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Using Chronobiological Phenotypes to Address Heterogeneity in Bipolar Disorder

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Abstract
Bipolar disorder (BD) is a neuropsychiatric mood disorder characterized by recurrent episodes of mania and depression in addition to disruptions in sleep, energy, appetite, and cognitive functions-rhythmic behaviors that typically change on daily cycles. BD symptoms can also be provoked by seasonal changes, sleep, and/or circadian disruption, indicating that chronobiological factors linked to the circadian clock may be a common feature in the disorder. Research indicates that BD exists on a clinical spectrum, with distinct subtypes often intersecting with other psychiatric disorders. This heterogeneity has been a major challenge to BD research and contributes to problems in diagnostic stability and treatment outcomes. To address this heterogeneity, we propose that chronobiologically related biomarkers could be useful in classifying BD into objectively measurable phenotypes to establish better diagnoses, inform treatments, and perhaps lead to better clinical outcomes. Presently, we review the biological basis of circadian time keeping in humans, discuss the links of BD to the circadian clock, and present recent studies that evaluated chronobiological measures as a basis for establishing BD phenotypes. We conclude that chronobiology may inform future research using other novel techniques such as genomics, cell biology, and advanced behavioral analyses to establish new and more biologically based BD phenotypes. © 2020 S. Karger AG, Basel

Introduction

Bipolar disorder (BD) is a common, severe, and debilitating mental illness that affects approximately 1–3% of the population [1, 2]. The negative impact associated with BD is immense. This chronic illness currently ranks as the sixth leading cause of disability worldwide [3] and is estimated to be the world's fourth largest cause of disability among young adults aged 15–44 years [4]. Among psychiatric disorders, BD has one of the highest suicide rates, with estimates that 10–20% of affected patients ultimately take their own lives [5]. Even though the vast majority of individuals suffering from affective episodes experience significant degrees of psy-

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chosocial impairment [6], many patients suffering from BD go untreated [1].

BD is defined primarily by recurrent manic and depressive episodes. Additional diagnostic criteria reveal underlying chronobiological disruptions in BD. BD is marked by fluctuations and disturbances in activity and energy, appetite, attention, subjective speeds of thought, and sleep – all processes that commonly show diurnal variation in healthy subjects. Additionally, some specifiers used to describe the illness, such as rapid cycling and seasonality, also suggest that rhythm disturbances are a core feature of the disorder [7]. Rhythm disruptions are a hallmark of BD [7, 8]. Variations in intrinsic circadian periods [9, 10], phase shifts [11–19], and less stable biological rhythms [20–25] have all been noted in association with the illness. Disturbances in lifestyle regularity [26–28], sleep disturbances [29–42], variations in melatonin secretion [17, 43], and disruptions in rhythmic locomotor activity [24, 25, 44, 45] have all been reported.

Among the challenges in studying and treating BD is the heterogeneity, defined as the variability in the clinical presentation, of the disorder. The illness is not fully characterized by existing diagnostic and classification systems, and many individuals with the same diagnosis show considerable differences in illness course and treatment response [46]. This heterogeneity in clinical presentation may reflect the presence of multiple, distinct pathophysiological mechanisms underlying the development and/or progression of BD [47]. While considerable progress has been made in understanding the biological mechanisms underlying BD, much remains to be known, and phenotypic heterogeneity has undoubtedly contributed to the challenges in identifying pathophysiological mechanisms associated with BD. One proposed method to address the issue of heterogeneity is to identify phenotypes, or observable traits and characteristics, for the illness [48]. A plausible phenotype should be supported by empirical evidence, be comprised of measurable characteristics, and be directly applicable to the disorder in question [48]. For BD, differences in the expression of chronobiological characteristics like circadian rhythm disturbances, sleep abnormalities, and seasonality among others may meet these criteria.

In this review we examine the heterogeneity of BD from a chronobiological perspective. We provide a background for the genetic and neurobiological foundations of the circadian clock system and evaluate evidence linking BD patients and chronobiological disturbances. Finally, the evidence supporting distinct chronobiological phenotypes in BD is reviewed, with discussion of the directions for future research in the field.

Structure and Function of the Circadian Timing System

Circadian rhythms play an essential role in life. They are self-sustained, ~24-h rhythms that are present in nearly every organism, including humans. The circadian timing system directly or indirectly influences the timing of nearly all rhythmic physiological activity in humans, including sleep and activity cycles as well as seasonal rhythms [49]. Additional physiological functions under the regulation of the circadian timing system include temperature regulation, feeding and metabolism, hormone secretion, and inflammation. In mammals, the suprachiasmatic nucleus of the hypothalamus functions as the master pacemaker [49]. However, many brain regions besides the suprachiasmatic nucleus contain circadian clocks, including areas that have been implicated in mood regulation and mood disorders, such as the frontal cortex, hippocampus, amygdala, and striatum [50, 51]. Recent estimates in nonhuman primate sampling from 64 tissues across the body indicates that >80% of the genome is rhythmically expressed in at least one tissue and that genes involved in critical cellular processes are typically rhythmic in the relevant tissue for that function [52]. Moreover, rhythms in the brain are widespread and show anatomically distinct profiles comprised of distinct ensembles of rhythmic genes in different brain regions [52]. Accordingly, behaviors and neurophysiological processes affected by mood disorders, such as cognitive function, reward processing, motivation, and mood regulation, are under the regulation of the circadian clock [50, 51].

At the core of the circadian timing system are endogenous molecular clocks comprised of transcriptional/translational feedback loops made up of circadian genes [53, 54] (Fig. 1). The positive feedback loop consists of heterodimeric transcriptional activator complexes (CLOCK/NPAS2-ARNTL) that bind to CACGTG E-box or related E-box-like sequences to regulate transcription of core clock genes (*PER1/2*, *CRY1/2*, *CIART*, *NR1D1/2*, and *DBP*) [55, 56]. The CLOCK/NPAS2-ARNTL complex regulates the expression of its own transcriptional repressors *PER1/2/3* and *CRY1/2* that gradually inhibit their own expression over ~24-h cycles to sustain a rhythmic circadian oscillator. Negative feedback is achieved upon accumulation of PER and CRY proteins in the cytoplasm, where they dimerize to form a PER-CRY repressor complex that translocate back to the nucleus upon phosphorylation by CSNK1D/E to negatively regulate their own transcription. CLOCK/NPAS2-ARNTL het-

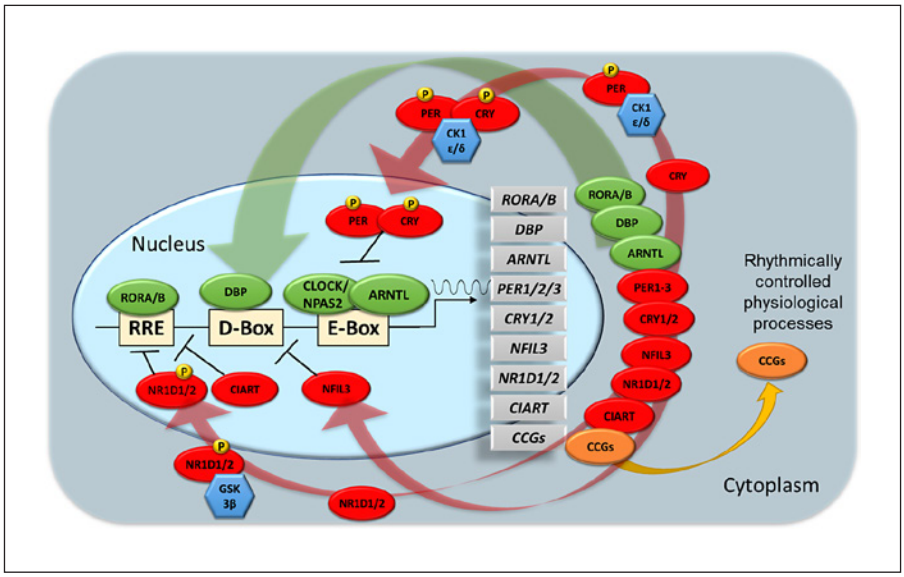

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Fig. 1. Transcriptional regulation of the human molecular clock. Transcriptional/translational feedback loops of molecular clocks are comprised of core circadian genes consisting of transcriptional activators (green) and repressors (red) responsible for the rhythmic expression of core clock genes and clock-controlled genes. Kinases (blue) are responsible for post-translation modification via phosphorylation (P) of key proteins within the cytoplasm required for translocation of proteins and protein complexes into the nucleus. ARNTL, aryl hydrocarbon receptor nuclear translocator-like; CCGs, clock-controlled genes; CIART, circadian-associated repressor of transcription; CK1ε/δ, casein kinase 1 epsilon/delta; CLOCK, clock circadian regulator; CRY1/2, cryptochrome circadian regulator 1/2; DBP, D-box-binding PAR BZIP transcription factor; GSK3β, glycogen synthase kinase 3 beta; NFIL3, nuclear factor, interleukin 3-regulated; NPAS2, neuronal PAS domain protein 2; NR1D1/2, nuclear receptor subfamily 1 group D member 1/2; PER1/2/3, period circadian regulator 1/2/3; RORA/B, RAR-related orphan receptor A/B; RRE, ROR response elements.

erodimers also activate the expression of transcription factors *NR1D1/2*, *CIART*, and *RORA/B*, which form a second feedback loop and activate and repress *ARNTL*, *NFIL3*, and *CRY1* transcription at ROR response elements containing a 5′-AGGTCA-3′ motif. D-box elements (5′-TTAYGTAA-3′) are activated and repressed by DBP and NFIL3, respectively, and regulate circadian transcriptional oscillations of *PER1/2/3*, *NR1D1/2*, and *RORA/B*. DBP and NFIL3 proteins are critical for determining the period length of the circadian oscillator [57] and have been implicated in phase resetting of the circadian clocks [58].

Virtually every cell in the body has an autonomous circadian clock [59, 60]. It is the expression of clock genes that results in the ability of cells to maintain time keeping rhythms in a cell-autonomous manner. In addition to governing molecular clock functions, clock genes also regulate the expression of clock-controlled output genes, i.e., genes that do not have a direct time keeping function but are involved in temporal regulation of tissue-specific, physiological processes in which timing plays an important role, including many implicated in mood regulation [61, 62]. The majority of rhythmically expressed genes in the body fall into this latter category of clock-controlled genes.

Effects of Circadian Misalignment on Health

One of the important functions of the circadian timing system is to coordinate physiological processes and behaviors across systems. It is believed that stable organization of biological rhythms is an indicator of good health and well-being [63]. Chronobiological disturbances are now widely recognized as a general health concern influencing a wide array of diseases [64–67], including psychiatric illnesses [68–73]. Circadian misalignment, or misalignment between the circadian pacemaker and behavioral or environmental cues, is associated with health problems [74] and with adverse physiological [75, 76] and mental sequelae [63, 76, 77].

Evidence has demonstrated that there is individual variability in the susceptibility towards temporal disorganization and the propensity to experience symptoms of

circadian misalignment [78–80]. In BD, this includes abnormalities in circadian phase [16, 18, 81–83], low-amplitude rhythms/rhythm fragmentation [83–86], and sleep disturbances [87, 88]. It may, therefore, be the case that a subset of BD patients suffer to a greater degree from chronobiological disturbances. If this is the case, chronobiological phenotyping may play a significant role in identifying BD groups that are most vulnerable or resistant to the adverse health effects of circadian misalignment and/or desynchronization.

Impact of Chronotype on BD

Circadian rhythm disorders represent the extreme ends of a broader spectrum of morning versus evening preferences that extends into the healthy population. This circadian phenotype is commonly called chronotype [89]. Chronotype, or the diurnal preference for daily activities, is often used to obtain a measure of interindividual variations in circadian rhythms and appears to be a relatively stable trait [90] likely associated with genetic markers [90]. People with different chronotypes can differ dramatically in responses to shift work [91], homeostatic sleep regulation [92–94], activity phase [95, 96], responses to sleep fragmentation [97, 98], total sleep deprivation [99, 100], and circadian phase [101, 102]. Chronotype is estimated to be about 50% heritable [103] and varies across populations and developmental stage [104–107]. Resting on a continuum, chronotype is likely to be polygenic in origin [90, 108].

It has been suggested that in BD patients, chronotype is a stable trait characteristic [16, 109]. BD patients consistently exhibit a significantly higher preference for eveningness compared to control subjects [16, 81, 110–113]. Chronotypic traits may impact the clinical presentation and course of bipolar illness. A greater degree of eveningness has been associated with rapid mood swings [82], higher recurrence rates [82, 114], and an earlier age of illness onset [82] and lithium response [115]. Chronotype has also been associated with physiological parameters [116, 117], including variations in body temperature [101, 116, 118], catecholamine secretion [116, 119], sleep patterns [116, 120–122], subjective activation and arousal [116, 119, 123], and circadian rhythms of hormone secretion [118] in healthy controls that may be important to the underlying pathophysiology of BD and/or phenotypic expression.

Physiological markers have been associated with BD. For example, an evening chronotype has been associated with insomnia [124], longer sleep latency [113], a higher percentage of total body fat and obesity [125, 126], higher homocysteine levels [127], increased atherogenic index of plasma [128], and a higher level of triglycerides [128]. Chronotype may also have clinical implications in BD. For example, an evening chronotype has been associated with higher response rates to the antidepressant response of total sleep deprivation plus light therapy [129].

Genome-Wide Associations of Clock Genes with Chronotype and BD

While genome-wide association studies (GWAS) have not identified core clock gene associations with BD; the sample size of the most recent BD GWAS [130] is still relatively underpowered compared to chronobiologically related GWAS studies with samples sizes surpassing 100,000 individuals [108, 131–135]. Variants in the core clock genes *ARNTL* [131, 136], *NPAS2* [131], *PER2* [108, 131, 132, 135, 136], *PER3* [135, 136], *CRY1* [131, 132], and *RORB* [131] have all shown significant GWAS association with chronotype. Other clock genes including *ARNTL* [56], *NFIL3* [137], and *CRY2* [136] demonstrated weaker associations with BD and chronotype that did not reach the threshold for genome-wide significance. Other GWAS chronotype-associated genes – *MEIS1/2* [131, 132] and *VIP* [131, 132, 136] – have previously well-established roles in regulating circadian rhythms [135, 136].

There is some indication that genetic markers of BD overlap with chronobiological phenotypes [138, 139]. For instance, a chronotype-associated locus lies in proximity to the clock gene *CIART* [56, 140] and overlaps with a newly reported risk locus (rs7544145) for BD [130]. Similarly, a variant in the clock gene *ARNTL* was among a small number of markers that differentiated polygenic risk for schizophrenia from BD [141]. Genetic variation in clock genes may not be limited to BD only. In addition to chronotype, differences in other chronobiological phenotypes also have a genetic basis [142]. Looking at related traits, *CRY1*, *PER2*, and *PER3* variants are associated with ease of getting up in the morning [132]. Markers on the genes *NFASC*, *SLC25A17*, and *MEIS* with roles in regulating circadian rhythms are associated with lower relative amplitude in locomotor activity [143] and relative amplitude of rest-activity cycles [143]. *RORB* and *MEIS1* variants are associated with insomnia [132–134, 144], and *MEIS1* variants are also related to sleep duration [145] and other sleep-related traits [133]. These data indicate that many chronotype-associated markers identified by

GWAS are not well functionally characterized, and there are likely to be numerous pathways and genes that influence rhythmic behaviors both within and beyond the core circadian clock. It is not yet clear to what degree the genes identified may demonstrate pleiotropic effects on other systems or what the impact of these identified markers are on chronobiological aspects of BD. For instance, *NR1D2* variants exhibit robust GWAS associations with intelligence [146–149] and cognitive ability [150–152], traits that have been previously linked to BD [153–157].

Cellular Models of Circadian Clocks in BD

In recent years, novel techniques have been developed to assess the cellular function of molecular clocks in healthy human subjects. These studies have begun to establish that there are significant interindividual differences in the functioning of molecular clocks [158, 159] and that this variation is associated with differences in behavior, chronotype, and physiology [158–160]. Brown et al. [158] characterized the expression of molecular clocks in fibroblasts of 19 individuals. While the average period of the sample was similar within the normal range previously reported for humans, the investigators noted a greater than expected variability in circadian phase. These investigators also found that period and phase of cellular clocks were associated with the chronotypes of human cell donors [159]. These findings were partially replicated by Hida et al. [160], who found a relationship between the period of molecular clocks and chronotype. While these observations have been made in the general population, similar chronobiological heterogeneity may exist in BD.

While GWAS are well suited to capture information from relatively large population cohorts, they typically cannot inform researchers about the functional consequences of a genetic variant as it relates to a time keeping function. Therefore, a complementary approach is to assess molecular clock functioning and chronobiological phenotypes in cells from BD patients. Since circadian clocks are cell-autonomous and present throughout the body, peripheral cell types like fibroblasts may be one useful model. These cells have the advantage of being relatively accessible and easy to grow. In one early study by Yang et al. [161] the expression of 12 clock genes was examined using PCR and protein analyses in fibroblast cultures in a time series over 72 h. Lower amplitude expression rhythms for *BMAL1* (*ARNTL*), *REV-ERBα* (*NR1D1*), and *DBP* as well as decreased phosphorylation of GSK3B were found in the BD compared to the control cells. Later studies again studied fibroblasts, but this time using a bioluminescent reporter gene (*PER2-luc*), which allowed for more frequent sampling over longer times. In this study, cells from BD patients were found to have a longer circadian period and abnormal amplitude response to treatment of the cells with lithium [162]. In follow-up studies the same authors again studied fibroblast cultures, but this time from cells obtained in the course of a prospective, multicenter, clinical trial of lithium monotherapy [115]. In lithium responder samples, cells had a shorter period compared to samples from non-responders. Moreover, there were other rhythm characteristics that differed between groups, with a linear relationship between period and phase and a period shortening effect in lithium responders, but not in cells from non-responders. These cellular models have provided some important functional context to genetic studies. However, since fibroblasts lack key features of neurons (e.g., neurotransmitters, electrical activity, synaptic connections), there may be additional BD-related chronobiological functions that are better examined in neuronal cells.

Sleep Abnormalities and BD

The two-factor theory of sleep predicts that circadian rhythms have a major impact on sleep behavior [163]. The American Academy of Sleep Medicine currently recognizes four intrinsic circadian rhythm sleep-wake disorders (CRSWDs) [164]. These include advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder, and non-24-h sleep-wake disorder, each disorder being marked by a particular characteristic. Advanced sleep phase disorder has been associated with shorter circadian acrophase and period (Fig. 2), while delayed sleep phase disorder has been associated with longer circadian acrophase and period. Irregular sleep-wake rhythm disorder is characterized by fragmented and pattern-lacking sleep-wake cycles. Non-24-h sleep-wake disorder presents with a progressive lengthening of circadian period.

Takaesu and colleagues [165–167] have conducted a series of studies examining the presence of CRSWD in BD. These investigators found that approximately one-third of bipolar patients met the criteria for a CRSWD [165, 166]. They further demonstrated that these comorbidities had clinical implications. BD patients with co-occurring CRSWD were associated with higher suicide rates [165], greater recurrence rates [166, 167], antide-

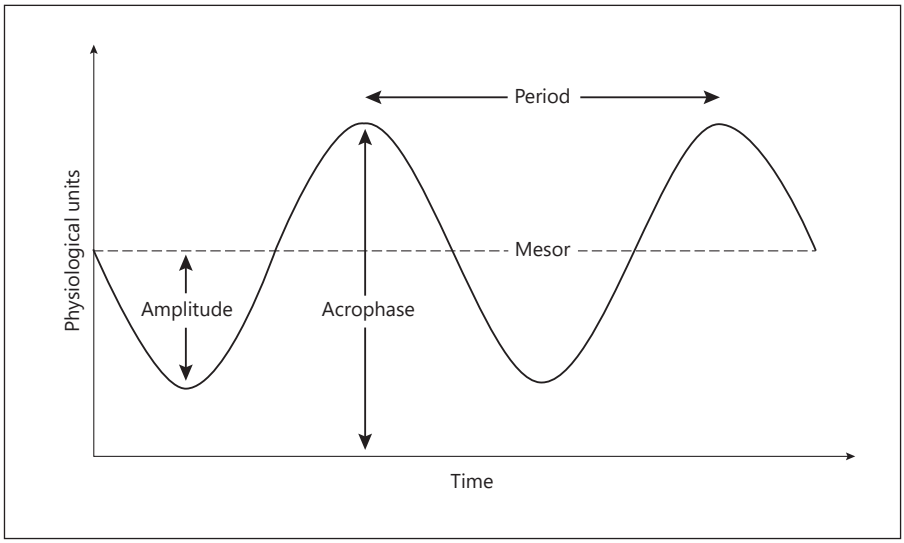

Fig. 2. Cosinor curve frequently used to represent circadian rhythms. In cosinor modeling, period is the duration of one cycle, amplitude is the peak value from a wave's mean, acrophase is a measure of the time of overall high values recurring in each cycle, and mesor is the rhythm-adjusted mean.

pressant-related manic switch [166], and higher rates of family history of psychiatric disorders [165].

Sleep characteristics may also prove to be important phenotypic signatures of BD and overlap with chronobiological mechanisms. Scott et al. [168] studied the relationship between sleep and BD in families. In this study, individuals with a family history of BD and subjects without a history of familial mood disorders were compared using actigraphy measures and Pittsburgh Sleep Quality Index scores. They found that the family history-positive group differed in mean nighttime sleep duration, variability in waking after sleep onset, sleep disturbances, and daytime dysfunction, indicating that sleep problems cosegregate with the genetic risk for BD in families. Studies also suggest that sleep phenotypes exist in BD. For example, short sleep duration has demonstrated association with more severe symptoms [42], while both short and long sleep duration have been associated with poor functioning and quality of life [42]. A worse course of illness [30, 169], increased symptom severity [30, 42, 169], and impairments in functioning and quality of life [30, 42, 169] have also been related to sleep disruption. Specific types of sleep disturbances may also be associated with specific mood states. Variability in sleep latency has been associated with depressive symptoms [169], and lower and more variable sleep efficiency has been associated with more lifetime depressive episodes [169]. Decreased sleep efficiency [169] and the duration of REM and slow-wave sleep [30] have also been associated with mania. Disturbances of sleep could potentially predispose a subset of BD patients towards disruptions in such circadian components as phase and acrophase, thus leading to a misalignment of circadian rhythms in BD.

Seasonal Rhythms and BD

Seasonality, including recurrent mood episodes and the level of functioning associated with seasonal changes, is another potential BD phenotype with chronobiological mechanisms. While seasonal rhythms occur over longer time intervals than the circadian rhythm (i.e., months versus hours), the suprachiasmatic nucleus and circadian clock genes are also critically involved in regulating these long cycles, in conjunction with melatonin and effects on thyroid hormones in the pars tuberalis of the anterior pituitary gland [170]. Therefore, circadian variation in BD patients may also be associated with seasonal mood changes [171]. A subpopulation of BD patients present with a seasonal pattern to their mood episodes [172–176]. For those with seasonal patterns, mania appears to peak in the early spring with a nadir in the late fall [172], mixed mania peaks in the late summer with a nadir in the late fall [172], and depression appears in the autumn to winter months [173].

Chronobiological Phenotypes and Clinical Features

The clinical characteristics of BD are heterogeneous, with differences in the course of illness, comorbidity of medical and psychiatric conditions, and treatment re-

sponses [177]. This variability is likely the result of biological and environmental variability across several etiological mechanisms [47]. Unfortunately, it is this heterogeneity that may have hindered discoveries of pathophysiological mechanisms associated with the illness. Better-defined BD phenotypes may unravel some of the diagnostic complexity and help to identify more coherent categorization schemes [48]. This in turn may yield better diagnostic approaches and improve treatment selection. Based on the work reviewed herein, we propose that variability in circadian and chronobiological measurements may be objective and quantifiable traits that could be used to more precisely organize BD patients into coherent phenotypes.

Humans show significant interindividual differences in a wide variety of chronobiological characteristics [90]. Individual differences in the free-running circadian period (tau) [178–180], circadian amplitude [102, 181], and circadian phase [101, 102, 179, 181] have all been reported. There is mounting evidence suggesting that chronobiological disturbances are not only associated with BD, but that specific clinical and physiological signatures point to circadian disruptions as potential chronobiological phenotypes in the illness. As with individuals intolerant to shift work [63], subsets of patients with BD may differ in susceptibility to the disruption of biological rhythms [182]. People who demonstrate an inability to adapt to shift work demonstrate alterations in sleep such as insomnia, short sleep duration, poor sleep quality, and mood alterations including irritability and mood lability [63, 183–188]. The question arises whether a similar mechanism may apply to BD and whether specific chronobiological phenotypes are present within the larger diagnostic category.

Pagani et al. [189] examined actigraphy-based phenotypes in 26 Costa Rican and Colombian pedigrees. The study included 136 euthymic BD individuals and 422 unaffected relatives. BD subjects expressed fragmented rhythms overall compared to unaffected controls (i.e., lower activity, longer sleep times, and low amplitude). Forty-nine activity-related phenotypes exhibited significant heritability, and 12 of these overlapped with heritability for BD. Using linkage analysis, the study identified a genome-wide significant locus on chromosome 12 for inter-daily stability of activity and suggestive linkage in the same region for the mean number of sleep bouts in the awake period and amplitude. Taken together, these studies indicate that a wide variety of rhythmic processes governing sleep and activity are altered in BD and that some of the factors underlying this variability may also overlap with the risk for BD.

Conclusion

In mammals, the circadian timing system keeps physiological rhythms synchronized with each other and the environment. Organism-wide coordination of rhythms influences multiple physiological systems, brain regions, and behaviors that are germane to both healthy mood regulation and mood disorders, including BD. Given the important and fundamental nature of the circadian clock, it is not surprising that rhythm disturbances are associated with detrimental mental health sequelae.

Humans show significant interindividual differences in a wide variety of chronobiological characteristics, suggesting that these traits lie on a continuum even in healthy subjects. As with many other human traits, this variability lends itself to potential dysfunction when located at extreme ends of the spectrum. It is now widely recognized that chronobiological disturbances predispose individuals experiencing them to health problems and disease states including psychiatric disorders. As in other complex trait disorders, individuals are not all prone to the development of adverse consequences related to chronobiological disruption. This may be particularly relevant in BD.

Rhythm disruptions are a hallmark of BD. While generally associated with the illness, chronobiological disturbances may be enriched in particular BD subgroups, suggesting they may be markers of certain illness chronobiological phenotypes, possibly with distinct etiological factors, illness course, and treatment response. Recent research has begun to support this notion. It is estimated that as many as one-third of bipolar patients may suffer from an independent CRSWD. These comorbid conditions may be related to a worse illness course. BD patients with significant chronobiological disturbances have been shown to have higher suicide rates, recurrence rates, and antidepressant-related manic switch rates. Another example is chronotype where a greater degree of eveningness has been associated with rapid mood swings, greater recurrence rates, and an earlier age of illness onset in the disorder, and less response to treatment with lithium.

The effects of chronobiology interacting with BD could arise in several different ways, none of which are mutually exclusive (Fig. 3). First, disruption of clock genes could be a primary factor that directly contributes to BD in some subjects. Next, inherited chronobiological disturbances could disturb rhythms in physiological processes that worsen BD through secondary effects on the illness (e.g., globally increased stress, decreased sleep). Finally, chronobiological disturbances could lead to unhealthy in-

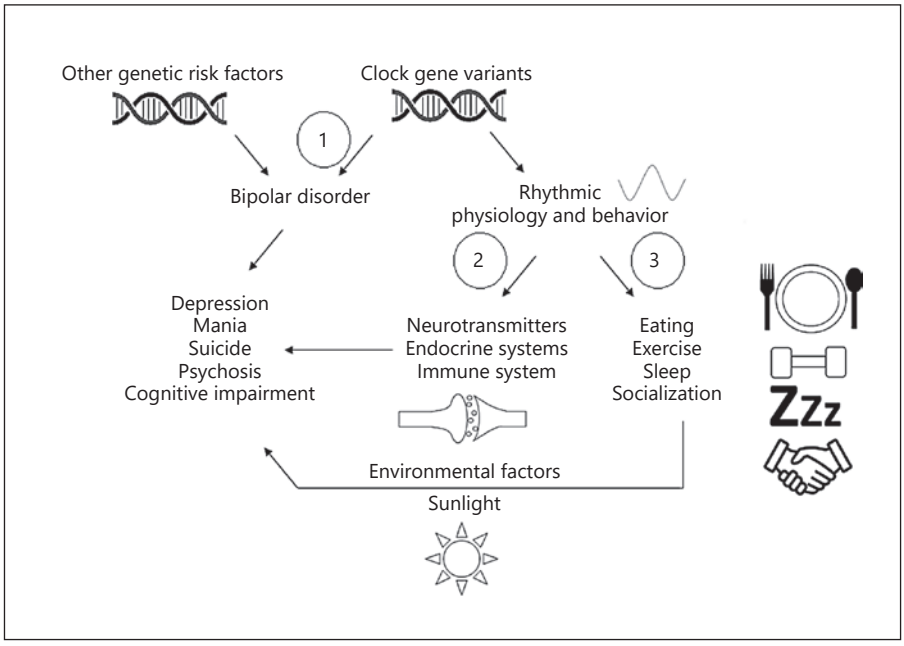

Fig. 3. Pathways by which clock gene variation could affect the illness progression of BD. (1) Clock gene variants may be causally related to BD and directly lead to the emergence of symptoms and mediate some aspects of the illness. (2) Clock genes may act in a pleiotropic manner to alter rhythms in biological processes like neurotransmission, endocrine systems, immune response, and others that affect relevant physiology and modulate the course BD. (3) Chronobiological factors also affect behaviors that affect interactions with environmental cofactors such as sunlight, diet, and socialization. These environmental factors interact with genetic and other biological substrates (including BD-specific risk alleles) to affect the course and progression of BD. It is unclear whether these environmental effects are mediators, modulators, or both. Of note, the three pathways outlined above are not mutually exclusive and could in principle run concurrently. BD, bipolar disorder.

teractions with environmental factors (e.g., light, diet, social contacts) that provoke symptoms or negatively affect illness course. Given the widespread involvement of the circadian clock in multiple organ systems and physiological processes, multiple mechanisms may be involved in each individual. It will be of interest in the future to determine whether BD patients who differ in circadian disruption differ in outcomes to chronobiologically based treatments such as melatonin or orexin receptor agonists, bright light therapy, partial sleep deprivation/phase advance, social rhythms therapy, and others.

While initial studies are promising, additional research is required to better define these putative chronobiological phenotypes in BD. New methods allow researchers to investigate the function of molecular clocks in living cells. The establishment of induced pluripotent stem cell-derived neurons may allow us to examine molecular rhythms in human neurons for the first time, perform transcriptome analysis over the circadian time course, and use integrative approaches for transcriptome-wide association studies to identify significant gene expression-trait associations. Using these approaches, it will be useful to identify the intersections of clock outputs with other biological risk factors for BD. Similarly, long-term sleep and activity measurements in human subjects are becoming more accessible and feasible in clinical populations. More refined analysis of larger cohorts with detailed clinical examination and collection of biomarkers will undoubtedly help to further resolve the target populations. It will be important to determine the clinical, course of illness, physiological/cellular/molecular mechanisms, and genetic differences that distinguish these groups. Finally, it also will be of considerable interest to correlate molecular and genetic factors with rhythmic behaviors in human subjects and to identify clinical features of BD that may differ as a function of chronobiological features. It is of vital importance to understand how the molecular gears of the ticking clock interlock with other biological and clinical factors underlying BD. These exciting new avenues for chronobiologically based research will continue to bring us closer to a bridge from the bench to the bedside.

Most importantly, research in this important area marks a step toward personalized medicine. Further research on chronobiological profiles in BD may improve diagnostic and classification criteria, inform research of the underlying pathophysiology of the disorder, and clarify the relationships with other clinical characteristics of the illness. Moreover, chronobiological phenotypes may help to identify subgroups of BD patients with distinct etiological factors and/or responses to treatment which may aid in the development of novel and specifically directed interventions [48, 190]. As activity and sleep rhythms are increasingly measured reliably and passively with electronic devices, future research could develop methods for monitoring the illness, allowing patients and clinicians to more effectively intervene when necessary.

We firmly believe that the identification and characterization of chronobiological phenotypes will represent a large step toward improving the characterization, management, and treatment of this debilitating disorder.

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Author Contributions

R. Gonzalez, S.D. Gonzalez, and M.J. McCarthy all contributed to the research and writing of the manuscript.

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