Chapter 19

Circadian biomarkers of bipolar disorder

Kathleen Ries Merikangas[1] and Ananya Swaminathan[1,2]
[1]*Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland, United States,* [2]*Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States*

19.1 Biomarkers of bipolar disorder

There is growing evidence from multiple sources that implicate disturbances of circadian rhythms as a key regulatory system underlying bipolar disorder (BD) (Dunster, Swendsen, & Merikangas, 2021). Studies that show differences in patterns of melatonin and reactivity to light, later chronotype and peak daily activity and sleep among people with BD, as well as regulation of these systems by treatments for BD, have spurred international efforts to gain insight into etiologic factors underlying circadian systems in BD. Here we provide an overview of evidence for the role of circadian regulatory systems and their biologic and behavioral correlates in people with BD. We examine biomarkers that are related to sleep, circadian rhythms, and motor activity that may characterize BD.

There is converging evidence regarding disturbances of circadian rhythms in BD (Logan & McClung, 2019; McCarthy, 2019). Increased manifestations of circadian disturbances in relatives, particularly offspring at risk suggest that these systems may be manifestations of familial or genetic biomarkers for BD (Carpenter et al., 2021). There is a growing body of research that seeks to identify potential genetic and regulatory factors that may underlie the behavioral manifestations of circadian rhythms in BD. Sleep is the most widely studied manifestation of circadian rhythms in BD as described below.

19.1.1 Sleep characteristics

Although much of the evidence regarding the associations between sleep patterns and BD was based on clinical interviews and subjective reports of patients, the use of objective measures has provided more reliable estimates

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of sleep patterns and disorders. Biomarkers derived from sleep electroencephalography (EEG), the gold standard for measurement of sleep architecture, have been demonstrated people with BD tend to thave decreased rapid eye movement (REM) latency and increased REM density during the manic phase, as well as a reduction in sleep efficiency and slow-wave sleep, a delay in sleep onset, and reduced time to first REM episode during the depressive phase (Dunster et al., 2021). During the depressive phase, patients with BD also have a later sleep midpoint compared to controls (Dunster et al., 2021).

BD may also be related to other sleep conditions such as delayed sleep-wake phase disorder and daytime sleepiness. In fact, delayed sleep-wake phase disorder has been found to be common in those with BD, specifically during the euthymic phase (Carpenter et al., 2021; Takaesu, 2018). Euthymic BD patients have also been found to suffer from insomnia, and BD patients as a whole tend to have a higher prevalence of daytime sleepiness compared to healthy controls (Takaesu, 2018; Walz et al., 2013).

19.1.1.1 Hormonal mechanisms

Because the sleep-wake cycle is regulated by the hormones melatonin and cortisol, there have been numerous studies of patterns of melatonin and cortisol levels and variability in people with BD. Several studies suggest that patients with BD have significantly lower levels of melatonin, the hormone responsible for initiating sleep, compared to controls (Dallaspezia & Benedetti, 2009). People with BD have been shown to produce melatonin later than those with Major Depressive Disorder (MDD) as well as less melatonin than those with MDD. This suggests that the melatonin release pattern could be used to differentiate between BD and MDD (Robillard et al., 2013). However, these findings suggest differences in these patterns between manic and depressive episodes. For example, some studies suggest that melatonin release occurs earlier in BD patients during the manic phase while other studies show that melatonin release is later than controls in BD patients during the depressive or euthymic phases (Dunster et al., 2021). Thus, there is a need for further research to study the extent to which melatonin patterns may reflect state vs trait manifestations of BD, as well as their specificity with respect to Mania, Depression or other mental disorders.

Several studies have also investigated changes in the cortisol release pattern in patients with BD. For example, patients with BD have been shown to have higher levels of nightime cortisol, the hormone responsible for initiating the process of waking up (Abreu & Bragança, 2015), whereas other studies have reported flatter diurnal slopes and larger cortisol fluctuations among people with BD compared to controls (Dunster et al., 2021). Morning cortisol levels have also been shown to be higher in people with BD compared to controls (Sigitova, Fišar, Hroudová, Cikánková, & Raboch, 2017).

19.1.1.2 Genetic factors

Rapid advances in deciphering the genetic systems implicated in the regulation of the circadian rhythms have generated substantial efforts to identify the potential role of genes involved in circadian rhythms. Identification of genes underlying circadian rhythms in basic science have led to greater understanding of the same genetic systems including the *CLOCK* gene, *BMAL1*, the *cryptochromes* genes, in humans. Several candidate gene studies have reported associations between some of the clock genes with BD such as *BMAL1* with sleep fragmentation, *CRY2* with sleep delay, and *PER3* with the evening chronotype and sleep delay (Abreu & Bragança, 2015). However, these reports require replication in larger samples.

There is a growing effort to identify sleep and circadian phenotypes in Genome-Wide Association Studies (GWAS) that are beginning to elucidate their genetic architecture for several sleep and rhythms phenotypes including insomnia, chronotype, sleep phase, and daytime sleepiness. Of particular interest is the genetic overlap between mood instability, MDD, and BD with sleep characteristics, including insomnia, and sleep duration (Lyall et al., 2018; Mullins et al., 2021; O'Connell et al., 2021), and one of the most compelling findings is genetic overlap between chronotype and mood symptoms and disorders (Jones et al., 2019).

19.1.2 Light sensitivity

Some studies have shown that patients with BD have greater sensitivity to light, suggesting that melatonin production is more easily suppressed in those with BD compared to controls (Dallaspezia & Benedetti, 2009). Some sources regard this sensitivity to light as a trait marker of BD, since it occurs during the manic, depressive, and euthymic phases of the disorder (Dunster et al., 2021). Interestingly, people with a family history of BD also appear to have a greater melatonin sensitivity to light compared to people without a family history of BD (Dallaspezia & Benedetti, 2009). More compelling evidence for differences in melatonin supression by light as a potential marker for BD has been provided by evidence that light supression of melatonin by lithium, the most efficacious treatment for BD (Dallaspezia & Benedetti, 2009). If confirmed, future studies should pursue the potential role of genetic factors such as the *PER3* gene that may be involved in melatonin suppression in response to light (Chellappa et al., 2012). Sensitivity to light may also explain findings of desynchronization of diurnal body temperature from heart rate in patients with BD compared to controls (Dunster et al., 2021).

19.2 Objectively measured sleep, activity, and circadian rhythms

The most widely used tool to track sleep in real life settings is actigraphy that has been used as an objective measure of sleep in mood disorders for

more than three decades (Scott et al., 2017). With the increasing recognition of dysregulation of motor activity in BD, many studies have also examined patterns of activity derived from actigraphy in people with BD compared to those of controls. Parameters extracted from actigraphy include the three domains of sleep, motor activity, and circadian rhythms as described below. The lack of independence of these three domains is now being examined systematically through the use of principal component analysis and machine learning techniques such as Joint and Individual Variance Explained (Di et al., 2019) to derive common factors that may influence these multiple systems.

19.2.1 Sleep

There have now been more than two dozen studies that have employed actigraphy as an objective measure of sleep in BD (see reviews: Abreu & Bragança, 2015; De Crescenzo, Economou, Sharpley, Gormez, & Quested, 2017; Dunster et al., 2021; Ritter, Marx, Bauer, Leopold, & Pfennig, 2011; Scott et al., 2017). These studies have consistently shown that people with BD have significantly increased sleep time, later sleep latency, more wake after sleep onset, and decreased sleep efficiency when compared to controls. There has also been some evidence of specificity with respect to differences in those with BD compared to those with MDD (Tazawa et al., 2019). However, similar patterns in actigraphy-based studies of patients with Schizophrenia raise questions regarding the specificity of sleep patterns as a marker for BD (Meyer et al., 2020).

19.2.2 Motor activity

There is now also compelling evidence that a central feature of mania is dysregulation of motor activity or related neural systems, and that energy is a more prominent subjective manifestation of mania than depressed mood (Carpenter et al., 2021; Johnson, Gershon, & Starov, 2015; Merikangas et al., 2019). Most objective research in BD has focused on sleep, and changes in motor activity have been relatively neglected in studies of BD (Scott et al., 2017). The most recent review of this work by a large team of experts in circadian rhythms and BD concluded that people with BD have lower 24-h activity compared to healthy controls (Murray et al., 2020). However, this may be state-related because several studies have shown that this difference may not persist outside of acute episodes of either mania or depression (De Crescenzo et al., 2017; Tazawa et al., 2019). Moreover, with respect to specificity, some studies have found no difference in patterns of motor activity among those with BD between episodes and those with MDD (Tazawa et al., 2019).

The patterns of motor activity and sleep have also been examined with respect to patterns of mood in studies using ecological momentary assessments (Merikangas et al., 2019). For example, analyses of the NIMH Family Study (see below) showed that increased activity was associated with greater changes in mood, energy, and sleep duration among those with Bipolar I Disorder (BP-I) compared to controls, suggesting desynchronization between circadian, motor, and emotional systems in BD (Merikangas et al., 2019).

This work has also shown that the peak activity of those with BD occurred later in the day compared to the activity of healthy controls and patients with MDD (Shou et al., 2017). This observation, in conjunction with hormone release and sleep patterns, suggests that people with BD have greater eveningness. The consistent findings of greater variability of and shift to later activity levels among those with BD warrants further study to investigate the directional associations between motor activity, sleep, and other homeostatic domains and their underlying determinants.

19.2.3 Circadian rhythms

The third set of variables derived from actigraphy concern circadian patterns of activity and sleep. Chronotype, a characteristic of a person's diurnal preference, or morningness−eveningness, is another potential biomarker for BD. Chronotype can be measured via subjective reports or objectively with actigraphy. Actigraphy-based studies of people with BD have consistently yielded evidence for a later chronotype in people with BD compared to those with either MDD or controls (Dunster et al., 2021; Melo, Abreu, Linhares Neto, de Bruin, & de Bruin, 2017; Shou et al., 2017). Patients with the two subtypes of BP-I and Bipolar II Disorder (BP-II) both appear to be more likely to have an evening chronotype, which in turn is associated with sleep delay and irregular bed-rise time (Abreu & Bragança, 2015). An evening chronotype is also linked to peak activity occurring later in the day, which is consistent with results regarding motor activity. Additionally, people with BD tend to have a later time of exposure to light, supporting the idea that patients with BD are more likely to have an evening chronotype (Dunster et al., 2021). There is some evidence that an evening chronotype has a stable association with BD over time (Carpenter et al., 2021). In fact, one study has suggested that an evening chronotype may be a trait marker, rather than a state marker, in those with BD; however, other studies do not support this conclusion (Takaesu, 2018).

Other actigraphy-derived features of circadian rhythms of daily activity including relative amplitude, interdaily stability, and intradaily variability have been shown to characterize people with BD across stages of the illness (Geoffroy et al., 2015; Gonzalez et al., 2018) or in the euthymic state (Krane-Gartiser et al., 2017). However, a more recent review (Meyer et al., 2020) did not demonstrate significant differences between BD and controls

in the relative amplitude of activity, interdaily stability, intradaily variability, or acrophase domains. These inconsistent findings can be attributable to the relatively small sample sizes, medication use, clinical state, and variation in the study methodology (De Crescenzo et al., 2017).

19.3 Endophenotypes for bipolar disorder

One of the most powerful approaches to determine whether the differences in biomarkers among people with BD may be disease rather than state markers is to examine whether the biomarkers also characterize the relatives of people with BD. The goal is to identify endophenotypes that may be closer reflections of genetic and biologic risk factors than clinical and behavioral phenotypes. An endophenotype is defined as a trait marker that: (1) discriminates between cases and controls; (2) discriminates between unaffected relatives of cases versus controls; (3) reflects traits rather than state markers of diseases; and (4) demonstrates familial aggregation (Gottesman & Gould, 2003).

Although this approach has been widely adopted in the schizophrenia field (Braff, Freedman, Schork, & Gottesman, 2007), there is now growing effort to identify endophenotypes for mood disorders (Guglielmo, Miskowiak, & Hasler, 2021). Findings from these studies demonstrate a range of potential endophenotypes in the domains of neurocognitive function, sleep, motor activity, temperament, and neuroimaging measures that discriminate between diagnostic subgroups and are significantly heritable. For example, actigraphy has been one of a series of potential endophenotypes in large extended pedigrees of people with BD (Pagani et al., 2016). Vreeker et al. (2019) further examined other measures including neuroimaging, cognitive, and temperamental factors as correlates of actigraphy parameters. There are also several other studies that have investigated sleep patterns in youth with BD (Harvey, Mullin, & Hinshaw, 2006) or among offspring of individuals with BD (Sebela, Novak, Kemlink, & Goetz, 2017). The section below illustrates our use of family study data to test circadian endophenotypes for BD.

The NIMH Family Study of affective spectrum disorder was designed to study the core components of mood disorders, as well as related psychiatric and physical endophenotypes and functional processes (Merikangas et al., 2014). Evaluation of the patterns of intergenerational transmission of mood disorders and related phenotypes are an important way to identify potential biomarkers or early manifestations of BD. The study includes 610 probands (200 with BD (128 BP-I; 72 BP-II), 193 MDD, 60 anxiety without mood, 150 controls) and 1157 of their relatives have completed the study, including 339 offspring under age 30. We conducted heritability (proportion of variance attributable to shared within vs between family correlations) and coheritability analyses (cross-disorder/trait/disorder associations, indicating common familial heritability) using SOLAR (Blangero & Almasy, 1997).

TABLE 19.1 Heritability and coheritability of circadian phenotypes among probands with Bipolar I Disorder and their relatives in the NIMH Family Study.

Condition	Heritability	ERV mania/BP-I
Chronotype	0.29**	0.72**
Delayed sleep Dx	0.55**	0.18
Insomnia Dx	0.25	0.22
Sleep midpoint	0.45*	0.61**
Sleepiness: Epworth scale	0.29**	0.25*

Endophenotype Ranking Value.
*$p < .05$.
**$p < .01$.

These estimates are used to derive an endophenotype ranking value (ERV) to identify traits with greatest common familial diatheses that can be used to rank putative endophenotypes of BD (Glahn et al., 2012).

In Table 19.1, we show estimates of the familial heritability for sleep and circadian phenotypes and BP-I disorder. Not shown here, the BP-I subtype is highly heritable ($h^2 = 0.89$, $P < .001$). The sleep phenotypes are moderately heritable with delayed sleep disorder ($h^2 = 0.55$, $P < .001$) and an h^2 of 0.45 ($P < .001$) for sleep midpoint, an objective index of chronotype. The second column shows the extent to which there is familial overlap between BP-I with the sleep phenotypes using the ERV (Glahn et al., 2012). There was substantial shared heritability between BP-I with questionnaire-based chronotype ($h = 0.72$) as well as with objective index of chronotype of sleep midpoint ($h^2 = 0.61$). We further found that the shared heritability differed significantly for BP-I compared to the other mood disorder subtypes of BP-II and MDD thereby demonstrating the heterogeneity of the BD spectrum.

These findings confirm that both objectively and subjectively assessed chronotypes have genetic factors in common with BP-I, suggesting that they may meet the criteria for an endophenotype for BD. More broadly, this work demonstrates the utility of the family study design to gain insight into clinical phenotypes to provide insight into both the genetic and environmental factors underlying BD.

19.4 Summary, challenges, and opportunities for future research

This chapter summarizes the aggregate evidence regarding circadian rhythms dysregulation as a biomarker for BD. The most compelling support is

provided by manifestations of sleep disturbances, greater sensitivity to light, and dysregulation of activity among offspring of parents with BD. Advances in unraveling the genetic architecture of the circadian system and sleep in humans will enhance our ability to identify genetic systems underlying relevant domains as well as environmental factors, particularly light, that may influence the reactivity in people with BD.

There are numerous methodologic challenges that complicate interpretation of the aggregate evidence on sleep and circadian rhythms in BD. These include: the cross-sectional nature of much of this work; generally small sample sizes; variability in study methodology; the heterogeneity of samples of BD; difficulty disentangling state versus trait influences; the impact of medications that may modify expression of circadian rhythms and gene expression studies; and the lack of adequate control for other potential confounders of these associations such as smoking, alcohol and drug use, comorbid medical conditions. Perhaps the most important challenge is our lack of information on the specificity of findings with respect to BD, Mania, or Depression, as well as with respect to other disorders such as psychosis, attention deficit disorder, or borderline personality disorder. This is due to the inclusion of unaffected controls in most studies rather than extending the work to include different clinical subgroups that could inform the specificity of the associations.

Future studies will require larger samples to distinguish subgroup effects and longitudinal prospective designs in order to examine the developmental manifestations as well as the stability of these findings across the lifespan. The evidence regarding patterns and disruptions of motor activity, chronotype, and related biological systems, rather than mood changes as the central feature of BD, provides new opportunities for translational cross-species studies of the circuitry and environmental and genetic influences on its regulation and interactions with other systems. This work is likely to yield greater insight into the biomarkers and environmental influences on BD that can be translated into evidence-based prevention and interventions.

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