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Abnormalities in sleep patterns in individuals at risk for psychosis and bipolar disorder

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ABSTRACT

Aim: To compare patterns of sleep and the presence of sleep disturbances in individuals in at-risk mental states (ARMS) for psychosis and bipolar disorder (BD) with a healthy control (HC) group.
Methods: This was a comparative study involving 20 individuals in ARMS for psychosis or BD, according to the Comprehensive Assessment of At-Risk Mental States, and 20 age- and sex-matched healthy controls. Quality of sleep in the previous month was assessed using the Pittsburgh Sleep Quality Index, diurnal somnolence was evaluated using The Epworth Sleepiness Scale, and chronotype was determined using the Questionnaire of Morningness/Eveningness (QME). All of the participants underwent polysomnography (PSG) during the entire night for two consecutive nights. The first night aimed to adapt the subject to the environment, and only the data from the second night were used for the analysis.
Results: Compared with the HC group, individuals in the ARMS group reported significantly worse sleep quality, as measured by the Pittsburgh Sleep Quality Index. Both groups had scores consistent with daytime sleepiness on the Epworth Sleepiness Scale, and there were no differences with regard to chronotype between the groups, with a predominance of the indifferent type in both groups. In the PSG assessment, we observed increased Sleep Latency (SL) and increased Rapid Eye Movement Sleep Onset Latency (REMOL) in the ARMS group, compared to the HC group.
Conclusion: The results of this study indicated that sleep abnormalities could be found early in the course of mental diseases, even in at-risk stages, and support the further investigation of their predictive value in the transition to psychosis and BD.

1. Introduction

Schizophrenia and bipolar disorder (BD) are potentially severe psychiatric disorders that affect, together, approximately 3% of the population over a lifetime (Kessler et al., 1994). Despite advances in psychopharmacology, available treatments are limited in reducing BD- and schizophrenia-associated morbidity and mortality (Brietzke et al., 2011; Yung et al., 1998). As a result, one of the most promising research lines in this field is the study of individuals who are most likely to develop severe mental disorders, focusing on prevention (Modinos et al., 2014).

Findings from several research lines have converged on an understanding that although they are distinct diseases, schizophrenia and BD have in common many pathophysiological processes such as the following: genetic susceptibility conferred by polymorphisms in the genes DISC1, Dysbidin, NRG1 and DAO-A (Ivleva et al., 2008); affected cognitive domains, (Murray et al., 2004); structural neuroimaging changes (McDonald et al., 2004); decreases in neurotrophins, particularly in *Brain-Derived Neurotrophic Factor* (BDNF) (Balu and Coyle, 2011; Cunha et al., 2006) and inflammatory mediators such as cytokines (Smesny et al., 2010).

The existence of a prodromal phase, a period during which symptoms are present with milder severity, with a shorter duration or lower frequency, preceding the onset of psychosis and BD has attracted increasing interest in the scientific community (Correll et al., 2014; Fusar-Poli et al., 2014; Noto et al., 2013). Some groups have developed criteria for identifying individuals with at-risk mental states (ARMS) for psychotic disorders (Amminger et al., 2006; Yung et al., 2004) and for BD (Bechdolf et al., 2010), using a combination of cognitive, behavioral, and emotional changes, in addition to non-specific genetic risk and functional decline. Prospective follow-up studies, using participants at ultra-high risk for psychosis, have shown that between 20 and 40% of the subjects developed psychotic episodes after 1 to 2 years of follow-up (Amminger et al., 2006; Yung et al., 2003).

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Complaints about changes in sleep patterns are common in patients with schizophrenia and BD, and these changes tend to intensify with the proximity of an episode of acute exacerbation of both diseases (Bechdolf et al., 2010; Yung et al., 2003). The circadian system modulates mood, and changes in this system, including sleep deprivation as a result of travel or overwork, have negative effects on mood, causing irritability and emotional lability (Murray et al., 2002). The relationship between sleep disturbances and mood swings is a two-way street because high levels of agitation affect the quality of sleep and can lead to a vicious cycle between sleep disturbance and emotional dysregulation (Murray et al., 2009; Thayer, 1987). Sleep loss not only increases the negative emotional response but also decreases the response to positive events (Boivin et al., 1997).

Sleep is an adaptive function of humans, during which the restoration of brain processes, including strengthening of the immune system, growth, major metabolic processes, memory consolidation and brain plasticity, occurs (Durmer and Dinges, 2005; Maquet, 1995; Stickgold et al., 2001). REM (rapid eye movements) sleep might be particularly important in processing and emotional modulation (Cartwright et al., 2006; Walker, 2009).

Psychosis in schizophrenia is associated with an abnormal pattern of brain self-activation in waking, and it is hypothesized that self-organized dynamics of neuronal activity in sleep should likewise be affected (Vukadinovic, 2011). Studies using high-density EEG have shown a decrease in sleep spindles in adult patients with schizophrenia compared to non-psychotic patients receiving neuroleptics and healthy controls (Ferrarelli et al., 2007; Wamsley et al., 2012). Tesler et al. (2015) found a reduced sleep spindle density in research with nine adolescents meeting the criteria for an early onset schizophrenia spectrum disorder and summarized that sleep spindles are thought to be a reliable electrophysiological marker reflecting deficits in the integrity of the thalamocortical system in schizophrenia.

Sleep alterations directly affect quality of life and interfere with emotional regulation in BD (Giglio et al., 2009; Michalak et al., 2007). Evidence exists for a relationship between the state of mood prior to sleep and EEG parameters during REM sleep, which seems to play an important role in emotional processing (Nishida et al., 2009). In a systematic review that investigated symptoms prior to outbreaks of manic or depressive episodes in bipolar patients, Jackson and colleagues concluded that changes in sleep patterns were the most common symptom predictor for mania (Jackson et al., 2003). A longitudinal study developed by Perlman et al. (2006) with 52 patients diagnosed with BD I, aged 18 to 75, reported that shorter sleep latencies were predictive of depressive episodes over 6 months of follow-up. Hirschfeld et al. (2003) investigated, through self-reported questionnaires, 600 patients with BD to determine the experiences of those with the disease; 78% reported some sleep disturbance as a common symptom when on the verge of a mood episode.

Correll et al. (2007) conducted a retrospective study with 52 euthymic bipolar patients, age 7 to 21, and reported reduced need for sleep as one of the symptoms prior to the development of a manic episode in 39% of patients. In a retrospective investigation of prodromal signs of the first psychotic episode, Yung and McGorry (1996) described changes in sleep as the most common finding in 70–100% of patients. In one study involving 59 euthymic bipolar outpatients, Bauer et al. (2006) found an increase in sleep latency to be the most common predictor of the recurrence of a mood episode.

Studies investigating sleep using PSG in individuals with schizophrenia have documented difficulties in initiating and maintaining sleep, increased total sleep time, little restful sleep, increased latency and reduced total REM sleep time, as well as a decrease in slow wave sleep (stage N3) (Keshavan et al., 1990; Poulin et al., 2003; Tandon et al., 1992). Keshavan et al. (2004) evaluated PSG findings from 81 first-degree relatives of schizophrenic patients, aged 6 to 25, and noted alterations such as disrupted sleep and reductions in Slow Wave Sleep (SWS). In a previous study, Keshavan and Tandon (1993), suggested that SWS reductions can be associated with negative symptoms, brain structural alterations, reduced prefrontal metabolism and cognitive impairment. In a study that compared 33 adolescents at ultra-high risk (UHR) for psychosis with 33 healthy controls, Lunsford-Avery et al. (2013) found increased latency to sleep onset and greater sleep disturbances in the UHR group.

Behavioral techniques such as sleep deprivation, light exposure, sound stimuli, and adjustments in feeding, working and social times are known to be effective ways to restore the sleep–wake cycle (Mistlberger et al., 2000). The effectiveness of such techniques is demonstrated clinically by phototherapy as a treatment for seasonal affective disorders and stabilization of biological rhythms to control TB relapses (Frank et al., 2007; Murray et al., 2006).

The detection of changes in sleep or sleep–wake cycles in vulnerable individuals might provide a valuable indicator of neurobiological developmental deviations and data about the pathophysiology of at-risk states, supporting the study of changes in sleep patterns as predictors of transitions to major psychiatric disorders (Zanini et al., 2013). Nevertheless, sleep has received little attention in the study of ARMS, and these individuals have never been assessed using robust standardized methods. In this study, we explored changes in sleep in individuals with ARMS, aiming to understand the clinical presentation and neurobiology of putatively prodromal stages of psychotic and severe mood disorders. The objective of this study was to investigate sleep complaints using structured questionnaires and PSG findings in ARMS patients compared with healthy controls.

2. Methods

2.1. Subjects

Twenty individuals in ARMS and 20 age- and sex-matched HC between the ages of 13 and 27 participated in the study. The subjects included in the ARMS group were selected from individuals seeking help from the Program for Recognition and Intervention in Individuals in At-Risk Risk Mental States (PRISMA), Federal University of São Paulo (UNIFESP). The HC group was recruited using posters calling for healthy volunteers for research and advertisements on Web sites.

The inclusion criteria for the individuals in the ARMS group were as follows: having never presented with any psychiatric illness, according to the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version — SCID-CV (First et al., 1996) and Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version — K-SADS-PL (Kaufman et al., 1997); having sought at least one health service for distress or functional impairment in the past year; and meeting the criteria for ultra-high risk for psychosis or high risk for BD. The criteria for ultra-high risk for psychosis were determined in accordance with those proposed by Yung et al. (2005), according to the classification of the Comprehensive Assessment of At-Risk Mental State (CAARMS) scale, translated and adapted to the Brazilian linguistic and cultural context. The criteria for high risk for BD followed those proposed by Bechdolf et al. (2010), measured by the CAARMS and clinical evaluation. Although the criteria to identify risk for BD remain under discussion, criteria developed by Bechdolf et al. (2010) were also adopted because they are similar to CAARMS and were prospectively validated. These criteria are summarized in Table 1. The inclusion criteria for the healthy controls were having never presented any psychiatric illness, according to the SCID-CV (First et al., 1996) and Schedule for Affective Disorders and Schizophrenia for K-SADS-PL (Kaufman et al., 1997), and no history of psychotic disorders or mood disorders in first-degree relatives.

Exclusion criteria for cases were as follows: diagnosis of BD type I or type II or a psychotic disorder, currently or during the lifetime, according to the SCID-CV (First et al., 1996), for individuals aged 16 years old or older or the K-SADS (Kaufman et al., 1997) for individuals younger than 16 years old; a current substance use disorder; risk of suicide or

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