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Sleep disturbances in individuals at clinical high risk for psychosis

Sarah-Lucy Poe[a,b,*], **Gary Brucato**[a,b], **Nicolina Bruno**[a,b], **Leigh Y. Arndt**[a,b], **Shelly Ben-David**[a,b], **Kelly E. Gill**[a,b], **Tiziano Colibazzi**[a,b], **Joshua T. Kantrowitz**[a,b], **Cheryl M. Corcoran**[a,b], and **Ragy R. Girgis**[a,b]

[a]Columbia University Medical Center, Department of Psychiatry, New York, NY, USA

[b]The New York State Psychiatric Institute, New York, NY, USA

Abstract

There has been recent interest in understanding the role that sleep disturbance plays in patients at Clinical High Risk for psychosis (CHR). We assessed sleep disturbance in 194 CHR patients and 66 healthy control subjects and their relationship to symptoms (positive, negative and general functioning). Patients experienced significantly more sleep disturbance than healthy control subjects and their sleep disturbance was related to greater positive and negative symptoms and worse overall functioning. Targeting sleep disturbance in CHR individuals may provide alternative means of treating the CHR syndrome.

Keywords

Sleep Disturbance; Clinical/Ultra high risk; Prodromal; Psychosis

1. Introduction

Schizophrenia and other psychoses are characterized by positive and negative symptoms, as well as functional impairments. Attenuated positive symptoms, negative symptoms, and other general psychiatric symptoms may be present for a period of time prior to the onset of threshold psychosis, and are assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS) (Miller et al., 2003). One general symptom is sleep disturbance, which is observed in a large number of patients with schizophrenia, approximately 30–80% (Cohrs, 2008). Even so, sleep disturbance is characteristic of many disorders, and is not always a focus of treatment. With better characterization of the relationship between sleep disturbance and symptoms, there is hope that sleep disturbance particular to CHR patients could be targeted as a means of preventing conversion to psychosis.

The mechanism by which sleep interacts with other known risks for psychosis is unclear, although evidence does suggest that individuals with schizophrenia with sleep disturbance experience more severe symptoms than patients without (Afonso et al., 2014). In a cross-

*Corresponding author at: Columbia University, 1051 Riverside Drive, Unit 31, New York, NY 10032, USA. slcp118@me.com (S.-L. Poe).

sectional study, Afonso et al. (2014) compared 811 schizophrenia outpatients based on whether or not they had sleep disturbance. Quality of sleep, symptom severity, adherence to treatment, and degree of family support were variables of interest. Patients with sleep disturbance were significantly more symptomatic and were found to have worse compliance and less family support than patients without disturbance. These findings suggest that the presence of sleep disturbance is an important clinical factor that may modify the presentation of psychosis. However, whether patients with sleep disturbance experience this extra level of dysfunction and symptom severity as a result of sleep disturbance or as a precursor to was not necessarily addressed in the aforementioned study.

Sleep disturbance has been described earlier in the disease process as well. Specifically, it is one of the most common prodromal features preceding a first episode of psychosis or psychosis relapse (Yung and McGorry, 1996). In a retrospective study investigating first-episodes of psychosis, sleep disturbance preceded first episode psychosis in the majority of patients (Tan and Ang, 2001). Others have reported a relationship between sleep disturbance and conversion to psychosis (Ruhrmann et al., 2010). While these studies shed light on the presence of sleep disturbance in early psychosis, they emphasize sleep disturbance as an important symptom that often occurs before conversion.

In one study, Lunsford-Avery et al. (2013) reported that, in 33 patients at ultra high risk for psychosis, patients had greater latency to sleep onset and greater disrupted continuity of sleep than controls. They found relationships between sleep disturbance and greater negative symptoms but not positive symptoms.

Studies that examine a general population and assess for psychotic-like experiences have also reported relationships between symptoms and sleep disturbance. A cross sectional study which questioned over 7000 adolescents about psychotic like experiences and sleep showed very strong relationships between sleep disturbance and psychotic like experiences (Lee et al., 2012). Taylor et al. (2015) assessed sleep, using the Pittsburgh Sleep Quality Index and Insomnia Severity Index, and psychotic like experiences in a general population of twins and found associations between sleep disturbance and positive symptoms. They found an association between sleep disturbance and negative symptoms as well, though the association was not as large. Day/night reversal is a well documented sleep disturbance in individuals with schizophrenia (Wulff et al., 2012).

Fisher et al. (2014) interviewed 6796 children and their parents from the general population at sequential time intervals to assess parasomnias and their relationship to psychotic-like experiences in childhood. The authors found that children who experienced frequent nightmares from ages 2.5 years to 9 years were more likely to experience psychotic-like symptoms at age 12 years. They also reported that 12 year old children reporting parasomnias were nearly four times as likely to have concurrent psychotic-like experiences than 12 year old children not reporting parasomnias.

These previous findings are helpful in that they suggest the prevalence and importance of sleep disturbances as they relate to attenuated psychotic symptoms. The goals of this study are to expand upon these results by examining sleep disturbance in a large CHR population

and their relationship with positive and negative symptoms and overall functioning as measured by the SIPS. We hypothesize that sleep disturbance will be present in a CHR population and will be related to greater symptoms and worse functioning. In addition we hypothesize based on the literature that day/night reversal (sleep item 5) would be related to positive symptoms and that CHR subjects would have significantly great sleep disturbance than controls.

2. Methods

2.1. Participants

194 help-seeking CHR patients, aged 13–30, were ascertained using the Structured Interview for Psychosis-Risk Syndromes (SIPS) (Miller et al., 2003), as were 66 matched healthy comparison participants. Recruitment and ascertainment relied on internet advertising and referrals from clinicians and schools in a large metropolitan area. Exclusion criteria for patients included attenuated psychosis symptoms solely in the context of substance use, history of threshold psychosis, IQ < 70, medical or neurological disorders and a serious risk of harm to self or others. Healthy comparison subjects were medically healthy, non-substance using, and had no history of any SCID or SIPS diagnosis. Groups were assessed at baseline for demographics and symptoms and all subjects were followed for up to 2.5 years or conversion to psychosis, whichever came first. The Institutional Review Board at NYSPI approved this study. Informed consent (or informed assent and parental consent if the patient was less than 18 years of age) was obtained before any research procedures were performed.

2.2. Assessments

The SIPS (Miller et al., 2003) was used to identify study subjects. G1 (“Sleep Disturbance”) was used to assess sleep and the seven items of G1 are 0, (Absence of sleep disturbance), 1 (Restless Sleep), 2 (Hyposomnia), 3 (Daytime Fatigue), 4 (Sleep Pattern Disruption), 5 (Day/Night reversal), and 6 (Insomnia for Two Days). A full list of item descriptions may be found in Table 3. The SIPS was also used to determine positive and negative symptoms and to assess conversion to psychosis. Demographic data were collected through self-report. The Global Assessment of Functioning (GAF) (Hall, 1995) is used to evaluate a person’s psychological, social and occupational functioning on a hypothetical continuum of mental health-illness and ranges from 1 (sickest), to 100, (healthiest). The GFS Social and Role scales were also used to examine social and role functioning in the cohort (Cornblatt et al., 2007). Role functioning includes personal self-care, cognitive/affective functioning, social/familial relationships, and vocational/educational functioning.

2.3. Statistical analysis

Comparisons between controls and patients across race, ethnicity and gender variables were made using chi square, and across age, sleep disturbance (SIPS Item G1), total positive symptoms, total negative symptoms, and general assessment of functioning using *t*-tests. Among the demographic variables, we found one statistically significant difference (age), so we performed a posthoc ANCOVA to assess whether the sleep differences we observed could be accounted for by differences in age. To better understand the nature of sleep

abnormalities, we reported frequencies of each type of sleep abnormality, as per the SIPS, in Table 2. We compared patients with controls on SIPS G1 subscores using ANOVA. Because control subjects had very limited sleep disturbance, the remainder of the analyses were only performed in the patient group. To better understand the relationship between G1 items with symptoms and functioning, we performed linear regression in which each of the 7 different types of sleep disturbance as per the SIPS (with '0' as the 'dummy variable') as the independent variables. To assess how G1 items predict conversion to psychosis, we performed logistic regression. We used SPSS version 22 and a significance level of $p < 0.05$.

3. Results

Chi square analysis revealed no significant difference in gender, race, nor ethnicity between patient and control groups (Table 1). Age was the only demographic variable that differed significantly across patient/control groups, (CHR mean=20 years, Healthy Control mean=21.9 years). We observed significant differences in positive symptoms, negative symptoms, sleep disturbance (SIPS G1), and general functioning. As hypothesized the former three were greater in CHR subjects, and the latter lesser in CHR. Because of the difference in age between controls and patients, we performed an ANCOVA to assess whether the difference in sleep disturbance could be accounted for by age, however the difference between patients and controls in sleep disturbance remained significant. To address the possibility that attenuated psychotic symptoms may explain the difference in sleep disturbance between patients and healthy controls, we performed an ANCOVA covarying for total positive symptoms and total negative symptoms. In both cases the difference remained significant. With 32% of CHR patients being medicated, we also wanted to address the concern whether medication status affects sleep disturbance. Using ANOVA, we assessed whether being on medication (or not) had a significant relationship with either sleep disturbance overall (i.e., total G1), or on any of the 6 sleep disturbance items in particular. We found no significance for any of these relationships and therefore did not control for medications in the final analyses (see Tables 1 and 2).

Frequency results from breaking down the sleep disturbance variable into its 6 items can be observed in Table 2. No controls scored between 4% and 6% and 73% scored a 0. The mode for patients is 3, but their scores ranged from 0 to 6. Results from ANOVA, whereby the means of patients and controls were compared on each item, demonstrated statistically significant differences for 0, (Absence of Sleep Disturbance), 1 (Restless Sleep), 3 (Daytime Fatigue), 4 (Sleep Pattern Disruption), and 5 (Day Night reversal), but not for 2 (Hyposomnia), or 6 (Insomnia for Two Days), the latter being underpowered to detect a difference. Healthy controls scored numerically higher on sleep items 0, and 1 (~73% and ~20% vs. ~22% and ~5%). CHR patients scored numerically higher on sleep items 2, 3, 4, 5, and 6 (~13%, ~29%, ~18%, ~12% and ~2% vs ~5%, ~3%, 0%, 0%, and 0%).

Results from the linear regression models to examine whether any of the sleep items (1–6; 0 was used as the 'dummy variable') was related to total positive symptoms, total negative symptoms, general functioning, social functioning or role functioning showed that both sleep item 4 (Sleep Pattern Disruption) and sleep item 5 (Day Night Reversal) were significantly related to total positive symptoms (B=3.37, p-value= < 0.01 and B=3.05, p-

value= < 0.01 respectively). Items 3 (Daytime Fatigue), 4 (Sleep Pattern Disruption) and 5 (Day Night Reversal) were significantly related to total negative symptoms (B=3.12, p-value=0.02; B=4.48, p-value= < 0.01; and B=5.54, p-value= < 0.01 respectively). Only sleep item 4 (Sleep Pattern Disruption) was significantly related to general functioning (B=−4.46, p-value= <0.01). In all cases, worse sleep predicted worse symptoms or worse functioning. Item 6 (Insomnia for two days) was related to role functioning (B=−4.75, p-value=0.051), social functioning (B=−3.29, p-value=0.072) and negative symptoms (B=6.48, p-value=0.05) at trend level. No sleep items at baseline significantly predicted conversion (at 2.5 year follow up).

4. Discussion

CHR patients were significantly more sleep disturbed than healthy controls, and the relationship between sleep disturbance and symptoms was significant. No specific sleep items predicted conversion or social and role functioning, though sleep disturbance item 4 (Sleep Pattern Disruption) and item 5 (Day Night reversal) were related to greater positive symptoms. These two specific sleep disturbances and item 3 (Daytime Fatigue) were also significantly related to negative symptom severity. Sleep disturbance item 4 (Sleep Pattern Disruption) was related to worse overall functioning.

These results add to the growing literature on the relationships between sleep and psychotic symptoms. Notably, with 194 CHR subjects, the current study is the largest to-date in the published literature, and broadens our understanding of sleep disturbances during the CHR period. Fisher et al. (2014) showed that nightmares in early childhood significantly predicted 12-years-old children's likelihood experiencing psychotic-like symptoms. While we reference Fisher et al.'s work to establish the chronology of sleep disturbance with attenuated psychotic symptoms, it is important to note that no associations were found between other persistent sleep problems during childhood (difficulty getting to sleep or night waking), and therefore the significance of the temporal relationship they found may not be generalizable to other types of sleep disturbance.

Our findings are also similar to those of Lunsford-Avery et al. (2013) who reported on sleep disturbance in a population at ultra high risk for psychosis and their relationship to negative, but not positive, symptoms. While we also observed relationships between positive symptoms and sleep disturbance, these findings are not necessarily discrepant as our sample sizes were substantially different, and we used different scales to measure sleep disturbance. Meanwhile, Taylor et al. (2015) also reported relationships between sleep disturbance and psychotic like experiences in a general twin population.

One limitation of this study is that sleep disturbance was not assessed solely for the purpose of this investigation. It was assessed as part of a number of items at baseline (i.e., the SIPS), which characterize the CHR subjects in our clinic. While the validity (Woods et al., 2009), and reliability (Miller et al., 2003) of the SIPS are well established, using any one item to measure an isolated symptom is less preferable than using a test designed to assess that specifically, like polysomnography. In addition, for this interview, when subjects report multiple sleep disturbances, we only mark the greater disturbance, which may account for

why controls scored a '1' more than patients. This study confirms previous findings of sleep disturbances, offers new support and specificity to these findings and is supportive of intervention studies targeting both negative symptoms and sleep disturbances (Kantrowitz et al., 2015). Intervention studies will be an important future focus.

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Table 1

Patient Demographic and Clinical Characteristics.

	Clinical high risk	Healthy controls	Measure of association	p-value[a]
N	194	66		
Age, mean years (± SD)	20.0 (3.8)	21.9 (3.6)	1.84	< **0.01**
Gender, male	142 (73.2%)	42 (63.6%)	3.26	0.196
Race, white	90 (47.6%)	30 (49.1%)	5.66	0.23
Ethnicity, not Hispanic	130 (67.0%)	48 (72.7%)	6.94	0.07
Medication	32%	0%	3.1	0.80
Positive Symptoms, mean (± SD)	14.6 (4.0)	1.2 (1.3)	−13.37	< **0.01**
Negative Symptoms, mean (± SD)	17.0 (6.5)	1.6 (1.9)	−15.39	< **0.001**
Sleep Disturbance, mean (± SD)	2.7 (2.2)	0.4 (0.7)	−2.32	< **0.01**
Overall Functioning, mean (± SD)	45.2 (6.9)	83.2 (7.0)	37.97	< **0.01**
ANCOVA	(Age)	68.52	< **0.001**	
	(Total Positive Symptoms)	5.49	**0.02**	
	(Total Negative Symptoms)	8.29	< **0.01**	

Table 2

Sleep Item Associations.

Sleep Item Number	0	1	2	3	4	5	6
Frequency, CHR	42 (21.6%)	9 (4.6%)	25(12.9%)	56 (28.9)	34 (17.5)	23 (11.9)	4 (2.1)
Frequency, HC	48 (72.7%)	13 (19.7%)	3 (4.5%)	2 (3%)	0	0	0
Medication	1.38 (0.24)	0.62 (0.43)	0.13 (0.72)	0.029 (0.87)	0.024 (0.88)	0.40(0.53)	0.60(0.44)
Sleep Disturbance, CHR	**72.06(< 0.01)**	**15.15(< 0.01)**	3.59(0.06)	**20.3(< 0.01)**	**13.92(< 0.01)**	**8.86(< 0.01)**	1.39(0.24)
General Functioning	–	−2.00 (0.42)	0.02(0.99)	−1.26 (0.36)	**−4.46 (< 0.01)**	−3.26 (0.07)	−0.78(0.83)
Negative Symptoms	–	−0.69 (0.77)	2.34(0.15)	**3.12 (0.02)**	**4.48 (< 0.01)**	**5.54(< 0.01)**	6.48(0.054)
Positive Symptoms	–	1.53 (0.30)	1.43(0.16)	1.49 (0.07)	**3.37 (< 0.01)**	**3.05(< 0.01)**	1.81(0.388)
Social Functioning	–	0.31 (0.73)	0.42(0.48)	0.15 (0.75)	0.63 (0.23)	−0.72 (0.23)	−3.29(0.072)
Role Functioning	–	−1.15 (0.32)	0.25(0.76)	−0.68 (0.27)	−0.42 (0.54)	−0.68 (0.39)	−4.75(0.051)

Table 3

G1 SIPS Sleep Items* (Miller, 2003).

Item	Description
6 (Insomnia for Two Days)	Unable to sleep at all for over 48 h.
5 (Day/Night Reversal)	Significant difficulty falling asleep or awakening early on most nights. May have Day Night Reversal. Usually not getting to scheduled activities at all.
4 (Sleep Pattern Disruption)	Sleep pattern significantly disrupted and has intruded on other aspects of functioning (e.g. trouble getting up for school or work). Difficult to awaken for appointment Spending a large part of the day asleep.
3 (Daytime Fatigue)	Daytime fatigue resulting from difficulty falling asleep at night or early awakening. Sleeping more than considered average.
2 (Hyposomnia)	Some mild difficulty falling asleep or getting back to sleep.
1 (Restless Sleep)	Restless sleep.
0 (Absence of sleep Disturbance)	

*Specific questions asked regarding sleep: 1. How have you been sleeping recently? What kinds of difficulty have you been having with you sleep? (include time to bed, to sleep, and to awake, hours of sleep in 24-h period, difficulty falling asleep, early awakening, day/night reversal). 2. Do you find yourself tired during the day? Is your problem with sleeping making it difficult to get through your day? Do you have trouble waking up?