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Sleep dysfunction and thalamic abnormalities in adolescents at ultra high-risk for psychosis

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ABSTRACT

Background: Sleep dysfunction is a pervasive, distressing characteristic of psychosis, yet little is known regarding sleep quality prior to illness onset. At present, it is unclear whether sleep dysfunction precedes the emergence of psychotic symptoms, signifying a core feature of the disorder, or if it represents a consequence of prolonged contact with aspects of schizophrenia and its treatment (e.g., medication use or neurotoxicity) or co-morbid symptoms (e.g., depressive and manic symptomatology). The current study examined sleep dysfunction in adolescents at ultra high-risk (UHR) for psychosis, relationships between sleep disturbances and psychosis symptoms, volume of an integral sleep-structure (thalamus), and associations between thalamic abnormalities and sleep impairment in UHR youth.

Method: Thirty-three UHR youth and 33 healthy controls (HC) participated in a self-assessment of sleep functioning (Pittsburgh Sleep Quality Index; PSQI), self and parent-report clinical interviews, and structural magnetic resonance imaging (MRI).

Results: UHR adolescents displayed increased latency to sleep onset and greater sleep disturbances/disrupted continuity compared to HC youth, over and above concurrent mood symptoms. Among UHR youth, increased sleep dysfunction was associated with greater negative symptom severity but not positive symptoms. Compared to HC adolescents, UHR participants displayed decreased bilateral thalamus volume, which was associated with increased sleep dysfunction.

Conclusions: Sleep dysfunction occurs during the pre-psychotic period, and may play a role in the etiology and pathophysiology of psychosis. In addition, the relationship of disrupted sleep to psychosis symptoms in UHR youth indicates that prevention and intervention strategies may be improved by targeting sleep stabilization in the pre-psychotic period.

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1. Introduction

Sleep dysfunction is a pervasive characteristic among individuals with psychosis, associated with increased illness severity, greater patient and family distress, and reduced quality of life (Cohrs, 2008; Waters and Manoach, 2012). Specifically, impairments in quality, continuity, efficiency, duration, non-rapid eye movement (NREM), and rapid eye movement (REM) sleep have been reliably observed in schizophrenia samples, irrespective of medication status (Chouinard et al., 2004) and mood state (e.g., Wulff et al., 2012). In addition, strong evidence suggests that disturbed sleep is related to increased negative and positive symptoms among affected patients (Cohrs, 2008), implicating a potential role for sleep disturbance in schizophrenia pathophysiology (Keshavan and Tandon, 1993; Monti and Monti, 2005). Indeed, dysfunctional sleep often precedes relapse (Benson, 2008), and when targeted in adults with schizophrenia, patients report improvements in both sleep quality and symptoms (Kantrowitz et al., 2010).

Despite ample support demonstrating sleep dysfunction in schizophrenia populations, little is known regarding the extent to which problematic sleep is present prior to psychosis onset, or how sleep disturbance may relate to symptoms in at-risk youth. Specifically, it is unclear whether sleep dysfunction precedes psychosis onset, if it represents a consequence of prolonged contact with schizophrenia

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and its treatment (e.g., medication use or neurotoxicity), or is a reflection of co-morbid depressive and hypomanic/manic symptoms. To the extent that problematic sleep precedes schizophrenia onset, it may represent a potential target for early identification, prevention, and intervention efforts for those at risk for psychosis.

Initial findings from retrospective investigations with schizophrenia patients suggest that general sleep disturbance, as well as specific deficits in duration and continuity, may precede schizophrenia onset (for reviews, see Yung and McGorry, 1996; Lunsford-Avery and Mittal, 2013). However, these studies are limited by potential recall inaccuracies and difficulties determining the temporal order of onset of sleep dysfunction versus frank psychosis. Circumventing these limitations, recent genetic risk (GR) and ultra high-risk (UHR) investigations show promise in providing a window for investigating potential processes contributing to schizophrenia etiology.

To date, two studies have examined dysfunctional sleep in at-risk populations. Using polysomnography, Keshavan et al. (2004) observed reduced NREM sleep, REM percentage, and REM counts/minute, and a trend toward disrupted continuity among GR youth compared to healthy controls. A second study utilizing a UHR sample found increased NREM sleep and decreased REM percentage compared to normal sleep distributions (Castro et al., 2012). These studies provide initial support for atypical sleep in at-risk populations; however, further investigation is critical for confirming and expanding upon these initial results. In addition, these investigations did not directly assess the relationship between sleep dysfunction and psychosis symptoms or underlying neural structures, information essential for clarifying a potential role of problematic sleep in schizophrenia pathophysiology.

Dovetailing with this literature, significant evidence suggests that neural structures underlying healthy sleep function are abnormal in patients with psychosis (e.g., Wright et al., 2000; Davidson and Heinrichs, 2003; Glahn et al., 2008; Fornito et al., 2009). In particular, the thalamus, a structure integral for sleep regulation (see Coulon et al., 2012 for a review), is consistently reduced bilaterally among schizophrenia patients (Konick and Friedman, 2001; Adriano et al., 2010), leading researchers to suggest that thalamic abnormalities may play a prominent role in schizophrenia development (Corson et al., 1999). Several GR studies have similarly found bilateral thalamic reductions (Lawrie et al., 1999, 2001; Bhojraj et al., 2011), suggesting that thalamic abnormalities may precede psychosis onset. The thalamus has also been the subject of spectroscopy and functional studies in the prodrome, which indicate that altered glutaminergic activity is characteristic of UHR individuals (Fusar-Poli et al., 2007, 2011). However, no studies have directly examined the relationship between thalamus reductions and sleep dysfunction in at-risk youth.

In the current study we assessed whether self-reported sleep (latency, duration, efficiency, continuity/disturbances, quality) is disrupted in UHR youth compared to healthy controls (HC), and if so, how aspects of sleep disturbance may relate to symptoms (i.e., positive, negative) in at-risk youth. The second aim was to determine if an important neural structure underlying sleep function (i.e., left/right thalamus) is abnormal in UHR youth and if so, whether thalamic abnormalities are associated with sleep deficiencies. Evidence of sleep and thalamus abnormalities in UHR youth, paired with associated elevations in symptom severity, may indicate a possible role for sleep dysfunction in psychosis pathophysiology, as well as potentially highlight a target for prevention/intervention strategies with this population.

2. Method

2.1. Participants

Participants were 33 UHR and 33 HC adolescents aged 12 to 21 years (mean: 18.29; SD: 2.31). A first-degree relative/parent (>age 18) was invited to participate for consent purposes and to corroborate interviews regarding symptoms. Participants were recruited through the Adolescent Development and Preventive Treatment (ADAPT) research program at the University of Colorado Boulder, and were referred by community health care providers or self-referred in response to media announcements. UHR inclusion criteria included: presence of a UHR syndrome defined by moderate levels of positive symptoms and/or a decline in global functioning accompanying the presence of schizotypal personality disorder and/or a family history of psychosis (Miller et al., 1999). Exclusion criteria for all participants included: lactation, tic disorder, history of significant head injury or other physical disorder affecting brain functioning, mental retardation, or history of a substance dependence disorder in the prior 6 months. In addition, life-long medical histories were gathered from a parent or guardian (in the case of minors) and/or the participant during the screening process and individuals with any history of neurological disorder were excluded. Imaging data from the MRI were also examined for any incidental pathology by a neuroradiologist. In the event of an anomaly, participants were referred for a neurological consultation. However, this was not necessary for any of the participants included in the present study. Additionally, UHR exclusion criteria included an Axis I psychotic disorder diagnosis, and HC exclusion criteria included any Axis I diagnosis or a first-degree relative with psychosis.

2.2. Clinical measures

The Structured Interview for Prodromal Symptoms (SIPS) was used to diagnose UHR syndromes, and included the scale of prodromal symptoms (SOPS; positive and negative subscales) (McGlashan et al., 2001; Rosen et al., 2002; Miller et al., 2003). The SIPS has sound predictive validity and interrater reliability (Miller et al., 2003). DSM-IV Axis I disorders were diagnosed using the Structured Clinical Interview for the DSM-IV (SCID, research version) (First et al., 1995), which has been shown to demonstrate excellent validity and reliability (Zanarini et al., 2000; Zanarini and Frankenburg, 2001; Lobbestael et al., 2011). Training of interviewers (who were advanced doctoral students) was conducted over a 2-month period, and inter-rater reliabilities exceeded the minimum study criterion of Kappa $\geq$ 80.

Given the established relationship between sleep dysfunction and mood symptoms in adolescents (Lunsford-Avery et al., 2012), and the prevalence of mood disorders in high-risk populations (Svirskis et al., 2005; Rosen et al., 2006; Shioiri et al., 2007; Salokangas et al., 2012), symptoms of depression and hypo(mania) were controlled for in the primary analyses (described below). The 21-item Beck Depression Inventory-II (BDI-II) self-report questionnaire assessed depressive symptoms over the prior two-week period (Beck et al., 1996). The BDI-II exhibits excellent internal consistency, test–retest reliability, and convergent, divergent, and construct validity in adolescent populations (Osman et al., 2008). The 10-item Parent General Behavior Inventory (P-GBI) Short Form — Hypomanic/Biphasic scale assessed parents' observations of (hypo)mania symptoms among participants. The P-GBI short form has strong reliability, and successfully discriminates adolescents with bipolar disorder from those with other axis I disorders (Youngstrom et al., 2008).

2.3. Sleep dysfunction

The 19-item, self-report Pittsburgh Sleep Quality Index assessed domains of sleep dysfunction, including sleep quality, latency, duration, efficiency, and disturbances/continuity (Buysse et al., 1989). Scoring of the PSQI total score ranges from 0 to 21 (sub-domains range = 0–3), with higher scores reflecting greater impairment. The PSQI has been shown to demonstrate acceptable reliability and validity (Buysse et al., 1989), and has been used widely in schizophrenia (e.g., Ritsner et al., 2004; Hofstetter et al., 2005; Afonso et al., 2011) and adolescent clinical populations (e.g., Jones et al., 2006; Kaneita et al., 2009).

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