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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.

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).

2.4. Imaging

A T1-weighted 3D magnetization prepared rapid gradient multi-echo sequence (MPRAGE; sagittal plane; repetition time [TR] = 2530 ms; echo times [TE] = 1.64 ms, 3.5 ms, 5.36 ms, 7.22 ms, 9.08 ms; GRAPPA parallel imaging factor of 2; 1 mm^3 isomorphic voxels, 192 interleaved slices; FOV = 256 mm; flip angle = 7°; time = 6:03 min) whole brain structural MRI scan was acquired using a Siemens 3-Tesla Magnetom TIM Trio MRI scanner (Siemens AG, Munich, Germany). The left and right thalamus were delineated automatically using FMRIB's Integrated Registration and Segmentation Tool (FIRST) algorithm within FMRIB's Software Library (FSL) image-processing suite (Patenaude, 2007). FIRST also returned values for each participant's total intracranial volume (TICV; the sum of whole-brain gray matter, white matter, and cerebrospinal fluid) and the thalamus structures (mm^3 metric) were divided by TICV to control for whole brain volume. Freesurfer segmentations were examined by an expert neuroanatomist (J.O.) using a combination of automated QA procedures and visual inspection. All subjects were determined to have accurate segmentation of the thalamus.

2.5. Statistical analyses

Stepwise linear regressions covarying for age and gender in step 1 and mood symptoms (BDI-II and P-GBI) in step 2 assessed group differences in PSQI scores (quality, latency, efficiency, duration, disturbances, total score). Linear regressions covarying for age, gender, and TICV compared left/right thalamus volume in UHR versus HC youth. Because medication was used in the UHR group alone, it was not appropriate to treat medication as a covariate in the group comparison analyses. Instead, analyses were repeated with the medication-free proportion of the sample, which did not affect the magnitude or direction of findings. Based on group differences indicating marked sleep and thalamic abnormalities in the UHR group alone, subsequent analyses examining associations focused on the UHR group. Among UHR youth, stepwise linear regressions covarying for mood symptoms in step 1 and dummy-coded medications (mood stabilizers, anti-psychotics, stimulants, SSRIs) in step 2 tested associations between sleep dysfunction and attenuated positive and negative symptoms on the SIPS. Finally, stepwise linear regressions covarying for mood symptoms in step 1 and medications in step 2 examined associations between thalamus volumes and PSQI variables among UHR adolescents.

3. Results

3.1. Demographics of the UHR and HC samples

Participants included 33 UHR and 33 HC adolescents. UHR adolescents included 22 males (67%) and 11 females (33%), with an average age of 18.73 (SD = 1.89). HC adolescents included 14 males (42%) and 19 females (58%), with an average age of 17.85 (SD = 2.62). Groups did not differ by age (F (1, 64) = 2.38, p = .13) or racial background (X^2 (3, 63) = 5.15, p = .16). A significantly greater number of males were in the UHR group compared to HC (X^2 (1, 65) = 3.91, p = .05). Due to this gender difference between groups, the analyses were replicated in a gender-matched sub-section of the sample. The direction and magnitude of our findings were unaltered; thus, results from the full sample are reported. UHR adolescents were more likely than HC to be taking mood stabilizers (X^2 (1, 65) = 4.26, p = .04), stimulants (X^2 (1, 65) = 9.10, p < .01), anti-psychotics (X^2 (1, 65) = 4.26, p = .04), and SSRIs (X^2 (1, 65) = 4.00, p < .05); however, the majority of UHR (n = 20) and HC (n = 32) adolescents were not medicated. See Table 1.

Table 1
Demographic characteristics of the UHR and HC samples.

Variable	UHR sample (n = 33)	HC sample (n = 33)	p value
Mean (SD)			
Age in years	18.73 (1.89)	17.85 (2.62)	*ns*
SIPS-Positive	11.85 (4.68)	.76 (1.44)	.00
SIPS-Negative	12.16 (7.22)	.73 (1.31)	.00
P-GBI	9.76 (7.11)	1.29 (2.66)	.00
BDI	18.81 (13.08)	4.61 (5.86)	.00
Number (%)			
Gender (male)	22 (67%)	14 (42%)	.05
Race			*ns*
Asian	0 (0%)	4 (12%)	
African American	1 (3%)	0 (0%)	
Caucasian	31 (94%)	28 (85%)	
Other	1 (3%)	1 (3%)	
Medications			
SSRI	6 (18%)	1 (3%)	.05
Stimulant	8 (24%)	0 (0%)	.00
Mood stabilizer	4 (12%)	0 (0%)	.04
Anti-psychotic	4 (12%)	0 (0%)	.04

Abbreviations: UHR, ultra high-risk; HC, healthy controls; SIPS, Structured Interview for Prodromal Symptoms (total symptoms); P-GBI, Parent General Behavior Inventory; BDI, Beck Depression Inventory; SSRI, Selective Serotonin Reuptake Inhibitor.

3.2. Group differences in sleep dysfunction

Controlling for age, gender, and mood symptoms, UHR adolescents endorsed significantly increased latency (F (5, 40) = 5.40, p = .01), greater disturbances (F (5, 40) = 5.53, p = .01), and a trend toward increased total PSQI score (F (5, 40) = 3.63, p = .10) compared to HC. Groups did not differ on duration (F (5, 40) = 0.64, p = .21), efficiency (F (5, 40) = 0.36, p = .28), or quality (F (5, 40) = 0.61, p = .22). See Fig. 1.

3.3. Relationships of psychosis symptoms to sleep dysfunction in UHR youth

Controlling for medications and mood symptoms, decreased duration (F (7, 15) = 11.61, p < .01), increased latency (F (7, 15) = 4.70, p = .02), decreased quality (F (7, 15) = 8.66, p < .01), and increased PSQI total score (F (7, 15) = 7.55, p < .01) were significantly related to increased negative symptom score on the SIPS in the UHR sample. Increased negative symptoms were not related to efficiency (F (7, 15) = 0.73, p = .20) or disturbances (F (7, 15) = 0.64, p = .22). None of the PSQI variables were related to positive symptoms among UHR youth. See Table 2.

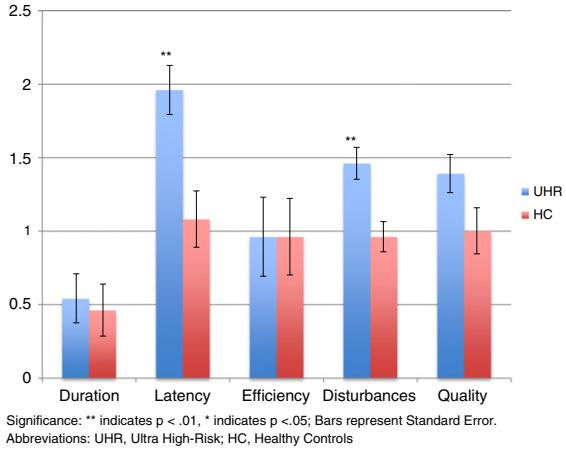

Fig. 1. Group differences in PSQI sleep variables.

Table 2
Relationship of sleep dysfunction to psychosis symptoms in the UHR sample.

	SIPS positive	SIPS negative
Duration	.050	−.514**
Latency	−.072	.378*
Efficiency	−.134	−.159
Disturbances	.150	−.170
Quality	.201	−.483**
Total Score	.013	.507*

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Abbreviations: SIPS, Structured Interview for Prodromal Symptoms.
Significance:
** Indicates $p < .01$.
* Indicates $p < .05$.

Table 3
Relationship of sleep dysfunction to thalamic abnormalities in the UHR sample.

	Left Thalamus	Right Thalamus
Duration	.207	.055
Latency	−.521**	−.425*
Efficiency	.446*	.471*
Disturbances	−.184	−.281
Quality	.696**	.562**
Total	−.779**	−.657**

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance:
** Indicates $p < .01$.
* Indicates $p < .05$.

3.4. Group differences in thalamus volumes

Compared to HC youth, UHR adolescents displayed significantly decreased gray matter volume of the left ($F(3, 53) = 4.59$, $p = .02$) and right ($F(3, 53) = 6.42$, $p < .01$) thalamus, controlling for age and gender. See Fig. 2.

3.5. Decreased thalamus volume and sleep dysfunction in UHR youth

Among UHR youth, reduced left thalamus volume was significantly associated with increased latency ($F(7, 14) = 6.68$, $p = .01$), decreased efficiency ($F(7, 13) = 4.32$, $p = .03$), reduced quality ($F(7, 14) = 13.91$, $p = .001$), and increased PSQI total score ($F(7, 13) = 13.07$, $p = .002$), over and above medications and mood symptoms. Volume of the left thalamus was not significantly related to duration ($F(7, 14) = 0.75$, $p = .20$) or disturbances ($F(7, 14) = 0.55$, $p = .47$). Similarly, controlling for medications and mood symptoms, reduced right thalamus volume was significantly associated with increased latency ($F(7, 14) = 3.55$, $p = .04$), decreased efficiency ($F(7, 13) = 5.02$, $p = .02$), reduced quality ($F(7, 14) = 6.56$, $p = .01$), and increased total PSQI score ($F(7, 13) = 7.21$, $p = <.01$) among UHR adolescents. Right thalamus volume was not associated with duration ($F(7, 14) = 0.05$, $p = .41$) or disturbances ($F(7, 14) = 1.32$, $p = .27$). See Table 3.

4. Discussion

Few empirical investigations have examined problematic sleep during the pre-psychotic period. Thus, it has been unclear whether dysfunctional sleep is present prior to psychosis onset, potentially reflecting the etiology and pathophysiology of the disorder, or represents comorbid mood symptoms or a consequence of schizophrenia exposure (neurotoxicity or medication use). Similarly, while abnormalities in sleep-related brain structures are pervasive in formal psychosis samples, little is known regarding whether these abnormalities exist in UHR youth, and how these brain anomalies may be related to problematic sleep in this population.

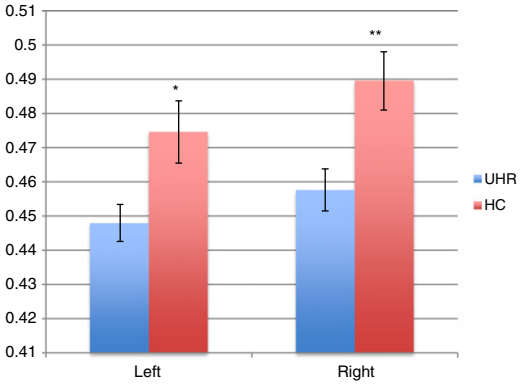

Fig. 2. Group differences in thalamic gray-matter volume.

Results indicated that UHR adolescents display increased latency and greater disturbances/disrupted continuity compared to HC, and greater difficulties with sleep (increased latency, reduced quality and duration, total PSQI score) were associated with increased negative symptoms among UHR youth. In addition, bilateral thalamic reductions were observed in UHR adolescents compared to HC, and these abnormalities were related to increased latency, reduced efficiency, and decreased quality in the UHR sample. These findings are highly consistent with the formal psychosis literature, in which increased latency (Cohrs, 2008), disrupted continuity (e.g., Chouinard et al., 2004; Afonso et al., in press), and bilateral thalamic reductions (Konick and Friedman, 2001; Adriano et al., 2010) are reliably observed. The current study builds on this prior evidence by examining sleep dysfunction, thalamic structure, and symptoms in a single sample of UHR adolescents, allowing for delineation of the interrelationships between specific brain abnormalities and clinical features of psychosis prior to illness onset.

Evidence of greater sleep dysfunction in UHR youth suggests that problematic sleep may represent a core feature of psychosis, over and above concurrent mood symptoms. In addition, findings of specific sleep deficits in UHR youth may indicate a possible role for particular domains of sleep dysfunction (latency, continuity) in the etiology of psychosis, and highlight the potential utility of these domains as risk factors (aiding in early identification) and targets for prevention/intervention strategies for youth at risk for schizophrenia. Supporting this assertion are the observed associations between sleep problems and negative symptoms in the current study, as phenomena closely tied to negative symptoms are believed to be more proximal to the true etiology of schizophrenia (Bleuler, 2010; Forbes, 2010).

Second, evidence of thalamic reductions in the UHR sample suggests that a critical brain structure supporting sleep function is compromised in adolescents at risk for psychosis. As these abnormalities are present prior to onset, these findings indicate that reductions in sleep-related structures may play a potential role in schizophrenia pathophysiology. Additionally, the relationships observed between thalamic reductions and sleep dysfunction in UHR youth suggest that structural abnormalities may be contributing to the problematic sleep observed in individuals vulnerable to psychosis, highlighting a potential brain-based source of the sleep disturbances reported by UHR youth.

In a recent review (Lunsford-Avery and Mittal, 2013), we hypothesized a developmental diathesis–stress model in which sleep dysfunction reflects an underlying psychosis vulnerability, which is exacerbated during later adolescence due to neuromaturational/endocrine factors and biological/psychological stressors. Sleep dysfunction, in turn, contributes to enhanced stress, cognitive dysfunction, and neural development abnormalities, thus driving psychosis onset. Findings of a relationship between sleep dysfunction and thalamic abnormalities in UHR youth provide support for the sleep-brain developmental pathways of this model;

however, extensive research utilizing multiple time points is essential for clarifying the role of sleep dysfunction in psychosis etiology.

This study should be considered in the context of several limitations. First, although a relative strength involved child and parent report of mood symptoms, sleep disturbances were assessed via a self-report questionnaire. While individuals tend to be fairly accurate reporters of sleep difficulties, self-assessment of some sleep domains (e.g., continuity, efficiency) may be less precise than objective measures (e.g., actigraphy and polysomnography) (Lockley et al., 1999). Future studies utilizing actigraphic and polysomnographic methods are essential for further clarifying the presence and characteristics of sleep dysfunction in UHR youth. Polysomnography has the added advantage of examining REM and NREM variables. As REM and NREM have been shown to be disrupted in schizophrenia populations (for reviews, see Monti and Monti, 2005; Benson, 2008; Cohrs, 2008) and two at-risk samples (Keshavan et al., 2004; Castro et al., 2012), observations of functioning in these domains in UHR youth remain an important question unaddressed by the current study.

Another limitation is that data were collected at a single time point. As only 35% of UHR adolescents subsequently develop psychosis (Cannon et al., 2008), discovering risk factors predictive of schizophrenia conversion is an important research priority. Specifically, discerning those most likely to covert allows for providing targeted pharmacological/psychosocial preventive treatment to individuals most vulnerable to psychosis. As the current study focuses on one time point, it is not possible to determine if sleep dysfunction represents a clinically significant risk factor for conversion, or how sleep may play a role in psychosis etiology.

Given the relationship of sleep dysfunction and increased symptom severity in UHR youth, prevention/intervention efforts incorporating sleep stabilization may prove highly beneficial for providing relief to affected youth. In particular, Cognitive Behavioral Therapy for Insomnia (CBT-I) has been shown to improve sleep in adult (Edinger et al., 2001) and adolescent (Gradisar et al., 2011) populations, and may be particularly beneficial for targeting the specific sleep difficulties observed in at-risk adolescents. Future research may determine if incorporation of sleep-specific strategies into UHR interventions not only alleviates current symptoms, but also delays or prevents schizophrenia onset.

An additional direction for future research may focus on determining the precise location of atrophy within the thalamus among UHR youth. The thalamus is a complex neuroanatomical structure with projections throughout the cerebral cortex. Higher resolution imaging and multimodal imaging strategies would allow for an analysis of the thalamus structure in greater depth, and further clarify how lesions to specific locations within the thalamus may relate to the sleep difficulties observed within UHR youth.

In conclusion, this study provides evidence for sleep disturbance in adolescents at risk for psychosis, related to increased symptoms and reductions in thalamic volume, a structure vital for healthy sleep. Because sleep dysfunction is present prior to illness onset, it may represent a core feature of schizophrenia, playing a role in psychosis etiology. However, future research is critical for determining the role of problematic sleep in the etiology and pathophysiology of psychosis.

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Contributors

Ms. Lunsford-Avery and Dr. Mittal conceptualized the study. Ms. Lunsford-Avery conducted the analyses and drafted the manuscript. Dr. Mittal obtained funding and helped to conduct the analyses and aided in drafting the manuscript. Mr. Dean, Ms. Pelletier-Baldelli, and Ms. Smith Watts helped to collect the data, interpret the results, and draft the manuscript. Dr. Orr, Dr. Bernard, Mr. Millman, and Ms. Gupta helped to interpret the data and draft the manuscript.

Conflict of interest

There are no conflicts of interest to report.

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