



## Research paper

# Performance of the biological rhythms interview for assessment in neuropsychiatry: An item response theory and actigraphy analysis



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## ABSTRACT

**Background:** Biological rhythm disturbances are widely associated with the pathophysiology of mood disorders. The Biological Rhythms Interview for Assessment in Neuropsychiatry (BRIAN) is a self-report that indexes rhythm disturbance in sleep, activity, social and eating patterns. The aim of this study was to perform an Item Response Theory (IRT) analysis of the BRIAN and investigate its associations with objective sleep and rhythm disturbance measures.

**Methods:** 103 subjects (31 bipolar, 32 major depression and 40 healthy volunteers) wore an actiwatch for fifteen days, and completed a first morning urine sample and the BRIAN on day 15. IRT analysis assessed individual BRIAN items and their relationship to total score. Individual actiwatch records were processed to produce a sequence of transitions between rest/activity, and a likelihood of transitioning between states was calculated to investigate sleep-wake dynamics. Cosinor analysis produced daily activity rhythms (DARs). Spearman correlations were used to assess the association between sleep/DAR variables and the BRIAN.

**Results:** IRT analyses showed that 11 of 18 BRIAN items displayed a high level of discrimination between item options across a range of BRIAN total scores. Total BRIAN score correlated with wake after sleep onset, total activity count during sleep, and urinary 6-sulphatoxymelatonin. BRIAN Activity domain correlated with the daytime transition probability from rest to activity.

**Limitations:** The sample size may have been underpowered for the graded-response model employed in IRT. The study lacked an objective comparison for BRIAN eating and social domain.

**Conclusion:** The present study reveals the BRIAN displays promising external validity compared to objective parameters of circadian rhythmicity.

## 1. Introduction

Sleep and biological rhythm disturbances have been widely associated with the pathophysiology of mood disorders (Boivin et al., 1997; Boland and Alloy, 2013; Buysse et al., 1997; Cretu et al., 2016; Leboyer and Kupfer, 2010; Soria et al., 2010). An example of such is the circadian disturbance characterized by insomnia in bipolar disorder (BD)

and major depressive disorder (MDD), which is considered a marker of both episode onset and the acute phase of mania and depression (Konno, 2013; Mendlewicz, 2009). Other circadian rhythms known to be strongly implicated in mood disorders include hormonal rhythms, temperature, eating patterns, social rhythm patterns, and day-to-day physical activity. Notably, accumulating evidence shows that residual symptoms of BD and MDD often persist into remission, causing further

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social, occupational and cognitive impairment (Boland and Alloy, 2013; Enns et al., 2005; Giglio et al., 2010; Nierenberg et al., 2010), all contributing to an increased risk of relapse (Judd et al., 2008). Furthermore, social rhythm irregularities are implicated in the onset of affective episodes in both BD and MDD (Shen et al., 2008; Wade and Kendler, 2000; Vilhjalmsson, 1993). A comprehensive evaluation of rhythmic activities such as sleep/wake, eating, social and functional activity in clinical practice is essential in order to manage affective disorders (Pinho et al., 2016), and, in light of this evidence, there is a need for quick and accurate diagnostic assessment of biological rhythm disruption in individuals with mood disorders. Comparing subjective reports of sleep and biological rhythm disruption to objective measures can offer insight into the feasibility of using subjective measures in the clinical setting.

There are several validated ways of assessing sleep and circadian rhythm disruption objectively. Perhaps the most widely used method of measuring markers of circadian rhythmicity involves profiling the daily fluctuations in endogenous melatonin and cortisol levels. Melatonin levels typically rise prior to habitual bedtime, peak in early morning hours roughly around 3:00 AM, and gradually decrease throughout the day during wakefulness (Burgess and Eastman, 2005). As melatonin levels increase, the homeostatic drive for sleep increases. Melatonin profiles can be obtained from plasma, serum or saliva. The dim light melatonin onset, which is typically obtained via an hourly or half-hourly saliva sample in the evening, is considered the most reliable measure of the timing of the biological clock (Lewy et al., 1982; Molina and Burgess, 2011). However, compliance for sampling melatonin requires participants to stay overnight in a laboratory. Urinary melatonin metabolite 6-sulphatoxymelatonin (6-SM) has demonstrated its usefulness in marking the peak of nocturnal melatonin secretion (Graham et al., 1998), which is known to be positively associated with the sleep/wake cycle. So, the collection of a first morning urine sample from subjects is quite feasible and cost-effective for these purposes in a research setting. Additionally, it is postulated that low nocturnal melatonin secretion is a biomarker of vulnerability to affective disturbance (Wetterberg et al., 1979). Several studies have reported deficient nocturnal melatonin levels in major depression (Brown et al., 1985; Claustat et al., 1984; Paparrigopoulos et al., 2001) and bipolar subjects (Kennedy et al., 1996; Lewy et al., 1981, 1985). Cortisol levels are typically quite high in the morning and decrease throughout the day, peaking roughly around 6:00 AM. Studies investigating plasma cortisol levels reveal that those with MDD and BD have increased cortisol levels (Bhagwagar et al., 2005; Cervantes et al., 2001; Deshauer et al., 2003), indicating biological dysregulation of the hypothalamic-pituitary-axis.

In addition to monitoring hormonal profiles, methods such as polysomnography (PSG) and actigraphy offer valuable information into daily activity patterns and sleep quality. PSG is a gold standard for the examination of sleep architecture, and has been used to demonstrate a shortened REM latency, increased REM density, variability of sleep duration, increased wake times, and delayed sleep onset in both manic and unipolar depressed patients compared to controls (Hudson et al., 1992). Actigraphy is a well-validated and non-invasive method of measuring daily activity rhythms (DARs) in BD (Kaplan et al., 2012; Millar et al., 2004), which has revealed less stable and more variable circadian activity, longer sleep durations and sleep onset latencies (Jones et al., 2005; Millar et al., 2004). Actigraphy shows high levels of agreement with PSG in BD, yet both objective measures have shown only modest agreement when compared with subjective sleep diaries (Kaplan et al., 2012). Matousek et al. (2004) corroborated these findings by showing that subjective reports of sleep quality are less reliable than PSG measures in depressed subjects.

Studies have shown longer sleep onset latency and sleep duration, as well as fewer awakenings, on subjective reports in sleep-disordered populations compared to objective measures (Kushida et al., 2001; Lichstein et al., 2006; Verbeek et al., 1994). Fewer nocturnal awakenings are also recorded in subjective reports compared to objective

estimates in healthy volunteers (Lockley et al., 1999). The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), a widely used self-reported measure of sleep quality, has revealed weak correlations with objective PSG and actigraphy (Backhaus et al., 2002; Buysse et al., 2008; Doi et al., 2000; Elsenbruch et al., 1999; Van Den Berg et al., 2008). Additionally, evening salivary melatonin concentrations as an objective measure of sleep disturbance have also been evaluated against total PSQI scores in healthy females where no relationship was observed (Ito et al., 2013). Boudebesse et al. (2014) sought to validate specific variables in three sleep and circadian questionnaires as behavioural equivalents against actigraphic measures in remitted BD: the PSQI, the Composite Scale of Morningness (CSM) (Smith et al., 1989), and the Circadian Type Inventory (CTI) (Folkard, 1987). The authors found that the PSQI and CSM highly correlated with sleep (latency and duration) and circadian variables (phase markers), respectively, however no relationship was found between the CTI and circadian variables (Boudebesse et al., 2014). A recent study demonstrated the capability of the Morningness-Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976) to predict acrophase, but not MESOR or amplitude in healthy subjects (Roveda et al., 2017). These findings highlight the considerable amount of variance between objective and subjective measures of sleep and circadian rhythmicity.

The BRIAN is a self-report questionnaire that was originally developed and validated in euthymic BD subjects to provide an index of biological rhythm disturbance (Giglio et al., 2009). This scale considers sleep disruptions, social rhythm irregularities, eating patterns, and abnormalities in daily activity at home and work in the last 15 days - all of which have been postulated to contribute to the onset and worsening of affective episodes (Ashman et al., 1999; Michalak et al., 2007; Shen et al., 2008; Ramacciotti et al., 2005), as well as worse psychosocial function and clinical outcomes (Faria et al., 2015; Pinho et al., 2015). The BRIAN is able to differentiate across mood states of euthymia, unipolar and bipolar depression, and mania (Faria et al., 2015; Pinho et al., 2015), and is an independent predictor of psychosocial functioning, severity of depression and quality of life (Cudney et al., 2016; Giglio et al., 2010; Pinho et al., 2015). Another favourable feature of the BRIAN is its sensitivity to rhythm disturbance in branching populations. Prospective changes in BRIAN scores predicted changes in depressive symptoms from pregnancy to the postpartum period (Krawczak et al., 2016a, 2016b). The BRIAN has also discriminated between levels of severity in depressed individuals with co-morbid metabolic syndrome (Moreira et al., 2016), and detected greater subjective rhythm disturbance in patients with fibromyalgia syndrome who did not have a comorbid affective disorder (Ucar et al., 2015).

The BRIAN fills a gap by offering a quick, self-reported measurement of biological rhythm disruption in individuals with mood disorders. However, to the best of our knowledge, the external validity of the BRIAN has not been tested against objective measures of sleep or circadian rhythms. Therefore, the objectives of the present study were (1) to provide an assessment of its construct validity using IRT, and (2) to compare the BRIAN with objective measures of sleep and circadian rhythmicity. We hypothesized that total BRIAN scores, BRIAN Sleep domain and Activity domain will show concordance with objective measures of sleep and circadian rhythmicity.

## 2. Methods

### 2.1. Participants

One hundred and eleven participants were enrolled in the study. All participants gave written informed consent to take part in the study, in accordance with Declaration of Helsinki. Eight participants withdrew from the study for various reasons (e.g. family emergency, work schedule, exams, failure to report current melatonin use). The final sample size consisted of 103 subjects (MDD = 32; BD = 31; healthy controls (HC) = 40) (Table 1). Subjects were recruited from the Mood Disorders

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