounding that could inform the integrative synthesis of currently disparate findings [301, 302]. Beyond providing philosophical rigor, efforts towards a cohesive testable multi-level synthesis of circadian regulation of mood would generate new questions, methodological challenges and clinically relevant insights.

#### **4.4 Limitations of the review**

The review had a number of limitations. Firstly, as explicated above (Table 3, section 4.2), the quality of the conclusions here is dependent on the range and quality of the reviewed literature. Secondly, in the absence of a systematic step in the current review, it is possible that key studies were overlooked or under-emphasized, and our conclusions await replication using other literature integration methods. It is hoped that the present critique of terminology and methodology will inform future efforts to use the literature to address questions about the chronobiology of BD. As a whole, the field is often limited by poorly defined variables and the associated effects on theoretical implications. Finally, the evidence reviewed suggests an absence of specificity, and implies that studies using BD diagnosis as their primary criterion relative to other mood disorders may be insensitive to identifying some circadian rhythm associations.

#### **4.5 Conclusions**

Within its limitations, the present critical review identifies a range of divergent data, broadly consistent with circadian associations with numerous and variably defined BD phenotypes. The

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balance of evidence suggests (consistent with the trend away from binary diagnoses) that this association is not specific to BD and extends at least to other psychiatric vulnerabilities. Existing literature is, however, limited in range and methodological quality, and to date there has been little effort towards a rigorous theoretical synthesis. In sum, the present review provides optimism that a future research program addressing these limitations is warranted.

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### **Conflicts of Interest**

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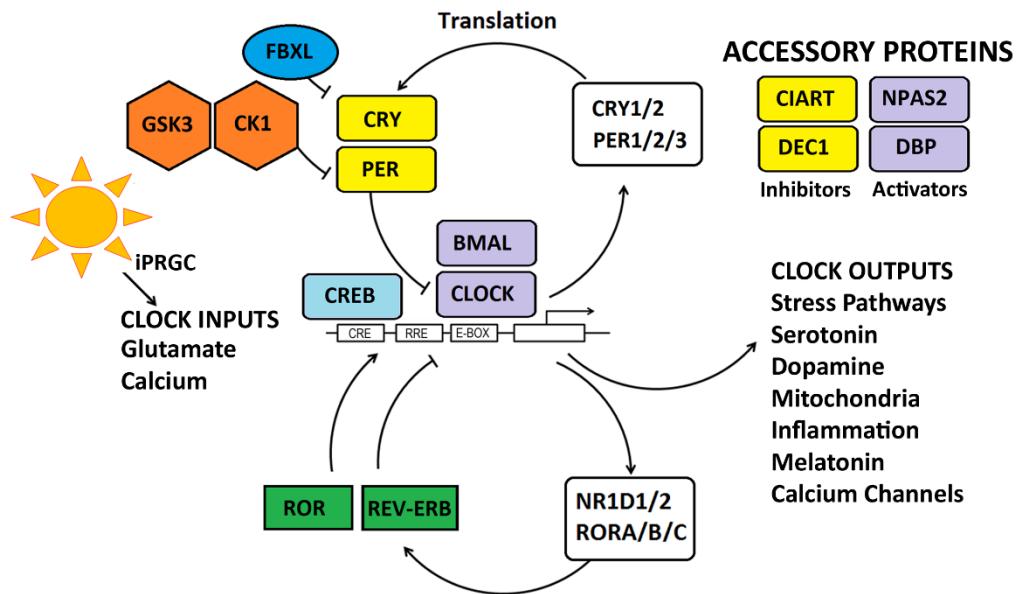
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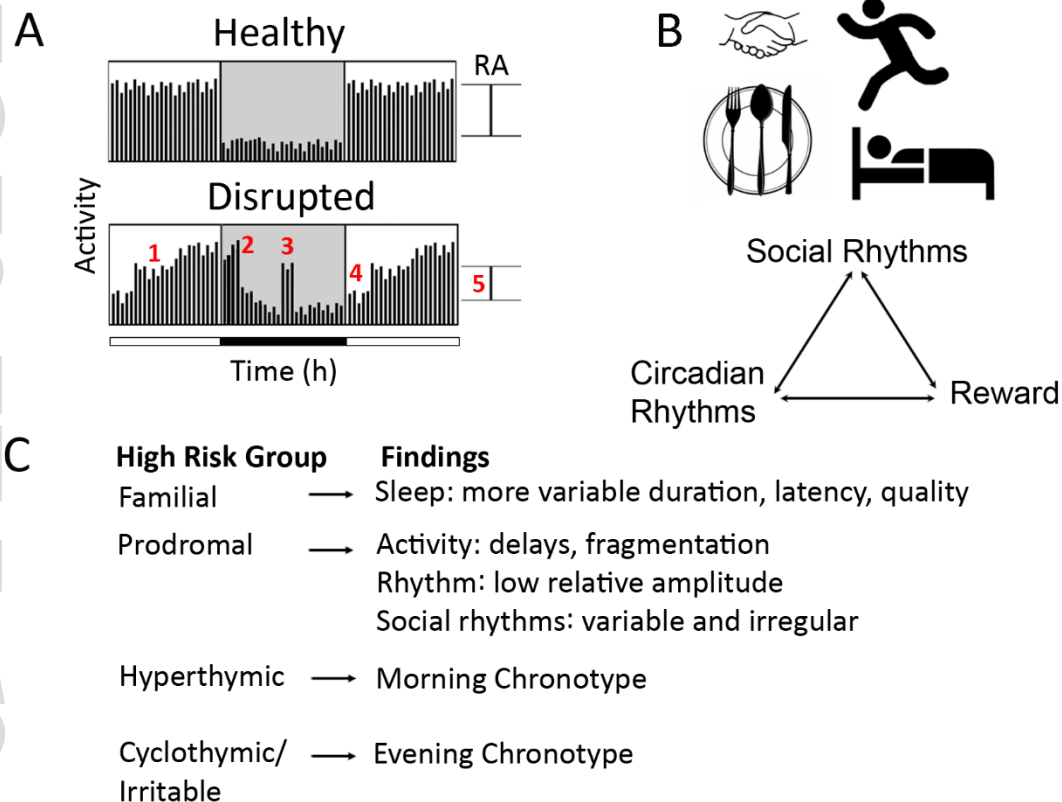
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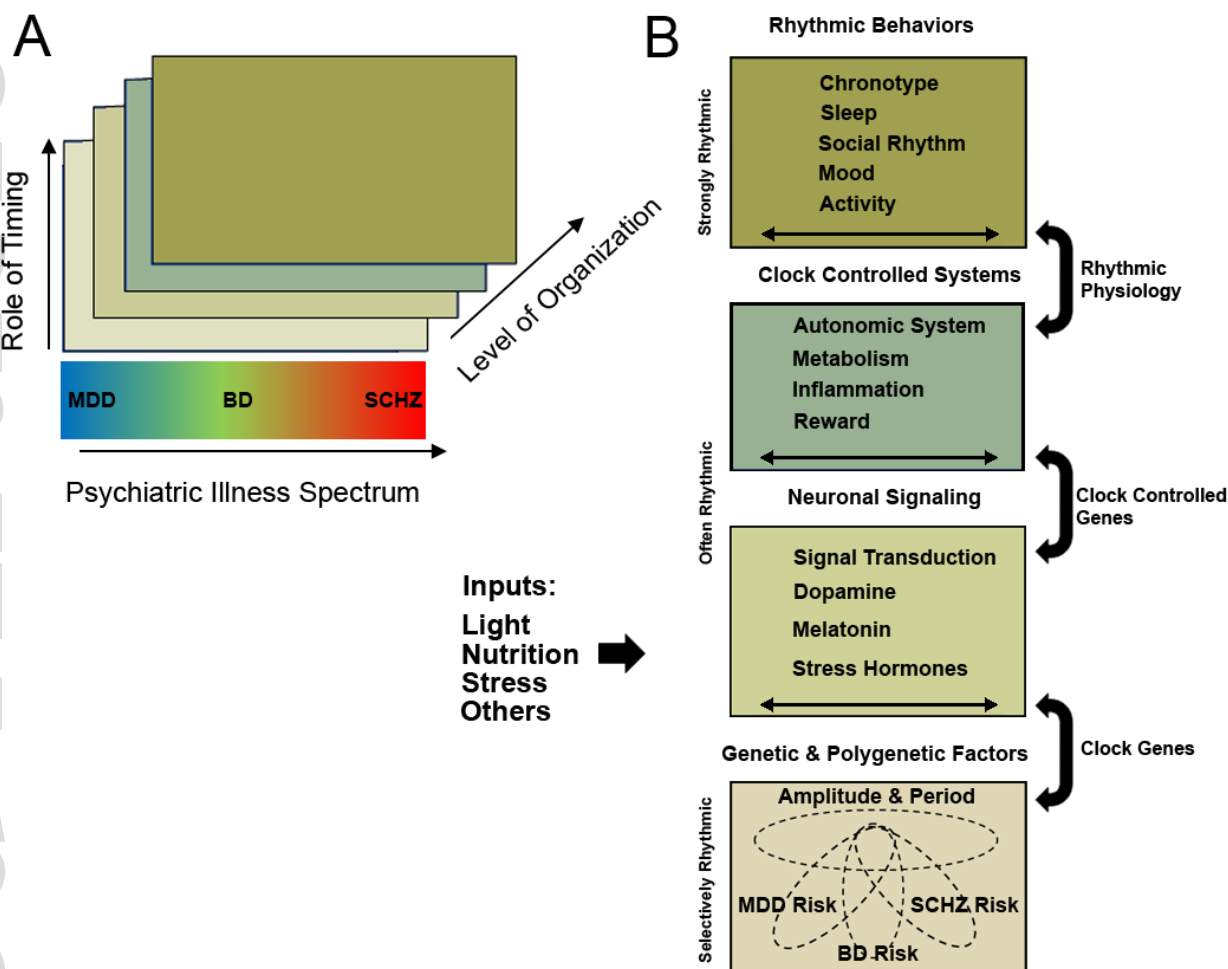
**Figure 1: The molecular clock is comprised of clock genes, organized in transcriptional/translational feedback loops.** Transcriptional activator proteins (purple), BMAL1 and CLOCK bind to DNA elements in promoters (E-Box) to stimulate transcription of *CRY1/2*, *PER1/2/3*, *NR1D1/2* and *RORA/B* genes that encode transcriptional repressors (yellow) or secondary loops (green) to regulate activity through protein and DNA interactions. These interactions yield oscillatory changes in gene expression and translation over ~24 h cycles causing cellular rhythms. Post-translational modification by protein kinases (glycogen synthase 3 kinases, GSK3, casein 1 kinases, CK1) or ubiquitin ligases (FBXL) adjust the rate of protein turnover. Light and environmental inputs to intrinsically photosensitive retinal ganglion cells (ipRGC) communicate with the clock through glutamate, pituitary adenylate-cyclase-activating polypeptide (PACAP) and intracellular calcium to shift circadian phase through actions on cAMP-response element binding protein (CREB). Accessory activators (NPAS2 and DBP) and inhibitors (CIART and DEC) play important roles in some cell types. The circadian clock affects the expression of clock-controlled genes that are rhythmically expressed, but do not play a role in the timekeeping mechanism. These rhythmic clock outputs are involved in physiological pathways that affect brain functions that require precise timing across the 24 h cycle.



**Figure 2. Actigraphy, social rhythm metrics and schematic summary of emerging findings from ongoing studies of cohorts at high risk for bipolar disorder.** A) A hypothetical actigraphy study of participants with healthy and disrupted activity patterns, demonstrating some of the commonly reported findings in BD including 1) reduced activity, 2) delayed sleep onset, 3) fragmented sleep, 4) delayed activity onset, 5) low relative amplitude (RA). Black vertical bars indicate epochs of activity. Background color indicates observations during the day (white) and night (gray). Horizontal line indicates environmental light conditions of light (white) and dark (black). B) Behaviors including social interactions, work, exercise, meals and sleep may serve both as time cues and outputs of circadian rhythms that can be quantified using social rhythm metrics (top). Social rhythms, brain reward mechanisms and circadian rhythms interact. Abnormal findings in one of these may reflect

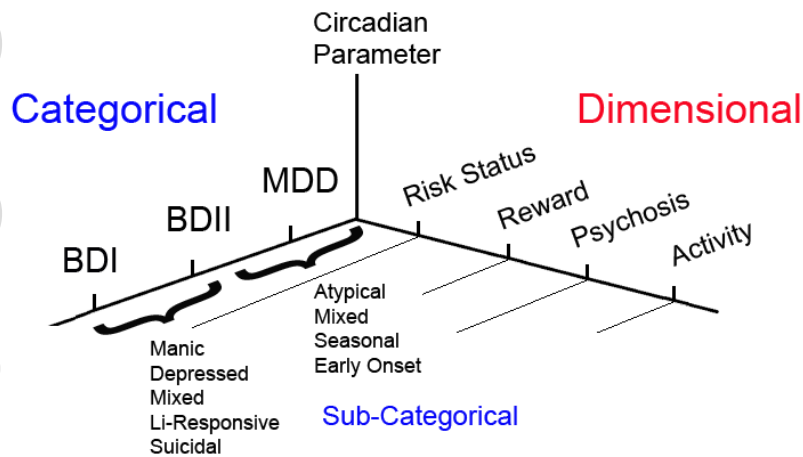
disruption in one or more of the others (bottom). C) Summary of major findings from studies of circadian rhythms in variously defined groups at high-risk for BD.

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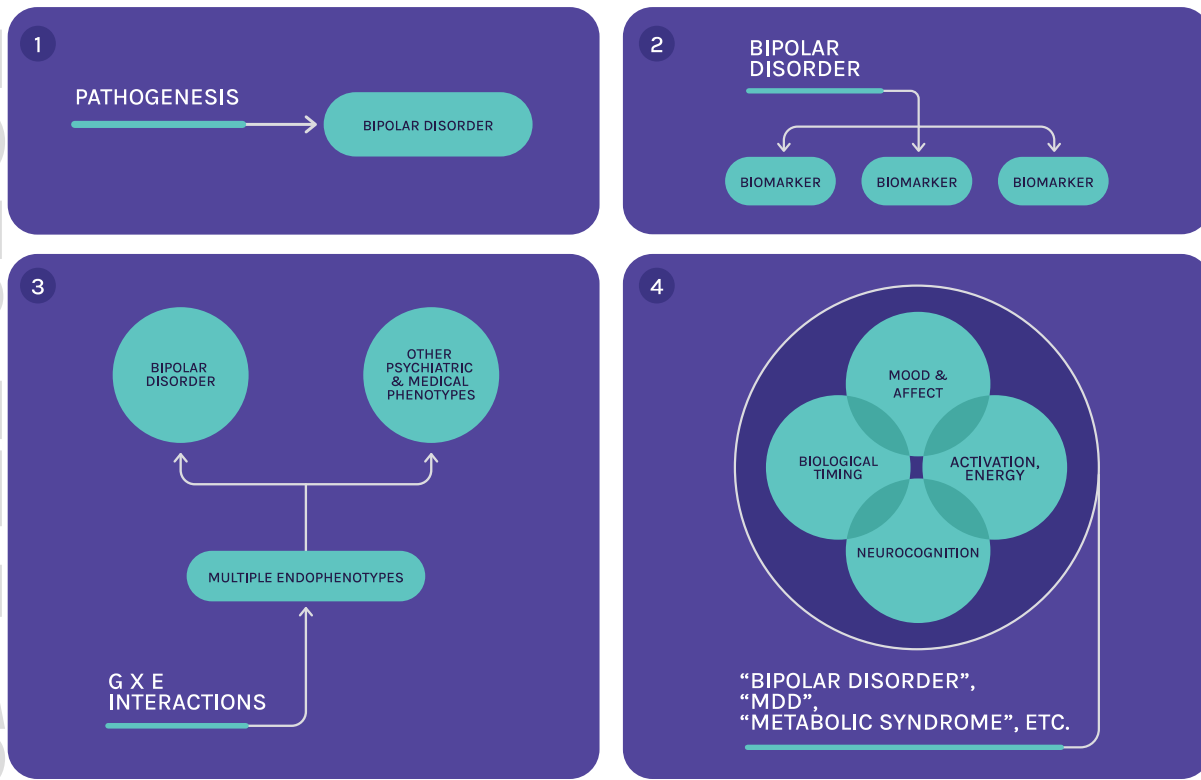


**Figure 3. Organizational scheme of circadian rhythm disruption in BD.** A) Circadian rhythms are manifest across multiple levels of biological and behavioral analysis, starting from genes and progressing upwards into rhythmic output pathways, systems and behaviors. At each level, there exists a spectrum for which disrupted circadian rhythms may cause a psychiatric illness including bipolar disorder (BD), but also major depressive disorder (MDD), schizophrenia (SCHZ) or features of personality and temperament (not shown). Simultaneously, there exists an independent dimension that defines the importance of circadian regulation for particular system. B) An expanded description of the scheme is shown with examples at each level. Colors are coded to correspond to levels in panel A. As the elements of rhythmic behaviors in BD are followed across lower levels of analysis, the set of rhythmic functions becomes more restricted: Circadian rhythms are important for all rhythmic behaviors, most physiological processes under many circumstances, but only a subset of BD and other

psychiatric risk genes. At each level, risk for psychiatric disorders exists across the spectrum to varying extents that are not well understood presently. Horizontal arrows indicate that the processes within a level cover a range of conditions within the spectrum of psychiatric disorders, encompassing but not necessarily specific for BD. Psychiatric disorders have discrete genetic factors, but also overlap with each other and with genetic components of the circadian clock. Environmental inputs affect the function of these systems typically at the level of outputs (affecting photoreceptors, nutrient sensors, etc.). Levels are reciprocally interconnected with activity at one level affecting others above and below.



**Figure 4: Dimensional, categorical and sub-categorical constructs used in BD.** Example categorical, sub-categorical and dimensional measures of BD and related mood disorders are shown. The number of categories allows for high degrees of freedom and increases the risk for false positive association (type 1 error). Dimensional constructs can in theory relate to categorical variables, but in practice are not well defined across schemes. The situation makes comparisons across the literature problematic, even when the same parameter of circadian rhythm is employed (e.g. chronotype, social rhythm metric, relative amplitude).



**Figure 5: Four approaches to conceptualizing circadian involvement in BD.** 1: Circadian function as causal explanation for emergence of disorder (specificity important, cause important); 2: Circadian function as biomarker (specificity and sensitivity important, cause irrelevant); 3: Circadian function as endophenotype (quantitative and dimensional, specificity not important, causality important, especially across developmental timeframes); 4: Circadian function as a component mechanism ('biological timing') in a complex system, the phenotype of which meets criteria for a variety of diagnoses including BD (specificity not applicable; causality is likely recursive and/or nonlinear).