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The interaction between subclinical psychotic experiences, insomnia and objective measures of sleep

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ABSTRACT

Investigations into schizophrenia have revealed a high incidence of comorbidity with disturbed sleep and circadian timing. Acknowledging this comorbidity on a dimensional level, we tested prospectively whether subclinical psychotic symptoms are more prevalent in individuals with insomnia. An insomnia group ($n = 21$) and controls ($n = 22$) were recruited on their subjective sleep quality, recorded actigraphically for 3 weeks and assessed for psychotic-like experiences with The Prodromal Questionnaire-16. Using multivariate Poisson regression analyses, we found that objective and subjective sleep measures interact to predict the highest risk for psychotic experiences. Objective measures of sleep and statistical modelling are rarely used in either clinical trials or practice for schizophrenia, yet this study highlights their value in these areas.

1. Introduction

Evidence is now accruing that sleep and circadian rhythm disruption (SCRD) is a ubiquitous feature of psychosis. A study by Cohrs (2008) highlighted that between 30% and 80% of patients with a diagnosis of schizophrenia report sleep disturbances (SD). This frequently manifests as patients exhibiting a range of SCRD related phenotypes, ranging from extended time to get to sleep (sleep onset latency), difficulties with sleep continuity (with a prevalence of 50–70%; Benson, 2006; Tandon et al., 2008; Waters and Manoach, 2012) to extreme circadian misalignment (sleep phase advances/delays, bidian cycles and non-24 h periods) and highly irregular and fragmented sleep patterns (Wulff et al., 2012). These disturbances are also associated with important clinical outcomes, including relapse (Waters and Manoach, 2012), poorer coping (Ritsner et al., 2004), higher distress (Hofstetter et al., 2005), and increased frequency of depression (Palmese et al., 2011) and completed suicide (Pompili et al., 2009).

It has been debated that SCRD may represent a vulnerability factor, or be involved in the development of psychosis, on the understanding that sleep/circadian abnormalities and the aetiology of psychosis are rooted in failures of genetic and synaptic functions of neurotransmitter systems (e.g. GABA, glutamate, dopamine) and neural/humoral circuits (e.g. hypothalamic-pituitary-adrenal axis; see reviews; Pritchett et al., 2012; Wulff et al., 2010). This is evidenced by the omnipotence of poor sleep across all of the core phases of the disorder, including the prodrome (with an estimated prevalence of 70–100%; Yung and McGorry, 1997), as well as acute (Kupfer et al., 1970), chronic, and residual phases (Waters et al., 2011).

More recently, the notion of a direct link between sleep/circadian dysfunction and the development of psychosis has been further addressed by examining of the presence of SCRD prior to the occurrence of psychotic episodes (see review Lunsford-Avery and Mittal, 2013). While there was overwhelming evidence for a link, the majority of data reviewed were subjective reports of sleep disturbance and only one published study had examined sleep in at-risk population using objective EEG methods (Keshavan et al., 2004). There are now two comprehensive systematic reviews examining the evidence to date in support of this relationship (Davies et al., 2016; Reeve et al., 2015). Davies et al. (2016) concluded that evidence to support the reliability of the observed association is limited due to considerable heterogeneity in samples and methods (non-affective, affective psychosis, 'other psychosis', prospective, retrospective, polysomnography, actigraphy, self-report, interview, etc.) and that the prevalence and nature of sleep disturbances cannot be defined as yet in ultra high-risk population. Nevertheless, the review highlights that poor sleep is related to greater severity in positive symptoms (Lunsford-Avery et al., 2015), higher distress (Andriopoulos et al., 2011) and, although unspecific, one out of six

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components in a prediction model for psychosis (Ruhrmann et al., 2010). Furthermore, there is also evidence that there may be a shared genetic and environmental lineage underlying psychotic experiences and SCRD (Taylor et al., 2015).

The differences observed in the prodromal phase equate to what is observed when the individual has transitioned to psychosis: extended sleep onset latency, difficulties with sleep continuity and lower circadian rest-activity amplitude (Castro et al., 2015; Zanini et al., 2013). It has also been noted that circadian phenotypic variation over 5 days of activity monitoring (lower daily activity, fragmented sleep patterning/misalignment with the light-dark cycle) predicted more severe psychotic symptoms and greater psychosocial impairment at a one-year follow-up in an adolescent cohort deemed clinically high-risk for psychosis (Lunsford-Avery et al., 2017). The authors concluded that circadian rhythm regulation might be a potential target for identification and interventions to stabilise social, eating and sleep-wake rhythms in early intervention services.

One of our goals continues to be the identification and characterisation of physiological sleep factors that impact mental function on an individual level. Given objective sleep differences have already been noted in individuals at risk of psychosis when compared to healthy controls (ex: Castro et al., 2015), it may then be more pertinent to note whether the signal is bi-directional: i.e. does a cohort with a complaint of poor sleep (insomnia) endorse a greater number of PLEs, and if so, what parameters of their sleep dictate this? We therefore tested whether the relationship between schizophrenia and sleep is bi-directional and hypothesised that healthy young adults with self-reported insomnia endorse a greater number of psychotic-like experiences than those with self-reported good sleep. We applied statistical models to examine whether parameters of sleep predict this relationship, and if so, which parameters: subjective, objective, or both.

A student sample was chosen because research on PLEs in this population may hold greater clinical relevance and these experiences may incur greater distress when compared to younger children and adolescents (Kelleher et al., 2012; Zammit et al., 2013). Furthermore, understanding sleep's role in PLEs is particularly pertinent in university students as they are a cohort particularly susceptible to disrupted sleep scheduling and day-time activity patterns (Brown et al., 2002).

2. Method

This sample included 43 healthy young adults (18–30 years), recruited from the University of Oxford and Oxford Brookes University. The Insomnia group were required to have a Pittsburgh Sleep Quality Index (PSQI) of 8 or above and an Insomnia Severity Index (ISI) of 10 or above, whilst controls were required to have a PSQI of 3 or below and an ISI of 6 or below, thereby creating a degree of separation in the groups' subjective reporting of sleep quality.

The PSQI (Buysse et al., 1989) measures subjective sleep quality over the previous month and yields a score ranging from 0 to 21, with higher scores representing poorer quality. The standardised cut-off score for poor sleep quality is 5. The ISI (Bastien, 2001) measures both night-time and day-time elements of insomnia, and ranges from 0 to 28. Scores of 10 and above are considered optimal for detecting insomnia in community samples (Morin et al., 2011). Both measures have shown good psychometric properties for use in both patients and healthy controls (Backhaus et al., 2002; Carpenter and Andrykowski, 1998; Morin et al., 2011).

Exclusion criteria for all participants included a diagnosis of a psychotic disorder (past or present); taking medication known to affect sleep; brain injury; epilepsy; shift work; hospitalisation in the previous six months; and travelling through two or more time zones in the previous fortnight. The study protocol was approved by the Medical Sciences Interdivisional Research Ethics Committee (MSD-IDREC-C1-2014-177) and all participants gave written informed consent.

As subjective sleep quality can reflect different sleep related experiences (ex: difficulty falling asleep, difficulty staying asleep) for different people and is correlated with non-sleep related phenomena (ex: mood; Krystal and Edinger, 2008), the sleep-wake cycle was objectively monitored for three weeks using wrist-worn actigraphs with an integrated light sensor (MotionWatch 8, CamNtech Ltd.). This was used in conjunction with a standardised diary of sleep timings and daily activities that was used to annotate the actigraphy data. Actigraphy data were sampled at one-minute epochs, and MotionWare software (version 1.1.15, CamNtech, Ltd.) was used to calculate sleep fragmentation (an index derived from the frequency and intensity of physical movement during the sleep period), sleep onset latency (SOL; the amount of time between bedtime and sleep onset), wake after sleep onset (WASO; the amount of time spent above a predefined activity threshold), total sleep time (TST; time between sleep onset and final wake time, excluding WASO), and variability in sleep onset and sleep duration (measured by their standard deviations).

Psychotic experiences were measured using the Prodromal Questionnaire 16 Item Version (PQ-16), which has acceptable psychometric properties in both healthy and high-risk populations (Ising et al., 2012). It contains 16 yes/no items, yielding a score out of 16. Scoring 5 or above warrants further screening for an at risk mental state (Ising et al., 2012). The Questionnaire assesses positive symptoms (visual and auditory hallucinations, delusional mood/perplexity, ideas of reference and persecutory thoughts), negative symptoms (excessive social anxiety) and avolition.

All measures were examined for their distributional properties. Actigraphic variables met the assumptions for parametric testing, as such Welch's two sample *t*-test (with continuity correction) was employed, and means were reported. All *p*-values reported were corrected for multiple testing using the Benjamini & Hochberg correction method (Benjamini and Hochberg, 1995). This correction controls for false discovery rate, as opposed to the more commonly employed Bonferroni method, which controls for the family-wise error rate.

3. Results

The sample comprised of 43 students: 21 in the insomnia group (mean age = 23.9 years, SD = 3.6, 13 women) and 22 controls (mean age = 22.8 years, SD = 3.2, 11 women). The mean PSQI of the insomnia group was 10.1 (SD = 2.2) compared to 2.4 (SD = 0.8) for the controls. The mean ISI was 14.4 (SD = 3.3) for the insomnia group compared to 1.3 (SD = 1.3) for the controls (Table 1). Independent-samples *t*-tests highlighted no significant differences between groups in any of the actigraphic measures taken after correcting for multiple comparisons with the exception of sleep period (time spent in bed excluding sleep onset latency; $t(38.3) = -3.02$; $p = 0.040$) using the Benjamini Hochberg correction method.

A Wilcoxon Rank-Sum test indicated that the median PQ-16 score in the insomnia group (median = 3) was significantly higher than the control group (median = 1, 95% CI [1.00–4.00], $W = 70.5$, $p < 0.001$, Fig. 1).

Multivariate Poisson regression analyses were used to investigate which parameters of sleep best predicted the difference in psychotic experiences (PQ-16) between groups. Possible predictor variables for PQ-16 were PSQI, ISI, WASO, TST, fragmentation, SOL, and variability in both sleep onset and duration. Due to concerns with collinearity, PSQI and ISI were not included in models together.

Model selection was based upon Akaike's Information Criterion (AIC), which measures the relative quality of a collection of models (Bozdogan, 1987). Standard automated model selection procedures (forward selection and backwards elimination) were used to propose candidate models. Beginning with a simple model with no predictor variables, forward selection iteratively adds the predictors offering maximal AIC reduction until no further reduction is possible. Backward

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