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Adolescents at clinical-high risk for psychosis: Circadian rhythm disturbances predict worsened prognosis at 1-year follow-up

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ABSTRACT

Background: Individuals with psychotic disorders experience disruptions to both the sleep and circadian components of the sleep/wake cycle. Recent evidence has supported a role of sleep disturbances in emerging psychosis. However, less is known about how circadian rhythm disruptions may relate to psychosis symptoms and prognosis for adolescents with clinical high-risk (CHR) syndromes. The present study examines circadian rest/activity rhythms in CHR and healthy control (HC) youth to clarify the relationships among circadian rhythm disturbance, psychosis symptoms, psychosocial functioning, and the longitudinal course of illness.

Methods: Thirty-four CHR and 32 HC participants were administered a baseline evaluation, which included clinical interviews, 5 days of actigraphy, and a sleep/activity diary. CHR ($n = 29$) participants were re-administered clinical interviews at a 1-year follow-up assessment.

Results: Relative to HC, CHR youth exhibited more fragmented circadian rhythms and later onset of nocturnal rest. Circadian disturbances (fragmented rhythms, low daily activity) were associated with increased psychotic symptom severity among CHR participants at baseline. Circadian disruptions (lower daily activity, rhythms that were more fragmented and/or desynchronized with the light/dark cycle) also predicted severity of psychosis symptoms and psychosocial impairment at 1-year follow-up among CHR youth.

Conclusions: Circadian rhythm disturbances may represent a potential vulnerability marker for emergence of psychosis, and thus, rest/activity rhythm stabilization has promise to inform early-identification and prevention/intervention strategies for CHR youth. Future studies with longer study designs are necessary to further examine circadian rhythms in the prodromal period and rates of conversion to psychosis among CHR teens.

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1. Introduction

Psychotic disorders are debilitating illnesses associated with marked distress and functional impairment, which often results in a significant socioeconomic burden (e.g., greater healthcare utilization, reduced occupational productivity; Jin and Mosweu, 2017). Thus, a critical programmatic priority has focused on elucidating risk factors for psychosis onset with the purpose of enhancing early identification and prevention/intervention approaches that reduce the rates of conversion (Cannon et al., 2008). Longitudinal investigations with adolescents with clinical-high risk (CHR) syndromes (e.g., subthreshold symptoms of

psychosis, reduced psychosocial functioning) is a promising approach to identify etiological mechanisms implicated in disorder onset (Addington and Heinssen, 2012), as a high proportion (up to 36%) of CHR adolescents convert to psychosis within a two-year period (Fusar-Poli et al., 2012).

The sleep/wake cycle, which is comprised of two interacting processes (i.e., homeostatic sleep “Process S” and circadian pacemaker “Process C”; Borbely et al., 2016), is frequently disturbed in adults with psychotic disorders, including both medicated and medication-naïve individuals (Chan et al., 2016) and those with and without comorbid mood symptoms (Wulff et al., 2012). Specifically, disrupted sleep/wake cycles increase the severity of psychosis (Cohrs, 2008) and precede relapse of psychotic episodes (Benson, 2015), and interestingly, when addressed therapeutically, reduce psychotic symptom severity (Kantrowitz et al., 2010). While sleep/wake cycle disturbances have

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been documented and investigated since the earliest conceptions of psychosis (Kraepelin et al., 1919), related clinical features have also recently garnered interest as potential biomarkers for CHR individuals (Lunsford-Avery and Mittal, 2013; Zanini et al., 2013).

To date, investigations with at-risk adolescents have largely focused on the sleep component of the sleep/wake cycle with results showing increased self-reported, actigraphic-measured, and polysomnographic-measured (PSG) sleep disturbances among at-risk participants compared to healthy controls (HC) (Brietzke et al., 2015; Castro et al., 2015; Castro et al., 2012; Keshavan et al., 2004; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Poe et al., 2017; Zanini et al., 2015). These disturbances in sleep are related to increased concurrent psychosis symptoms, poorer psychosocial functioning, and sleep-related neural abnormalities (i.e., thalamus reductions) (Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Poe et al., 2017). Perhaps most importantly, self-reported and actigraphic-measured sleep disturbances at clinical intake predict increased positive symptom severity over a 1-year period among CHR adolescents (Lunsford-Avery et al., 2015), suggesting potential risk markers for psychosis onset. Indeed, prior work has revealed self-reported sleep disturbances as an important factor in predicting transition to psychosis among CHR youth (Ruhmann et al., 2010).

However, less is known about disruptions to the circadian process of the sleep/wake cycle (24-hour, time-dependent, light-dependent, oscillatory variation in sleep propensity; Borbely et al., 2016) among at-risk adolescents or how circadian disturbances may contribute to worsened clinical outcomes for affected youth. Although sleep and circadian processes are closely interrelated, they are also separate processes with distinct biological markers, neural underpinnings, and implications for treatment (Borbely et al., 2016). Thus, clarifying a role of circadian disruptions in addition to sleep problems in the development of psychosis has important implications for understanding the etiology of the illness as well as developing interventions. In a recent study, Castro et al. (2015) investigated circadian rest/activity rhythms in teens displaying At Risk Mental States (i.e., ARMS; risk of psychosis and/or bipolar disorder) and found rhythms to be more irregular, fragmented, and desynchronized with the light/dark cycle among at-risk youth compared to HC. In a follow-up case study of three youth from the ARMS project, there was evidence of irregular rest/activity rhythms in the period directly prior to psychosis conversion (Goncalves et al., 2016), suggesting that circadian disturbances may play a role in psychosis development. However, given the small sample size, this issue warrants further attention.

This study had three principal objectives. First, we aimed to replicate Castro et al.'s (2015) findings and hypothesized that CHR adolescents would display disrupted circadian rhythms compared to HC youth. Second, to extend this work, we tested whether circadian rhythm disturbances relate to concurrent psychosis symptom severity and psychosocial impairment among CHR youth. Finally, among CHR youth, we investigated whether circadian rhythm disturbances at intake predicted psychosis symptom severity and worsened psychosocial functioning at the 1-year follow-up assessment. Evidence linking circadian disturbances and worsened prognosis for CHR youth would support a possible role of rest/activity disruptions in psychosis pathophysiology as well as inform potentially beneficial prevention/intervention efforts for individuals at risk for psychosis.

2. Method

2.1. Procedure

Participants were recruited via internet and print advertisements and physician referrals as part of the Adolescent Development and Preventative Treatment (ADAPT) program's ongoing longitudinal study of CHR youth. At the intake evaluation (time 1; T1), informed consent and assent were obtained and adolescents participated in clinical

interviews to determine eligibility, and if deemed eligible, completed self-report forms as well as 5 days of actigraphy and a sleep/activity diary (described below). Participants returned for a 1-year follow-up (time 2; T2), at which time clinical interviews were repeated to assess for changes in symptom severity and psychosocial functioning during the follow-up period.

2.2. Participants

Participants (CHR = 45, HC = 42) included youth aged 12–21 years. Several adolescents in each group (CHR = 11, HC = 10) were excluded after the intake evaluation due to deficient data regarding rest/activity patterns (<5 days of registration or removing the actigraph for >3 h), and only the final sample (CHR = 34, HC = 32) were included in T1 analyses. Participants who were excluded based on insufficient actigraphy data did not differ from included adolescents on any demographic or clinical variables. Inclusion criteria for the CHR group included: 1) attenuated positive psychosis symptoms (moderate severity) or 2) global functioning declines accompanied by family history of psychosis or schizotypal personality disorder (Miller et al., 1999). Histories of head injury/loss of consciousness, intellectual disability, and neurological disorder were exclusionary for both groups. Formal psychotic disorder was a further exclusionary criterion for CHR youth as was Axis I disorder and family history of psychosis for HC. Twenty-nine of 34 CHR participants had returned for the 1 year follow-up at the time T2 analyses were completed.

2.3. Clinical assessments

The Structured Interview for Prodromal Symptoms (i.e., SIPS; McGlashan et al., 2001; Miller et al., 2003; Rosen et al., 2006), Structured Clinical Interview for DSM-IV (i.e., SCID, Research Version; First et al., 1995), and Global Assessment of Functioning (i.e., GAF; Jones et al., 1995) assessed CHR syndromes, Axis I disorders, and psychosocial functioning respectively at both time points (interrater reliability Kappa > 0.80). As depression is common in CHR youth (Rosen et al., 2006; Salokangas et al., 2012; Shioiri et al., 2007; Svirskis et al., 2005) and related to circadian rhythms among adolescents (Robillard et al., 2013), youth completed the 21-item Beck Depression Inventory-II at T1 (BDI-II; Beck et al., 1996) which served as a covariate in statistical analyses.

2.4. Actigraphic measurement of circadian rhythms

Circadian rhythms were measured at T1 via an ActiSleep wrist monitor (approximate cost = \$225; ActiGraph; Pensacola, FL), which was continuously worn by participants over a 5 day period. Participants concurrently completed a daily sleep/activity diary, which required participants to record bedtimes, wake times, and nap times, as well as information about activity participation, school attendance, and any medical concerns (Acebo and LeBourgeois, 2006; Ancoli-Israel et al., 2003). Participants were also asked to record any times they removed the actigraph (e.g., bathing), which was confirmed by ActiLife validation scoring (version 5.10.0).

Circadian rhythms variables were derived from the actigraphy data using the method described by Castro et al. (2015), including: autocorrelation function (Ac; slope of the time correlation line (log-transformed); indicative of rhythm fragmentation; lower values represent less fragmented rhythms), interdaily stability (IS; value for 1440 min provided by Sokolove–Bushell periodogram analysis; denotes synchronization of circadian rhythms with the light/dark cycle), intradaily variability (IV; mean of the first derivative of the actigraphy data normalized by the total variance; a measure of rest-activity rhythm fragmentation), M10 (mean activity level during the most active 10 h of the day; higher values are indicative of a more active lifestyle), F10 (onset of M10), L5 (sum activity during the least active 5 h of the

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