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An actigraphy study investigating sleep in bipolar I patients, unaffected siblings and controls

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ABSTRACT

Objectives: Disturbances in sleep and waking patterns are highly prevalent during mood episodes in bipolar disorder. The question remains whether these disturbances persist during phases of euthymia and whether they are heritable traits of bipolar disorder. The current study investigates objective sleep measures in a large sample of bipolar I patients, non-affected siblings and controls.

Methods: A total of 107 bipolar disorder I patients, 74 non-affected siblings, and 80 controls were included. Sleep was measured with actigraphy over the course of 14 days. Seven sleep parameters were analyzed for group differences and their relationship with age at onset, number of episodes and psychotic symptoms using linear mixed model analysis to account for family dependencies.

Results: Patients had a longer sleep duration and later time of sleep offset compared to the non-affected siblings but these differences were entirely attributable to differences in mood symptoms. We found no difference between patients and controls or siblings and controls when the analyses were restricted to euthymic patients. None of the bipolar illness characteristics were associated with sleep.

Limitations: Medication use was not taken into account which may have influenced our findings and controls were younger compared to non-affected siblings.

Conclusions: In the largest study to date, our findings suggest that recovered bipolar I patients and their siblings do not experience clinically significant sleep disturbances. Sleep disturbances are primarily a reflection of current mood state, but are unrelated to the course of the disorder.

1. Introduction

Bipolar disorder is a chronic psychiatric disorder characterized by severe fluctuations in mood, which affects 1–2% of the general population (Belmaker, 2004). According to the DSM-V criteria, one prominent manifestation of a mood episode is a shift in sleep-wake behavior (American Psychiatric Association, 2013). The majority of patients experience insomnia or hypersomnia during depression and a reduced need for sleep during mania (Harvey, 2008). These disturbances are thought to be a hallmark of a current mood episode, and often precede mood episodes, suggesting utility as a marker of prodromal symptoms (Jackson et al., 2003).

Studies focusing on bipolar patients have tried to delineate whether these sleep disturbances can be considered as more than a state marker of the disorder and represent a general deregulation of the endogenous circadian cycle independent from current episodes. In accordance with

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that idea, phase advances, phase delays and general phase instabilities have been reported for several measures of rhythmicity, such as body temperature, nocturnal cortisol levels and peak melatonin time in euthymic bipolar patients (Milhiet et al., 2011; Nurnberger et al., 2000). Sleep (the most evident behavioral reflection of circadian rhythms) has also been reported to be disturbed during non-clinical phases of the disorder. According to Harvey et al. (2005), 70% of euthymic patients reported clinically significant sleep problems, with 55% of patients also meeting the criteria for insomnia. Several other studies using self-report measures identified worse sleep quality and more disturbed sleep-timing preferences in non-clinical bipolar patients compared to controls (Cretu et al., 2016; Rocha et al., 2013; Seleem et al., 2015). Actigraphy has proven to be an indispensable tool in the objective assessment of sleep-wake parameters (Sadeh et al., 1995). Actiwatches are wrist-worn devices that continuously record movement and allow for measurements in a natural environment over several weeks. Validation showed better performance compared to observational measurements, sleep logs and diaries (Ancoli-Israel et al., 2003). When assessed in a bipolar sample, actigraphy showed high correlations with polysomnography and high to moderate correlations with subjective measures of sleep (Boudebesse et al., 2014). Nevertheless, studies using actigraphy in the analysis of sleep in bipolar disorder have come up with conflicting results. While some studies found differences between bipolar patients and controls on several sleep parameters (e.g. sleep duration, sleep onset latency, sleep efficiency) (Geoffroy et al., 2014; Harvey et al., 2005; Millar et al., 2004; Salvatore et al., 2008), other studies failed to replicate these findings (Jones et al., 2005; Kaplan et al., 2012; St-Amand et al., 2013). These contradictory results can potentially be explained by differences in methodology. Measurement periods varied between 2 and 54 nights and different diagnostic criteria may have resulted in heterogeneous patient samples. Moreover, sample sizes were generally small (< 36 cases and controls), raising the possibility that some studies were underpowered. Recently, two meta-analyses concluded that bipolar patients differed from controls on measures of sleep duration, sleep onset latency and wake after sleep onset (Geoffroy et al., 2015a; Ng et al., 2014). Sleep efficiency of bipolar patients was significantly lower in only one of the two meta-analyses. According to the authors, the number of actigraphy studies in bipolar disorder is limited and lags behind similar research in depression and ADHD. Furthermore, Geoffroy et al. pointed to heterogeneity in methodologies and found that age matching, level of depressive symptoms and actigraphy device potentially influence the actigraphy analyses and should be taken into account in future research (Geoffroy et al., 2015a, 2015b). Moreover, associations between objective sleep parameters and bipolar illness characteristics have so far not been studied. If sleep disturbances indeed reflect a continuous aberration of the circadian rhythm, it is conceivable that these disturbances correlate with an unfavorable course of the disorder.

Although the presence of sleep disturbances in bipolar patients has gained increasing attention, the question whether disturbances in sleep patterns can be considered as a heritable trait of bipolar disorder, has scarcely been investigated. As of yet, only two studies objectively studied the difference in sleep-wake behavior between bipolar patients and their relatives. Jones et al. (2006) studied children of bipolar patients and concluded that sleep onset latency and sleep fragmentation were lower in children of bipolar parents compared to control children. However, when affected bipolar offspring was excluded the effects were no longer significant. Pagani et al. (2016) analyzed 26 pedigrees ascertained for bipolar I disorder and showed that bipolar patients slept longer and woke up later compared to their non-affected relatives. The authors also provided evidence that a number of sleep measures are heritable. Extending this pedigree study by also including independent control subjects gives the opportunity to study the sleep-wake pattern in individuals who are genetically susceptible for the disorder, but lack the direct illness and its sequelae such as medication use. If first-degree relatives indeed show disturbed sleep patterns similar to probands, it would support the hypothesis that the sleep-wake pattern is a trait of bipolar disorder.

The current study aims at extending previous research in a large, homogenous sample of bipolar I patients using an elaborate collection of objective measures of sleeping behavior. First, the question will be addressed whether euthymic bipolar patients show differences in sleep pattern compared to controls and whether the non-affected siblings display similar patterns of sleeping behavior. Sleep duration, timing of sleep onset, timing of sleep offset, sleep onset latency, sleep efficiency, wake after sleep onset (WASO) and sleep inertia will be measured objectively using actigraphy. Subsequently, the association with current mood symptom level and life-time illness characteristics (i.e. age at onset, number of mood episodes, presence of psychotic symptoms and history of suicidal behavior) will be analyzed.

2. Methods

2.1. Sample

The current study is a follow up of the Dutch Bipolar Cohort (DBC) study, which is a collaboration between the University Medical Center Utrecht (UMCU), various health care institutes in the Netherlands and the University of California Los Angeles (UCLA). In short, the DBC study is designed to provide a deep-phenotype characterization of bipolar I patients and their first-degree relatives. The cohort included 1700 bipolar I patients, 586 relatives and 265 controls. After completion of the DBC protocol, a subgroup of patients, siblings and controls were re-approached to participate in the actigraphy protocol. Both the DBC study and the current study were approved by the medical ethical committee of the UMCU and were in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants prior to participation.

All participants had a minimum age of 18, at least three grandparents of Dutch descent. Exclusion criteria for all participants were self-reported major somatic illness (e.g. sleep apnea) and pregnancy. Inclusion criteria for patients was a bipolar I diagnosis, verified using the Structural Clinical Interview for DSM-IV (SCID-I) (First et al., 1997) and no current admission for their bipolar illness. None of the patients reported being in a current mood episode. However, 17 patients scored above the IDS-SR threshold for mild depressive symptoms. Additionally, 4 patients had an ASRM score indicative of a manic or hypomanic state. Siblings and control subjects with a diagnosis of bipolar disorder or other psychotic disorders were excluded, as were control subjects who had a first or second degree relative with such diagnoses. Both siblings and controls were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998). In total, 466 eligible candidates were approached for participation via telephone, post or e-mail. 106 subjects did not respond to our invitation, 57 subjects refused to participate and 17 subjects did not show up for their appointment. In 5 participants with an appointment the Actiwatch never started recording and in 5 participants the data showed consecutive nights in which the minimum activity never reached 0, indicative of measurement errors. These 10 participants were excluded from further analyses. After excluding participants who did not meet the inclusion criteria (sleep apnea n=3, other somatic illness n=1, non-compliance to the protocol due to a mood episode n=3, sibling not meeting diagnostic criteria n=7, controls not meeting diagnostic criteria n=1) the sample consisted of 107 patients, 74 siblings and 80 controls.

2.2. Actigraphy recordings and sleep logs

Sleep-wake measurements were recorded with the Actiwatch 2 (Philips Respironics Inc, Murrysville, PA, USA). The Actiwatch has a solid state piezo-electric accelerometer and a lithium rechargeable