SLEEP DYSFUNCTION IN ADOLESCENTS AT HIGH RISK FOR PSYCHOSIS

by

JESSICA RUTH LUNSFORD AVERY

B.A., University of Virginia, 2006

M.A., University of Colorado Boulder, 2010

A thesis submitted to the

Faculty of the Graduate School of the

University of Colorado in partial fulfillment

of the requirement for the degree of

Doctor of Philosophy

Department of Psychology and Neuroscience

2013

This thesis entitled:
Sleep Dysfunction in Adolescents at High Risk for Psychosis
written by Jessica R. Lunsford Avery
has been approved for the Department of Psychology and Neuroscience

_____
Vijay A. Mittal, Ph.D. Chair

_____
Angela Bryan, Ph.D.

_____
Monique LeBourgeois, Ph.D.

_____
David Miklowitz, Ph.D.

_____
Mark Whisman, Ph.D.

Date_____

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

IRB Protocol # 10-0398

Avery, Jessica Ruth Lunsford (Ph.D., Psychology and Neuroscience)

Sleep Dysfunction in Adolescents at High Risk for Psychosis

Thesis directed by Assistant Professor Vijay A. Mittal

Sleep dysfunction is a pervasive and distressing symptom in schizophrenia, yet little is known regarding the extent to which problematic sleep is present prior to the onset of illness, or how sleep impairment may relate to symptoms in at-risk individuals. The current thesis explores two primary aims. First, I examined whether adolescents at ultra high-risk (UHR; n = 33) for psychosis display increased sleep dysfunction (duration, continuity, latency, efficiency, total movement counts, disturbances, quality) on subjective (Pittsburgh Sleep Quality Index; PSQI) and objective (actigraphy) measures compared to healthy controls (HC; n = 33), and if present, how sleep disturbances relate to symptoms (positive, negative, disorganized) among UHR youth. Second, magnetic resonance (MRI) and diffusion tensor (DTI) imaging were employed to determine if neural structures (thalamus) and tracts (anterior thalamic radiations) underlying sleep function are abnormal in UHR adolescents compared to HC participants, and if so, how neural abnormalities relate to sleep impairment in UHR youth. An exploratory aim examined relationships between subjective and objective measures of sleep disturbance in UHR youth. Results indicated that UHR adolescents displayed increased latency, greater disturbances, decreased efficiency, disrupted continuity, and increased sleep movements compared to HC youth. Reduced duration, increased latency, and decreased quality predicted elevated negative symptoms in UHR youth, and decreased efficiency, disrupted continuity, and increased movements during sleep predicted increased positive and disorganized symptoms. Bilateral thalamus volume reductions were found in UHR compared to HC adolescents, and these

abnormalities predicted increased latency, decreased efficiency, reduced sleep quality, disrupted continuity, and increased movements among UHR youth. There were no group differences in anterior thalamic radiation integrity; however, in UHR patients, integrity decreases predicted greater disturbances, reduced quality, decreased efficiency, disrupted continuity, and increased movements. UHR adolescents accurately reported sleep efficiency, and subjective report of disturbances predicted sleep movements. These results suggest that sleep dysfunction occurs during the pre-psychotic period, and may play a role in the developmental diathesis-stress cascade driving schizophrenia onset. 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.

In honor of

Matthew Vincent Avery

John Jeffrey and Carol Walton Lunsford

David Jeffrey Lunsford

ACKNOWLEDGMENTS

First, I would like to thank my family for their unfailing love and support. In particular, thank you to my husband, Matt Avery, for journeying across the country from Washington, D.C., to Boulder, C.O., to Durham N.C. so that I could pursue my dream of achieving a Doctor of Philosophy in Clinical Psychology. He makes everyday a wonderful adventure. I also want to express my eternal gratitude to my parents, Jeff and Carol Lunsford, who have instilled in me the values of family, education, and service to others. The world is a better place for their presence, and I could not have achieved this accomplishment without their belief in my abilities. Finally, thank you to my brother, Dave Lunsford, whose wisdom, ready wit, and gentle good humor always sustain me in the face of seemingly insurmountable obstacles. I am lucky to have been born with a built-in best friend.

Secondly, I wish to recognize my excellent mentors, Drs. Vijay Mittal and David Miklowitz, for their enduring support and encouragement, insightful supervision, and instructive feedback throughout my graduate education. Their dedication to improving the lives of individuals impacted by psychiatric disorders continually inspires me to be the best clinician and researcher possible, and the quality of this project is a testament to their invaluable guidance. Thank you also to the members of my committee, Drs. Angela Bryan, Monique LeBourgeois, and Mark Whisman, who generously dedicated their time and expertise to the development and successful execution of this dissertation. Words cannot fully express my appreciation for their intellectual contributions and enthusiasm for this project. Lastly, thank you to the members of the Adolescent Development and Preventive Treatment lab for their efforts on behalf of this study: Tina Gupta, Joseph Orr, Andrea Pelletier-Baldelli, Derek Dean, Blair Kleiber, Ashley Smith Watts, Daniel Leopold, Briana Robustelli, Zachary Millman, Olivia Russak, and Jessica Bernard.

CONTENTS

TABLES

Table

FIGURES

Figure

CHAPTER I

INTRODUCTION

Kraepelin and Bleuler first posited that schizophrenia and sleep are intricately intertwined in the early part of the twentieth century (Bleuler, 2010; Manoach & Stickgold, 2009). Since that time, a significant body of research has focused on sleep disruption in psychosis, with clinicians observing difficulties in initiating or maintaining sleep in 30 to 80% of patients with schizophrenia (Cohrs, 2008; Waters & Manoach, 2012). Consistent with these observations, deficits in general sleep function, continuity, duration, non-rapid eye movement (NREM), and rapid eye movement (REM) have been found in patients with schizophrenia, irrespective of medication status (Chouinard, Poulin, Stip, & Godbout, 2004) and mood state (e.g., Wulff, Dijk, Middleton, Foster, et al., 2012). Further, there is now considerable evidence to suggest that sleep is integrally tied to the pathophysiology of schizophrenia (Keshavan & Tandon, 1993; Monti & Monti, 2005). For example, sleep dysfunction often precedes relapse (Benson, 2008), and when targeted in adults with schizophrenia, patients report improvements in both sleep quality and psychiatric symptoms (Kantrowitz, Oakman, Bicket, Citrome, et al., 2010).

Despite widespread evidence associating dysfunctional sleep and the pathophysiology of schizophrenia, there has been little research investigating the presence of sleep disturbance in the integral period immediately preceding the onset of the disorder. More specifically, the degree to which sleep dysfunction predictably precedes psychosis onset is unknown, and it is unclear which specific domains of sleep are affected or how disturbed sleep may relate to symptoms in at-risk populations. As domains of sleep function reflect specific neurological processes, understanding this information may significantly elucidate our etiological conceptualization of psychosis, as well as potentially highlight one or more new vulnerability markers for identifying

those at imminent risk for developing schizophrenia. Delineating the role of sleep in the pathogenesis of schizophrenia may also strengthen conceptual models of psychosis.

There are several benefits to examining high-risk samples and in studying sleep dysfunction in particular. First, studying sleep function in schizophrenia patients treated with antipsychotic medication is complicated by the sedative and sleep-inducing effects of antipsychotics, which have been attributed to antihistaminergic, antiadrenergic, and anticholinergic properties (Gerlach & Peacock, 1995; Monti, BaHammam, Pandi-Perumal, Bromundt, et al., 2013; Waters & Manoach, 2012). Indeed, the primary contributing factors to variability between sleep studies in schizophrenia are methodological differences such as the medication status of sampled participants (Chouinard et al., 2004; Tandon, Shipley, Taylor, Greden, et al., 1992). As only a fraction of high-risk youth are treated with similar medications (e.g., 15%), this confound may be circumvented. Second, specifically studying sleep states in general has a unique benefit for improving etiological understanding of psychosis. Confounds that are relevant in schizophrenia and high-risk waking states, such as cognitive function, attention, and motivation, may not be as pertinent when comparing sleep-related brain activations in patients versus controls (Ferrarelli, Peterson, Sarasso, Rieder, et al., 2010; Vukadinovic, 2011). Thus, investigations of sleep dysfunction in samples at high-risk may clarify whether sleep disturbance is a byproduct of processes underlying the development of psychosis or alternatively, a key contributor to psychosis onset.

The Psychosis Prodrome

The onset of schizophrenia is typically preceded by a prodromal phase characterized by subtle attenuated symptoms such as positive phenomena, cognitive dysfunction, and socio-occupational functional decline (Cannon, Cadenhead, Cornblatt, Woods, et al., 2008; Haroun,

Dunn, Haroun, & Cadenhead, 2006). The prodromal period is of particular interest as a window for investigating processes involved in disease onset, as well as a potential point of prevention and intervention (Haroun et al., 2006; McGlashan, Addington, Cannon, Heinimaa, et al., 2007; Mittal, Karlsgodt, Zinberg, Cannon, et al., 2010). More specifically, recent studies have suggested that adolescents with a prodromal syndrome (i.e., showing moderate attenuated positive symptoms accompanied by a global decline in functioning; Miller, McGlashan, Rosen, Somjee, et al., 2002; Miller, McGlashan, Woods, Stein, et al., 1999; Miller, Zipursky, Perkins, Addington, et al., 2003) are at imminent risk for psychosis conversion, as approximately 35% convert to a psychotic disorder within a two-year period (Cannon et al., 2008).

From a research perspective, studying this prodromal population within the period prior to conversion may significantly inform etiological conceptualizations of psychosis, as this period is prior to when medications and neurotoxicity confound research (Haroun et al., 2006; McGlashan, 2006). It is also significant from a clinical perspective, as detecting potential risk factors will aid in the development of early intervention and prevention efforts with the potential to reduce the duration of untreated psychosis, ameliorate the course of illness, and delay or potentially prevent psychosis onset (Haroun et al., 2006; McGlashan, Zipursky, Perkins, Addington, et al., 2003; McGorry, Yung, Phillips, Yuen, et al., 2002; Morrison, French, Walford, Lewis, et al., 2004; White, Anjum, & Schulz, 2006; Woods, Breier, Zipursky, Perkins, et al., 2003). Because schizophrenia eliminates or severely limits the most productive years of an individual's life and may require lifelong family or institutional care, its costs to society are enormous (Wu, Birnbaum, Shi, Ball, et al., 2005). Thus, through potential contributions to early detection and intervention, the discovery of premorbid risk factors represents an opportunity to lessen suffering and costs to vulnerable individuals, families, and society. Sleep dysfunction

represents one potential marker that may have significant implications for clarifying etiological questions and supporting the development of early interventions.

Healthy Sleep Function

In healthy populations, the sleep-wake cycle is a complicated phenomenon composed of interactions between sleep homeostasis and circadian processes. Specifically, the sleep homeostasis process (process S) is an accumulating drive to sleep that increases the longer an individual remains awake and rapidly dissipates following sleep onset. Over the course of a day, process S interacts with a sleep-independent circadian process (process C), a 24-hour oscillatory variation in the propensity for sleep, which is dependent on the time of day and variability in exposure to light (Borbely, 1982; Borbely & Achermann, 1992).

Sleep architecture in healthy individuals is characterized by cycles of light sleep, deep slow-wave sleep (SWS), and REM sleep. Initially, sleep stages proceed sequentially, but as the night progresses, cycles through sleep stages occur in an out-of-sequence progression. Sleep begins in stage 1 (i.e., 5 – 10 minute transitional period between wakefulness and sleep, characterized by mixed frequency theta waves, slow rolling eye movements, and slightly reduced eye movement) and progresses into stages 2 (i.e., 20 minutes involving mixed-frequency brain waves with rapid bursts of rhythmic brain wave activity known as sleep spindles; decreased body temperature and slowing heart rate), 3 (i.e., transitional period between light sleep and very deep sleep characterized by 20–50% delta waves), and 4 (approximately 30 minutes of delta sleep). After stage 4 sleep, stages 3 and then 2 are repeated before REM sleep begins (i.e., characterized by mixed frequency electroencephalogram (EEG) with theta waves in combination with rapid eye movements and nearly absent chin electromyogram (EMG)). The body usually returns to stage 2 sleep following the REM cycle. The first cycle of REM sleep occurs approximately 80 -

100 minutes after sleep onset and lasts a very short amount of time (with each cycle, REM sleep lasts longer) (Hudson & Bush, 2010).

A complex network of neural structures and pathways supports healthy sleep patterns, and current models of sleep promotion focus on the dynamic interaction between wakefulness/arousal-promoting and sleep-promoting regions of the brain. Specifically implicated in the interaction of arousal- and sleep-promoting mechanisms are areas of the thalamus, hypothalamus, basal forebrain (BF), brainstem, and cortex, and thalamocortical pathways connecting these regions (Fuller, Gooley, & Saper, 2006; Stiller & Postolache, 2005; Taber & Hurley, 2006).

Sleep Dysfunction in Schizophrenia and At-Risk Populations

Sleep disturbances are prominent and distressing symptoms experienced by patients with schizophrenia (Benson, 2006; Cohrs, 2008; Monti & Monti, 2005; Waters & Manoach, 2012); at present, however, little is known regarding the extent to which problematic sleep is present prior to illness onset. Specifically, it is unclear whether sleep dysfunction precedes the emergence of psychotic symptoms, reflecting/driving pathophysiology and 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).

Three types of studies have the potential to inform the extent to which sleep dysfunction precedes emergence of frank psychotic symptoms: schizophrenia samples focusing on retrospective report of symptoms in the premorbid/prodromal period, genetic high-risk samples (GR: individuals under age 18 with a first-degree relative with schizophrenia and no symptoms or functional decline), and ultra high-risk samples (UHR, also known as “prodromal”: individuals displaying attenuated psychotic symptoms, adolescents under age 18 meeting criteria

for schizotypal personality disorder, or adolescents under age 18 displaying functional decline in the presence of genetic risk; Yung, McGorry, McFarlane, Jackson, et al., 1996).

Retrospective studies of patients diagnosed with schizophrenia provide an important perspective into the prodromal phase of illness. Although there are justified concerns due to potential recall inaccuracies, these studies represent initial attempts to identify risk factors prior to illness onset, and constitute the largest base of information regarding experiences in the premorbid period. GR studies, the first generation of prospective high-risk studies, evolved from the recognition that due to the strong genetic component of schizophrenia, a significant proportion of schizophrenia patients' offspring or younger first-degree relatives would inevitably develop psychosis. Further, as GR youth do not exhibit symptoms, a number of third variable confounds are eliminated. These intensive and long-term studies began between the 1960s and 1970s, and have continued to provide valuable insight into psychosis etiology (Ehrlich, Morrow, Roffman, Wallace, et al., 2010).

The newest generation of high-risk studies, or UHR investigations, capitalize on evidence that the majority of individuals (> 70%; Bleuler, 1950; Cannon, Rosso, Bearden, Sanchez, et al., 1999) who succumb to psychosis manifest prodromal signs of behavior disturbance, beginning in early adolescence and progressively worsening as the individuals approach young adulthood (the mean age of onset). Because as many as 35% of this group will develop a full psychotic disorder within 2 years (Cannon et al., 2008), and these studies are less labor intensive and more feasible than GR studies (higher base rate of UHR), a series of prospective UHR studies have commenced in the last decade. Further, because the psychosis prodrome represents both a viable intervention point (Haroun et al., 2006) and a developmental period with high potential to shed

light on psychosis etiology (Mittal & Walker, 2011), this method has been widely adopted for early intervention studies and lends particularly well to neurodevelopmental questions.

In the following sections, preliminary evidence of sleep dysfunction from retrospective, GR, and UHR investigations is reviewed. To the extent that sleep impairment is present prior to onset and involved in the etiology of schizophrenia, prevention and intervention efforts focusing on improving sleep functioning may benefit youth at risk for psychosis. See Table 1.

Table 1. Studies of sleep dysfunction prior to onset of psychosis

Type	Author	Population	Method	Results
General Sleep Disturbance	Bourgeois & Etchepare, 1986	Retrospect	Parent Interview	Increased sleep problems in childhood.
	Massou dit Bourdet & Laffy-Beufils, 2000	Retrospect	Parent Interview	Increased sleep problems in childhood.
	Verdoux et al., 1998	Retrospect	Parent Interview	Increased sleep problems in childhood.
	Frazee, 1953	Retrospect	Medical Record Review	Increased sleep problems in childhood.
	Birchwood et al., 1989	Retrospect	Family Interview	Sleep disturbance is a prodromal symptom.
	Häfner et al., 1992	Retrospect	Clinical Interview	Sleep disturbance present prior to onset.
	Hambrecht et al., 1994	Retrospect	Family Interview	Sleep disturbance present prior to onset.
	Heinrichs & Carpenter 1985	Retrospect	Clinical Interview	Sleep disturbance is a prodromal symptom.
	Parnas, 1999	Retrospect	Review	Sleep disturbance present prior

				to onset.
	Yung & McGorry, 1996a	Retrospect	Review	Sleep disturbance present prior to onset.
	Donlon & Blacker 1973; 1975	Retrospect	Self report/ Clinical Interview	Sleep disturbance present prior to onset.
	Tan & Ang, 2001	Retrospect	Clinical Interview	Sleep disturbance present prior to onset.
	Kim et al., 2009	Retrospect	Clinical Interview	Sleep disturbance present prior to onset.
	Gourzis et al., 2002	Retrospect	Clinical Interview	Sleep disturbances present prior to onset.
Sleep Duration	Bowers, 1968	Retrospect	Clinical Interview	Insomnia present prior to onset.
	Bowers & Freedman, 1966	Retrospect	Self report/ Clinical Interview	Insomnia/sleeplessness present prior to onset.
	Huber et al., 1980	Retrospect	Clinical Interview	Sleep deprivation as a prodromal symptom.
	Cameron, 1938	Retrospect	Family/Friend Interview	Sleeplessness present prior to onset.
	Yung & McGorry, 1996b	Retrospect	Clinical/ Family Interview	Abnormalities in sleep duration (insomnia/hypersomnia) present prior to onset.
	Miller et al., 2003	UHR	Clinical Interview	Abnormalities in sleep duration (insomnia/hypersomnia present prior to onset.
	Keshavan et al., 2004	GR	Polysomno-graphy	No significant reduction in TST.
Sleep Latency	Keshavan et al., 2004	GR	Polysomno-graphy	No difference in sleep latency between GR and controls.
Sleep Continuity	Beisser et al., 1967	GR	Parent Interview	Disruptions in sleep continuity present prior to onset.
	Keshavan et al., 2004	GR	Polysomno-graphy	Trend toward increased TAT.

Abbreviations: Retrospect, Retrospective Studies; GR, Genetic High Risk; UHR, Ultra High-Risk

General Sleep Disturbances

Sleep dysfunction represents a multifaceted dimension, including abnormalities in duration, REM and NREM stages, sleep-related behaviors (e.g., talking or walking during sleep), continuity, subjective quality, latency, and efficiency (Carskadon & Dement, 2005; Hori, Sugita, Koga, Shirakawa, et al., 2001; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Some studies involving schizophrenia and at-risk populations combine one or more specific dimensions of sleep disturbance into a general category. In these investigations, sleep disturbances are generally defined as irregularities or detrimental changes in sleep experiences, and are most often assessed via clinical interview, patient self-report, or interview with significant others, family members, and friends (Detre, 1966; Haffmans, Hoencamp, Knegtering, & van Heycop ten Ham, 1994; Royuela, Macias, Gil-Verona, Pastor, et al., 2009; Serretti, Mandelli, Lattuada, & Smeraldi, 2004).

As mentioned previously, general sleep dysfunction is commonly experienced by patients with psychotic disorders (for a review, see Cohrs, 2008), and is comparable to that experienced by individuals with primary insomnia (Doi, Minowa, Uchiyama, Okawa, et al., 2000). Specifically, broadly defined sleep disturbances are found in 30 to 80% of patients with schizophrenia (variability in results due to confounds such as medications) (Haffmans et al., 1994; Royuela et al., 2009; Serretti et al., 2004), and are present during both the acute and chronic phases of the disorder (Detre, 1966).

In addition to affecting patients with psychosis, there is considerable evidence to suggest that general sleep disturbances are common occurrences for individuals prior to schizophrenia onset. For instance, several retrospective studies assessing patients with psychotic disorders suggest that sleep problems in early childhood may differentiate individuals who subsequently

develop schizophrenia from healthy controls and/or individuals who develop other (non-psychotic) psychiatric disorders. Based on parental report, patients who developed schizophrenia in adulthood displayed a significantly greater number of non-specific sleep disturbances during early development (ages 0 – 5) than normal controls, suggesting that sleep irregularities are an important childhood antecedent to the development of psychosis (Bourgeois & Etchepare, 1986; Massou dit Bourdet & Laffy-Beaufils, 2000; Verdoux, Pauillac, Fournet, Bergey, et al., 1998).

Similar results were found in a sample of clinic-referred youth. Frazee (1953) examined the medical records of males (aged 5 to 16) referred to a juvenile clinic for the treatment of emotional and behavioral disorders. Although no participants reported psychotic symptoms at clinical intake, incidence of sleep disturbances reported at initial contact (e.g., nightmares, excessive sleep, or walking, talking, or screaming during sleep) was higher for those who would subsequently develop schizophrenia compared to individuals who developed non-psychotic internalizing or externalizing symptoms (as revealed by records of hospitalization in adulthood). While preliminary, these findings suggest that general sleep dysfunction is not only present prior to the onset of frank psychotic symptoms, but may distinguish individuals who develop psychosis from those who do not in early developmental stages.

In addition to abnormalities in childhood, individuals may experience detrimental changes in sleep in the prodromal period directly prior to schizophrenia onset. According to retrospective studies, patients with psychotic disorders and their family members report general sleep problems as one of the earliest signs of psychiatric illness, present in the period immediately preceding transition into psychosis (Birchwood, Smith, Macmillan, Hogg, et al., 1989; Hafner, Riecher-Rossler, Hambrecht, Maurer, et al., 1992; Hambrecht, Hafner, & Loffler,

1994; Heinrichs & Carpenter, 1985; Parnas, 1999; Yung & McGorry, 1996b). Consistent with these findings, Donlon and Blacker (1973, 1975) combined information from self-reports, clinical studies, and controlled experiments to propose that initial sleep disturbances represent a key symptom experienced in the first stage of psychotic decompensation, occurring before the emergence of overt psychotic symptoms.

More recent research focusing on first-episode patients' recall of symptoms prior to illness onset corroborates this notion. In a retrospective study of male members of the military in Singapore (where all males between ages 17 and 23 enlist in the National Service), unstructured and semi-structured interviews implicated sleep disturbances as significant prodromal experiences present prior to the manifestation of a first episode of psychosis (Tan & Ang, 2001). Similarly, utilizing the clinician-rated Korean Nottingham Onset Schedule (K-NOS), Kim and colleagues (2009) found that unfavorable changes in sleep patterns were a commonly reported symptom of the prodrome among individuals recruited from a university clinic. Finally, sleep disturbances may represent a prodromal symptom common across subtypes of schizophrenia. According to retrospective patient and family report on the Structured Clinical Interview for the DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995), sleep disturbances were present prior to emergence of a first episode in patients suffering from paranoid, disorganized, and undifferentiated schizophrenia (Gourzis, Katrivanou, & Beratis, 2002).

Taken together, the reviewed studies suggest that general sleep disturbances are prevalent symptoms experienced by individuals with schizophrenia. Importantly, findings from retrospective investigations support the hypothesis that non-specific sleep problems appear to manifest prior to the emergence of frank psychotic illness. Evidence of sleep abnormalities in the prodromal period suggest that irregularities in sleep may represent a core feature of psychotic

disorders, rather than a byproduct of neurotoxicity or protracted exposure to anti-psychotic medications.

Sleep Duration

In healthy populations, specific abnormalities in sleep duration are typically defined as difficulties initiating or maintaining sleep (Carskadon & Dement, 2005). Sleep duration is quantified either by objective measures, such as polysomnography or actigraphy, or subjective report from individuals and their family members. In sleep studies using objective measures, sleep duration is defined as "total sleep time (TST)", which sums the total time spent in each of the REM and NREM stages (Hori et al., 2001; Keenan & Hirshkowitz, 2011; Ohayon et al., 2004). In investigations relying on self- or collateral report of sleep duration, symptoms of sleep disorders, such as insomnia and hypersomnia, are assessed (Lockley, Skene, & Arendt, 1999).

For individuals with schizophrenia, sleep duration is frequently reduced (for reviews, see Cohrs, 2008; Monti & Monti, 2005), and these difficulties initiating and maintaining sleep are consistently present, regardless of medication status or phase of illness. Specifically, decreased TST has been observed in never-medicated or previously treated (Chouinard et al., 2004; Monti & Monti, 2004) and medicated patients (Haffmans et al., 1994) with schizophrenia, as well as in those in the acute and chronic phases of the disorder (Hudson, Lipinski, Keck, Aizley, et al., 1993; Lauer, Schreiber, Pollmacher, Holsboer, et al., 1997; Tandon et al., 1992). These findings suggest that attenuation of sleep duration is not only a pervasive and distressing symptom of schizophrenia, but may represent an intrinsic feature of psychotic disorders.

Consistent with this hypothesis, converging evidence from at-risk populations suggests that reduced sleep duration may be present prior to the onset of schizophrenia. For instance, several retrospective studies of individuals with schizophrenia have revealed diminution of sleep

time as a common symptom of the prodrome prior to onset of a first episode. Based on interviews and survey measures, sleeplessness and insomnia have been identified as preceding development of psychosis by patients (Bowers, 1968; Bowers & Freedman, 1966), clinicians (Bowers & Freedman, 1966; Huber, Gross, Schuttler, & Linz, 1980), and those in close contact with patients, including family members, friends, employers, and doctors (Cameron, 1938).

In addition, one retrospective study has indicated that reduced sleep time is not only a common symptom of the psychosis prodrome, but may be universal. Recruiting a sample from an early psychosis prevention and intervention center, Yung and McGorry (1996a) employed the clinician-administered Multidimensional Assessment of Psychotic Prodrome (MAPP) to assess symptoms experienced in the time between initial "non-psychotic changes" and onset of frank psychotic symptoms. According to responses provided by patients and their family members, abnormalities in sleep duration, including symptoms of insomnia and hypersomnia, were observed during the prodromal period for 100% of patients (n = 21), suggesting a potential prominent role for reduced sleep time in the developmental course of the disorder.

Individuals at risk for developing schizophrenia also experience reductions in sleep duration. Miller and colleagues interviewed individuals meeting criteria for UHR syndromes (mean age of participant = 17.8; Miller, Zipursky, Perkins, Addington, et al., 2003). Participants were initially diagnosed with the clinician-administered Structured Interview for Prodromal Syndromes (SIPS; McGlashan, Miller, & Woods, 2001; Miller, McGlashan, Rosen, Cadenhead, et al., 2003; Rosen, Woods, Miller, & McGlashan, 2002), which also assesses symptoms of the prodrome, including an item assessing sleep dysfunction (primarily focused on difficulties in initiation and maintenance of sleep). Specifically, out of the nineteen domains assessed by the SIPS, one domain measures abnormalities in sleep (i.e., G.1 Sleep Disturbance). Adolescents are

queried, “How have you been sleeping recently?”, and clinicians indicate the type of sleep disturbance described (i.e., having difficulty falling asleep, waking earlier than desired and not able to fall back asleep, sleeping during the day, day night reversal, or hypersomnia). Results indicated that 37% of UHR participants endorsed moderate to severe abnormalities in sleep duration on the SIPS, with females more likely to endorse sleep duration abnormalities than males.

To date, only one study has used an objective method to examine sleep duration in a high-risk (i.e., GR) population. Using data from two consecutive nights of polysomnography, Keshavan and colleagues (2004) compared TST among young first-degree relatives (aged 6 – 25) of patients with schizophrenia and healthy controls. While GR relatives displayed reduced TST in minutes (496 $\pm$ 55.9) compared to their healthy counterparts (528 $\pm$ 48.7), this difference did not reach statistical significance. Further research investigating TST in individuals at high genetic risk for psychosis is necessary to determine whether reduction in sleep duration is present in this population prior to onset of illness.

In sum, irregularities in sleep duration, assessed by either objective or interview measures, are prevalent and distressing symptoms commonly experienced by individuals with schizophrenia, regardless of phase of illness and medication status. In addition, findings from studies with at-risk populations, including studies with UHR or GR populations and retrospective investigations examining symptoms present prior to onset of psychosis suggest that abnormalities in sleep duration may represent an intrinsic feature of the disorder, playing a potential role in the etiology and development of psychosis in at-risk individuals.

Sleep Latency

Similar to abnormalities in sleep duration, impairment in sleep latency also reflects difficulties initiating a sleep period. However, rather than focusing on TST, studies of sleep latency in healthy populations focus specifically on the length of time preceding sleep onset. Sleep latency is quantified by objective measures (i.e., polysomnography and actigraphy), and is defined as the elapsed time from the clock time of lights out (i.e., when an individual initiates an attempt to sleep) to the first occurrence of sleep (or in polysomnography studies, the first epoch of NREM sleep; Hori et al., 2001, Keenan & Hirshkowitz, 2011). Over the typical lifespan, sleep latency increases, remaining stable throughout childhood and adolescence, and progressively amplifying over the course of adulthood (Ohayon et al., 2004).

Among patients with schizophrenia, sleep latency is persistently elevated in comparison to their healthy counterparts (for a review, see Cohrs, 2008). Importantly, several meta-analyses and recent studies have shown that sleep latency is increased in never-treated or drug-free patients with schizophrenia, highlighting a potential role for prolonged sleep latency in the development of psychosis (Chouinard et al., 2004; Salin-Pascual, Herrera-Estrella, Galicia-Polo, Rosas, et al., 2004; Yang & Winkelman, 2006).

Despite the pervasiveness of increased sleep latency in schizophrenia populations, only one study has examined sleep latency in a high-risk population. In a polysomnographic study with offspring and young relatives of psychosis patients, GR participants did not exhibit significantly increased sleep latency (22.3 $\pm$ 12.1 minutes) compared to healthy controls (18.2 $\pm$ 12.1) ($p = 0.18$; Keshavan, Diwadkar, Montrose, Stanley, et al., 2004). Thus, while increased sleep latency is a pervasive impairment in schizophrenia, the extent to which elevations in sleep latency are present prior to the emergence of psychosis remains unknown, and the role of this

type of sleep dysfunction in the etiology of schizophrenia an important subject for empirical inquiry.

Sleep Continuity

Irregularities in sleep continuity typically manifest as interruptions during the sleep period, and include frequency and length of awakenings once sleep is successfully initiated (e.g., Carskadon & Dement, 2005). In studies investigating sleep profiles in healthy populations, sleep continuity is measured either by objective measures (i.e., polysomnography or actigraphy) or by patient and family member account during clinical or self-report assessments. On objective measures of sleep, sleep continuity may be defined as "frequency of awakenings" and/or "total awake time (TAT)", calculated by summing the minutes awake during a sleep recording (Hori et al., 2001; Keenan & Hirshkowitz, 2011; Ohayon et al., 2004). Clinical or self-report measures typically query individuals and significant others regarding their subjective experience of interruptions during the sleep period (Baker, Maloney, & Driver, 1999; Lockley et al., 1999).

Sleep continuity, as measured by both subjective and objective assessment, is often disturbed in individuals with schizophrenia (for a review, see Chouinard et al., 2004). Specifically, numerous studies utilizing polysomnographic measures have demonstrated increased TAT following sleep initiation in medicated (Afonso, Figueira, & Paiva, 2013) and drug-free and anti-psychotic naïve patients with psychosis (Benson, Sullivan, Lim, Lauriello, et al., 1996; Benson & Zarcone, 1993; Gaillard, Iorio, Campajola, & Kemall, 1984; Keshavan, Reynolds, Miewald, Montrose, et al., 1998; Salin-Pascual et al., 2004; Tandon et al., 1992; Yang & Winkelman, 2006). While frequently present, abnormalities in sleep continuity are not universal in schizophrenia, with some studies failing to find a significant difference in TAT for individuals with schizophrenia versus healthy controls (Ganguli, Reynolds, & Kupfer, 1987; Jus,

Bouchard, Jus, Villeneuve, & Lachance, 1973; Kempenaers, Kerkhofs, Linkowski, & Mendlewicz, 1988; Van Cauter, Linkowski, Kerkhofs, Hubain, et al., 1991). One potential reason for this disparity in findings involves use of anti-psychotic medications, as both first- and second-generation anti-psychotics have an attenuating impact on TAT (for a review, see Cohrs, 2008). Indeed, a meta-analysis revealed increased TAT for drug-naïve, but not previously treated drug-free, patients with schizophrenia (Chouinard et al., 2004).

To date, only two studies have examined interruptions in sleep continuity in at-risk populations, and both studies have focused on GR samples. In their study investigating the psychosocial adjustment of children of mothers with schizophrenia, Beisser and colleagues (1967) found a higher incidence of parent-reported sleep interruptions in offspring of patients with schizophrenia as compared to healthy controls. More recently, Keshavan and colleagues (2004) examined TAT using polysomnographic methods with young first-degree relatives and offspring (aged 6 – 25) of patients with psychotic disorders. Results from the sleep recording indicated a trend toward increased TAT in the GR group versus healthy comparison subjects ($p = .06$).

Conclusively, interruptions in sleep continuity are common phenomena in schizophrenia, but are not universal. Disparate results in this area may be due to previous use of anti-psychotic medication, as disruptions in sleep continuity are present in drug-naïve patients, but not in those who have been withdrawn from a previous medication regimen. Initial evidence suggests that abnormalities in sleep continuity may occur prior to onset of psychosis; however, further replication in GR and UHR populations is essential for clarifying the role of interrupted sleep in the development of schizophrenia.

Sleep Efficiency

In healthy populations, sleep efficiency represents the percentage of time in bed spent asleep (Buysse, Reynolds, Monk, Berman, et al., 1989). Reductions in sleep efficiency are revealed by decreases in the ratio of TST to total recording time (TRT), with TRT representing the elapsed time from the clock time of lights out (i.e., the time an individual initiates an attempt to sleep) to the clock time of lights on (i.e., the time an individual awakens). Sleep efficiency is measured by objective measures of sleep function, including polysomnography and actigraphy (Hori et al., 2001; Keenan & Hirshkowitz, 2011; Ohayon et al., 2004). Among healthy individuals, continuous reduction in sleep efficiency is observed over the course of the lifespan, peaking in childhood and adolescence, and decreasing throughout adulthood and old age (Ohayon et al., 2004).

Sleep efficiency is pervasively impaired in individuals with schizophrenia compared to healthy controls (for reviews, see Benson, 2008; Cohrs, 2008; Monti & Monti, 2005). Specifically, reductions in sleep efficiency have been consistently observed in never-treated or drug-free patients with schizophrenia (Chouinard et al., 2004; Monti & Monti, 2004; Tekell, Hoffmann, Hendrickse, Greene, et al., 2005; Yang & Winkelman, 2006), suggesting an important role for deficits in sleep efficiency in the pathophysiology of psychotic disorders. Interestingly, both first- and second-generation anti-psychotic medications have been shown to reliably enhance sleep efficiency, such that deficits in this domain may be less frequently observed in patients successfully treated by pharmacological interventions (Cohrs, 2008).

Despite the consistency with which deficiencies in sleep efficiency are observed in individuals with schizophrenia, to date, no studies have investigated sleep efficiency in adolescents and young adults at high risk for developing psychosis. Thus, while the presence of

deficits in sleep efficiency are reliably observed in never-treated patients with psychosis, suggesting a potential role in the etiology of the disorder, whether similar impairment exists prior to the onset of frank psychosis, and the possible function of sleep efficiency deficiency in the development of schizophrenia, remain open questions warranting empirical investigation.

Sleep Development, Brain Changes during Adolescence, and Risk for Psychosis

Investigators have observed evidence for normative gray matter loss indicative of pruning beginning in sensorimotor areas in puberty and spreading into 'higher-order' cortical regions during late adolescence (Gogtay, Giedd, Lusk, Hayashi, et al., 2004). In addition, research has shown a significantly greater normative change in cerebral white-matter proportion than change in total cerebral gray-matter proportion over the course of adolescence, suggesting that the relative gray-matter reduction may co-occur with significant increases in white matter (Bartzokis, Beckson, Lu, Nuechterlein, et al., 2001; Sowell, Peterson, Thompson, Welcome, et al., 2003). Because studies have reported observations of grey and white matter abnormalities in frontal regions of adults with psychotic illness (Foong, Symms, Barker, Maier, et al., 2001; Hoptman, Volavka, Johnson, Weiss, et al., 2002) and sleep disorders (Altena, Vrenken, Van Der Werf, van den Heuvel, et al., 2010), researchers are currently questioning whether disruptions in this normative maturational pattern may be contributing to 1) sleep abnormalities and 2) the etiology of schizophrenia.

Sleep Changes Across Development

Reflective of these neurodevelopmental processes, sleep behaviors and architecture change as a function of developmental stage. At birth, newborns' sleep (14 hours per day) is evenly distributed across the 24-hour period, with sleep consolidating in the nighttime by approximately 9 months of age. REM and NREM are evenly divided (50 REM:50 NREM ratio,

in 50 minute cycles) but disorganized, and a tracé alternant EEG pattern (high voltage slow activity interrupted by electrical silence) is common. Initially, infant sleep commences with a REM stage, but at 3 months, initial sleep stage reflects that of adults (NREM), and by 6 months, NREM is organized into its 4 stages. Over the first year of life, NREM EEG voltage shows a significant increase. In early childhood, sleep duration decreases due to reduction in naps, although sleep is subject to interruptions (e.g., 50% of children 1 – 5 years old wake up at least one night per week). By school age (6 – 12 years), children demonstrate a circadian sleep phase preference (evening or morning type). Throughout early childhood, REM proportion decreases to the adult level (20 REM:80 NREM ratio, in 90-110 minute cycles), and beginning at age 9, EEG voltages are significantly decreased (Jenni & Carskadon, 2005).

In adolescence, the level of sleep changes rival those in infancy. Adolescent sleep is characterized by a phase delay in sleep such that adolescents stay up late and sleep late compared to school age children (Jenni & Carskadon, 2005). In addition, Feinberg (1982) noted that the sleep changes during adolescence are quantitative rather than qualitative. For example, the time spent in deep (i.e., stage 4) sleep declines by about 50%, the amplitude of delta waves decline markedly (Feinberg, Hibi, & Carlson, 1977; Williams, Karacan, & Hursch, 1974; Williams, Karacan, Hursch, & Davis, 1972), SWS declines by approximately 40% between ages 10-12 and ages 14-16 (Carskadon, Acebo, & Jenni, 2004), and the total duration of sleep is reduced by approximately two hours (Williams et al., 1974). Consistent with these findings, research teams are working to determine if the decline in SWS is reflected in altered sleep-wake processes as well (see Carskadon et al., 2004 for a review). In addition to changes in total sleep and SWS duration, investigators have observed that sleep latencies during initial hours of extended wakefulness were longer in more mature adolescents than pre-pubertal children. Of particular

interest, it appears that adolescents are uniquely sensitive to early rising demands, often resulting in chronic patterns of insufficient sleep. Based on the notion that a function of sleep is to reverse the effects of waking on plastic brain neurons, investigators have posited that these changes reflect decreases of brain metabolic rate and plasticity occurring during adolescence (greater neuronal connectedness requires a greater number/higher delta waves; Feinberg, 1982; Keshavan, Anderson & Pettegrew, 1994). As such, abnormalities in adolescent neurodevelopment may lead to deficits in sleep, which in turn, may further negatively impact brain development.

Sleep in adulthood is also characterized by developmental changes. Across the course of adulthood, age-related decreases are observed in sleep duration (by about 10 minutes per decade of age), efficiency (3% per decade after age 40), SWS (2% per decade), REM percentage (4% between age 20 and 69), and REM latency. Concurrently, increases in sleep latency, percentages of Stage 1 and 2 NREM (5% between ages 20 and 70), and TAT after sleep onset (10 minutes per decade after 30 years old) occur across the adult lifespan. In elderly individuals, sleep efficiency continues to significantly decline after the age of 60 (Ohayon et al., 2004).

Increases in Stress During Adolescence

The adolescent period is both an exciting and demanding time. Teenagers are required to develop adult responsibilities, build independence, and manage an increasingly rigorous academic schedule. At the same time, adolescents do not have the benefit of a functioning "adult" brain (Spear, 2004). The normative levels of stress in adolescence can be demanding for healthy and well-adapted teenagers, but for those at-risk for serious mental illness, these changes can significantly exacerbate vulnerability factors. Further, individuals experiencing prodromal symptoms face an additional set of stressors, including burgeoning social, occupational, and

neurocognitive deficits, which significantly limit prognosis and quality of life (Niendam, Jalbrzikowski, & Bearden, 2009; Woods, Addington, Cadenhead, Cannon, et al., 2009). Indeed, the deterioration of social functioning has been shown to significantly distinguish those high-risk teenagers who go on to develop psychosis from those who do not (Cannon et al., 2008; Mason & Beavan-Pearson, 2005; Yung, Phillips, Yuen, Francey, et al., 2003; Yung, Phillips, Yuen, & McGorry, 2004).

Similarly, there are noteworthy stressors in the normative adolescent environment impacting sleep function. Specifically, widespread evidence suggests a strong trend for later bedtimes and later resting times during the teen years, irrespective of school based constraints (e.g., the early rising times dictated by schools do not affect the late bedtimes seen in adolescents; Carskadon, Wolfson, Acebo, Tzischinsky, et al., 1998). These sleep disruptions are related to social factors and stressors associated with the teenage years. Adolescents, particularly in western cultures such as the United States, are vulnerable to the relatively unforgiving educational structure demanding early morning school attendance. Compared to 6th graders, who engage in 500 minutes of sleep during the school week, the average time spent asleep is 453 minutes in grade 10 and 420 minutes in grade 12 (Carskadon & Dement, 1982; Gaudreau, Carrier, & Montplaisir, 2001).

Abnormalities in Neural Structures Associated with Sleep

As noted above, a complex network of neural structures supports healthy sleep patterns, and includes both wakefulness/arousal-promoting and sleep-promoting regions (Stiller & Postolache, 2005; Taber & Hurley, 2006). Patients with schizophrenia display gray-matter abnormalities in several of the neural structures associated with sleep, including the thalamus, cortex, hypothalamus, brainstem, and BF. Regarding the thalamus, individuals with

schizophrenia consistently display bilateral reductions in gray matter volume, with abnormalities present in both first-episode and chronic schizophrenia (for reviews, see Adriano, Spoletini, Caltagirone, & Spalletta, 2010; Konick & Friedman, 2001). Bilateral reductions in gray matter volume have also been reliably observed in several areas of the cortex, including the frontal (Davidson & Heinrichs, 2003; Wright, Rabe-Hesketh, Woodruff, David, et al., 2000), temporal (Davidson & Heinrichs, 2003; Vita, De Peri, Silenzi, & Dieci, 2006; Wright et al., 2000; Zakzanis, Poulin, Hansen, & Jolic, 2000), and parietal (Fornito, Yucel, Patti, Wood, et al., 2009; Glahn, Laird, Ellison-Wright, Thelen, et al., 2008) lobes in first-episode and chronic psychoses.

Findings regarding abnormalities in other brain structures involved in sleep have been mixed. Regarding the hypothalamus, individuals with psychotic disorders have been shown to exhibit both increased (Goldstein, Seidman, Makris, Ahern, et al., 2007) and decreased (Koolschijn, van Haren, Hulshoff Pol, & Kahn, 2008) volumes compared to healthy controls; however, in the Kooschijn et al. (2008) study, the significant difference between groups disappeared after correcting for total brain volume, suggesting the decrease in hypothalamic volume is non-specific. Similarly, a recent study found no hypothalamic volume differences between individuals with schizophrenia and their healthy counterparts (Klomp, Koolschijn, Pol, Kahn, et al., 2012).

Abnormalities in the brainstem have been observed in patients with schizophrenia, including smaller cross-sectional areas of the pons (Sachdev & Brodaty, 1999), reduced N-acetyl aspartate (NAA)/creatine (CR)-phosphocreatine ratios in the pons (Eluri, Paul, Roemer, & Boyko, 1998), and decreased activity in the pons during resting states (He, Kuang, & Tan, 2008). Another study, however, found significant reductions in the volume of the midbrain, but no differences in size of the pons and medulla, in patients with schizophrenia compared to healthy

controls (Nopoulos, Ceilley, Gailis, & Andreasen, 2001). Finally, while less frequently studied, abnormalities in the BF may be present in schizophrenia; interestingly, volume differences may be sex-dependent, with males with schizophrenia exhibiting larger BF volume compared to male controls, and female patients displaying reductions in volume compared to female controls (Goldstein, Seidman, O'Brien, Horton, et al., 2002).

Although not investigated in the context of sleep, there is some evidence to suggest that abnormalities in the cortex and thalamus may be present prior to the emergence of frank psychotic symptoms. Among UHR individuals, reductions in gray matter volume have been consistently observed in the frontal (Bohner, Milakara, Witthaus, Gallinat, et al., 2012; Fusar-Poli, Broome, Woolley, Johns, et al., 2011; Fusar-Poli, Crossley, Woolley, Carletti, et al., 2011a; Iwashiro, Suga, Takano, Inoue, et al., 2012; Jung, Kim, Jang, Choi, et al., 2011; Koutsouleris, Schmitt, Gaser, Bottlender, et al., 2009; Mechelli, Riecher-Rossler, Meisenzahl, Tognin, et al., 2011; Meisenzahl, Koutsouleris, Gaser, Bottlender, et al., 2008; Witthaus, Kaufmann, Bohner, Ozgurdal, et al., 2009), temporal (Borgwardt, Riecher-Rossler, Dazzan, Chitnis, et al., 2007; Hurlemann, Jessen, Wagner, Frommann, et al., 2008; Jung et al., 2011; Koutsouleris et al., 2009; Mechelli et al., 2011; Meisenzahl et al., 2008; Pantelis, Velakoulis, McGorry, Wood, et al., 2003; Phillips, Velakoulis, Pantelis, Wood, et al., 2002; Stone, Day, Tsagaraki, Valli, et al., 2009; Takahashi, Wood, Yung, Sousby, et al., 2009; Takahashi, Wood, Yung, Walterfang, et al., 2010; Witthaus et al., 2009; Witthaus, Mendes, Brune, Ozgurdal, et al., 2010; Wood, Kennedy, Phillips, Seal, et al., 2010; Ziermans, Schothorst, Schnack, Koolschijn, et al., 2012), and parietal (Jung et al., 2011) lobes compared to healthy controls. However, these findings are not universal, with some studies finding no neuroanatomical differences between UHR patients and controls (Ziermans, Durston, Sprong, Nederveen, et al., 2009).

In addition to volumetric decreases, cortical thickness asymmetry in the frontal, temporal, and parietal lobes may distinguish UHR youth from healthy controls (Haller, Borgwardt, Schindler, Aston, et al., 2009), and abnormalities (elevations or reductions) in NAA to CR, NAA to choline (CHO), and CR to CHO ratios in the frontal lobe have been observed in UHR individuals compared to their healthy counterparts (Jessen, Scherk, Traber, Theyson, et al., 2006; Wood, Berger, Velakoulis, Phillips, et al., 2003).

Results are similar among GR youth, including reductions in the frontal (Bhojraj, Francis, Montrose, & Keshavan, 2011; Bhojraj, Sweeney, Prasad, Eack, et al., 2011; Diwadkar, Montrose, Dworakowski, Sweeney, et al., 2006; Ho, 2007; Job, Whalley, Johnstone, & Lawrie, 2005; McIntosh, Owens, Moorhead, Whalley, et al., 2011), temporal (Bhojraj, Francis, et al., 2011; Bhojraj, Sweeney, et al., 2011; Diwadkar et al., 2006; Job et al., 2005; Keshavan, Dick, Mankowski, Harenski, et al., 2002; Keshavan, Montrose, Pierri, Dick, et al., 1997; Lawrie, Whalley, Kestelman, Abukmeil, et al., 1999; Lawrie, Whalley, Abukmeil, Kestelman, et al., 2001; Lawrie, Whalley, Abukmeil, Kestelman, et al., 2002; McIntosh et al., 2011; Moorhead, French, Walford, Lewis, et al., 2009; Rajarethinam, Sahni, Rosenberg, & Keshavan, 2004; Schreiber, Baur-Seack, Kornhuber, Wallner, et al., 1999; Sismanlar, Anik, Coskun, Agaoglu, et al., 2010), and parietal (Bhojraj, Francis, et al., 2011; Job et al., 2005) lobes. In addition, elevations in glutamate and glutamine in the frontal lobe distinguish adolescents at high genetic risk for psychosis from healthy adolescents (Tibbo, Hanstock, Valiakalayil, & Allen, 2004).

GR individuals may also display reductions in the gray matter volume of the thalamus (Bhojraj, Francis, et al., 2011; Lawrie et al., 1999; Lawrie et al., 2001), although this finding is not universal (Sismanlar et al., 2010). Additionally, among UHR individuals, reductions in glutamate and NAA in the thalamus have been observed as compared to healthy controls

(Brugger, Davis, Leucht, & Stone, 2011; Stone et al., 2009). Moreover, reductions in thalamic glutamate, glutamine, and NAA have been associated with abnormal frontal auditory event-related potentials in UHR individuals (Stone, Bramon, Pauls, Sumich, et al., 2010), suggesting a role for thalamic abnormalities in the development of thought disorders (Corson, Nopoulos, Andreasen, Heckel, et al., 1999).

In sum, a complex network of brain structures, including the thalamus, hypothalamus, BF, brainstem, and cortex, supports sleep-promoting mechanisms. Ample evidence suggests that many of the structures involved in sleep are compromised in individuals with schizophrenia. In addition, findings from studies examining UHR and GR individuals indicate that these brain abnormalities may be present prior to the onset of psychotic disorders, suggesting that reductions in the gray-matter volumes of sleep-related neural structures may participate in the etiology and development of schizophrenia. See Table 2.

Table 2. Grey Matter Volumes of Key Structures Implicated in Sleep Function and Schizophrenia (MRI)

Dysfunction	Author	Population/ Sample Size	Results
Gray Matter Volumes In Neural Structures Supporting Sleep	Mechelli et al., 2011	UHR (182) HC (167)	Reduction in frontal & temporal lobes.
	Pantelis et al., 2003	UHR	Reduction in temporal lobe.
	Takahashi et al., 2009	UHR (35) HC (22)	Reduction in temporal lobe.
	Wood et al., 2010	UHR (66) HC (29)	Reduction in temporal lobe.
	Takahashi et al., 2010	UHR (97) HC (42)	Reduction in temporal lobe.
	Meisenzahl et al., 2008	UHR (40) HC (75)	Reduction in frontal & temporal lobes.
	Koutsouleris	UHR (46)	Reduction in frontal & temporal lobes.

et al., 2009	HC (75)	
Stone et al., 2009	UHR (27) HC (27)	Reduction in temporal lobe.
Fusar-Poli et al., 2011a	UHR (15) HC (15)	Reduction in frontal lobe.
Fusar-Poli et al., 2011b	UHR (39) HC (41)	Reduction in frontal lobe.
Borgwardt et al., 2007	UHR (35) HC (22)	Reduction in temporal lobe.
Haller et al., 2009	UHR (20) HC (20)	Asymmetry in cortical thickness in frontal, parietal, & temporal lobes.
Bhojraj et al., 2011a	GR (94) HC (81)	Reduction in frontal, temporal, & parietal lobes; thalamus.
Bhojraj et al., 2011b	GR (27) HC (23)	Reduction in frontal & temporal lobes.
Witthaus et al., 2009	UHR (30) HC (29)	Reduction in frontal & temporal lobes.
Witthaus et al., 2010	UHR (29) HC (29)	Reduction in temporal lobe.
Bohner et al., 2012	UHR (25) HC (29)	Reduction in frontal lobe.
Hurlemann et al., 2008	UHR (36) HC (30)	Reduction in temporal lobe.
Lawrie et al., 1999	GR (100) HC (30)	Reduction in temporal lobe.
Lawrie et al., 2001	GR (147) HC (36)	Reduction in temporal lobe; thalamus.
Lawrie et al., 2002	GR (66) HC (20)	Reduction in temporal lobe.
Job et al., 2005	GR (65) HC (19)	Reduction in frontal, temporal, & parietal lobes.
McIntosh et al., 2011	GR (146) HC (36)	Reduction in frontal & temporal lobes.
Moorhead et al., 2009	UHR (53) HC (45)	Reduction in temporal lobe.

Ziermans et al., 2009	UHR (54) HC (54)	No grey matter reductions.
Ziermans et al., 2012	UHR (43) HC (30)	Reduction in temporal lobe over time.
Keshavan et al., 1997	GR (11) HC (12)	Reduction in temporal lobe.
Keshavan et al., 2002	GR (17) HC (22)	Reduction in temporal lobe.
Rajarethinam et al., 2004	GR (29) HC (27)	Reduction in temporal lobe.
Diwadkar et al., 2006	GR (33) HC (34)	Reductions in frontal & temporal lobes.
Ho, 2007	GR (46) HC (46)	Reduction in frontal lobe.
Schreiber et al., 1999	GR (15) HC (15)	Reduction in temporal lobe.
Jung et al., 2011	UHR (29) HC (29)	Reduction in frontal, temporal, & parietal lobes.
Iwashiro et al., 2012	UHR (20) HC (20)	Reduction in frontal lobe.
Sismanlar et al., 2010	GR (26) HC (23)	Reduction in temporal lobe; No reduction in thalamus.

Abbreviations: GR, Genetic High Risk; UHR, Ultra High-Risk; HC, Healthy Controls
Note: Indentions represent data collected within a research group.

Abnormalities in White Matter Integrity

As noted, the adolescent period is characterized by white matter growth, indicative of thicker myelin sheathes, increased axonal diameter, and improved organization of white matter tracts, resulting in improved signal transduction (Barnea-Goraly, Menon, Eckert, Tamm, et al., 2005). Maturation of white matter pathways in the prefrontal regions, the internal capsule, basal

ganglia, and thalamus has also been observed during adolescence (Ashtari, Cervellione, Hasan, Wu, et al., 2007; Barnea-Goraly et al., 2005; Schmithorst, Wilke, Dardzinski, & Holland, 2002).

Several white matter pathways are integral in supporting sleep functioning in healthy individuals. Specifically, two thalamocortical pathways running through the anterior internal capsule mediate arousal and sleep processes: a dorsal pathway originating in the upper brainstem and projecting to the cortex through the thalamus, and a ventral pathway originating in the brainstem and projecting to the cortex through the hypothalamus and basal forebrain (Fuller et al., 2006; Stiller & Postolache, 2005; Taber & Hurley, 2006). Abnormalities in thalamocortical tracts, such as the left and right anterior thalamic radiations (running through the anterior internal capsule) have been found in individuals with disordered sleep (Unger, Belke, Menzler, Heverhagen, et al., 2010). In healthy individuals, the thalamocortical tracts involved in sleep function are among the neural pathways demonstrating significant white matter growth in adolescence (Paus, Zijdenbos, Worsley, Collins, et al., 1999).

In patients with schizophrenia, white matter integrity is compromised (Davis, Stewart, Friedman, Buchsbaum, et al., 2003). Additionally, there is some evidence to suggest that anomalies in the neural pathways implicated in sleep are present in patients with schizophrenia. Specifically, dysfunction of the thalamic-reticular nucleus and thalamocortical tracts is prominent in individuals with psychosis (Ferrarelli & Tononi, 2011; Vukadinovic, 2011). For instance, decreases in the number, amplitude, duration, and integrated activity of stage 2 sleep spindles (i.e., products of thalamic-reticular and thalamocortical mechanisms) have been found in patients with schizophrenia compared to individuals with depression and healthy controls (Ferrarelli, Huber, Peterson, Massimini, et al., 2007), independent of the effects of anti-psychotic medication (Ferrarelli et al., 2010).

There is also evidence to suggest that white matter integrity is compromised in high-risk populations. Diffusion tensor imaging (DTI) studies in prodromal adolescents have detected decreased fractional anisotropy (FA, an index of white matter integrity) in the superior longitudinal fasciculus (SLF, a fronto-parietal connection; Karlsgodt, van Erp, Poldrack, Bearden, et al., 2008) and temporal lobe white matter tracts (i.e., hippocampus and inferior longitudinal fasciculus; Karlsgodt, Niendam, Bearden, & Cannon, 2009) in prodromal patients relative to control subjects. Similarly, one study using DTI found that FA for UHR individuals in the SLF, inferior fronto-occipital fasciculus, commissural fibers (corpus callosum), and cortico-subcortical pathways (corona radiata, corticospinal tract, and corticopontine tract) was intermediate between individuals with schizophrenia and healthy controls (Carletti, Woolley, Bhattacharyya, Perez-Iglesias, et al., 2012). In addition, MRI studies have indicated that high-risk individuals demonstrate significant reductions in global white matter growth (Ziermans et al., 2012), as well as reduced white matter underlying the superior temporal gyrus (Fusar-Poli, Crossley, et al., 2011b; Witthaus, Brune, Kaufmann, Bohner, et al., 2008) and the frontal lobe (Fusar-Poli, Crossley, et al., 2011b; Peters, Schmitz, Dingemans, van Amelsvoort, et al., 2009) compared to their healthy counterparts. Despite this preliminary evidence for white matter reductions in prodromal individuals, to date, no studies have examined the thalamocortical pathways implicated in sleep functioning in high-risk individuals. Thus, whether the pathways supporting sleep functioning are abnormal prior to the onset of psychosis is an open question.

Sleep Impairment and Symptoms of Psychosis

Several categories of sleep dysfunction are associated with symptoms in schizophrenia. First, broadly defined sleep disturbances, reduced sleep duration, and impaired sleep efficiency are correlated with reduced quality of life (Afonso, Brissos, Figueira, & Paiva, 2011; Hofstetter,

Lysaker, & Mayeda, 2005; Ritsner, Kurs, Ponizovsky, & Hadjez, 2004; Xiang, Weng, Leung, Tang, et al., 2009) and increased severity of illness (Neylan, van Kammen, Kelley, & Peters, 1992) in patients with schizophrenia. In addition, abnormalities in sleep duration, efficiency, and latency are associated with worsened positive symptoms in affected individuals (Chemerinski, Ho, Flaum, Arndt, et al., 2002; Zarcone & Benson, 1997).

Second, SWS (i.e., stages 3 and 4 NREM) abnormalities, a consistent sleep finding in schizophrenia (e.g., Cohrs, 2008), are related to increased illness severity (Neylan et al., 1992), poorer clinical outcomes (Keshavan, Reynolds, Miewald, & Montrose, 1995), and most importantly, increased negative symptoms (Ganguli et al., 1987; Kajimura, Kato, Okuma, Sekimoto, et al., 1996; Kato, Kajimura, Okuma, Sekimoto, et al., 1999; Keshavan, Miewald, Haas, Sweeney, et al., 1995; Keshavan, Pettegrew, Reynolds, Panchalingam, et al., 1995; Sekimoto, Kato, Watanabe, Kajimura, et al., 2011; Tandon, DeQuardo, Taylor, McGrath, et al., 2000; Tandon, Shipley, Eiser, & Greden, 1988; van Kammen, van Kammen, Peters, Goetz, et al., 1988), suggesting that this aspect of sleep dysfunction may be closely tied to the etiology of schizophrenia. Reductions in sleep spindles (i.e., stage 2 NREM) have been associated with increased positive symptoms in psychosis-affected individuals (Wamsley, Tucker, Shinn, Ono, et al., 2012).

Third, atypical REM sleep has been associated with symptoms in schizophrenia. Specifically, reduced REM latency is correlated with increased illness severity (Tandon et al., 1992; Taylor, Tandon, Shipley, & Eiser, 1991; Thaker, Wagman, & Tamminga, 1990), greater positive (Lauer et al., 1997; Poulin, Daoust, Forest, Stip, et al., 2003; Tandon et al., 1992; Taylor, Tandon, Shipley, & Eiser, 1991; Thaker et al., 1990) and negative symptoms (Tandon et al., 2000; Tandon, Lewis, Taylor, Shipley, et al., 1996; Tandon et al., 1988; Tandon et al., 1992;

Taylor, Tandon, Shipley, & Eiser, 1991), and psychosocial impairment (Goldman, Tandon, DeQuardo, Taylor, et al., 1996; Taylor, Tandon, Shipley, Eiser, & Goodson, 1991). Similarly, increased REM density is related to worsened illness severity (Poulin et al., 2003; Yang & Winkelman, 2006), and increased positive (Benson & Zarcone, 1993; Rotenberg, Hadjez, Indursky, Martin, et al., 1997; Yang & Winkelman, 2006) and negative (Riemann, Hohagen, Krieger, Gann, et al., 1994) symptoms. Finally, abnormalities in REM percentage are related to amplified illness severity (Keshavan, Reynolds, Ganguli, Brar, et al., 1991; Poulin et al., 2003) and suicidality (Keshavan et al., 1991; Lewis et al., 1996).

Taken together, evidence from the schizophrenia literature suggests that sleep dysfunction is correlated with detrimental increases in illness severity and positive and negative symptoms, as well as poorer clinical outcomes and psychosocial functioning. Several dimensions of sleep disturbance, including abnormalities in SWS and REM, have been closely associated with negative symptoms, suggesting that sleep dysfunction may play a role in the etiology of schizophrenia.

To date, only one cross-sectional study has investigated objective measures of sleep dysfunction in individuals at risk for developing schizophrenia. Keshavan and colleagues (2004) observed decreased delta counts per minute (i.e., reduced SWS), reduced REM percentage and counts per minute, and trends toward increased awake time in minutes (i.e., impaired sleep continuity, $p = 0.06$) and REM latency in minutes ($p = 0.08$) among GR youth compared to healthy controls. In the same sample, GR youth demonstrated increased schizotypy symptoms compared to controls, including elevations in magical ideation and perceptual aberration scores, and a high rate of axis I disorders. Thus, sleep dysfunction may be related to symptoms in at-risk

populations; however, extensive, longitudinal research is necessary to determine the relationship between disturbed sleep and symptoms in individuals at risk for schizophrenia.

Summary

Widespread evidence suggests that sleep dysfunction is a common symptom among individuals with schizophrenia, associated with increased symptoms, distress, and impairment; however, despite the prominent role of sleep impairment in schizophrenia, there has been little research investigating disturbed sleep in at-risk populations. Initial evidence from retrospective, GR, and UHR studies suggests that disturbances in sleep (i.e., general sleep disturbances and reduced sleep duration) may precede the emergence of frank psychotic symptoms. However, many of these studies are limited by retrospective designs and self-report or clinical interview methodology, rendering their results subject to demand characteristics, memory biases, and difficulties determining the temporal order of onset of sleep dysfunction versus psychotic symptoms. The current study accounts for these limitations by employing a prospective design assessing sleep functioning with an objective measure of sleep (i.e., actigraphy). In addition, the current study used multiple methods to assess the sleep dysfunction construct, including an objective measure as well as a self-report measure of sleep (Pittsburgh Sleep Quality Index). Thus, this study is particularly sensitive to detecting sleep difficulty, and explores the validity of self-report in assessing sleep dysfunction in at-risk populations.

To date, there has been only one study using an objective method to examine sleep in an at-risk population. Keshavan and colleagues (2004) employed all-night polysomnographic methods to investigate sleep in the young relatives of patients with schizophrenia. This study was pivotal, as it provided the first preliminary support for atypical sleep in at-risk populations; however, further investigation is critical for confirming and expanding upon these initial results.

The current study builds on the Keshavan et al. (2004) study in multiple ways. First, polysomnography studies are conducted in sleep laboratories, typically in hospital settings. As a result of the research venue, stress and anxiety associated with sleeping in a novel environment result in altered sleep patterns (commonly known as the "first night effect"; Agnew, Webb, & Williams, 1966). Although most polysomnography studies account for this limitation by examining the second night of sleep in a study, altered sleep patterns as a result of laboratory setting may extend up to four nights (e.g., Le Bon, Staner, Hoffmann, Dramaix, et al., 2001). As actigraphy relies on information collected from a wristwatch device used at home, it accounts for this potential confound by examining adolescents' sleep in the natural setting. In addition, the actigraph used in the current study collects data over a longer period of time than most polysomnographic methods (i.e., 5 night period).

Second, the Keshavan et al. (2004) study utilized a GR sample. As outlined above, UHR/prodromal youth, who already exhibit attenuated/brief symptoms and/or a drop in functioning, may be a particularly important sample in which to examine risk factors such as sleep impairment. As one-third of these individuals are likely to convert to schizophrenia, research with this population is particularly germane to informing etiological conceptualizations and developing targeted prevention and intervention efforts. In addition, these studies are more feasible than GR studies, as the low base rate of schizophrenia in the population renders generating a sufficiently powered GR sample extremely challenging. Further, because the prodrome represents a developmental period with high potential to shed light on the etiology of psychosis (Mittal & Walker, 2011), focusing on UHR samples lends particularly well to neurodevelopmental questions.

Third, although a relationship between sleep dysfunction and symptoms can be inferred from the Keshavan et al. (2004) study, as both sleep impairment and symptoms of schizotypy were observed in the same sample, the investigators did not directly examine this relationship. In the current study, in which most adolescents are demonstrating symptoms in several domains of psychosis (positive, negative, disorganized), the association between categories of sleep dysfunction and various types of symptoms are directly assessed.

Finally, in addition to studies specifically investigating sleep functioning in at-risk youth, there is some evidence to suggest abnormalities in the neural structures and pathways underlying sleep regulation, including anomalies in the structure and function of the thalamus and cortex and reductions in white matter tracts. However, no prior studies have examined gray matter abnormalities (e.g., thalamus) in the context of sleep, and no research has specifically investigated the white matter tracts (e.g., thalamocortical pathways running through the anterior internal capsule) involved in healthy sleep functioning in at-risk populations. The current study addresses these specific questions.

Current Study

In the current study, 33 adolescents and young adults meeting criteria for a prodromal syndrome and 33 healthy controls were evaluated for sleep characteristics utilizing both instrumental and self-report strategies. The 66 participants also completed a range of clinical measures and both magnetic resonance (MRI) and diffusion tensor imaging (DTI) to address two primary questions relating to sleep dysfunction in the pathophysiology of psychosis. The first aim was to determine whether sleep (i.e., latency, duration, continuity, efficiency, disturbances, subjective quality, total movement count) is disrupted in UHR youth when compared to healthy controls using self-report (Pittsburgh Sleep Quality Index, PSQI) and objective (Actigraphy)

methods. Also part of Aim 1 was to determine if aspects of sleep disturbance (as measured by PSQI and actigraphy) are related to symptoms (i.e., positive, negative, disorganized) in high-risk youth. The second aim was to determine if neural structures and tracts underlying sleep function are abnormal in high-risk youth compared to controls (i.e., thalamus and thalamocortical pathways), and if so, the extent to which these abnormalities are associated with indices of sleep dysfunction.

Specific Aims

Specific Aim 1a: To determine whether distinct domains of sleep impairment (i.e., latency, duration/TST, continuity/TAT, efficiency, total movement count, disturbances, subjective quality) are present prior to the onset of psychosis in UHR youth compared to healthy controls. *Based on evidence suggesting that general sleep impairment is present in other high-risk populations (e.g., Keshavan et al., 2004; Yung & McGorry, 1996a), and highly prevalent in formal psychosis (Cohrs, 2008), it was predicted that individuals meeting criteria for an UHR syndrome would show a) increased latency, b) decreased duration/TST, c) disrupted continuity/TAT, d) reduced efficiency, e) greater total movement count during the sleep period, f) greater sleep disturbances, and g) poorer reported quality of sleep on actigraphic and PSQI measures.*

Specific Aim 1b: To determine the relationship of sleep dysfunction (latency, duration/TST, continuity/TAT, efficiency, total movement count, disturbances, subjective quality), as measured by both subjective and objective methods, with domains of prodromal symptoms (positive, negative, disorganized) in UHR youth. *To date there has been a significant discrepancy in the research literature regarding the relationship between symptoms and sleep dysfunction in psychosis populations (Cohrs, 2008). For example, some studies have found relationships*

between sleep dysfunction and positive symptoms (Lauer et al., 1997; Poulin et al., 2003; Tandon et al., 1992; Taylor, Tandon, Shipley, & Eiser, 1991; Thaker et al., 1990), whereas other studies have found an association between disturbed sleep and negative symptoms (Ganguli et al., 1987; Kajimura et al., 1996; Kato et al., 1999; Keshavan, Miewald, et al., 1995; Keshavan, Pettegrew, et al., 1995; Sekimoto et al., 2011; Tandon et al., 2000; Tandon et al., 1988; van Kammen et al., 1988). Delineating associations between sleep impairment and specific symptoms is critical, as a stronger relationship with negative symptoms (which significantly precede positive symptoms and do not change course) would speak to a more core position for sleep in the development of psychosis. Specifically, phenomena closely tied to negative symptoms are believed to be more proximal to the true underlying etiology of the disorder (Bleuler, 2010). With regard to the discrepancy in findings, researchers have posited that methodological differences involving confounds such as medications may be involved. A distinct benefit of examining these questions in high-risk youth relates to the smaller percentage of youth treated with potential confounding medications (< 18% are treated). It was predicted that each of the domains of sleep dysfunction found in the high-risk youth would be associated with positive, negative, and disorganized symptoms, but that the magnitude of the relationship between sleep dysfunction and negative symptoms would be greatest.

Specific Aim 2: To determine if neural structures (i.e., left and right thalamus) and tracts (i.e., left and right anterior thalamic radiations) underlying sleep function are abnormal in UHR youth compared to controls, and if so, the extent to which neural abnormalities are related to indices of sleep dysfunction. *There is a significant body of evidence to suggest that structures and tracts implicated in healthy sleep function are abnormal in patients with formal psychosis (e.g., Davidson & Heinrichs, 2003; Ferrarelli & Tononi, 2011; Fornito et al., 2009; Glahn et al.,*

2008; Vukadinovic, 2011; Wright et al., 2000) as well as UHR youth (e.g., Bhojraj, Francis, et al., 2011; Diwadkar et al., 2006; McIntosh et al., 2011; Mechelli et al., 2011; Takahashi et al., 2010). In particular, the thalamus has shown reliable reductions in volume in schizophrenia (Adriano et al., 2010; Konick & Friedman, 2001) and at-risk (GR; Bhojraj, Francis, et al., 2011; Lawrie et al., 1999; Lawrie et al., 2001) samples, leading researchers to suggest that thalamic abnormalities may play an especially important role in the development of schizophrenia (Corson et al., 1999). However, to date, there have been no studies designed to examine the relationship between the thalamus structure/thalamocortical tracts and sleep dysfunction in UHR youth. Based on the reviewed literature, we predicted that significant volume reductions in the thalamus would characterize the UHR group when compared with the healthy control group. In addition, it was predicted that abnormalities in the thalamus and thalamocortial tracts would be associated with indices of sleep impairment.

<u>*Exploratory Aim 1:*</u> To determine the relationship between self-report (PSQI) and objective (actigraphy) measures of sleep impairment. *Because we are utilizing both subjective and objective measures of sleep dysfunction, it is possible to examine an exploratory question regarding the reliability of self-report of sleep in this critical group. In healthy populations, subjective and actigraphic measures of sleep functioning (duration, continuity, efficiency) are correlated; however, self-assessment of sleep is more accurate for duration than for measures assessing transitions between sleep and wake states (continuity and efficiency) (Lockley et al., 1999). Thus, we predicted that subjective and objective indices of sleep impairment would be associated in our full sample of adolescents, but that measures of duration would be more highly related than continuity or efficiency. We explored whether UHR adolescents showed less accurate reporting of sleep functioning than healthy controls.*

Exploratory Aim 2: To determine the relationship of sleep dysfunction (latency, duration/TST, continuity/TAT, efficiency, total movement counts, disturbances, subjective quality), as measured by both subjective and objective methods, with domains of mood symptoms (depressive and hypomanic/manic) in UHR youth. *Because the prodrome is often accompanied by comorbid mood disorders (e.g., major depressive disorder, bipolar I and II) (Rosen, Miller, D'Andrea, McGlashan, et al., 2006; Salokangas, Ruhrmann, von Reventlow, Heinimaa, et al., 2012; Shioiri, Shinada, Kuwabara, & Someya, 2007; Svirskis, Korkeila, Heinimaa, Huttunen, et al., 2005), and a body of evidence suggests a relationship between mood symptoms and sleep dysfunction (Gruber, Miklowitz, Harvey, Frank, et al., 2011; Lunsford-Avery, Judd, Axelson, & Miklowitz, 2012) we were interested to determine if mood symptoms (depressive and hypomanic/manic) influenced the level of sleep dysfunction in the UHR sample. While the number of participants exhibiting clinically significant mood symptoms was relatively small, and this analysis was underpowered, trends or effects will guide future research projects.*

CHAPTER II

METHODS

Participants

Inclusion and Exclusion Criteria

Participants were 33 adolescents and young adults at risk for psychosis and 33 healthy controls between 12 and 21 years of age. A first-degree relative/parent/significant other (> age 18) for each proband/control was also invited to participate for consent purposes and to corroborate interviews regarding symptoms and criteria related to inclusion. Participants were referred by community health care providers or self-referred in response to media announcements. Community health care providers provided patients exhibiting signs of unusual thought content, suspiciousness, grandiosity, and/or perceptual abnormalities with our contact information. Inclusion criteria for cases included: presence of a prodromal/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 schizophrenia (Miller et al., 1999).

Exclusion criteria for all subjects included: age less than 12 or greater than 21 years, lactation, presence of a neurological or tic disorder, history of significant head injury or other physical disorder affecting brain functioning, mental retardation, or history of a substance dependence disorder within 6 months of the screening interview. For the UHR group, additional exclusion criteria included the presence of an Axis I psychotic disorder. For the healthy comparison group, additional exclusion criteria included the presence of any Axis I disorder or a first degree relative with a psychotic disorder. Every attempt was made to select healthy controls for demographic characteristics comparable to UHR patients regarding age, sex, handedness,

parental educational level (a proxy for social class), race/ethnicity, and community of residence, and to assemble UHR and control samples that were representative of the ethnically diverse Denver-Aurora-Boulder community.

Mood Symptoms

In addition to attenuated positive symptoms, comorbid mood disorders are prevalent in prodromal samples. Indeed, major depressive disorder (MDD) is the most common comorbidity experienced by UHR youth, with most studies finding that a majority of UHR participants meet criteria for a lifetime unipolar depression disorder (Rosen et al., 2006; Salokangas et al., 2012; Shioiri et al., 2007; Svirskis et al., 2005). Similarly, depression represents a common presenting problem reported by prodromal individuals (Lencz, Smith, Auther, Correll, et al., 2004). In addition, a large multisite study revealed that approximately 7% of UHR adolescents meet criteria for lifetime diagnoses of non-psychotic bipolar disorders, which are predictive of later transition to schizophrenia (Salokangas et al., 2012). Given the high prevalence of mood disorders in this population, and the established relationship between sleep dysfunction and mood disorders in adults (Gruber et al., 2011) and adolescents (Lunsford-Avery et al., 2012), symptoms of depression and hypo(mania) were controlled for in the primary analyses (described below). In addition, exploratory analyses focused specifically on potential relationships between indices of sleep dysfunction and mood symptoms in this population.

Medications

Although priority was given to the recruitment of participants who have never received psychotropic medication, prior studies with UHR/prodromal samples suggest that some participants are prescribed one or more psychotropic drugs naturalistically in the community. For example, in a recent study examining neurocognition in 90 prodromal adolescents,

antipsychotic medication was naturalistically prescribed to 23% of the participants (Mittal et al., 2010). This observation is consistent with a national pattern, in which an increase in the number of adolescents diagnosed with mental health and adjustment problems has resulted in an increase in adolescents taking psychotropic medications, particularly stimulants, antidepressants and, to a lesser extent, antipsychotics (Zito, Safer, DosReis, Gardner, et al., 2003). Importantly, these medications have also been shown to affect sleep functioning. Both first- and second-generation anti-psychotics, for instance, have been shown to result in increased sleep duration and improved sleep efficiency (for a review, see Cohrs, 2008). To address this potential confound, medication was modeled statistically (described below).

Procedures

The current study was conducted in the Adolescent Development and Preventative Treatment (ADAPT) clinic at the University of Colorado Boulder. Participants and their family members signed informed consent to participate in a screening evaluation consisting of a psychiatric interview and questionnaires. This interview included the positive symptom section of the Structured Interview for Prodromal States (SIPS, Section 1; Miller, McGlashan et al., 2003) and the psychotic disorder section of the Structured Clinical Interview for the DSM-IV (SCID, Section B; First et al., 1995). The screening interview determined the presence of an UHR syndrome and ruled out the presence of an Axis I psychotic disorder. During this initial interview, the family member/parent/significant other and patient were interviewed together for two sections of the SIPS (developmental and medical/psychiatric history), as well as for questions concerning current functioning and presenting problems. However, all other sections of the SIPS and SCID were conducted separately with the patient and the family member/parent/significant other. If, during the screening, patients or family members indicated

the presence of potential exclusion criteria, appropriate release forms were obtained, and subjects' medical records were reviewed for more details to inform an inclusion/exclusion decision (i.e., head injury, tic disorder, neurological disorder, substance dependence). Individuals who were excluded were given appropriate community referrals, and their data were not included in the study.

If a subject met inclusion criteria and was interested in further participation, a full clinical interview was scheduled. Once informed consent for this section of the study was obtained, the subject underwent an extensive clinical evaluation, including the remainder of the SIPS (negative, disorganized, and general symptom sections) and SCID (all remaining sections). In addition, a first-degree relative or significant other (> age 18) was consented and interviewed to provide information concerning the birth and developmental history of the subject and any recent changes in medical/psychiatric history or presenting problem (SIPS, pages 5-7). For subjects without close relatives (> age 18) available for interview, the subject him- or herself was interviewed for family/medical/developmental history. Participants older than age 18 were encouraged to sign a release to discuss findings and treatment options with caretakers.

Following the clinical interview, participants were provided with a sleep monitor (ActiSleep wristwatch), worn for a 5-day period following the initial assessment. Participants were required to wear the wrist-monitor during the daytime and nighttime in order to provide a baseline measure for assessing sleep initiation. In order to apply precise analysis of activity and sleep times, participants were asked to keep a sleep/activity diary to record the times where they took the wrist watch off, times they went to bed or got out of bed, times when they napped, whether they went to school that day, whether they were physically ill that day, and any activity in which they participated throughout the day. Prior to provision of the sleep/activity diary to the

patient, the examiner filled in the dates and day of the week for each day the sleep watch was to be worn. In addition to keeping the sleep/activity log, the participant completed the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The participants were given the sleep/activity log, monitor, and PSQI at the baseline assessment, and scheduled for a follow-up meeting (5 – 7 days after provided the watch) for the examiner to collect and review the sleep materials with the participant.

During the sleep follow-up interview, each participant reviewed the collected sleep data with an examiner. Specifically, the examiner looked for discrepancies between the sleep/activity log and the actigraph data, and queried the participant to ensure accurate sleep/wake data collection using the ECSSii Actigraphy Questioning Form (obtained from the Sleep and Development Laboratory at the University of Colorado, Monique LeBourgeois, Ph.D.; see Appendix A). The examiner queried about low activity times during typical wake periods (e.g., due to napping, falling asleep, watching television on the couch, taking watch off) and high activity times during typical sleep periods (e.g., nighttime awakenings due to noise, bathroom trip, bed partner, pet, bad dream, sick, too hot/too cold) to ensure the participant was actually awake during periods of high activity and truly asleep during periods of low activity. The examiner recorded responses to these queries and any missing data on the sleep/activity log in a different colored pen, in order to clearly indicate information collected after the watch was returned.

Following the sleep study, patients and healthy controls participated in a structural Magnetic Resonance (MRI) and Diffusion Tensor (DTI) imaging session. Pregnancy tests were administered prior to scanning to all female participants unless they signed a specific waiver declining this test. If the participant was a minor, her parent/guardian was asked to sign this

waiver. Pregnant subjects were excluded from the imaging section. A professionally licensed radiologist reviewed scans to detect clinical abnormalities. In the event of an anomaly, participants were informed and if requested, offered a referral to a professional at no cost to the participant.

Healthy controls followed identical clinical, sleep, and imaging procedures as the UHR individuals; however, as healthy individuals were less likely to endorse symptoms, the clinical interviews generally lasted a shorter amount of time. Therefore, for healthy controls, the screening and full clinical interviews were scheduled for a single session.

Measures

Structured Interview for Prodromal Symptoms (SIPS)

The Structured Interview for Prodromal Symptoms (SIPS) was used to diagnose the three prodromal syndromes included in the current study (i.e., brief intermittent psychotic symptom syndrome, attenuated positive symptom syndrome, genetic risk and deterioration syndrome), and includes the scale of prodromal symptoms (SOPS), Schizotypal Personality Disorder Checklist (American Psychiatric Association, 2000), family history questionnaire, and global assessment of functioning (GAF; Hall, 1995) (McGlashan et al., 2001; Miller, McGlashan, et al., 2003; Rosen et al., 2002). The SOPS is a 19-item scale measuring the severity of prodromal symptoms, including four subscales: positive (i.e., unusual thoughts, suspiciousness, grandiosity, perceptual abnormalities, disorganized communication), negative (i.e., social anhedonia, avolition, expression of emotion, experience of emotion/self, ideational richness, occupational functioning), disorganized (i.e., odd behavior/appearance, bizarre thinking, trouble with focus/attention, impairment in personal hygiene), and general (i.e., sleep disturbance, dysphoric

mood, motor disturbances, impaired tolerance to normal stress). The SIPS has sound predictive validity and interrater reliability (Miller, McGlashan, et al., 2003).

Structured Clinical Interview for the DSM-IV (SCID)

The research version of the Structured Clinical Interview for the DSM-IV (SCID) is a semi-structured interview used to diagnose DSM-IV axis I disorders in psychiatric populations (First et al., 1995). Specifically, symptoms of mood, psychosis, anxiety, substance use, somatization, and eating disorders were marked as absent, subthreshold, or present, and once a prescribed number of symptoms were endorsed, the individual received a DSM-IV diagnosis. The SCID has been shown to demonstrate excellent validity and reliability (Lobbestael, Leurgans, & Arntz, 2011; Zanarini & Frankenburg, 2001; Zanarini, Skodol, Bender, Dolan, et al., 2000).

ActiSleep Monitor (Wristwatch) and Sleep/Activity Diary

The ActiSleep monitor is a sleep-specific device developed by ActiGraph (Pensacola, Fl). It has 4MB of non-volatile memory and a rechargeable battery capable of providing power for 8 days between charges. When worn during sleep episodes, the ActiSleep monitor provides sleep quality measurements such as sleep onset, total sleep time (TST, in minutes), number and duration (in minutes) of awakenings, total awake time (TAT, in minutes), sleep efficiency, and total movement counts during the sleep period. The ActiSleep monitor has a sleek, lightweight, and compact design for maximum comfort. The sleep/activity diary accompanied the ActiSleep monitor and required participants to record the time of sleep initiation, time of awakening, school attendance, naps, physical illness, and participation in activities throughout each day (see Appendix B).

The ActiSleep monitor and sleep/activity diary collected data regarding sleep and activity variables over a 5-day period. Total activity counts are recorded in 60-second intervals. The sleep/activity diary (subjective recordings of time in bed and time out of bed) was used to determine the sleep period used in the actigraphy analyses. Target sleep variables for analyses were calculated using the Sadeh algorithms (Sadeh, Sharkey, & Carskadon, 1994) in the ActiLife version 5.10.0 scoring program. The Sadeh algorithms were specifically chosen due to their previous use with adolescent and young adult populations (Sadeh et al., 1994). The ActiLife scoring program also provides validation data confirming how long the ActiSleep wristwatch was worn based on measurements of activity.

Following automatic scoring in the ActiLife scoring program, the data were hand-checked for accuracy by the experimenter. Using the sleep diary to determine the sleep period, the experimenter ensured accurate sleep onset time (determined as the first sleep epoch of three successive sleep epochs, following an awake epoch) and sleep offset time (determined as the last sleep epoch of five sleep epochs, prior to an awake epoch). To address any incidents of ambiguous data, consensus meetings with the experimenter (Jessica Lunsford Avery, M.A.), sleep consultant (Dr. Monique LeBourgeois), ADAPT's director (Dr. Vijay Mittal), and ADAPT lab coordinator (Tina Gupta, B.S.) determined whether nights with an anomaly (e.g., large movement in the night, the watch being taken off) were fit for inclusion in analyses. Participants required at least three (and up to five) nights with accurate actigraph data to be included in analyses; two UHR participants were excluded from the actigraph analyses due to insufficient number of nights supporting valid data.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI (Appendix C) is a 19-item self-report questionnaire assessing seven domains: subjective sleep quality, latency, duration, efficiency, disturbances, use of sleeping medication, and daytime dysfunction (Buysse et al., 1989). Scoring of the PSQI total score ranges from 0 – 21, with higher scores reflecting increasing levels of sleep impairment. Similarly, scores for each sub-domain ranges from 0 to 3, with higher numbers reflecting greater impairment. For a detailed description of how the PSQI is scored, see Appendix D. The PSQI has been shown to demonstrate acceptable reliability and validity (Buysse et al., 1989), and has been used widely in schizophrenia research (e.g., Afonso et al., 2011; Hofstetter et al., 2005; Ritsner et al., 2004), as well as with adolescent clinical populations (e.g., Jones, Tai, Evershed, Knowles, et al., 2006; Kaneita, Yokoyama, Harano, Tamaki, et al., 2009). This questionnaire was intended as a supplement to the sleep/activity log and provided a meaningful subjective measure of sleep quality.

Beck Depression Inventory-II (BDI-II)

The Beck Depression Inventory-II (BDI-II) is a 21-item self-report questionnaire designed to assess the intensity of depressive symptoms in adolescents and adults aged 13 to 80 years, and includes items assessing sadness, anhedonia, pessimism, feelings of guilt or punishment, self-dislike, self-criticalness, suicidal ideation, crying, agitation, indecisiveness, feelings of worthlessness or failure, lack of energy, sleep impairment, irritability, appetite or weight changes, concentration difficulties, fatigue, and loss of interest in physical intimacy. For each item, participants were instructed to indicate which statement best described their experience over the past two-week period. Items are rated on a 4-point (0 to 3) scale, and the total score is obtained by summing the scores for all items. Scores ranging between 0 and 13 are

indicative of minimal depression; scores between 14 and 19 reflect a mild level of depression; scores of 20 to 28 are considered moderate; and scores between 29 and 63 are indicative of severe depression (Beck, Steer, Ball, & Ranieri, 1996). The BDI-II exhibits excellent internal consistency, test-retest reliability, convergent and divergent validity, and construct validity in both adult (Beck et al., 1996; Dozois & Covin, 2004; Segal, Coolidge, Cahill, & O'Riley, 2008) and adolescent (Osman, Barrios, Gutierrez, Williams, et al., 2008) populations.

Parent General Behavior Inventory (P-GBI) Short Form – Hypomanic/Biphasic scale

The Parent General Behavior Inventory (P-GBI) Short Form - Hypomanic/Biphasic scale is a 10-item, parent-report questionnaire assessing symptoms of hypomania and mania (euphoria, restlessness, rapid shifts in mood, increased energy, decreased need for sleep, irritability, pressured speech) (Youngstrom, Frazier, Demeter, Calabrese, et al., 2008). The P-GBI short form is adapted from the original 73-item P-GBI (Youngstrom, Findling, Danielson, & Calabrese, 2001), and correlates .95 with the original Hypomanic/Biphasic scale. The P-GBI short form has strong reliability, and successfully discriminates adolescents with bipolar disorder from those with other axis I disorders, including unipolar depression and attention-deficit/hyperactivity disorder (Youngstrom, et al., 2008). A parent-report measure of hypomania was selected in accordance with evidence suggesting that parent report is more valid than adolescent self-report concerning the presence and severity of manic symptoms (Baroni, Lunsford, Luckenbaugh, Towbin, et al., 2009; Youngstrom, Meyers, Youngstrom, Calabrese, & Findling, 2006).

Imaging

Data Collection. The imaging section of the study was conducted at the University of Colorado Inter-mountain Imaging Consortium (INC) center. Magnetic resonance imaging (MRI)

of the brain was acquired on each subject using a Siemens 3-Tesla Magnetom TIM Trio MRI scanner (Siemens AG, Munich, Germany) with a 12-channel head coil. 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) covering the whole brain was acquired for anatomic segmentation. A turbo spin echo proton density (PD)/ T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line (AC-PC line); TR= 3720ms; TE = 89 ms; GRAPPA parallel imaging factor of 2; .9 x .9 mm voxels; FOV = 240 mm; flip angle: 120°; 77 interleaved 1.5 mm slices; time = 5:14 min) was acquired to check for incidental pathology. The entire imaging protocol including localizing images, gradient echo field mapping, the arterial spin labeling scan, and the BOLD weighted resting state scan took approximately 30 minutes.

MRI Post Processing. The thalamus was delineated automatically on MRI using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) algorithm within the FMRIB's Software Library (FSL) image-processing suite (Patenaude, 2007). Researchers have found close correspondences between FIRST and manually derived volume values (de Jong, van der Hiele, Veer, Houwing, et al., 2008). To employ FIRST, each subject's whole-brain IR-FSPGR was converted from DICOM to Analyze format and cropped below the head. The resulting volume was re-sliced to an axial-oblique orientation aligned with the AC-PC plane. It was then transformed into MNI152 space before being loaded into FIRST.

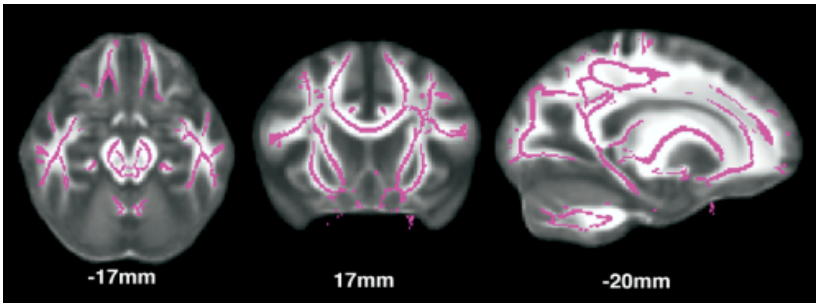
FIRST was developed by the FMRIB Centre in the Department of Clinical Neurology at Oxford and represents a cutting-edge addition to the widely used FSL medical image-processing

package, incorporating several major advances in brain voluming of the last decade. Briefly, the individual subject's brain MRI was compared to a large database of standard brains maintained by Harvard/Massachusetts General Hospital. These brains have been carefully parcellated into numerous volumes-of-interest (VOIs), each representing a different brain anatomic structure, by hand. A surface mesh was then applied to the VOI in the current study (thalamus) in the subject's brain, (i.e., the actual surface is approximated by a contiguous net of a large number of tiny polygons (e.g., triangles) each with vertices (mesh points) and an interior area (facet). The shape formed by the points mesh is then described quantitatively as a 3D distribution in space, composed of varying amounts of a set of standard deformable distributions. The T1 MRI intensity at each facet of the mesh surface was normalized to correct for instrumental and other inter-subject differences in intensity. A separate 3D distribution was then derived for the intensity. A "training set" of standard VOIs was extracted from the database. Iterative curve fitting was then applied until a linear combination of the standard VOIs was found that best reproduced the shape and intensity distributions of the subject's VOI. That yielded the final volume. FIRST also returned values for each participant's total intracranial volume (TICV; the sum of whole-brain grey matter plus white matter plus cerebrospinal fluid) and the thalamus structure was then divided by the TICV to control for whole brain volume. To confirm volumes derived using FIRST, results for each subject were visually inspected by ADAPT team experts including Drs. Marie Banich and Joseph Orr.

DTI Post-Processing. DTI was utilized to measure tract integrity for each participant; respective FA values were used to estimate white matter integrity including myelin thickness, axonal diameter, and similarity in the direction of fibers within the tract (the improved organization of white matter tracts bolster the signal transduction). Eddy current correction was

completed using Flirt (FMRIB Software Library [FSL], Oxford, United Kingdom; Smith, Jenkinson, Woolrich, Beckmann, et al., 2004), and images were skull-stripped using the Brain Extraction Tool. FA images were calculated using DTIFit (FMRIB's Diffusion Toolbox), which fits a diffusion tensor model at each voxel, and then registered to Montreal Neurological Institute (MNI)-152 space using a 12-parameter affine registration with a mutual information cost function implemented in Flirt (FSL). A group map was created using a rigorous approach of Tract-Based Spatial Statistics (TBSS) (Smith, Jenkinson, Johansen-Berg, Rueckert, et al., 2006). FA is a robust intravoxel measure that yields values between 0 (perfectly isotropic diffusion) and 1 (the hypothetical case of cylinder infinitely long and infinitely thin). An average FA image was created and the tracts were narrowed to generate an FA "skeleton" representing the center of all tracts common to the entire group. The area around the skeleton in each subject's aligned FA map was searched and the highest local FA value was assigned to the skeleton. This ensured that each subject's skeleton was in the group space, yet represented the center of that subject's own unique fiber tracts. Regions of interest (ROIs) included thalamocortical pathways running through the anterior internal capsule (i.e., left and right anterior thalamic radiations). Taken together, these ROIs will be used to guide analyses.

Figure 1. Tract based Spatial Skeleton



Regions were created by overlying the TBSS-generated skeleton (see Figure 1) with the John Hopkins University DTI-based probabilistic tractography atlas for the tracts of interest (Hua, Zhang, Wakana, Jiang, et al., 2008; Wakana, Caprihan, Panzenboeck, Fallon, et al., 2007). This process achieves alignment without the need for perfect non-linear pre-registration and further,

any systematic differences in exact tract location between groups of subjects thus did not bias the comparison of FA values between the groups. To ensure the validity of the tractography-based ROIs for our TBSS skeleton, in any instance in which the skeleton and JHU tract differs, the ROI was edited to incorporate contiguous and inclusive sections of the skeleton. Each participant's FA skeleton was masked using the ROIs, and the average FA was calculated for that segment of the skeleton in each region.

Data Analyses

Specific Aim 1a: To determine whether subjective (self-report) and objective (actigraph) domains of sleep impairment (i.e., latency, duration/TST, continuity/TAT, efficiency, total movement count, subjective quality, disturbances) are present in UHR youth compared to healthy controls. To test hypotheses that UHR individuals have greater sleep dysfunction compared to controls, linear regressions covarying for age, gender, and mood symptoms (BDI-II and P-GBI) tested for group differences in ActiSleep wristwatch variables (continuity/TAT, efficiency, duration/TST, total movement counts), five self-report PSQI indices (subjective sleep quality, latency, efficiency, duration, disturbances), and total PSQI score. Because medications were only utilized in one group (i.e., UHR), medications were not included as covariates in these analyses, as medications would have represented a proxy for group membership.

Specific Aim 1b: To determine the relationship of sleep dysfunction with domains of prodromal symptoms (positive, negative, disorganized) in UHR youth. Linear regression models covarying for mood symptoms (BDI-II and P-GBI) and dummy-coded medications (mood stabilizers, anti-psychotics, stimulants, SSRIs) tested associations between subjective (duration, latency, efficiency, disturbances, subjective quality, total PSQI score) and objective (duration/TST, continuity/TAT, total movement counts, efficiency) measures of sleep dysfunction and

attenuated symptoms (positive, negative, disorganized) on the SIPS. These analyses were conducted on the entire sample as well as with the UHR group alone.

Specific Aim 2: To determine if neural structures (i.e., right and left thalamus) and tracts (i.e., right and left anterior thalamic radiations) underlying sleep function are abnormal in UHR youth compared to controls, and if so, the extent to which neural abnormalities are related to indices of sleep dysfunction. For Aim 2, the variables of interest were MRI/DTI data concerning neural structures and white matter tracts widely believed to underlie sleep dysfunction and psychosis. The neural structures include the left and right thalamus, and the left and right thalamocortical white matter tracts running through the anterior internal capsule (Fuller et al., 2006; Stiller & Postolache, 2005; Taber & Hurley, 2006). Linear regressions covarying for age, gender, and total intracranial volume (TICV) compared the volume of the specified structures and estimates of white matter integrity in UHR individuals and healthy controls to test the hypotheses that individuals at high-risk for psychosis have decreased volume of the thalamus and reduced integrity of thalamocortical white matter in comparison to controls. In addition, linear regressions covarying for mood symptoms (BDI, P-GBI) and dummy-coded medications (mood stabilizers, anti-psychotics, stimulants, SSRIs) examined associations between grey and white matter variables and subjective and objective measures of sleep.

Exploratory Aim 1: To determine the relationship between self-report (PSQI) and objective (actigraphy) measures of sleep impairment. Linear regressions covarying for dummy-coded medications (mood stabilizers, anti-psychotics, stimulants, SSRIs) and mood symptoms (BDI, P-GBI) tested the associations between subjective and objective measures of sleep dysfunction (i.e., duration with TST, subjective efficiency with objective efficiency, self-reported sleep

disturbances with TAT and total movement counts). These analyses were conducted on the entire sample as well as with the UHR group alone.

Exploratory Aim 2: To determine the relationship of sleep dysfunction (latency, duration/TST, continuity/TAT, efficiency, disturbances, subjective quality, total movement count), as measured by both objective and subjective methods, with domains of mood symptoms (depressive and hypomanic/manic) in UHR youth. Linear regression models covarying for medications (mood stabilizers, anti-psychotics, stimulants, SSRIs) tested associations between measures of sleep dysfunction (TST/duration, TAT/continuity, total movement counts, latency, efficiency, disturbances, subjective quality, total PSQI score) and depressive and hypomanic/manic symptoms (BDI-II and P-GBI). These analyses were conducted on the entire sample as well as with the UHR group alone.

CHAPTER III

RESULTS

In addition to the data analysis strategy outlined above, analyses were conducted in several additional ways to ensure the validity of the results. Specifically, analyses were conducted a) with and without medications as covariates, b) including and excluding patients on medications, c) including and excluding patients with significantly elevated symptoms of (hypo)mania, d) with and without patients with significantly elevated symptoms of depression, and for the actigraphy analyses, e) using structured sleep periods (restrained by environmental demands such as waking for school, job, etc.) and unstructured sleep periods (the adolescent slept naturally). As these additional strategies did not significantly alter the direction or magnitude of findings, results are reported following a general strategy of including all participants. As described in the data analysis section, analyses assessing group differences in sleep variables controlled for age, gender, and mood symptoms. Analyses examining associations between sleep variables and prodromal symptoms covaried for mood symptoms and medications. Group differences in brain volumes and tracts were assessed covarying for age, gender, and intracranial volume, and relationships between sleep variables and brain volume/integrity reductions were examined controlling for mood symptoms and medications. Medications were controlled for in analyses assessing associations between sleep variables and mood symptoms.

Demographics of the Ultra High-Risk and Healthy Control Samples

Participants included 33 UHR adolescents and 33 healthy controls. UHR adolescents included 22 males (67%) and 11 females (33%), with an average age of 18.73 (SD = 1.89). Healthy control 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 (6, 60) =11.13, p = .08). A significantly greater number of males were in the UHR group compared to controls (X^2 (1, 65) = 3.91, p = .05).

As would be expected, UHR adolescents were more likely than healthy controls to be taking medications, including 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 adolescents (n = 20) and healthy controls (n = 32) were not taking medications. See Table 3.

Table 3. Demographic characteristics of the 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
SIPS-Disorganized	6.16 (3.66)	.45 (.87)	.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*
First Nations	0 (0%)	1 (3%)	
East Asian	0 (0%)	3 (9%)	
Southeast Asian	0 (0%)	1 (3%)	
Black	1 (3%)	0 (0%)	
Central/South American	5 (15%)	11 (33%)	
Caucasian	26 (79%)	17 (52%)	
Other	1 (3%)	0 (0%)	
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

Group Differences in Symptoms

Regarding psychosis symptoms, UHR adolescents displayed significantly higher levels of positive symptoms on the SIPS (M = 11.85, SD = 4.68) than healthy controls (M = 0.76, SD = 1.44) (F (1, 63) = 153.85, p = .00), as well as significantly higher levels of negative symptoms on the SIPS (M = 12.16, SD = 7.22) than their healthy counterparts (M = 0.73, SD = 1.44), (F (1, 63) = 78.18, p = .00). Similarly, groups significantly differed on levels of disorganized symptoms on the SIPS, with UHR youth displaying higher levels (M = 6.16, SD = 3.66) than controls (M = 0.45, SD = 0.87) (F (1, 63) = 70.75, p = .00). Groups also differed on levels of mood symptoms, with UHR adolescents displaying increased depression levels on the BDI (M = 18.75, SD = 4.33) compared to healthy controls (M = 4.61, SD = 5.86) (F (1, 63) = 34.41, p = .00), and increased (hypo)mania levels on the P-GBI (M = 9.76, SD = 7.11) than healthy controls (M = 1.29, SD = 2.66) (F (1, 41) = 19.46 , p = .00). See Table 3.

Aim 1a. Group Differences in Subjective and Objective Sleep Dysfunction

Pittsburgh Sleep Quality Index

Controlling for age, gender, and mood symptoms, UHR adolescents endorsed significantly greater latency to sleep onset (F (5, 40) = 5.40, p = .01), higher rates of sleep disturbances (F (5, 40) = 5.53, p = .01), and a trend toward greater total score (F (5, 40) = 3.63, p = .10) on the PSQI compared to healthy controls. Groups did not differ on PSQI duration (F (5, 40) = 0.64, p = .21), efficiency (F (5, 40) = 0.36, p = .28), or sleep quality (F (5, 40) = .61, p = .22) over and above the effects of age, gender, and mood symptoms.

Actigraphy

UHR adolescents displayed significantly reduced actigraph-measured efficiency (F (5, 30) = 2.85, p = .05), increased TAT/disrupted continuity (F (5, 30) = 3.65, p = .03), and

increased movements during sleep (F (5, 30) = 4.06, p = .03) compared to healthy controls, over and above the effects of age, gender, and mood symptoms. Controlling for age, gender, and mood symptoms, groups did not differ on TST/duration (F (5, 30) = 0.32, p = .29). See Table 4.

Table 4. Group differences in sleep dysfunction

	UHR mean (SD)	HC mean (SD)	Beta Value	*F* Statistic	*p* Value
PSQI					
Duration	.54 (.88)	.46 (.91)	-.112	0.64	.21
Latency	1.96 (.88)	1.08 (.98)	.315*	5.40	.01
Efficiency	.96 (1.40)	.96 (1.31)	-.093	0.36	.28
Disturbances	1.46 (.58)	.96 (.53)	.322*	5.53	.01
Quality	1.39 (.69)	1.00 (.80)	.106	0.61	.22
Total	8.04 (3.54)	5.44 (3.37)	.177^{+}	3.63	.10
Actigraphy					
TST	389.30 (62.71)	399.85 (61.0)	.124	0.32	.29
Efficiency	86.23 (5.72)	87.14 (5.21)	-.389*	2.85	.05
TAT	62.80 (29.61)	59.08 (26.42)	.438*	3.65	.03
Total Movements	24984.03 (13503.07)	21345.85 (9250.44)	.469*	4.06	.03

Significance: * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: UHR, Ultra High-Risk; HC, Healthy Controls; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Aim 1b. Relationships of Psychosis Symptoms to Sleep Dysfunction

UHR Sample

Positive Symptoms. Among UHR adolescents, increased positive symptom total score on the SIPS was not significantly related to duration (F (7, 15) = 0.04, p = .42), latency (F (7, 15) = 0.09, p = .38), efficiency (F (7, 15) = 0.34, p = .28), sleep disturbances (F (7, 15) = 0.33, p = .29), sleep quality (F (7, 15) = 0.64, p = .22), or total score (F (7, 15) = 0.00, p = .48) on the PSQI, over and above the effects of medications and mood symptoms. Controlling for medications and mood symptoms, decreased actigraph-measured efficiency (F (7, 13) = 5.57, p = .02), increased TAT (F (7, 13) = 5.37, p = .02), and increased movements during the sleep period (F (7, 13) = 3.51, p = .04) were significantly correlated with increased positive symptom total score on the SIPS in the UHR sample. Among UHR youth, positive symptom total score was

not associated with TST (F (7, 13) = 0.23, p = .32) over and above the effects of medications and mood symptoms.

Negative Symptoms. 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 sleep quality (F (7, 15) = 8.66, p < .01), and increased total score (F (7, 15) = 7.55, p < .01) on the PSQI were significantly associated with increased negative symptom score on the SIPS in the UHR sample. Increased negative symptom total score was not related to PSQI efficiency (F (7, 15) = 0.73, p = .20) or sleep disturbances (F (7, 15) = 0.64, p = .22) among UHR youth. In the UHR sample, increased negative symptom total score was not significantly associated with actigraph-measured efficiency (F (7, 12) = 0.43, p = .26), TST (F (7, 12) = 1.32, p = .14), TAT (F (7, 12) = 0.89, p = .18), or total movements during sleep (F (7, 12) = 0.71, p = .21) over and above the effects of medications and mood symptoms.

Disorganized Symptoms. Among UHR youth, decreased duration (F (7, 15) = 5.80, p = .02) and increased total score (F (7, 15) = 4.08, p = .03) on the PSQI were significantly associated with increased disorganized symptom score on the SIPS, over and above the effects of medications and mood symptoms. Increased disorganized symptom score was not significantly related to latency (F (7, 15) = 0.52, p = .24), efficiency (F (7, 15) = 1.46, p = .12), sleep quality (F (7, 15) = 1.58, p = .12), or sleep disturbances on the PSQI (F (7, 15) = 0.01, p = .46) in UHR adolescents. Controlling for medications and mood symptoms, decreased actigraph-measured efficiency (F (7, 12) = 3.78, p = .04), increased TAT (F (7, 12) = 4.08, p = .03), and increased total movements during sleep (F (7, 12) = 3.01, p = .05) were significantly correlated with increased disorganized symptom total score in the UHR sample. Disorganized symptom total

score was not significantly associated with TST (F (7, 12) = 0.36, p = .28) in UHR youth over and above the effects of medications and mood symptoms. See Table 5.

Table 5. Relationship of sleep dysfunction to psychosis symptoms in the UHR sample

	SIPS Positive	SIPS Negative	SIPS Disorganized
PSQI			
Duration	.050	-.514**	-.511*
Latency	-.072	.378*	.176
Efficiency	-.134	-.159	-.272
Disturbances	.150	-.170	.026
Quality	.201	-.483**	-.308
Total Score	.013	.507*	.504*
Actigraphy			
TST	.166	.287	.129
Efficiency	-.525*	-.131	-.428*
TAT	.515*	.183	.436*
Total Movements	.438*	.165	.388*

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: SIPS, Structured Interview for Prodromal Symptoms; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Full Sample

Positive Symptoms. Controlling for medications and mood symptoms, total positive score on the SIPS was not significantly related to PSQI duration (F (7, 32) = 0.87, p = .18), latency (F (7, 32) = 0.00, p = .49), efficiency (F (7, 31) = 0.56, p = .23), sleep disturbances (F (7, 32) = 0.35, p = .28), sleep quality (F (7, 32) = 0.26, p = .31) or total score (F (7, 31) = 0.06, p = .41) in the full sample. Among all participants, decreased actigraph-measured efficiency (F (7, 28) = 10.93, p < .01), increased TAT (F (7, 28) = 10.77, p = .002), and increased movements during sleep (F (7, 28) = 10.71, p = .002) were significantly correlated with increased total positive symptom score over and above mood symptoms and medications. Controlling for mood

symptoms and medications, total positive symptom score was not associated with TST (F (7, 28) = 0.24, p = .31) in the full sample.

Negative Symptoms. Controlling for mood symptoms and medications, decreased duration (F (7, 31) = 3.25, p = .04), increased latency (F (7, 31) = 3.49, p = .04), reduced sleep quality (F (7, 31) = 4.10, p = .03), and increased total score (F (7, 30) = 3.02, p < .05) on the PSQI were significantly correlated with increased total negative symptom score on the SIPS in the full sample. Among all participants, total negative symptom score was not significantly associated with PSQI efficiency (F (7, 30) = 1.26, p = .14) or sleep disturbances (F (7, 31) = 0.93, p = .17) over and above medications and mood symptoms. Decreased efficiency (F (7, 27) = 1.76, p < .10), increased TAT (F (7, 27) = 2.52, p = .06), and increased total movements during sleep (F (7, 27) = 2.57, p = 0.06) were correlated with increased total negative symptom score at the trend level in the full sample, controlling for medications and mood symptoms. Among all participants, TST was not related to total negative symptom score over and above the effects of medications and mood symptoms (F (7, 27) = 0.95, p = .17).

Disorganized Symptoms. Among all participants, decreased duration (F (7, 31) = 1.76, p < .10) and increased PSQI total score (F (7, 30) = 1.71, p = .10) were associated with increased total disorganized symptom score on the SIPS at the trend level, over and above medications and mood symptoms. Controlling for mood symptoms and medications, total disorganized symptom score was not related to PSQI latency (F (7, 31) = 0.25, p = .31), efficiency (F (7, 30) = 1.31, p = .13), sleep disturbances (F (7, 31) = 0.01, p = .45), or sleep quality (F (7, 31) = 0.35, p = .28) in the full sample. Among all participants, decreased actigraph-measured efficiency (F (7, 27) = 7.65, p < .01), increased TAT (F (7, 27) = 7.66, p < .01), and increased total movement counts (F (7, 27) = 7.86, p < .01) were significantly correlated with increased total disorganized symptom

score. Controlling for mood symptoms and medications, total disorganized symptom score was not associated with TST in the full sample (F (7, 27) = 0.22, p = .32). See Table 6.

Table 6. Relationship of sleep dysfunction to psychosis symptoms in the full sample

	SIPS Positive	SIPS Negative	SIPS Disorganized
PSQI			
Duration	.117	-.191*	-.177^{+}
Latency	.002	.214*	.074
Efficiency	-.092	-.119	-.151
Disturbances	.090	-.126	.122
Quality	.064	-.213*	-.081
Total Score	-.037	.220*	.201^{+}
Actigraphy			
TST	.082	.131	.074
Efficiency	-.392**	-.148^{+}	-.328**
TAT	.385**	.172^{+}	.322**
Total Movements	.384**	.174^{+}	.362**

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: SIPS, Structured Interview for Prodromal Symptoms; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Aim 2a. Group Differences in Brain Structures and Tracts

Compared to healthy controls, UHR adolescents displayed significantly decreased grey matter volume of the left (F (3, 53) = 4.59, p = .02) and right (F (3, 53) = 6.42, p < .01) thalamus, over and above the effects of age and gender. Controlling for age and gender, fractional anisotrophy in the left (F (3, 49) = 2.39, p = .13) and right (F (3, 49) = 1.29, p = .26) anterior thalamic radiations did not differ between groups. See Table 7.

Table 7. Group differences in thalamus volume and anterior thalamic radiation integrity

	UHR	HC	Beta	F Statistic	*p* Value
Brain Structure					
Left Thalamus	.45 (.03)	.47 (.05)	.263*	4.59	.02
Right Thalamus	.46 (.03)	.49 (.05)	.276**	6.42	.01
Brain Tract					
Left ATR	.49 (.02)	.49 (.02)	-.217^{+}	2.39	.12
Right ATR	.48 (.01)	.47 (.02)	-.156	1.29	.26

Note: Thalamus volume indicated as percentage TICV, ATR integrity represents FA.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: UHR, Ultra High-Risk; HC, Healthy Controls; ATR, Anterior Thalamic Radiation

Aim 2b. Relationship of Reduced Brain Volumes and Tracts to Sleep Dysfunction

UHR Sample

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

Decreased Thalamus Volume and Actigraphy-Measured Sleep. Controlling for medications and mood symptoms, reduced left thalamus volume was significantly correlated

with increased movements during the sleep period (F (7, 10) = 3.19, p = .05) in UHR youth, and increased TAT (F (7, 10) = 2.74, p = .06) and decreased efficiency (F (7, 10) = 2.25, p = .08) at the trend level. Among UHR adolescents, left thalamus volume was not significantly related to TST (F (7, 10) = 0.80, p = .20) over and above the effects of mood symptoms and medications. In the UHR sample, deceased right thalamus volume was significantly associated with decreased efficiency (F (7, 10) = 7.61, p = .01), increased TAT (F (7, 10) = 9.35, p < .01), and increased total movements during sleep (F (7, 10) = 8.09, p < .01), controlling for medications and mood symptoms. Covarying for mood symptoms and medications, right thalamus volume was not significantly related to TST among UHR youth (F (7, 10) = 1.00, p = .17).

Decreased Thalamocortical Tract Integrity and PSQI Sleep. Among UHR youth, decreased FA in the left anterior thalamic radiation was significantly associated with increased sleep disturbances (F (7, 14) = 4.04, p = .03), more problems with sleep quality (F (7, 14) = 5.78, p = .02), and a trend toward increased total score (F (7, 13) = 1.84, p < .01) on the PSQI, controlling for medications and mood symptoms. FA of the left anterior thalamic radiation was not significantly related to duration (F (7, 14) = .26, p = .31), latency (F (7, 14) = 0.69, p = .21), or efficiency (F (7, 13) = 0.00, p = .45) on the PSQI within the UHR sample, over and above mood symptoms and medications.

Controlling for mood symptoms and medications, decreased FA in the right anterior thalamic radiation was significantly correlated with more problems with sleep quality (F (7, 14) = 4.04, p = .03) in the UHR sample, and with increased sleep disturbances (F (7, 14) = 1.91, p = .09) and increased total score (F (7, 13) = 2.35, p = 0.07) at the trend level. In the UHR sample, FA in the right anterior thalamic radiation was not significantly related to duration (F (7, 14) =

0.75, $p = .20$), latency (F (7, 14) = 1.04, $p = 0.16$), or efficiency (F (7, 13) = 0.06, $p = 0.40$) on the PSQI, controlling for medications and mood symptoms.

Decreased Thalamocortical Tract Integrity and Actigraph-Measured Sleep. Controlling for mood symptoms and medications, decreased FA of the left anterior thalamic radiation was significantly related to increased total movement count in the sleep period (F (7, 10) = 3.31, $p <$ .05) among UHR adolescents, but was not associated with TST (F (7, 10) = 0.13, $p = .36$), actigraph-measured efficiency (F (7, 10) = 0.69, $p = .21$), or TAT (F (7, 10) = 1.32, $p = .14$). Over and above medications and mood symptoms, decreased FA in the right anterior thalamic radiation was significantly correlated with increased TAT (F (7, 10) = 3.88, $p = .04$) and increased total movements during sleep (F (7, 10) = 8.06, $p < .01$) in the UHR sample, and decreased actigraph-measured efficiency (F (7, 10) = 2.30, $p = .08$) at the trend level. Among UHR youth, FA in the right anterior thalamic radiation was not associated with TST (F (7, 10) =0.54, $p = .24$) over and above the effects of medications and mood symptoms. See Table 8.

Table 8. Relationship of sleep dysfunction to thalamic abnormalities in the UHR sample

	Left Thalamus	Right Thalamus	Left ATR	Right ATR
PSQI Variable				
Duration	.207	.055	.134	.235
Latency	-.521**	-.425*	- .206	-.264
Efficiency	.446*	.471*	.001	.069
Disturbances	-.184	-.281	-.483*	-.373^{+}
Quality	.696**	.562**	.574*	.530*
Total	-.779**	-.657**	-.412^{+}	-.478^{+}
Actigraphy				
TST	.317	.343	-.151	-.317
Efficiency	.399^{+}	.595**	.266	.473^{+}
TAT	-.424^{+}	-.619**	-.348	-.565*
Total Movements	-.440*	-.582**	-.501*	-.704**

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: ATR, Anterior Thalamic Radiation; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Full Sample

Decreased Thalamus Volume and PSQI Sleep. Controlling for medications and mood symptoms, decreased volume of the left thalamus was significantly correlated with increased latency (F (7, 27) = 5.03, p = .02), decreased efficiency (F (7, 25) = 2.86, p = .05), reduced sleep quality (F (7, 34) = 12.85, p < .001), and increased total score (F (7, 25) = 8.77, p < .01) on the PSQI in the full sample. Among all participants, volume of the left thalamus was not significantly related to PSQI duration (F (7, 27) = 1.20, p = .14) or sleep disturbances (F (7, 27) = 0.00, p = .50) over and above the effects of medications and mood symptoms. Similarly, controlling for medications and mood symptoms, decreased volume of the right thalamus was significantly associated with increased latency (F (7, 27) = 4.12, p = .03), decreased efficiency (F (7, 25) = 4.81, p = .02), reduced sleep quality (F (7, 27) = 10.62, p < .01), and increased total score (F (7, 25) = 6.93, p < .01) in the full sample. Among all participants, volume of the right thalamus was not significantly related to PSQI duration (F (7, 27) = 0.22, p = .32) or sleep disturbances (F (7, 27) = 0.23, p = .82) over and above the effects of mood symptoms and medications.

Decreased Thalamus Volume and Actigraph-Measured Sleep. Controlling for medications and mood symptoms, decreased left thalamus volume was significantly correlated with decreased efficiency (F (7, 22) = 3.64, p = .03) and increased TAT during the sleep period (F (7, 22) = 3.69, p = .03) in the full sample. Among all participants, left thalamus volume was not significantly associated with TST (F (7, 22) = 0.24, p = .32) or total movements during sleep (F (7, 22) = 1.61, p = .11) over and above the effects of medications and mood symptoms. Similarly, in the full sample, deceased right thalamus volume was associated with decreased efficiency (F (7, 22) = 8.40, p = .004), increased TAT (F (7, 22) = 8.30, p = .005), and increased

total movement count during sleep (F (7, 22) = 3.87, p = .03) over and above medications and mood symptoms. Controlling for mood symptoms and medications, right thalamus volume was not significantly associated with TST in the full sample (F (7, 22) = 0.29, p = .30).

Decreased Thalamocortical Tract Integrity and PSQI Sleep. Among all participants, decreased FA of the left anterior thalamic radiation was significantly correlated with increased sleep disturbances (F (7, 25) = 6.58, p < .01), but not with duration (F (7, 25) = 0.37, p = .27), latency (F (7, 25) = 0.03, p = .43), efficiency (F (7, 23) = .03, p = .49), quality (F (7, 25) = 0.02, p = .44), or total score on the PSQI (F (7, 23) = 0.65, p = .22), over and above mood symptoms and medications. Controlling for medications and mood symptoms, decreased FA of the right anterior thalamic radiation was significantly associated with greater sleep disturbances (F (7, 25) = 3.94, p = .03) in the full sample, but was not related to duration (F (7, 25) = 0.15, p = .35), latency (F (7, 25) = 0.01, p = .46), efficiency (F (7, 23) = 0.43, p = .26), sleep quality (F (7, 25) = 0.03, p = .43), or total sleep score on the PSQI (F (7, 23) = 1.58, p = .11).

Decreased Thalamocortical Tract Integrity and Actigraph-Measured Sleep. Controlling for mood symptoms and medications, decreased FA of the left anterior thalamic radiation was significantly related to increased total movements during sleep (F (7, 20) = 3.14, p < .05) in the full sample, and increased TAT (F (7, 20) = 1.80, p < .10) at the trend level. Among all participants, FA of the left anterior thalamic radiation was not associated with TST (F (7, 20) = 0.81, p = .19) or actigraph-measured efficiency (F (7, 20) = 0.90, p = 0.18) over and above medications and mood symptoms. Controlling for mood symptoms and medications, decreased FA of the right anterior thalamic radiation was significantly correlated with increased TAT (F (7, 20) = 4.19, p = .03) and increased total movements (F (7, 20) = 6.13, p = .01) in the full sample,

and increased TST (F (7, 20) = 2.32, p = .08) and decreased actigraph-measured efficiency (F (7, 20) = 2.38, p = .07) at the trend level. See Table 9.

Table 9. Relationship of sleep dysfunction to thalamic abnormalities in the full sample

	Left Thalamus	Right Thalamus	Left ATR	Right ATR
PSQI Variable				
Duration	.202	.087	-.121	-.082
Latency	-.404*	-.367*	.034	.020
Efficiency	.300*	3.73*	-.003	.134
Disturbances	.000	-.050	-.514**	-.435*
Quality	.554**	.513**	.029	.035
Total	-.586**	-.531**	-.179	-.291
Actigraphy				
TST	.113	.122	-.233	-.391^{+}
Efficiency	.361*	.492**	.203	.334^{+}
TAT	-.356*	-.482**	-.270^{+}	-.409*
Total Movements	-.242	-.351*	-.341*	-.469**

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: ATR, Anterior Thalamic Radiation; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Exploratory Aim 1. Relationship of Subjective and Objective Measures of Sleep Dysfunction

UHR Sample

Self-reported number of minutes slept on the PSQI was not significantly related to actigraph-measured TST in the UHR sample (F (1, 20) = 1.81, p = .19). Among UHR youth, subjective ratings of efficiency on the PSQI were significantly associated with actigraph-measured efficiency (F (1, 20) = 5.48, p = .03), such that decreased self-reported efficiency predicted decreased efficiency on the objective measure. Self-reported sleep disturbances were related to total movements during sleep at the trend level (F (1, 20) = 3.84, p = .06) in the UHR sample, such that increased difficulty with sleep disturbances on the PSQI predicted increased movements during sleep. Among UHR adolescents, subjective ratings of difficulty with sleep

disturbances were not associated with actigraph-measured TAT (F (1, 20) = 0.60, p = .45). See Table 10.

Table 10. Relationship of subjective and objective measures of sleep dysfunction in the UHR sample

	PSQI Minutes Slept	PSQI Efficiency	PSQI Disturbances
Actigraph TST	.288	-	-
Actigraph Efficiency	-	.464*	-
Actigraph TAT	-	-	.170
Actigraph Total Movements	-	-	.401^{+}

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Efficiency reverse-coded.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Full Sample

Among all participating adolescents, self-reported number of minutes slept on the PSQI was significantly related to actigraph-measured TST (F (1, 44) = 4.22, p < .05), such that increased subjective account of minutes slept predicted increased TST on the objective measure. Self-reported sleep efficiency was significantly associated with actigraph-measured efficiency in the full sample (F (1, 43) = 5.90, p = .02), such that decreased efficiency on the PSQI predicted decreased efficiency on the objective measure. Among all participants, subjective ratings of sleep disturbances were significantly correlated with actigraph-measured total movements during sleep (F (1, 44) = 5.94, p = .02), such that increased problems with sleep disturbances on the PSQI predicted increased movements during sleep on the objective measure. Subjective ratings of difficulty with sleep disturbances were not associated with actigraph-measured TAT in the full sample (F (1, 44) = 1.79, p = .19). See Table 11.

Table 11. Relationship of subjective and objective measures of sleep dysfunction in the full sample

	PSQI Minutes Slept	PSQI Efficiency	PSQI Disturbances
Actigraph TST	.296*	-	-
Actigraph Efficiency	-	.348*	-
Actigraph TAT	-	-	.198
Actigraph Total Movements	-	-	.334*

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Efficiency reverse-coded.
Significance: ** indicates $p < .01$, * indicates $p < .05$, $^{+}$ indicates $p < .10$
Abbreviations: PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Exploratory Aim 2. Relationships of Mood Symptoms to Sleep Dysfunction

UHR Sample

Depression Symptoms. Controlling for medications, increased total depression score on the BDI was significantly associated with reduced sleep quality (F (5, 21) = 5.73, p = .01), increased latency (F (5, 21) = 3.83, p = .03) and increased total score (F (5, 20) = 11.56, $p < .01$) on the PSQI in the UHR sample. Among UHR youth, increased total depression score was related to decreased PSQI efficiency (F (5, 20) = 1.93, p = .09) and increased sleep disturbances (F (5, 21) = 1.96, p = .09) at the trend level, over and above the effects of medications. Controlling for medication, PSQI duration (F (5, 21) = 0.02, p = .44) was not related to total depression score in the UHR sample. Among UHR adolescents, total depression score was not significantly related to TST (F (5, 18) = 0.88, p = .36), TAT (F (5, 18) = 0.30, p = .60), efficiency (F (5, 18) = 0.07, p = .80), or total movements during sleep (F (5, 18) = 0.36, p = .54) over and above the effects of medications.

(Hypo)mania Symptoms. Controlling for medications, total (hypo)mania score on the P-GBI was not significantly associated with duration (F (5, 19) = 1.41, p = .26), latency (F (5, 19) = 0.76, p = .40), efficiency (F (5, 18) = 0.66, p = .42), sleep disturbances (F (5, 19) = 0.18, p = .68), sleep quality (F (5, 19) = 0.74, p = .40), or total score (F (5, 18) = 0.38, p = .54) on the PSQI in the UHR sample. Among UHR youth, total (hypo)mania score on the P-GBI was not

significantly related to TST (F (5, 15) = 0.06, p = 0.82), TAT (F (5, 15) = 0.47, p = .50), efficiency (F (5, 15) = 0.41, p = .54), or total movements during sleep (F (5, 15) = 0.42, p = .52), over and above the effects of medications. See Table 12.

Table 12. Relationship of mood symptoms and sleep dysfunction in the UHR sample

	BDI	P-GBI
PSQI		
Duration	.031	-.240
Latency	.365*	.169
Efficiency	-.287^{+}	.168
Disturbances	.291^{+}	.087
Quality	-.453*	-.176
Total Score	.574**	.127
Actigraphy		
TST	-.255	-.061
Efficiency	.059	.134
TAT	-.126	-.140
Total Movements	-.144	-.133

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: BDI, Beck Depression Inventory; P-GBI, Parent General Behavior Inventory; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

Full Sample

Depression Symptoms. Controlling for medications, increased total depression score on the BDI was significantly related to increased latency (F (5, 46) = 15.37, p < .01), increased sleep disturbances (F (5, 46) = 9.33, p < .01), decreased sleep quality (F (5, 46) = 6.74, p = .01), and increased total score (F (5, 44) = 19.84, p < .01) on the PSQI in the full sample. Among all participants, PSQI duration (F (5, 46) = 0.70, p = .41) and efficiency (F (5, 44) = 0.44, p = .51) were not significantly associated with total depression score over and above the effects of medications. Controlling for medications, total depression score was not significantly related to TST (F (5, 48) = 2.55, p = .12), actigraph-measured efficiency (F (5, 48) = 0.00, p = .99), TAT (F (5, 48) = 0.20, p = .66), or total movements during sleep (F (5, 48) =0.05, p = .82) in the full sample.

(Hypo)mania Symptoms. In the full sample, increased total (hypo)mania score on the P-GBI was associated with increased latency (F (5, 36) = 3.78, p = .06), increased sleep disturbances (F (5, 36) = 3.68, p = .06), and increased total PSQI score (F (5, 34) = 2.78, p = .10) at the trend level, over and above medications. Controlling for medications, PSQI duration (F (5, 35) = 2.58, p = .12) and quality (F (5, 36) = 1.63, p = .20) were not significantly correlated with total (hypo)mania score in the full sample. Among all participants, total (hypo)mania score was not related to PSQI efficiency (F (5, 34) = 0.97, p = .34) over and above the effects of medications. Total (hypo)mania score was not significantly associated with TST (F (5, 30) = 1.17, p = .30), actigraph-measured efficiency (F (5, 30) = 0.01, p = .94), TAT (F (5, 30) = 0.00, p = .96), or total movements during the sleep period (F (5, 30) = 0.11, p = .74) in the full sample over and above medications. See Table 13.

Table 13. Relationship of mood symptoms and sleep dysfunction in the full sample

	BDI	GBI
PSQI		
Duration	-.109	-.224
Latency	.391**	.267^{+}
Efficiency	-.089	.145
Disturbances	.384**	.274^{+}
Quality	-.318**	-.180
Total Score	.499**	.239^{+}
Actigraphy		
TST	-.211	-.172
Efficiency	-.001	-.011
TAT	-.056	- .009
Total Movements	-.029	.048

Note: Relationships indicated as beta values. For ease of interpretation, PSQI Duration, Efficiency, Quality reverse-scored.
Significance: ** indicates p < .01, * indicates p <.05, $^{+}$ indicates p <.10
Abbreviations: BDI, Beck Depression Inventory; P-GBI, Parent General Behavior Inventory; PSQI, Pittsburgh Sleep Quality Index; TST, Total Sleep Time; TAT, Total Awake Time

CHAPTER IV

DISCUSSION

Sleep is an important biological phenomenon in humans; disturbances in sleep function have deleterious effects on cognition, social and occupational functioning, and physical and mental health (Durmer & Dinges, 2005). In addition, ample evidence has demonstrated that sleep dysfunction, including abnormalities in duration, continuity, latency, and efficiency, are prevalent and greatly impairing symptoms experienced by patients with schizophrenia (e.g., Cohrs, 2008). However, despite the consistency of this finding, few empirical investigations have examined the incidence and characteristics of problematic sleep during the pre-psychotic period. Due to this paucity of research, it has been unclear whether dysfunctional sleep is present prior to psychosis onset, potentially reflecting the etiology and pathophysiology of the disorder, or represents a consequence of extended exposure to aspects of schizophrenia (e.g., neurotoxicity) and its treatment (e.g., medication use).

The current study utilized subjective (i.e., PSQI) and objective (i.e., actigraphy) sleep measures, clinical measures, and imaging (MRI and DTI) to address two primary aims: to determine 1) whether domains of sleep dysfunction differed between UHR adolescents and healthy controls, and if so, the extent to which domains of sleep dysfunction predicted psychosis symptoms, and 2) if sleep-related brain structures (i.e., thalamus) and tracts (i.e., anterior thalamic radiations) differed between UHR youth and healthy controls, and if so, the extent to which brain abnormalities are associated with increased sleep disturbance. Of note, this is the first study to 1) investigate sleep efficiency in a high-risk population, 2) provide evidence for statistically significant declines in sleep efficiency and continuity disruptions in the pre-psychosis period, 3) directly assess associations between sleep dysfunction and psychosis

symptoms in a UHR sample, 4) demonstrate decreased thalamus volumes in UHR youth compared to healthy controls, 5) directly investigate the thalamus-sleep link in an at risk population, and 6) assess white matter integrity of thalamocortical tracts in UHR adolescents.

In the following sections, the results of the present study are reviewed and discussed within the broader schizophrenia, at-risk, and sleep literature. In addition, a potential role for sleep dysfunction within the context of a neurodevelopmental diathesis-stress conception of schizophrenia is discussed. Finally, limitations of the current study are outlined and novel directions for future empirical investigations are proposed.

Findings from the Current Study

Aim 1a. Group Differences in Subjective and Objective Sleep Dysfunction

Adolescents at high risk for psychosis displayed increased sleep dysfunction on both subjective and objective measures compared to healthy controls, over and above the effects of age, gender, and mood symptoms. Specifically, UHR youth displayed increased latency and greater rates of sleep disturbances on the PSQI, as well as decreased efficiency, disrupted continuity, and greater movements during sleep on the actigraph compared to their healthy counterparts.

Latency. Sleep latency refers to the length of time preceding sleep onset. In typical adolescents, increased latencies are associated with a range of troubling outcomes, including daytime sleepiness, inattention, academic and behavior problems, accidents, and physical health problems (Carskadon, 2011). Increased latency in individuals at-risk for psychosis is highly consistent with the schizophrenia literature, which has reliably demonstrated increased time to sleep onset among affected patients (Cohrs, 2008). This result also builds on Keshavan and colleagues' (2004) finding of increased (but non-significant) latency in GR youth; the increased

sample size used by the current study (UHR n = 33/HC n = 33, versus GR n = 9/HC n = 10) may be one explanation for the significant result in the present sample.

Continuity, Disturbances, and Movements. Sleep continuity reflects frequency and length of awakenings once sleep is initiated (e.g., Carskadon & Dement, 2005). In healthy adolescents, experimentally disrupting sleep continuity results in daytime fatigue, tiredness, and detrimental emotional changes (Bonnet, 1994). Disrupted sleep continuity in the UHR sample, reflected by increased TAT and related to greater PSQI disturbances (e.g., waking in the middle of the night due to room temperature, coughing/snoring, bathroom, etc.) and greater movements during the sleep period, also fits with many schizophrenia studies supporting continuity difficulties in affected patients (e.g., Afonso et al., 2013; Chouinard et al., 2004). In the schizophrenia literature, findings regarding continuity have been mixed, with some studies finding increased TAT in schizophrenia patients and other investigations finding no differences between affected individuals and healthy controls. One prominent explanation for this discrepancy is use of antipsychotic medications among included participants, which have been shown to reduce TAT (Cohrs, 2008). The current finding of disrupted continuity in mostly un-medicated UHR youth supports this theory, suggests that increased TAT may be present in the pre-psychosis period, and is consistent with two previous studies showing sleep interruptions in at-risk (GR) youth (Beisser et al., 1967; Keshavan et al., 2004).

Efficiency. Sleep efficiency represents the percentage of time in bed spent asleep (Buysse et al., 1989), and efficiency reductions in healthy adolescents result in decreased cognitive (e.g., working memory) and academic performance (Kopasz, Loessi, Hornyak, Riemann, et al., 2010). The current finding of attenuated sleep efficiency among UHR adolescents is reflective of the broader schizophrenia literature, in which reductions in efficiency is a consistent finding among

never-treated and drug-free patients (e.g., Monti & Monti, 2004). Because antipsychotics have been shown to enhance sleep efficiency (Cohrs, 2008), it is noteworthy that efficiency reductions are present in mostly un-medicated youth prior to schizophrenia onset, potentially suggesting an important role for this deficit in the pathophysiology of psychotic disorders.

Duration. Duration refers to the length of time spent asleep, and in healthy adolescents, reductions in duration result in increased physical and mental health problems, reduced cognitive performance, and increases in risk for accidents (Leger, Beck, Richard, & Godeau, 2012). Contrary to our hypothesis, the expected decreases in sleep duration in UHR youth compared to healthy adolescents were not observed. This is particularly surprising given the pervasive finding of duration abnormalities in schizophrenia (e.g., Monti & Monti, 2005). One explanation for this finding is that reductions in duration are common to mood disorders (depression and bipolar disorder; e.g., Gruber et al., 2011), and mood symptoms are prevalent in psychotic disorders (50% experience comorbid depression; Buckley, Miller, Lehrer, & Castle, 2009) and some prodromal populations (Rosen et al., 2006; Salokangas et al., 2012; Shioiri et al., 2007; Svirskis et al., 2005). In the current study, only 8 UHR adolescents (27%) were experiencing clinically significant levels of depression and/or (hypo)mania at intake. If duration difficulties are more specific to mood disorders than psychosis, the low incidence of significant depression and (hypo)mania in the current sample may have contributed to the null finding in the current study. Supporting this suggestion, the only other study to use an objective measure to study sleep in an at-risk (GR) sample similarly found no duration abnormalities (Keshavan et al., 2004). Alternatively, abnormalities in duration may not manifest until after the onset of psychosis, potentially reflecting aspects of exposure to the disorder and its treatment (e.g., neurotoxicity or medications).

Taken together, the findings of greater sleep dysfunction in the UHR sample compared to healthy adolescents suggest that problematic sleep may represent a core feature of psychosis, over and above the effects of 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, efficiency, sleep movements) in the etiology of schizophrenia, 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.

Aim 1b. Relationships of Psychosis Symptoms to Sleep Dysfunction

As predicted, indices of sleep disturbance were associated with positive, negative, and disorganized symptoms in both UHR youth and the full sample. Among UHR adolescents, disrupted continuity and increased movements during sleep were significantly associated with increased positive symptoms, controlling for medication status and mood symptoms. Additionally, actual reductions in sleep efficiency, but not perceived difficulties with efficiency, were also significantly related to increased positive symptoms. Positive symptoms were not predicted by difficulties with duration, latency, disturbances, or quality in the UHR sample. Analogous results were found in the full sample.

Controlling for medications and mood symptoms, increased latency and decreased quality were significantly correlated with increased negative symptoms among UHR youth. In addition, in the UHR sample, perceived problems with duration, but not actual duration difficulties, predicted increased negative symptoms. Problems with disturbances, continuity, efficiency, and movements were not related to negative symptoms in UHR adolescents. Results were similar in the full sample; furthermore, among all participants, disrupted continuity, increased movements, and actual decreases in efficiency were predictive (trend) of increased

negative symptoms. Because the non-significant associations between sleep variables and negative symptoms in UHR youth were in the expected direction, these trend-level associations observed in the full sample may reflect the increased statistical power associated with doubling the sample size used in the analyses. Perceived problems with efficiency, however, were not associated with negative symptoms in the full sample.

In the UHR sample, disrupted continuity and increased movements during sleep were significantly associated with increased disorganized symptoms, over and above the effects of medications and mood symptoms. In addition, actual difficulties with sleep efficiency were significantly related to increased disorganized symptoms among UHR youth; this was not the case for perceived difficulties with efficiency. Perceived duration problems, but not actual reductions in duration, were also associated with higher levels of disorganized symptoms. Difficulties with latency, disturbances, and sleep quality were not associated with disorganized symptoms in UHR adolescents. Equivalent results were found in the full sample.

Of note, in a few cases, actual and perceived sleep problems were discrepant in prediction of psychosis symptoms; this may be due to inaccuracies in self-reports (individuals are fairly accurate, but imperfect, reporters of sleep difficulties; Lockley et al., 1999), or in some cases, UHR youth may be starting to experience declines in sleep functioning, but these decreases are not yet meeting distress levels to warrant reporting.

Many of these relationships between sleep variables and psychosis symptoms are reflected in the broader schizophrenia literature. For instance, the current finding of a relationship between perceived duration reductions and increased negative and disorganized symptoms in UHR youth is consistent with Neylan and colleagues' (1992) suggestion of a relationship between decreased duration and increased severity of psychotic illness. In addition,

the associations between attenuated sleep efficiency and positive, negative, and disorganized symptoms are also consistent with those observed in schizophrenia, in which reduced efficiency has been shown to correlate with increased severity of psychotic illness (Neylan et al., 1992) and increased level of positive symptoms (Zarcone & Benson, 1997). Finally, the relationship between disrupted continuity and positive symptoms in the current study is similar to the results from the Keshavan et al. (2004) at-risk study, in which a trend toward disrupted continuity ($p = .06$) and positive symptoms of schizotopy (perceptual aberrations, magical thinking) where found in the same GR sample (although in that study, the sleep-symptom relationship was not directly assessed).

Consistent with our predictions, these findings suggest that aspects of sleep dysfunction, as measured by both subjective and objective measures, are associated with greater positive, negative, and disorganized symptoms in UHR youth as well as in the full sample. Importantly, relationships between disturbed sleep and psychosis symptoms suggest that sleep functioning may represent an important target for prevention and intervention efforts in this critical population. In addition, associations between sleep problems and negative symptoms suggest that sleep dysfunction may be closely tied to the etiology of schizophrenia, representing a core feature of the disorder.

Aim 2a. Group Differences in Brain Structures and Tracts

Consistent with expectations, decreased grey matter volume of the thalamus was observed bilaterally in the UHR sample compared to their healthy counterparts, controlling for age and gender. These results are similar to the thalamic reductions observed in schizophrenia samples (Adriano et al., 2010; Konick & Friedman, 2001), as well as prior studies of GR youth (Bhojraj, Francis, et al., 2011; Lawrie et al., 1999; Lawrie et al., 2001). No group differences

were found in the integrity of the thalamocortical white matter tracts running through the anterior internal capsule.

Evidence demonstrating decreased thalamus volumes in UHR youth compared to healthy controls is important in several ways. First, it suggests that a critical brain structure supporting sleep function is compromised in adolescents at high risk for schizophrenia. Second, as thalamic abnormalities are present in UHR youth prior to onset, it appears that reductions in sleep-related structures may precede psychosis, and may play an essential role in the pathophysiology of schizophrenia. Third, abnormal thalamus reductions in UHR youth support the theory that abnormalities in developmental neuromaturational processes (e.g., pruning) may play a significant role in the etiology of psychotic disorders (Corcoran, Walker, Huot, Mittal, et al., 2003; Walker, Mittal, & Tessner, 2008).

Aim 2b. Relationship of Reduced Grey and White Matter to Sleep Dysfunction

Consistent with our hypothesis, bilateral reductions in thalamic volume and decreases in thalamocortical tract integrity were associated with increased sleep dysfunction in UHR youth, as well as in the full sample. Among UHR adolescents, bilateral reductions in the thalamus were related (significantly or trend level) to increased latency, decreased efficiency, reduced sleep quality, disrupted continuity, and increased movements during sleep, over and above the effects of medication status and mood symptoms. Results were comparable when investigated in the full sample, except left thalamus volume was not associated with total movement count. Bilateral reductions in the thalamus were not significantly related to problems with duration or disturbances in either the UHR or full sample.

Although there were no group differences in anterior thalamic white matter tracts, decreased integrity of bilateral anterior thalamic radiations in the UHR group was predictive

(significantly or trend level) of increased sleep disturbances, decreased quality, and increased movements during sleep, over and above mood symptoms and medications. Additionally, decreased right anterior thalamic radiation integrity was significantly associated with disrupted continuity in UHR youth. Regarding efficiency, reduced right thalamic radiation integrity was related (trend) to actual reductions in efficiency, but not perceived problems with efficiency. Decreased integrity of the anterior thalamic radiations was not associated with problems with duration or latency in the UHR sample. Similarly, in the full sample, bilateral reductions in the integrity of the anterior thalamic tracts were related to greater sleep disturbances, disrupted continuity, and increased movements during sleep. In addition, among all participants, reduced right anterior thalamic radiation integrity was predictive (trend) of actual decreases in duration and efficiency, but not perceived difficulties with these indices of sleep. Again, discrepancies in relationships between actual and perceived sleep problems and brain abnormalities may be due to inaccuracies in self-reports (Lockley et al., 1999) or experiences of declines in sleep functioning not yet distressing enough to warrant reporting.

Relationships between thalamus volume/thalamocortical integrity with domains of sleep function is well documented in healthy populations (e.g., see Jan, Reiter, Wasdell, & Bax, 2009 for a review), and an important new theory in schizophrenia posits that the sleep abnormalities observed in psychosis may result from deficient thalamic-cortical communication (Vukadinovic, 2011). The current findings of associations between thalamic volume/thalamocortical tract abnormalities and indices of disturbed sleep in UHR youth are consistent with this literature. In addition, these results suggest that abnormalities in developmental neuromaturational processes in UHR youth may be contributing to the sleep dysfunction observed in individuals vulnerable to psychosis.

Exploratory Aim 1. Relationship of Subjective and Objective Measures of Sleep Dysfunction

Based on their responses to the PSQI, UHR adolescents are accurate reporters of their sleep efficiency, and their endorsement of sleep disturbances (awakenings due to room temperature, bathroom, cough/snore, etc.) was also accurately associated with their number of movements during the sleep period. They were not accurate reporters of the time they spent asleep (duration), and their account of sleep disturbances did not predict their actual sleep continuity. In the full sample, in which healthy controls are also assessed, the participating adolescents as a whole were reliable reporters of sleep efficiency and duration, and their account of sleep disturbances was correlated with how much they moved during the night, but not sleep continuity.

Findings in the full sample suggesting that adolescents are accurate reporters of sleep duration and efficiency are consistent with literature in healthy populations, suggesting that subjective and actigraphic measures of duration and efficiency are correlated (Lockley et al., 1999). In addition, given that healthy individuals have been shown to be better reporters of duration than sleep/wake transitions (Lockley et al., 1999), it is not surprising that accounts of sleep disturbances provided by the UHR adolescents and full sample participants were not associated with continuity. However, it is notable that for both the UHR and full samples, reports of sleep disturbances were correlated with movement during the sleep period, suggesting youth have some insight into sleep disturbances necessitating movement/repositioning during the sleep period. The finding that UHR adolescents were not accurate reporters of their sleep duration was unexpected; it may be that UHR adolescents lack insight into the length of their sleep period, or alternatively, the smaller sample size utilized in the UHR analysis may have rendered this exploratory question underpowered to find an effect in the patient group.

Exploratory Aim 2. Relationships of Mood Symptoms to Sleep Dysfunction

Among UHR youth, increased depression was related (significantly or at the trend level) to reduced sleep quality, increased latency, and increased sleep disturbances, controlling for medications. In addition, depression was associated with perceived reductions in efficiency, but not actual efficiency. Increased depression was not associated with difficulties with duration, continuity, or movement count. Results were comparable among the full sample, except that perceived efficiency was not associated with elevations in depression. (Hypo)mania was not associated with any sleep variables in the UHR population, but was related (trend level) to increased latency and sleep disturbances in the full sample.

Associations between problems with sleep quality, latency, efficiency, and continuity and increased depression in the UHR and full samples is highly consistent with a long-standing literature confirming associations between disruptions in these sleep domains and depression (e.g., Jones, Gershon, Sitaram, & Keshavan, 1987); however, given that problems with insomnia/hypersomnia represent a criterion for major depressive disorder in the DSM-IV-TR (American Psychiatric Association, 2000), the lack of a relationship between depression and duration in the current study was unanticipated. This null finding may be due in part to the restricted range of duration among both UHR and healthy youth. For instance, on the PSQI, the modal and median score for duration for both groups was 0 (indicating no problems with duration). Similarly, TST on the actigraph indicated adequate mean and median duration for both groups, with scores falling in a comparable range (each sleeping approximately 6.66 hours/night, range 3.5 - 8.5 for both). Another potential explanation is that different processes underlie sleep disturbances in schizophrenia than in depression, and while depression may amplify or exacerbate sleep abnormalities in UHR youth, it is not a main contributor to the sleep

dysfunction observed in UHR patients. Supporting this assertion, findings of sleep problems in UHR adolescents were consistently present, even when participants with clinically significant depression were omitted from analyses.

Relationships between (hypo)mania and difficulties with latency and disturbances in the full sample are also reflective of the literature, which has demonstrated relationships between elevated mood and latency/disturbance problems in both adults (e.g., Ritter, Marx, Lewtschenko, Pfeiffer, et al., 2012) and youth (Lunsford-Avery et al., 2012). Again, given the symptomatic profile of mania (i.e., decreased need for sleep; American Psychiatric Association, 2000), the lack of an association between mood elevation and sleep duration was unexpected; as previously noted, this may be due to the restricted range of sleep duration, or to the low levels of mood elevation endorsed by participants and their parents (i.e., only 15% of UHR youth experienced clinically significant mood elevation according to the P-GBI). In addition, mood symptoms may not play a significant role in sleep abnormalities in UHR adolescents; findings of sleep dysfunction in UHR youth persisted when individuals with clinically significant (hypo)mania were removed from the primary analyses.

Sleep Dysfunction and a Proposed Neurodevelopmental Diathesis-Stress Model for Schizophrenia

A diathesis-stress conceptualization of schizophrenia posits that both inherited and early environmental factors contribute to structural and functional brain changes in intrauterine/perinatal periods, and the resulting vulnerability interacts with neuroendocrine, neurodevelopmental, and environmental psychosocial factors during late adolescence to manifest in psychosis (Walker & Diforio, 1997). The current study suggests that abnormalities in sleep latency, disturbances, continuity, and efficiency characterize UHR youth compared to healthy

controls. In this section, these conclusions are considered and incorporated into the broader sleep, psychosis, and high-risk literature to posit a possible role for sleep dysfunction within a neurodevelopmental diathesis-stress model for schizophrenia. As yet untested, this model is intended as a theoretical template to guide future research.

A Constitutional Vulnerability

Inherited Factors. Several studies have implicated specific genetic factors in the development of schizophrenia and sleep dysfunction. Using mouse models, sleep and/or circadian dysfunction have been associated with Snap-25 (Oliver, Sobczyk, Maywood, Edwards, et al., 2012), Vipr2 (Hughes & Piggins, 2008), Nrg1 (Johnson, Devay & Role, 2002), PERIOD3 (Mansour, Wood, Logue, Chowdari, et al., 2006), TIMELESS (Mansour et al., 2006), CLOCK (Lamont, Coutu, Cermakian, & Boivin, 2010; Moons, Claes, Martens, Peuskens, et al., 2011), and Cckar (Shimazoe, Morita, Ogiwara, Kojiya, et al., 2008) genes (for a review, see Pritchett, Wulff, Oliver, Bannerman, et al., 2012), all of which have been widely associated with psychosis (Koefoed, Hansen, Woldbye, Werge, et al., 2009; Muller, Klempan, De Luca, Sicard, et al., 2005; Munafo, Thiselton, Clark, & Flint, 2006; Vacic, McCarthy, Malhotra, Murray, et al., 2011). In addition, recent research has shown a direct association between Snap-25 and CLOCK genes and the disrupted sleep patterns observed in schizophrenia (Oliver et al., 2012). Findings from this literature have suggested that these genetic factors may provide both direct and indirect vulnerability for sleep problems in psychosis (Pritchett et al., 2012; Waters & Manoach, 2012).

There are also significant relationships between dopamine, glutamate, serotonin, and noradrenaline and various sleep-wake functions (Kantrowitz, Citrome & Javitt, 2009; Monti & Jantos, 2008; Siegel, 2004), and genes underlying these neurotransmitters have been widely implicated in schizophrenia (e.g., COMT, DRD2, and DRD3; Dzirasa, Ribeiro, Costa, Santos, et

al., 2006; Kantrowitz et al., 2009). In addition, genes involved with neural development, maintenance, and repair are implicated, as key neural structures and circuits for sleep such as the thalamus, pineal gland, and thalamocortical pathways are also compromised in psychosis (Ferrarelli et al., 2010). Whether these genetic relationships reflect an additive, covariation, or interaction model remains to be seen. Regardless, it is probable that sleep deficits and psychosis etiology reflect the confluence of multiple genes, each exerting a small influence (Cannon & Keller, 2006).

Prenatal/Postnatal Environment. Prenatal malnutrition and exposure to psychological or physical stress have been shown to negatively impact sleep architecture in adult rats (Duran, Galler, Cintra, & Tonkiss, 2006; Weinstock, 2001) and are widely implicated in the development of schizophrenia (for a review, see Mittal, Ellman & Cannon, 2008). For example, maternal stressors during pregnancy, such as exposure to war (van Os & Selten, 1998), unwanted pregnancy (Herman, Brown, Opler, Desai, et al., 2006), and death of a loved one (Khashan, Abel, McNamee, Pederson, et al., 2008) have been associated with increased risk of schizophrenia among offspring. These factors may be particularly relevant to the sleep dysfunction seen in psychosis. Indeed, animal models have shown prenatal stress to be associated with phenomena consistent with schizophrenia (e.g., reduced social interaction, reduced cerebral asymmetry and dopamine turnover, increased anxiety in novel situations) alongside disturbances in sleep and circadian functioning (Weinstock, 2001).

Prenatal hypoxia may also contribute to the development of sleep dysfunction in schizophrenia. Animal models indicate that prenatal hypoxia is associated with multiple brain abnormalities involved in both sleep dysregulation and schizophrenia, including increased transcript expression of the NR1 subunit in frontal and temporal regions, nucleus accumbens,

and hippocampus (Schmitt, Fendt, Zink, Ebert, et al., 2007), increased dopamine release and persistent alterations in the function of mesolimbic and mesostriatal pathways (Boksa & El-Khodor, 2003), and neuronal death in the cerebellum, hippocampus, and cerebral cortex (Rees & Inder, 2005). Importantly, one animal study has shown direct relationships between hypoxia and deficits associated with schizophrenia (e.g., impaired dopamine signaling) and sleep impairment (e.g., disrupted development of mesotelencephalic pathways modulating the expression of sleep/wakefulness and disturbed sleep-wake architecture; Decker & Rye, 2002).

The early postnatal environment is a critical developmental window for both brain formation and sleep. As noted prior, mirroring the rate of early brain development, sleep development in infancy is characterized by exponentially high rates of change. An environmental insult during this crucial period could have lasting consequences for the development of sleep dysfunction and psychosis. For example, traumatic brain injury (TBI) is widely linked to sleep abnormalities (Castriotta, Wilde, Lai, Atanasov, et al., 2007; Verma, Anand & Verma, 2007) and increased risk for psychotic disorders (David & Prince, 2005; Fugii & Ahmed, 2002; Zhang & Sachdev, 2003).

It is likely that this constitutional (genetic and early environmental) vulnerability results in sleep deficits across early and late childhood in at-risk youth, which are then exacerbated during adolescence. Other potential risk markers for schizophrenia, including movement abnormalities (Mittal, Jalbrzikowski, Daley, Roman, et al., 2011; Walker, Savoie, & Davis, 1994) and cognitive deficits (Cannon & Murray, 1998; Reichenberg & Harvey, 2007), show a similar pattern, in which impairments are present in early childhood and worsen during the adolescent years. As retrospective studies have revealed significant sleep problems in early childhood among individuals who later develop schizophrenia (Bourgeois & Etchepare, 1986;

Frazee, 1953; Massou dit Bourdet & Laffy-Beufils, 2000; Verdoux et al., 2000), sleep deficits are likely to follow a course comparable to other risk factors for psychosis. However, as no studies have directly examined the developmental course of sleep dysfunction in risk for schizophrenia, this remains an empirical question.

Adolescent Neural Development and Psychosocial Stress

As noted in the introduction, adolescence is characterized by brain changes (normative grey matter loss co-occurring with significant increases in white matter; Bartzokis et al., 2001; Gogtay et al., 2004; Sowell et al., 2003) and increases in psychosocial stress (social, academic, and increasing independence; Spear, 2004). These processes are disrupted or exacerbated in individuals at risk for schizophrenia. For instance, adolescents at high risk for psychosis display abnormal brain development (declining grey matter volume in the thalamus and frontal, temporal, and parietal lobes and decreased integrity of white matter tracts; Bhojraj, Sweeney, et al., 2011; Karlsgodt et al., 2009) and greater susceptibility and exposure to psychosocial stress (escalating social, occupational, and neurocognitive deficits; Niendam et al., 2009; Woods et al., 2009). Reflective of these neural and psychosocial developmental processes, sleep in adolescence is characterized by many changes, including a phase delay in sleep (Jenni & Carskadon, 2005), declines in delta wave amplitude, SWS, and duration, and increases in sleep latency (Carskadon, Acebo & Jenni, 2004; Feinberg, Hibi & Carlson, 1977; Williams, Karacan & Hursch, 1974; Williams et al., 1972).

Sleep dysfunction in UHR youth may be both a result of abnormalities in neurodevelopmental and psychosocial processes and a contributor to the cascade of diathesis-stress interactions leading to the development of psychosis. For instance, the current study demonstrates bilateral thalamic gray matter reductions in a UHR sample compared to healthy

controls, and shows that these abnormalities are directly associated with pronounced sleep deficits, including increased latency, decreased efficiency, reduced quality, and disrupted continuity. These findings support the notion that difficulties with sleep dysfunction may result from underlying irregularities in neural development in adolescents at high risk for psychosis. Similarly, although no abnormalities in sleep-related thalamocortical tracts were observed in the current study of UHR youth, decreased integrity of anterior thalamic radiations was associated with increases in sleep dysfunction among youth at risk for psychosis, suggesting those experiencing abnormal decreases in thalamocortical tracts may be at particular risk for experiencing greater disturbances in sleep.

In addition, although not directly examined in the current study, disturbed sleep may also participate in driving the developmental diathesis-stress cycle leading to psychosis. For instance, a posited function of sleep is to reverse the effects of waking on plastic brain neurons (Feinberg, 1982; Keshavan, Anderson & Pettegrew, 1994). Given this potential important role of sleep in supporting neurodevelopment, sleep abnormalities originating from brain-based anomalies in UHR adolescents may in turn negatively impact brain development among at risk individuals, creating a vicious cycle.

Similarly, sleep dysfunction experienced by UHR youth may compound stress associated with social, academic, and neurocognitive deficits. For instance, disturbed sleep is associated with social impairment (Wolfson & Carskadon, 1998) and learning problems and poor academic performance (Wolfson & Carskadon, 2003) in adolescents. In addition, sleep may play a role in declarative and procedural memory consolidation (e.g., Stickgold & Walker, 2005), a process found to be disrupted in schizophrenia (e.g., Goder, Fritzer, Gottwald, Lippmann, et al., 2008; Manoach, Thakkar, Stroynowski, et al., 2010). As memory function underlies a host of higher-

order cognitive abilities, sleep-related interruptions in the process may contribute to greater stress associated with neurocognitive deficits. Taken together, the downstream consequences of sleep deficits in increasing social, cognitive, and occupational stress among vulnerable adolescents may play a significant role in the broader pathogenesis of schizophrenia.

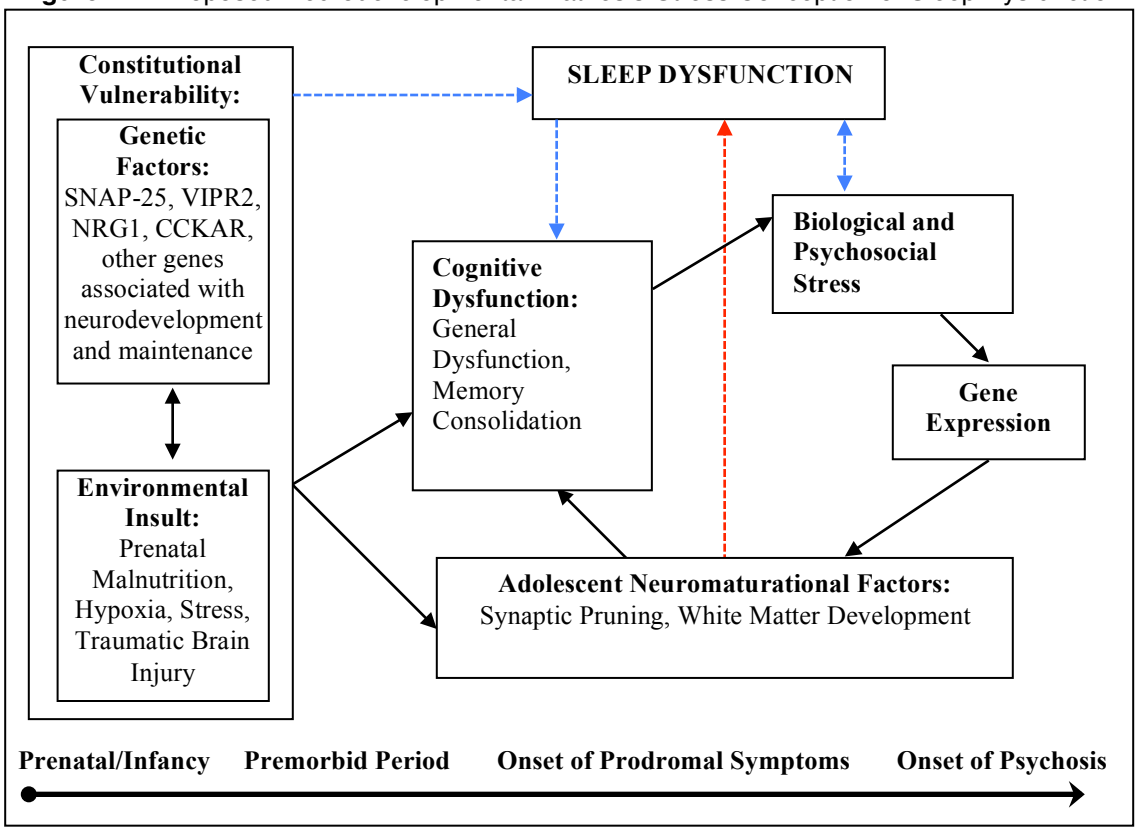
Sleep Dysfunction and Conversion to Psychosis

There is strong evidence that common genetic and early environmental factors lead to a constitutional vulnerability for schizophrenia (Mittal et al., 2008), which interacts with a host of neuromaturational, endocrine, and psychosocial/biological factors during adolescence. This leads to a viscous cycle of genetic and environmental interactions, ultimately driving psychosis onset. In this cycle, the Hypothalamic-Pituitary-Axis becomes increasingly sensitive to stress, which in turn modulates the expression of genes underlying neuromaturational factors, leading to abnormal synaptic pruning and white matter growth (Corcoran et al., 2003; Walker et al., 2008). This process may lead to a number of deleterious effects, including cognitive dysfunction and further susceptibility to stress. Because cortisol has a synergistic relationship with dopamine, this relationship may exacerbate attenuated positive symptoms (Walker et al., 2008). In addition, given that the neural system is already vulnerable, excessive pruning or poor white matter growth may also drive psychosis onset (Feinberg, 1982; McGlashan, 2005).

Sleep, which is also affected by the confluence of inherited and early environmental factors, plays a critical role at multiple points in development and may contribute to driving the cycle leading to schizophrenia onset (see Figure 2; the broken lines illustrate the hypothesized role of sleep dysfunction). Normative and pathological adolescent neurodevelopmental factors alter sleep-related structures (e.g., thalamus and thalamo-cortical tracts; Shimizu, Fujiwara, Hirao, Namiki, et al., 2008), which, as shown in the current study, are related to increased sleep

dysfunction. In turn, sleep dysfunction appears to negatively impact neurodevelopment (Feinberg, 1982). Further, sleep dysfunction affects memory consolidation (affecting numerous higher-order cognitive functions; Stickgold & Walker, 2005) and enhances social and academic stress (Wolfson & Carskadon, 1998; 2003), driving this cycle. Thus, sleep abnormalities may play a role in pathophysiology of schizophrenia and contribute to increasing dysfunction in domains underlying the development of psychosis.

Figure 2. A Proposed Neurodevelopmental Diathesis-Stress Conception of Sleep Dysfunction



Note: The broken lines indicate the hypothesized relationships between sleep dysfunction and factors underlying a neurodevelopmental diathesis-stress conceptualization. The red line indicates the hypothesized relationship investigated in the current study; blue lines indicate hypothesized relationships for future inquiry.

The current study informs this model in several ways. First, this investigation indicates that sleep dysfunction is present in UHR youth. Second, abnormalities in brain structures integral to sleep function (e.g., bilateral thalamic lesions) were found in UHR youth. Third, these neurodevelopmental anomalies were associated with the disturbed sleep observed in UHR

adolescents (indicated by the red arrow). However, several pathways outlined in the model are untested and require empirical support from future studies. Specifically, associations between genetic and early environmental risk factors and sleep dysfunction, impact of sleep disturbances on cognitive performance (and specifically, memory consolidation), and bidirectional relationships of problematic sleep and psychosocial/biological stress are open questions for future empirical inquiry.

Limitations

This study should be considered in the context of several limitations. First, although actigraphic methods have several advantages over polysomnographic methods for investigating sleep in adolescent populations (e.g., naturalistic setting, recording over 5 successive days), actigraph monitors do not provide measures of several important domains of sleep functioning, including REM and NREM sleep. As REM and NREM have been shown to be disrupted in schizophrenia populations (for reviews, see Benson, 2008; Cohrs, 2008; Monti & Monti, 2005), observations of functioning in these domains in UHR youth remain an important question unaddressed by the current study. Future research will utilize polysomnographic methods to investigate REM and NREM variables in this critical population.

A second limitation of the current study is that data are collected at a single time point. As only 35% of UHR adolescents subsequently develop a psychotic disorder (Cannon et al., 2008), discovering risk factors predictive of conversion to schizophrenia is an important mission in the field. Specifically, given the costs associated with medications (e.g., financial burden, side effects), discerning those most likely to covert allows for providing targeted pharmacological and psychosocial preventive treatment to individuals most vulnerable to development of 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. However, future longitudinal studies will aim to determine sleep impairment's role in risk for conversion to schizophrenia.

Third, the current study did not assess for circadian rhythm abnormalities in UHR youth. Thus, while the current study suggests that UHR and healthy adolescents are not differing in sleep duration, the present findings do not speak to which hours (night versus day) the adolescents are asleep. Several severe mental illnesses, such as bipolar disorder and major depression, are associated with sleep phase delays, in which individuals' sleep onset and offset is later than in their healthy counterparts (Lewy, 2009). This phenomenon is believed to result from delayed secretion of melatonin, an important hormone regulating sleep (Srinivasan, Smits, Spence, Lowe, et al., 2006). While less frequently studied in schizophrenia, disruptions of biological rhythms (shifting the sleep phase) have been associated with exacerbating underlying psychotic conditions (Katz, 2011). Importantly, disruptions in circadian rhythm have a harmful impact on social functioning and quality of life (Szentkirályi, Madarász, & Novák, 2009), and if present, may contribute to the impairment observed in pre-psychosis populations. Future studies will utilize the Morningness-Eveningness Preferences scale (Carskadon, Vieira, & Acebo, 1993) and actigraphy to assess circadian rhythms in UHR youth.

A fourth limitation is that while the current study controlled for age in its primary analyses, participants' pubertal status was not assessed. Because both sleep changes in adolescence (Hagenauer, Perryman, Lee, & Carskadon, 2009) and neural development (Sisk & Foster, 2004) are dependent on pubertal status of individuals, future studies of sleep and brain development in UHR youth will incorporate Carskadon & Acebo's (1993) Self-Administered Rating Scale for Pubertal Development. However, it should be noted that in the current study,

the mean age (Controls = 17.85, UHR = 18.73), median age (19 for both), and modal age (Controls = 19, UHR = 20) suggest that the majority of participants have concluded puberty, and pubertal status may have had a very limited impact on the current results.

Fifth, as data in the present investigation were collected at a single time point, it is difficult to tease apart relationships of sleep experiences with negative symptoms versus depression in UHR adolescents. Both symptom categories are present in UHR youth (e.g., Rosen et al., 2006), and share common features, such as avolition, anhedonia, and social withdraw (American Psychiatric Association, 2000). In the current study, UHR specialists assessed both symptom categories, and are highly trained in successfully discriminating affective and negative experiences. In addition, in the present study, negative symptoms and depression related to sleep in different ways. For example, depression was related to increased sleep disturbances, while negative symptoms were not. Similarly, in the full sample, negative symptoms were related to disrupted continuity and increased movements, while depression was not. These findings suggest that the relationships between sleep dysfunction and negative symptoms are not primarily driven by depression. However, longitudinal studies establishing symptom course (depression waxes and wanes, while negative symptoms are constant) and level of distress associated with symptoms (depression is distressing to patients, negative symptoms are not associated with distress) are essential for further differentiating associations between sleep dysfunction and negative symptoms versus depression. Use of schizophrenia-specific mood scales, such as the Calgary Depression Scale for Schizophrenia (Addington, Addington, & Schissel, 1990) may be particularly helpful for distinguishing relationships between disturbed sleep and affective versus psychotic experiences in UHR populations.

Finally, a major limitation of the present study is that we did not correct for multiple comparisons. As such, the current findings should be viewed as preliminary until they are replicated in a larger sample. While this is a common strategy for studies with smaller samples of patients who are difficult to recruit and expensive to follow (e.g., Bohner, Milakara, Witthaus, Gallinat, et al., 2012; Kelleher, Murtagh, Clarke, Murphy, et al., 2013; Koh, Shin, Kim, Choi, et al., 2011), incorporation of sleep variables into larger, better-powered investigations, such as the North American Prodrome Longitudinal Study (NAPLS; Addington, Cadenhead, Cannon, Cornblatt, et al., 2007), is an important next step in confirming the occurrence of dysfunctional sleep in individuals at risk for psychosis.

Future Studies

In addition to impending investigations listed in the limitations section, future studies of sleep in UHR populations should assess the potential role of sleep dysfunction in driving psychosis onset, as proposed within the neurodevelopmental diathesis-stress model for schizophrenia. First, future studies should investigate associations between genetic factors implicated in both schizophrenia and sleep function (e.g., SNAP-25, CLOCK, TIMELESS; Oliver et al., 2012) and indices of sleep disturbance in UHR populations. Similarly, investigations should examine early environmental vulnerability to psychosis (e.g., prenatal/postnatal stress) and sleep dysfunction among adolescents at-risk for schizophrenia. While animal models suggest common genetic and environmental vulnerabilities underlying sleep function and psychosis (e.g., Oliver et al., 2012; Weinstock, 2001), the hypothesis that a constitutional vulnerability to schizophrenia contributes to the problematic sleep observed in UHR youth is yet untested.

Second, future investigations should assess the impact of sleep dysfunction on general cognitive functioning in UHR youth, and specifically, on memory consolidation processes. While sleep-dependent memory consolidation has been shown to be an important function of sleep (e.g., Stickgold & Walker, 2005) and impaired in schizophrenia (Manoach & Stickgold, 2009), it remains unexamined in individuals vulnerable to psychosis. Because cognitive deficits have been shown to increase biological/psychosocial stress in UHR individuals (contributing to the stress cascade resulting in psychosis; Niendam, Jalbrzikowski, & Bearden, 2009; Woods et al., 2009), future investigations focusing on sleep-dependent memory consolidation in UHR populations may further inform our understanding of the role of sleep dysfunction in the development of psychotic disorders.

Third, the potential bidirectional relationship between sleep dysfunction and biological/psychosocial stress in high-risk populations should be examined. Widespread evidence has shown that sleep dysfunction negatively impacts social and academic functioning in adolescents (Wolfson & Carskadon, 1998; 2003), and in turn, stress increases psychological and physiological activation and impairs sleep functioning (for a review, see Âkerstedt, 2006). However, the proposed bidirectional relationship between biological/psychosocial stress and sleep dysfunction in UHR youth, and the potential role of this interaction in driving psychosis onset, remain open questions. Elucidating associations between sleep impairment and increased stress among UHR adolescents has the potential to enhance understanding of how sleep factors contribute to the etiology of schizophrenia.

Fourth, given the role of the HPA axis in conversion to schizophrenia, future studies should examine hormones supporting sleep function in UHR populations. For instance, there is substantial evidence supporting melatonin and pineal gland dysfunction in schizophrenia

(Anderson & Maes, 2012), suggesting possible roles for melatonin and cortisol in the pathophysiology of psychosis (Monti et al., 2013). In addition, a recent investigation demonstrated an association between delayed or free-running melatonin rhythms and circadian rhythm desynchronization in patients with schizophrenia (Wulff et al., 2012). However, to date, no studies have examined how changes in melatonin or cortisol secretion manifest in youth at risk for schizophrenia. Future investigations examining melatonin, cortisol response to awakening (CRW), and pineal gland function in UHR populations hold promise, as preliminary research suggests that these functions may be implicated in the pathogenesis of psychosis (Mittal et al., 2010).

Finally, the presence of sleep dysfunction in UHR youth, as well as the observed relationships between impaired sleep and increased positive, negative, and disorganized symptoms in the current study, suggest that sleep dysfunction may represent a viable target for prevention and intervention efforts for this important population. Future studies may evaluate the efficacy of interventions focused on sleep stabilization in the treatment of UHR youth. In particular, a 6-week administration of Cognitive Behavioral Therapy for Insomnia (CBT-I) has been shown to improve sleep efficiency and continuity in adult (Edinger, Wohlgemuth, Radtke, Marsh, et al., 2001) and adolescent (Gradisar, Dohnt, Gardner, Paine, et al., 2011) populations, and may be particularly beneficial for targeting the specific sleep difficulties observed in adolescents at risk for schizophrenia. Future research may determine if incorporation of sleep-specific strategies into interventions for UHR adolescents alleviates not only current symptoms, but also delays or prevents onset of schizophrenia.

Conclusions

Despite conclusive evidence suggesting the prevalence and detrimental impact of sleep dysfunction in schizophrenia, few empirical studies have examined sleep impairment in the prodromal period. The current project addresses the paucity of research on sleep dysfunction in adolescents at high risk for developing psychotic disorders, and enhances our understanding of the role of sleep in schizophrenia in several ways. First, this project suggests that sleep dysfunction may be a core feature and risk marker for psychosis, and informs etiological models of schizophrenia. Specifically, sleep dysfunction was observed in the pre-psychosis period, is associated with increased symptoms (including negative symptoms, believed to lie at the heart of the disorder), and was related to abnormalities in neural development of structures/tracts subsuming sleep function in at-risk youth. Within the context of a neurodevelopmental model of schizophrenia, these findings suggest that sleep dysfunction may represent a result of abnormal brain development, as well as a potential contributor to the diathesis-stress cascade resulting in schizophrenia. However, future research is necessary to confirm the role of impaired sleep in conversion to psychosis. Second, this study has implications for designing prevention and intervention efforts for vulnerable youth. Specifically, as sleep dysfunction is present in UHR adolescents and young adults, and is associated with worsened positive, negative, and disorganized symptoms, interventions targeting sleep stabilization may be beneficial for delaying or preventing onset of schizophrenia.

BIBLIOGRAPHY

1. Addington, D., Addington, J., & Schissel, B. (1990). A depression rating scale for schizophrenics. *Schizophrenia Research, 3*(4), 247-51.

2. Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B., McGlashan, T. H., Perkins, D. O., Seidman, L J., Tsuang, M., Walker, E. F., Woods, S. W., & Heinssen, R. (2007). North American prodrome longitudinal study: a collaborative multisite approach to prodromal schizophrenia research. *Schizophrenia Bulletin, 33,* 665-672.

3. Adriano, F., Spoletini, I., Caltagirone, C., & Spalletta, G. (2010). Updated meta-analyses reveal thalamus volume reduction in patients with first-episode and chronic schizophrenia. *Schizophrenia Research, 123*(1), 1-14.

4. Afonso, P., Brissos, S., Figueira, M. L., & Paiva, T. (2011). Schizophrenia patients with predominantly positive symptoms have more disturbed sleep-wake cycles measured by actigraphy. *Psychiatry Research, 189*(1), 62-66.

5. Afonso, P., Figueira, M. L., & Paiva, T. Sleep-wake patterns in schizophrenia patients compared to healthy controls [published ahead of print January 15 2013]. *The World Journal of Biological Psychiatry.*

6. Agnew, H. W., Webb, W. B., & Williams, R. L. (1966). The first night effect: an EEG study of sleep. *Psychophysiology, 2*(3), 263-266.

7. Âkerstedt, T. (2006). Psychosocial stress and impaired sleep. *Scandinavian Journal of Work, Environment & Health, 32,* 493-501.

8. Altena, E., Vrenken, H., Van Der Werf, Y. D., van den Heuvel, O. A., & Van Someren, E. J. (2010). Reduced orbitofrontal and parietal gray matter in chronic insomnia: a voxel-based morphometric study. *Biological Psychiatry, 67*(2), 182-185.

9. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th Ed., text rev.). Washington, D.C.: Author.

10. Anderson, G. & Maes, M. (2012). Melatonin: an overlooked factor in schizophrenia and in the inhibition of anti-psychotic side effects. *Metabolic Brain Disease, 27*(2), 113-119.

11. Ashtari, M., Cervellione, K. L., Hasan, K. M., Wu, J., McIlree, C., Kester, H., Ardenkani, B. A., & Kumra, S. (2007). White matter development during late adolescence in healthy males: a cross-sectional diffusion tensor imaging study. *Neuroimage, 35*(2), 501-510.

12. Baker, F. C., Maloney, S., & Driver, H. S. (1999). A comparison of subjective estimates of sleep with objective polysomnographic data in healthy men and women. *Journal of Psychosomatic Research, 47*(4), 335-341.

13. Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C. C., & Reiss, A. L. (2005). White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cerebral Cortex, 15*(12), 1848-1854.

14. Baroni, A., Lunsford, J. R., Luckenbaugh, D. A., Towbin, K. E., & Leibenluft, E. (2009). Practitioner review: the assessment of bipolar disorder in children and adolescents. *Journal of Child Psychology and Psychiatry, 50*(3), 203-215.

15. Bartzokis, G., Beckson, M., Lu, P. H., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Archives of General Psychiatry, 58*(5), 461-465.

16. Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment, 67*(3), 588-597.

17. Beisser, A. R., Glasser, N., & Grant, M. (1967). Psychosocial adjustment in children of schizophrenic mothers. *Journal of Nervous and Mental Disease, 145*(6), 429-440.

18. Benson, K. L. (2006). Sleep in schizophrenia: impairments, correlates, and treatment. *Psychiatric Clinics of North America, 29*(4), 1033-1045.

19. Benson, K. L. (2008). Sleep in Schizophrenia. *Sleep Medicine Clinics, 3*, 251-260.

20. Benson, K. L., Sullivan, E. V., Lim, K. O., Lauriello, J., Zarcone, V. P., & Pfefferbaum, A. (1996). Slow wave sleep and computed tomographic measures of brain morphology in schizophrenia. *Psychiatry Research, 60*(2-3), 125-134.

21. Benson, K. L. & Zarcone, V. P. (1993). Rapid eye movement sleep eye movements in schizophrenia and depression. *Archives of General Psychiatry, 50*(6), 474-482.

22. Bhojraj, T. S., Francis, A. N., Montrose, D. M., & Keshavan, M. S. (2011). Grey matter and cognitive deficits in young relatives of schizophrenia patients. *Neuroimage, 54*(Suppl 1), S287-S292.

23. Bhojraj, T. S., Sweeney, J. A., Prasad, K. M., Eack, S. M., Francis, A. N., Miewald, J. M., Montrose, D. M., & Keshavan, M. S. (2011). Gray matter loss in young relatives at risk for schizophrenia: relation with prodromal psychopathology. *Neuroimage, 54*(Suppl 1), S272-S279.

24. Birchwood, M., Smith, J., Macmillan, F., Hogg, B., Prasad, R., Harvey, C., & Bering, S. (1989). Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. *Psychological Medicine, 19*(3), 649-656.

25. Bleuler, E. (1950). [A new type of arithmetic book for special classes and institutional schools]. *Pro Infirmis, 9*(4), 108-109; Italian transl, 117-118.

26. Bleuler, E. (2010). [Dementia praecox or the group of schizophrenias]. *Vertex, 21*(93), 394-400.

27. Bohner, G., Milakara, D., Witthaus, H., Gallinat, J., Scheel, M., Juckel, G., & Klingebiel, R. (2012). MTR abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. *Schizophrenia Research, 137*(1-3), 85-90.

28. Boksa, P. & El-Khodor, B. F. (2003). Birth insult interacts with stress at adulthood to alter dopaminergic function in animal models: possible implications for schizophrenia and other disorders. *Neuroscience & Biobehavioral Reviews, 27*(1-2), 91-101.

29. Bonnet, M. (1994). Sleep deprivation. In M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine, 2nd Ed.* (pp. 50-68). Philadelphia: W. B. Sanders.

30. Borbely, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology, 1*(3), 195-204.

31. Borbely, A. A. & Achermann, P. (1992). Concepts and models of sleep regulation: an overview. *Journal of Sleep Research, 1*(2), 63-79.

32. Borgwardt, S. J., Riecher-Rossler, A., Dazzan, P., Chitnis, X., Aston, J., Drewe, M., Gschwandtner, U., Haller, S., Pfluger, M., Rechsteiner, E., D'Souza, M., Stieglitz, R. D., Radu, E. W., & McGuire, P. K. (2007). Regional gray matter volume abnormalities in the at risk mental state. *Biological Psychiatry, 61*(10), 1148-1156.

33. Bourgeois, M. & Etchepare, J. J. (1986). [Schizophrenics prior to schizophrenia. Comparative and statistical inquiry on the infantile antecedents of 35 schizophrenics and 35 control subjects]. *Annales Medico-Psychologiques, 144*(7), 757-766.

34. Bowers, M. B. (1968). Pathogenesis of acute schizophrenic psychosis. An experimental approach. *Archives of General Psychiatry, 19*(3), 348-355.

35. Bowers, M. B. & Freedman, D. X. (1966). "Psychedelic" experiences in acute psychoses. *Archives of General Psychiatry, 15*(3), 240-248.

36. Brugger, S., Davis, J. M., Leucht, S., & Stone, J. M. (2011). Proton magnetic resonance spectroscopy and illness stage in schizophrenia-a systematic review and meta-analysis. *Biological Psychiatry, 69*(5), 495-503.

37. Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin, 35(2),* 383-402.

38. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research, 28*(2), 193-213.

39. Cameron, D. E. (1938). Early Schizophrenia. *American Journal of Psychiatry, 95*(3), 567-582.

40. Cannon, M. & Murray, R. M. (1998). Neonatal origins of schizophrenia. *Archives of Disease in Childhood, 78,* 1-3.

41. Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., Seidman, L. J., Perkins, D., Tsuang, M., McGlashan, T., & Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of General Psychiatry, 65*(1), 28-37.

42. Cannon, T. D. & Keller, M. C. (2006). Endophenotypes in the genetic analyses of mental disorders. *Annual Review of Clinical Psycholology, 2*, 267-290.

43. Cannon, T. D., Rosso, I. M., Bearden, C. E., Sanchez, L. E., & Hadley, T. (1999). A prospective cohort study of neurodevelopmental processes in the genesis and epigenesis of schizophrenia. *Development and Psychopathology, 11*(3), 467-485.

44. Carletti, F., Woolley, J. B., Bhattacharyya, S., Perez-Iglesias, R., Fusar Poli, P., Valmaggia, L., Broome, M. R., Bramon, E., Johns, L., Giampietro, V., Williams, S. C., Barker, G. J., & McGuire, P. K. Alterations in white matter evident before the onset of psychosis [published ahead of print April 3 2012]. *Schizophrenia Bulletin*.

45. Carskadon, M. A. & Acebo, C. (1993). A self-administered rating scale for pubertal development. *Journal of Adolescent Health, 14,* 190-195.

46. Carskadon, M. A. (2011). Sleep in adolescents: the perfect storm. *Pediatric Clinics of North America, 58,* 637-647.

47. Carskadon, M. A., Acebo, C., & Jenni, O. G. (2004). Regulation of adolescent sleep: implications for behavior. *Annals of the New York Academy of Sciences, 1021*, 276-291.

48. Carskadon, M. A. & Dement, W. C. (1982). Nocturnal determinants of daytime sleepiness. *Sleep 5*(2), S73-81.

49. Carskadon, M. A. & Dement, W. C. (2005). Normal human sleep: an overview. In M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine, 4th Ed.* (pp. 13 - 23). Philadelphia: W. B. Sanders.

50. Carskadon, M. A., Vieira, C., & Acebo, C. (1993). Association between puberty and delay phase preference. *Sleep, 16,* 258-262.

51. Carskadon, M. A., Wolfson, A. R., Acebo, C., Tzischinsky, O. & Seifer, R. (1998). Adolescent sleep patterns, circadian timing, and sleepiness at a transition to early school days. *Sleep 21*(8), 871-81.

52. Castriotta, R. J., Wilde, M. C., Lai, J. M., Atanasov, S., Masel, B. E., & Kuna, S. T. (2007). Prevalence and consequences of sleep disorders in traumatic brain injury. *Journal of Clinical Sleep Medicine, 3*(4), 349-356.

53. Chemerinski, E., Ho, B. C., Flaum, M., Arndt, S., Fleming, F., & Andreasen, N. C. (2002). Insomnia as a predictor for symptom worsening following antipsychotic withdrawal in schizophrenia. *Comprehensive Psychiatry, 43*(5), 393-396.

54. Chouinard, S., Poulin, J., Stip, E., & Godbout, R. (2004). Sleep in untreated patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin, 30*(4), 957-967.

55. Cohrs, S. (2008). Sleep disturbances in patients with schizophrenia : impact and effect of antipsychotics. *CNS Drugs, 22*(11), 939-962.

56. Corcoran, C., Walker, E., Huot, R., Mittal, V., Tessner, K., Kestler, L., & Malaspina, D. (2003). The stress cascade and schizophrenia: etiology and onset. *Schizophrenia Bulletin, 29*(4), 671-692.

57. Corson, P. W., Nopoulos, P., Andreasen, N. C., Heckel, D., & Arndt, S. (1999). Caudate size in first-episode neuroleptic-naive schizophrenic patients measured using an artificial neural network. *Biological Psychiatry, 46*(5), 712-720.

58. David, A. S. & Prince, M. (2005). Psychosis following head injury: a critical review. *Journal of Neurology, Neurosurgery, and Psychiatry, 76*(Suppl 1), i53-60.

59. Davidson, L. L. & Heinrichs, R. W. (2003). Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: a meta-analysis. *Psychiatry Research, 122*(2), 69-87.

60. Davis, K. L., Stewart, D. G., Friedman, J. I., Buchsbaum, M., Harvey, P. D., Hof, P. R., Buxbaum, J., & Haroutunian, V. (2003). White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Archives of General Psychiatry, 60*(5), 443-456.

61. de Jong, L. W., van der Hiele, K., Veer, I. M., Houwing, J. J., Westendorp, R. G., Bollen, E. L., de Bruin, P. W., Middelkoop, H. A., van Buchem, M. A., & van der Grond, J. (2008). Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. *Brain, 131*(Pt 12), 3277-3285.

62. Decker, M. J. & Rye, D. B. (2002). Neonatal intermittent hypoxia impairs dopamine signaling and executive functioning. *Sleep and Breathing, 6*(4), 205-210.

63. Detre, T. (1966). Sleep disorder and psychosis. *Canadian Psychiatric Association Journal*(Suppl 11), S169-S177.

64. Diwadkar, V. A., Montrose, D. M., Dworakowski, D., Sweeney, J. A., & Keshavan, M. S. (2006). Genetically predisposed offspring with schizotypal features: an ultra high-risk group for schizophrenia? *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 30*(2), 230-38.

65. Doi, Y., Minowa, M., Uchiyama, M., Okawa, M., Kim, K., Shibui, K., & Kamei, Y. (2000). Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Research, 97*(2-3), 165-172.

66. Donlon, P. T. & Blacker, K. H. (1973). Stages of schizophrenic decompensation and reintegration. *Journal of Nervous and Mental Disease, 157*(3), 200-209.

67. Donlon, P. T. & Blacker, K. H. (1975). Clinical recognition of early schizophrenic decompensation. *Diseases of the Nervous System, 36*(6), 323-327.

68. Dozois, D. J. A. & Covin, R. (2004). The Beck Depression Inventory-II (BDI-II), Beck Hopelessness Scale (BHS), and Beck Scale for Suicide Ideation (BSS). In D. L. Segal & M. Hilsenroth (Eds.), *Comprehensive Handbook of Psychological Assessment: Vol. 2. Personality Assessment and Psychopathology* (pp. 50-69). Hoboken, N.J.: John Wiley & Sons.

69. Duran, P., Galler, J. R., Cintra, L., & Tonkiss, J. (2006). Prenatal malnutrition and sleep states in adult rats: effects of restraint stress. *Physiology & Behavior, 89*(2), 156-163.

70. Durmer, J. S. & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology, 25,* 117-129.

71. Dzirasa, K., Ribeiro, S., Costa, R., Santos, L. M., Lin, S. C., Grosmark, A., Sotnikova, T. D., Gainetdinov, R. R., Caron, M. G., & Nicolelis, M. A. (2006). Dopaminergic control of sleep-wake states. *The Journal of Neuroscience, 26*(41), 10577-10589.

72. Edinger, J. D., Wohlgemuth, W. K., Radtke, R. A., Marsh, G. R., & Quillian, R. E. (2001). Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA, 285*(14)*,* 1856-1864.

73. Ehrlich, S., Morrow, E. M., Roffman, J. L., Wallace, S. R., Naylor, M., Bockholt, H. J., Lundquist, A., Yendiki, A., Ho, B. C., White, T., Manoach, D. S., Clark, V. P., Calhoun, V. D., Gollub, R. L., & Holt, D. J. (2010). The COMT Val108/158Met polymorphism and medial temporal lobe volumetry in patients with schizophrenia and healthy adults. *Neuroimage, 53*(3), 992-1000.

74. Eluri, R., Paul, C., Roemer, R., & Boyko, O. (1998). Single-voxel proton magnetic resonance spectroscopy of the pons and cerebellum in patients with schizophrenia: a preliminary study. *Psychiatry Research, 84*(1), 17-26.

75. Feinberg, I. (1982). Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatry Research, 17*(4), 319-334.

76. Feinberg, I., Hibi, S., & Carlson, V. R. (1977). Changes in EEG amplitude during sleep with age. In K. Nandy & L. Sherwin (Eds.), *The Aging Brain and Senile Dementia* (pp. 85-98). New York: Plenum Press.

77. Ferrarelli, F., Huber, R., Peterson, M. J., Massimini, M., Murphy, M., Riedner, B. A., Watson, A., Bria, P., & Tononi, G. (2007). Reduced sleep spindle activity in schizophrenia patients. *American Journal of Psychiatry 164*(3), 483-492.

78. Ferrarelli, F., Peterson, M. J., Sarasso, S., Riedner, B. A., Murphy, M. J., Benca, R. M., Bria, P., Kalin, N. H., & Tononi, G. (2010). Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. *American Journal of Psychiatry, 167*(11), 1339-1348.

79. Ferrarelli, F. & Tononi, G. (2011). The thalamic reticular nucleus and schizophrenia. *Schizophrenia Bulletin, 37*(2), 306-315.

80. First, M., Spitzer, R., Gibbon, M., & Williams, J. (1995). *Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I), Patient Edition.* Washington DC: American Psychiatric Press.

81. Foong, J., Symms, M. R., Barker, G. J., Maier, M., Woermann, F. G., Miller, D. H., & Ron, M. A. (2001). Neuropathological abnormalities in schizophrenia: evidence from magnetization transfer imaging. *Brain, 124*(Pt 5), 882-892.

82. Fornito, A., Yucel, M., Patti, J., Wood, S. J., & Pantelis, C. (2009). Mapping grey matter reductions in schizophrenia: an anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research, 108*(1-3), 104-113.

83. Frazee, H. (1953). Children who later became schizophrenic. *Smith College Studies in Social Work, 23*, 125-149.

84. Fugii, D. & Ahmed, I. (2002). Psychotic disorder following traumatic brain injury: a conceptual framework. *Cognitive Neuropsychiatry, 7*(1), 41-62.

85. Fuller, P. M., Gooley, J. J., & Saper, C. B. (2006). Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *Journal of Biological Rhythms, 21*(6), 482-493.

86. Fusar-Poli, P., Broome, M. R., Woolley, J. B., Johns, L. C., Tabraham, P., Bramon, E., Valmaggia, L., Williams, S. C., & McGuire, P. (2011). Altered brain function directly related to structural abnormalities in people at ultra high risk of psychosis: longitudinal VBM-fMRI study. *Journal of Psychiatric Research, 45*(2), 190-198.

87. Fusar-Poli, P., Crossley, N., Woolley, J., Carletti, F., Perez-Iglesias, R., Broome, M., Johns, L., Tabraham, P., Bramon, E., & McGuire, P. (2011a). Gray matter alterations related to P300 abnormalities in subjects at high risk for psychosis: longitudinal MRI-EEG study. *Neuroimage, 55*(1), 320-328.

88. Fusar-Poli, P., Crossley, N., Woolley, J., Carletti, F., Perez-Iglesias, R., Broome, M., Johns, L., Tabraham, P., Bramon, E., & McGuire, P. (2011b). White matter alterations related to P300 abnormalities in individuals at high risk for psychosis: an MRI-EEG study. *Journal of Psychiatry & Neuroscience, 36*(4), 239-248.

89. Gaillard, J. M., Iorio, G., Campajola, P., & Kemall, D. (1984). Temporal organization of sleep in schizophrenics and patients with obsessive-compulsive disorder. *Advances in Biological Psychiatry, 15*, 76-83.

90. Ganguli, R., Reynolds, C. F., & Kupfer, D. J. (1987). Electroencephalographic sleep in young, never-medicated schizophrenics. A comparison with delusional and nondelusional depressives and with healthy controls. *Archives of General Psychiatry, 44*(1), 36-44.

91. Gaudreau, H., Carrier, J. & Montplaisir, J. (2001). Age-related modifications of NREM sleep EEG: from childhood to middle age. *Journal of Sleep Research 10*(3), 165-72.

92. Gerlach, J. & Peacock, L. (1995). New antipsychotics: the present status. *International Clinical Psychopharmacology, 10*(Suppl 3), 39-48.

93. Glahn, D. C., Laird, A. R., Ellison-Wright, I., Thelen, S. M., Robinson, J. L., Lancaster, J. L., Bullmore, E., & Fox, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological Psychiatry, 64*(9), 774-781.

94. Goder, R., Fritzer, G., Gottwald, B., Lippmann, B., Seeck-Hirschner, M., Serafin, I., & Aldenhoff, J. B. (2008). Effects of olanzapine on slow wave sleep, sleep spindles and sleep-related memory consolidation in schizophrenia. *Pharmacopsychiatry, 41*(3), 92-99.

95. Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Acadamy of Science, 101*(21), 8174-8179.

96. Goldman, M., Tandon, R., DeQuardo, J. R., Taylor, S. F., Goodson, J., & McGrath, M. (1996). Biological predictors of 1-year outcome in schizophrenia in males and females. *Schizophrenia Research, 21*(2), 65-73.

97. Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biological Psychiatry, 61*(8), 935-945.

98. Goldstein, J. M., Seidman, L. J., O'Brien, L. M., Horton, N. J., Kennedy, D. N., Makris, N., Caviness, V. S., Faraone, S. V., & Tsuang, M. T. (2002). Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Archives of General Psychiatry, 59*(2), 154-164.

99. Gourzis, P., Katrivanou, A., & Beratis, S. (2002). Symptomatology of the initial prodromal phase in schizophrenia. *Schizophrenia Bulletin, 28*(3), 415-429.

100. Gradisar, M., Dohnt, H., Gardner, G., Paine, S., Starkey, K., Menne, A., Slater, A., Wright, H., Hudson, J. L., Weaver, E., & Trenowden, S. (2011). A randomized controlled trial of cognitive-behavior therapy plus bright light therapy for adolescent delayed sleep phase disorder. *Sleep, 34(12)*, 1671-1680.

101. Gruber, J., Miklowitz, D. J., Harvey, A. G., Frank, E., Kupfer, D., Thase, M. E., Sachs, G. S., & Ketter, T. A. (2011). Sleep matters: sleep functioning and course of illness in bipolar disorder. *Journal of Affective Disorders, 134*(1-3), 416-420.

102. Haffmans, P. M., Hoencamp, E., Knegtering, H. J., & van Heycop ten Ham, B. F. (1994). Sleep disturbance in schizophrenia. *The British Journal of Psychiatry: The Journal of Mental Science, 165*(5), 697-698.

103. Hafner, H., Riecher-Rossler, A., Hambrecht, M., Maurer, K., Meissner, S., Schmidtke, A., Fatkenheuer, B., Loffler, W. & van der Heiden, W. (1992). IRAOS: an instrument for the assessment of onset and early course of schizophrenia. *Schizophrenia Research, 6*(3), 209-223.

104. Hagenauer, M. H., Perryman, J. I., Lee, T. M., & Carskadon, M. A. (2009). Adolescent changes in the homeostatic and circadian regulation of sleep. *Developmental Neuroscience, 31,* 276-284.

105. Hall, R. C. W. (1995). Global assessment of functioning: a modified scale. *Psychosomatics, 36,* 267-275.

106. Haller, S., Borgwardt, S. J., Schindler, C., Aston, J., Radue, E. W., & Riecher-Rossler, A. (2009). Can cortical thickness asymmetry analysis contribute to detection of at-risk mental state and first-episode psychosis? A pilot study. *Radiology, 250*(1), 212-221.

107. Hambrecht, M., Hafner, H., & Loffler, W. (1994). Beginning schizophrenia observed by significant others. *Social Psychiatry and Psychiatric Epidemiology, 29*(2), 53-60.

108. Haroun, N., Dunn, L., Haroun, A., & Cadenhead, K. S. (2006). Risk and protection in prodromal schizophrenia: ethical implications for clinical practice and future research. *Schizophrenia Bulletin, 32*(1), 166-178.

109. He, Z., Kuang, F., & Tan, L. (2008). Resting state functional magnetic resonance imaging in patients with schizophrenia and control subjects. *Chinese Journal of Clinical Psychology, 16*(2), 154-156.

110. Heinrichs, D. W., & Carpenter, W. T. (1985). Prospective study of prodromal symptoms in schizophrenic relapse. *The American Journal of Psychiatry, 142*(3), 371-373.

111. Herman, D. B., Brown, A. S., Opler, M. G., Desai, M., Malaspina, D., Bresnahan, M., Schaefer, C. A. & Susser, E. S. (2006). Does unwantedness of pregnancy predict schizophrenia in the offspring? Findings from a prospective birth cohort study. *Social Psychiatry and Psychiatric Epidemiology, 41*(8), 605-610.

112. Ho, B. C. (2007). MRI brain volume abnormalities in young, nonpsychotic relatives of schizophrenia probands are associated with subsequent prodromal symptoms. *Schizophrenia Research, 96*(1-3), 1-13.

113. Hofstetter, J. R., Lysaker, P. H., & Mayeda, A. R. (2005). Quality of sleep in patients with schizophrenia is associated with quality of life and coping. *BMC Psychiatry, 5*, 13.

114. Hoptman, M. J., Volavka, J., Johnson, G., Weiss, E., Bilder, R. M., & Lim, K. O. (2002). Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. *Biological Psychiatry, 52*(1), 9-14.

115. Hori, T., Sugita, Y., Koga, E., Shirakawa, S., Inoue, K., Uchida, S., Kuwahara, H., Kousaka, M., Kobayashi, T., Tsuji, Y., Terashima, M., Fukuda, K., & Fukuda, N. (2001). Proposed supplements and amendments to 'A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects', the Rechtschaffen & Kales (1968) standard. *Psychiatry and Clinical Neurosciences 55*(3), 305-10.

116. Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., Calabresi, P. A., Pekar, J. J., van Zijl, P. C., & Mori, S. (2008). Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage, 39*(1), 336-347.

117. Huber, G., Gross, G., Schuttler, R., & Linz, M. (1980). Longitudinal studies of schizophrenic patients. *Schizophrenia Bulletin, 6*(4), 592-605.

118. Hudson, J. I., Lipinski, J. F., Keck, P. E., Aizley, H. G., Vuckovic, A., Zierk, K. C., & Pope, H. G. (1993). Polysomnographic characteristics of schizophrenia in comparison with mania and depression. *Biological Psychiatry, 34*(3), 191-193.

119. Hudson, T. & Bush, B. (2010). The role of cortisol in sleep. *Natural Medicine Journal, 2*(6), 26-29.

120. Hughes, A. T. & Piggins, H. D. (2008). Behavioral responses of Vipr2-/- mice to light. *Journal of Biological Rhythms, 23*(3), 211-219.

121. Hurlemann, R., Jessen, F., Wagner, M., Frommann, I., Ruhrmann, S., Brockhaus, A., Picker, H., Scheef, L., Block, W., Schild, H. H., Moller-Hartmann, W., Krug, B., Falkai, P., Klosterkotter, J., & Maier, W. (2008). Interrelated neuropsychological and anatomical evidence of hippocampal pathology in the at-risk mental state. *Psychological Medicine, 38*(6), 843-851.

122. Iwashiro, N., Suga, M., Takano, Y., Inoue, H., Natsubori, T., Satomura, Y., Koike, S., Yahata, N., Murakami, M., Katsura, M., Gonoi, W., Sasaki, H., Takao, H., Abe, O., Kasai, K., & Yamasue, H. (2012). Localized gray matter volume reductions in the pars triangularis of the inferior frontal gyrus in individuals at clinical high-risk for psychosis and first episode for schizophrenia. *Schizophrenia Research, 137*(1-3), 124-31.

123. Jan, J. E., Reiter, R. J., Wasdell, M. B., & Bax, M. (2009). The role of the thalamus in sleep, pineal melatonin production, and circadian rhythm sleep disorders. *Journal of Pineal Research, 46,* 1-7.

124. Jenni, O. G. & Carskadon, M. A. (2005). Normal human sleep at different ages: infants to adolescents. In: M. Opp, T. Kilduff, C. Marcus, R. Armitage, & E. Nofzinger (Eds), *Sleep Research Society Basics of Sleep Guide* (pp. 11–19). Westchester, IL: SRS.

125. Jessen, F., Scherk, H., Traber, F., Theyson, S., Berning, J., Tepest, R., Falkai, P., Schild, H. H., Maier, W., Wagner, M., & Block, W. (2006). Proton magnetic resonance spectroscopy in subjects at risk for schizophrenia. *Schizophrenia Research, 87*(1-3), 81-88.

126. Job, D. E., Whalley, H. C., Johnstone, E. C., & Lawrie, S. M. (2005). Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage, 25*(4), 1023-1030.

127. Johnson, M. A., Devay, P., & Role, L. W. (2002, November). The cystine-rich domain of the neuregulin-1 gene (crd-NRG-1) is required for survival of a subset of neurons in the suprachiasmatic nucleus (SCN). Poster session presented at the 32nd annual meeting of the *Society for Neuroscience,* Orlando, FL.

128. Jones, D., Gershon, S., Sitaram, N., & Keshavan, M. (1987). Sleep and depression. *Psychopathology, 20,* S20 - 31.

129. Jones, S. H., Tai, S., Evershed, K., Knowles, R., & Bentall, R. (2006). Early detection of bipolar disorder: a pilot familial high-risk study of parents with bipolar disorder and their adolescent children. *Bipolar Disorders, 8*(4), 362-372.

130. Jung, W. H., Kim, J. S., Jang, J. H., Choi, J. S., Jung, M. H., Park, J. Y., Han, J. Y., Choi, C. H., Kang, D. H., Chung, C. K., & Kwon, J. S. (2011). Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophrenia Bulletin, 37*(4), 839-849.

131. Jus, K., Bouchard, M., Jus, A. K., Villeneuve, A., & Lachance, R. (1973). Sleep EEG studies in untreated, long-term schizophrenic patients. *Archives of General Psychiatry, 29*(3), 386-390.

132. Kajimura, N., Kato, M., Okuma, T., Sekimoto, M., Watanabe, T., & Takahashi, K. (1996). Relationship between delta activity during all-night sleep and negative symptoms in schizophrenia: a preliminary study. *Biological Psychiatry, 39*(6), 451-454.

133. Kaneita, Y., Yokoyama, E., Harano, S., Tamaki, T., Suzuki, H., Munezawa, T., Nakajima, H., Asai, T., & Ohida, T. (2009). Associations between sleep disturbance and mental health status: a longitudinal study of Japanese junior high school students. *Sleep Medicine, 10*(7), 780-786.

134. Kantrowitz, J., Citrome, L., & Javitt, D. (2009). GABA(B) receptors, schizophrenia and sleep dysfunction: a review of the relationship and its potential clinical and therapeutic implications. *CNS Drugs, 23*(8), 681-691.

135. Kantrowitz, J. T., Oakman, E., Bickel, S., Citrome, L., Spielman, A., Silipo, G., Battaglia, J., & Javitt, D. C. (2010). The importance of a good night's sleep: an open-label trial of the sodium salt of gamma-hydroxybutyric acid in insomnia associated with schizophrenia. *Schizophrenia Research, 120*(1-3), 225-226.

136. Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., & Cannon, T. D. (2009). White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biological Psychiatry, 66*(6), 562-569.

137. Karlsgodt, K. H., van Erp, T. G., Poldrack, R. A., Bearden, C. E., Nuechterlein, K. H., & Cannon, T. D. (2008). Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. *Biological Psychiatry, 63*(5), 512-518.

138. Kato, M., Kajimura, N., Okuma, T., Sekimoto, M., Watanabe, T., Yamadera, H., & Takahashi, K. (1999). Association between delta waves during sleep and negative symptoms in schizophrenia. Pharmaco-eeg studies by using structurally different hypnotics. *Neuropsychobiology, 39*(3), 165-172.

139. Katz, G. (2011). Jet lag and psychotic disorders. *Current Psychiatry Reports, 13,* 187-192.

140. Keenan, S. & Hirshkowitz, M. (2011). Monitoring and staging sleep. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine, 5th Ed.* (pp. 1602-1609). St. Louis: Elsevier Saunders.

141. Kelleher, I., Murtagh, A., Clarke, M. C., Murphy, J., Rawdon, C., & Cannon, M. (2013). Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: Support for the processing speed hypothesis. *Cognitive Neuropsychiatry, 18,* 9-25.

142. Kempenaers, C., Kerkhofs, M., Linkowski, P., & Mendlewicz, J. (1988). Sleep EEG variables in young schizophrenic and depressive patients. *Biological Psychiatry, 24*(7), 833-838.

143. Keshavan, M. S., Anderson, S., & Pettegrew, J. W. (1994). Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. *Journal of Psychiatric Research, 28*(3), 239-65.

144. Keshavan, M. S., Dick, E., Mankowski, I., Harenski, K., Montrose, D. M., Diwadkar, V., & DeBellis, M. (2002). Decreased left amygdala and hippocampal volumes in young offspring at risk for schizophrenia. *Schizophrenia Research, 58*(2-3), 173-183.

145. Keshavan, M. S., Diwadkar, V. A., Montrose, D. M., Stanley, J. A., & Pettegrew, J. W. (2004). Premorbid characterization in schizophrenia: the Pittsburgh High Risk Study. *World Psychiatry: Official Journal of the World Psychiatric Association, 3*(3), 163-168.

146. Keshavan, M. S., Miewald, J., Haas, G., Sweeney, J., Ganguli, R., & Reynolds, C. F. (1995). Slow-wave sleep and symptomatology in schizophrenia and related psychotic disorders. *Journal of Psychiatric Research, 29*(4), 303-314.

147. Keshavan, M. S., Montrose, D. M., Pierri, J. N., Dick, E. L., Rosenberg, D., Talagala, L., & Sweeney, J. A. (1997). Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: preliminary studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 21*(8), 1285-1295.

148. Keshavan, M. S., Pettegrew, J. W., Reynolds, C. F., Panchalingam, K. S., Montrose, D., Miewald, J., & Kupfer, D. J. (1995). Biological correlates of slow wave sleep deficits in functional psychoses: 31P-magnetic resonance spectroscopy. *Psychiatry Research, 57*(2), 91-100.

149. Keshavan, M. S., Reynolds, C. F., Ganguli, R., Brar, J., & Houck, P. (1991). Electroencephalographic sleep and cerebral morphology in functional psychoses: a preliminary study with computed tomography. *Psychiatry Research, 39*(3), 293-301.

150. Keshavan, M. S., Reynolds, C. F., Miewald, M. J., Montrose, D. M., Sweeney, J. A., Vasko, R. C., & Kupfer, D. J. (1998). Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. *Archives of General Psychiatry, 55*(5), 443-448.

151. Keshavan, M. S. & Tandon, R. (1993). Sleep abnormalities in schizophrenia: pathophysiological significance. *Psychological Medicine, 23*(4), 831-835.

152. Keshavan, M. S., Reynolds, C. F., Miewald, J., & Montrose, D. (1995). Slow-wave sleep deficits and outcome in schizophrenia and schizoaffective disorder. *Acta Psychiatrica Scandinavica, 91*(5), 289-292.

153. Khashan, A. S., Abel, K. M., McNamee, R., Pedersen, M. G., Webb, R. T., Baker, P. N., Kenny, L. C., & Mortensen, P. B. (2008). Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Archives of General Psychiatry, 65*(2), 146-152.

154. Kim, Y., Lee, J. Y., Kim, Y. S., Jung, H. Y., & Lee, K. Y. (2009). Reliability of the Korean Nottingham Onset Schedule (K-NOS) in Korean first-episode psychosis patients. *Clinical Psychopharmacology and Neuroscience, 7*(2), 51-56.

155. Klomp, A., Koolschijn, P. C., Pol, H. E., Kahn, R. S., & Haren, N. E. (2012). Hypothalamus and pituitary volume in schizophrenia: a structural MRI study. *The International Journal of Neuropsychopharmacology: Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum, 15*(2), 281-288.

156. Koefoed, P., Hansen, T. V., Woldbye, D. P., Werge, T., Mors, O., Hansen, T., Jakobsen, K. D., Nordentoft, M., Wang, A., Bolwig, T. G., & Rehfeld, J. F. (2009). An intron 1 polymorphism in the cholecystokinin-A receptor gene associated with schizophrenia in males. *Acta Psychiatrica Scandinavica, 120*(4), 281-287.

157. Koh, Y. Shin, K. S., Kim, J. S., Choi, J., Kang, D., Jang, J. H., Cho, K., O'Donnell, B. F., Chung, C. K., Kwon, J. S. (2011). An MEG study of alpha modulation in patients with schizophrenia and in subjects at high risk of developing psychosis. *Schizophrenia Research, 126,* 36-42.

158. Konick, L. C. & Friedman, L. (2001). Meta-analysis of thalamic size in schizophrenia. *Biological Psychiatry, 49*(1), 28-38.

159. Koolschijn, P. C., van Haren, N. E., Hulshoff Pol, H. E., & Kahn, R. S. (2008). Hypothalamus volume in twin pairs discordant for schizophrenia. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology, 18*(4), 312-315.

160. Koutsouleris, N., Schmitt, G. J., Gaser, C., Bottlender, R., Scheuerecker, J., McGuire, P., Burgermeister, B., Born, C., Reiser, M., Moller, H. J., & Meisenzahl, E. M. (2009). Neuroanatomical correlates of different vulnerability states for psychosis and their

clinical outcomes. *The British Journal of Psychiatry: the Journal of Mental Science, 195*(3), 218-226.

161. Kopasz, M., Loessi, B., Hornyak, M., Riemann, D., Nissen, C., Piosczyk, H., & Voderholzer, U. (2010). Sleep and memory in healthy children and adolescents - a critical review. *Sleep Medicine Reviews, 14,* 167-177.

162. Lamont, E. W., Coutu, D. L., Cermakian, N., & Boivin, D. B. (2010). Circadian rhythms and clock genes in psychotic disorders. *The Israel Journal of Psychiatry and Related Sciences, 47*(1), 27-35.

163. Lauer, C. J., Schreiber, W., Pollmacher, T., Holsboer, F., & Krieg, J. C. (1997). Sleep in schizophrenia: a polysomnographic study on drug-naive patients. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 16*(1), 51-60.

164. Lawrie, S. M., Whalley, H., Kestelman, J. N., Abukmeil, S. S., Byrne, M., Hodges, A., Rimmington, J. E., Best, J. J., Owens, D. G., & Johnstone, E. C. (1999). Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet, 353*, 30-33.

165. Lawrie, S. M., Whalley, H. C., Abukmeil, S. S., Kestelman, J. N., Donnelly, L., Miller, P., Best, J. J., Owens, D. G., & Johnstone, E. C. (2001). Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biological Psychiatry, 49*(10), 811-823.

166. Lawrie, S. M., Whalley, H. C., Abukmeil, S. S., Kestelman, J. N., Miller, P., Best, J. J., Owens, D. G., & Johnstone, E. C. (2002). Temporal lobe volume changes in people at high risk of schizophrenia with psychotic symptoms. *The British Journal of Psychiatry, 181*, 138-143.

167. Le Bon, O., Staner, L., Hoffmann, G., Dramaix, M., San Sebastian, I., Murphy, J. R., Kentos, M., Pelc, I., & Linkowski, P. (2001). The first-night effect may last more than one night. *Journal of Psychiatric Research, 35*(3), 165-172.

168. Leger, D., Beck, F., Richard, J., & Godeau, E. (2012). Total sleep time severely drops during adolescence. *PLoS One, 7,* e45204.

169. Lencz, T., Smith, C. W., Auther, A., Correll, C. U., & Cornblatt, B. (2004). Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. *Schizophrenia Research, 68*(1), 37-48.

170. Lewis, C. F., Tandon, R., Shipley, J. E., DeQuardo, J. R., Jibson, M., Taylor, S. F., & Goldman, M. (1996). Biological predictors of suicidality in schizophrenia. *Acta Psychiatrica Scandinavica, 94*(6), 416-420.

171. Lewy, A. J. (2009). Circadian misalignment in mood disorders. *Current Psychiatry Reports, 11,* 459-465.

172. Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy, 18*(1), 75-79.

173. Lockley, S. W., Skene, D. J., & Arendt, J. (1999). Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *Journal of Sleep Research, 8*(3), 175-183.

174. Lunsford-Avery, J. R., Judd, C. M., Axelson, D. A., & Miklowitz, D. J. (2012). Sleep impairment, mood symptoms, and psychosocial functioning in adolescent bipolar disorder. *Psychiatry Research, 200,* 265-271.

175. Manoach, D. S. & Stickgold, R. (2009). Does abnormal sleep impair memory consolidation in schizophrenia? *Frontiers in Human Neuroscience, 3*, 21.

176. Manoach, D. S., Thakkar, K. N., Stroynowski, E., Ely, A., McKinley, S. K., Wamsley, E., Djonlagic, I., Vangel, M. G., Goff, D. C., & Stickgold, R. (2010). Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. *Journal of Psychiatric Research 44*(2), 112-120.

177. Mansour, H. A., Wood, J., Logue, T., Chowdari, K. V., Dayal, M., Kupfer, D. J., Monk, T. H., Devlin, B., & Nimgaonkar, V. L. (2006). Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. *Genes, Brain, and Behavior, 5*(2), 150-157.

178. Mason, O. J. & Beavan-Pearson, J. (2005). Understanding the genesis of psychotic disorder: issues in the prediction and prophylaxis of those at 'ultra-high risk'. *The British Journal of Clinical Psychology, 44*(3), 383-404.

179. Massou dit Bourdet, J. M. & Laffy-Beaufils, B. (2000). [Child development and schizophrenic risk: a retrospective study]. *Annales Medico-Psychologiques, 158*(2), 148-157.

180. McGlashan, T. H. (2005). Early detection and intervention in psychosis: an ethical paradigm shift. *The British Journal of Psychiatry, 48*, S113-115.

181. McGlashan, T. H. (2006). Is active psychosis neurotoxic? *Schizophrenia Bulletin, 32*(4), 609-613.

182. McGlashan, T. H., Addington, J., Cannon, T., Heinimaa, M., McGorry, P., O'Brien, M., Penn, D., Perkins, D., Salokangas, R. K., Walsh, B., Woods, S. W., & Yung, A. (2007). Recruitment and treatment practices for help-seeking "prodromal" patients. *Schizophrenia Bulletin, 33*(3), 715-726.

183. McGlashan, T. H., Miller, T. J., & Woods, S. W. (2001). Pre-onset detection and intervention research in schizophrenia psychoses: current estimates of benefit and risk. *Schizophrenia Bulletin, 27*(4), 563-570.

184. McGlashan, T. H., Zipursky, R. B., Perkins, D., Addington, J., Miller, T. J., Woods, S. W., Hawkins, K. A., Hoffman, R., Lindborg, S., Tohen, M., & Breier, A. (2003). The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophrenia Research, 61*(1), 7-18.

185. McGorry, P. D., Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adiard, S., & Jackson, H. (2002). Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry, 59*(10), 921-928.

186. McIntosh, A. M., Owens, D. C., Moorhead, W. J., Whalley, H. C., Stanfield, A. C., Hall, J., Johnstone, E. C., & Lawrie, S. M. (2011). Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. *Biological Psychiatry, 69*(10), 953-958.

187. Mechelli, A., Riecher-Rossler, A., Meisenzahl, E. M., Tognin, S., Wood, S. J., Borgwardt, S. J., Koutsouleris, N., Yung, A. R., Stone, J. M., Phillips, L. J., McGorry, P. D., Valli, I., Velakoulis, D., Woolley, J., Pantelis, C., & McGuire, P. (2011). Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. *Archives of General Psychiatry, 68*(5), 489-495.

188. Meisenzahl, E. M., Koutsouleris, N., Gaser, C., Bottlender, R., Schmitt, G. J., McGuire, P., Decker, P., Burgermeister, B., Born, C., Reiser, M. & Moller, H. J. (2008). Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. *Schizophrenia Research, 102*(1-3), 150-162.

189. Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Cannon, T., Ventura, J., McFarlane, W., Perkins, D. O., Pearlson, G. D., & Woods, S. W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin, 29*(4), 703-15.

190. Miller, T. J., McGlashan, T. H., Rosen, J. L., Somjee, L., Markovich, P. J., Stein, K., & Woods, S. W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry, 159*(5), 863-865.

191. Miller, T. J., McGlashan, T. H., Woods, S. W., Stein, K., Driesen, N., Corcoran, C. M., Hoffman, R., & Davidson, L. (1999). Symptom assessment in schizophrenic prodromal states. *Psychiatry Quarterly, 70*(4), 273-287.

192. Miller, T. J., Zipursky, R. B., Perkins, D., Addington, J., Woods, S. W., Hawkins, K. A., Hoffman, R., Preda, A., Epstein, I., Addington, D., Lindborg, S., Marquez, E., Tohen, M., Breier, A., & McGlashan, T. H. (2003). The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the "prodromal" sample. *Schizophrenia Research, 61*(1), 19-30.

193. Mittal, V. A., Ellman, L. M., & Cannon, T. D. (2008). Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. *Schizophrenia Bulletin, 34*(6), 1083-1094.

194. Mittal, V. A., Jalbrzikowski, M., Daley, M., Roman, C., Bearden, C. E., & Cannon, T. D. (2011). Abnormal movements are associated with poor psychosocial functioning in adolescents at high risk for psychosis. *Schizophrenia Research, 130,* 164-169.

195. Mittal, V. A., Karlsgodt, K. H., Zinberg, J., Cannon, T., & Bearden, C. E. (2010). Identification and treatment of a pineal gland tumor in an adolescent with prodromal psychotic symptoms. *American Journal of Psychiatry, 167*(9), 1033-1037.

196. Mittal, V. A. & Walker, E. F. (2011). Minor physical anomalies and vulnerability in prodromal youth. *Schizophrenia Research, 129*(2-3), 116-121.

197. Mittal, V. A., Walker, E. F., Bearden, C. E., Walder, D., Trottman, H., Daley, M., Simone, A., & Cannon, T. D. (2010). Markers of basal ganglia dysfunction and conversion to psychosis: neurocognitive deficits and dyskinesias in the prodromal period. *Biological Psychiatry, 68*, 93-99.

198. Monti, J. M., BaHammam, A. S., Pandi-Perumal, S. R., Bromundt, V., Spence, D. W., Cardinali, D. P., & Brown, G. M. (2013) Sleep and circadian rhythm dysregulation in schizophrenia. *Progress in Neuropsychopharmacology & Biological Psychiatry, 43*(3), 209-216.

199. Monti, J. M. & Jantos, H. (2008). Activation of the serotonin 5-HT3 receptor in the dorsal raphe nucleus suppresses REM sleep in the rat. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*(4), 940-947.

200. Monti, J. M. & Monti, D. (2004). Sleep in schizophrenia patients and the effects of antipsychotic drugs. *Sleep Medicine Reviews, 8*(2), 133-148.

201. Monti, J. M. & Monti, D. (2005). Sleep disturbance in schizophrenia. *International Review of Psychiatry, 17*(4), 247-253.

202. Moons, T., Claes, S., Martens, G. J., Peuskens, J., Van Loo, K. M., Van Schijndel, J. E., De Hert, M., & van Winkel, R. (2011). Clock genes and body composition in patients with schizophrenia under treatment with antipsychotic drugs. *Schizophrenia Research, 125*(2-3), 187-193.

203. Moorhead, T. W., Stanfield, A., Spencer, M., Hall, J., McIntosh, A., Owens, D. C., Lawrie, S., & Johnstone, E. (2009). Progressive temporal lobe grey matter loss in adolescents with schizotypal traits and mild intellectual impairment. *Psychiatry Research, 174*(2), 105-109.

204. Morrison, A., French, P., Walford, L., Lewis, S. W., Kilcommons, A., Green, J., Parker, S., & Bentall, R. P. (2004). Cognitive therapy for the prevention of psychosis in people at ultra-high risk: Randomised controlled trial. *British Journal of Psychiatry, 185*, 291-297.

205. Muller, D. J., Klempan, T. A., De Luca, V., Sicard, T., Volavka, J., Czobor, P., Sheitman, B. B., Lindenmayer, J. P., Citrome, L., McEvoy, J. P., Lieberman, J. A., Honer, W. G., & Kennedy, J. L. (2005). The SNAP-25 gene may be associated with clinical response and weight gain in antipsychotic treatment of schizophrenia. *Neuroscience Letters, 379*(2), 81-89.

206. Munafo, M. R., Thiselton, D. L., Clark, T. G., & Flint, J. (2006). Association of the NRG1 gene and schizophrenia: a meta-analysis. *Molecular Psychiatry, 11*(6), 539-546.

207. Neylan, T. C., van Kammen, D. P., Kelley, M. E., & Peters, J. L. (1992). Sleep in schizophrenic patients on and off haloperidol therapy. Clinically stable vs relapsed patients. *Archives of General Psychiatry, 49*(8), 643-649.

208. Niendam, T. A., Jalbrzikowski, M., & Bearden, C. E. (2009). Exploring predictors of outcome in the psychosis prodrome: implications for early identification and intervention. *Neuropsychology Review*, *19*(3), 280-293.

209. Nopoulos, P. C., Ceilley, J. W., Gailis, E. A., & Andreasen, N. C. (2001). An MRI study of midbrain morphology in patients with schizophrenia: relationship to psychosis, neuroleptics, and cerebellar neural circuitry. *Biological Psychiatry, 49*(1), 13-19.

210. Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep, 27*(7), 1255-1273.

211. Oliver, P. L., Sobczyk, M. V., Maywood, E. S., Edwards, B., Lee, S., Livieratos, A., Oster, H., Butler, R., Godinho, S. I., Wulff, K., Peirson, S. N., Fisher, S. P., Chesham, J. E., Smith, J. W., Hastings, M. H., Davies, K. E., & Foster, R. G. (2012). Disrupted circadian rhythms in a mouse model of schizophrenia. *Current Biology, 22*(4), 314-319.

212. Osman, A., Barrios, F. X., Gutierrez, P. M., Williams, J. E., & Bailey, J. (2008). Psychometric properties of the Beck Depression Inventory-II in nonclinical adolescent samples. *Journal of Clinical Psychology, 64*(1), 83-102.

213. Pantelis, C., Velakoulis, D., McGorry, P. D., Wood, S. J., Suckling, J., Phillips, L. J., Yung, A. R., Bullmore, E. T., Brewer, W., Soulsby, B., Desmond, P., & McGuire, P. K. (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet, 361*, 281-288.

214. Parnas, J. (1999). From predisposition to psychosis: progression of symptoms in schizophrenia. *Acta Psychiatrica Scandinavica. Supplementum, 395*, 20-29.

215. Patenaude, B. (2007). *FMRIB Technical Report TR07BP1*. London: Oxford.

216. Paus, T., Zijdenbos, A., Worsley, K., Collins, D. L., Blumenthal, J., Giedd, J. N., Rapoport, J. L., & Evans, A. C. (1999). Structural maturation of neural pathways in children and adolescents: in vivo study. *Science, 283*, 1908-1911.

217. Peters, B. D., Schmitz, N., Dingemans, P. M., van Amelsvoort, T. A., Linszen, D. H., de Haan, L., Majoie, C. B., & den Heeten, G. J. (2009). Preliminary evidence for reduced frontal white matter integrity in subjects at ultra-high-risk for psychosis. *Schizophrenia Research, 111*(1-3), 192-193.

218. Phillips, L. J., Velakoulis, D., Pantelis, C., Wood, S., Yuen, H. P., Yung, A. R., Desmond, P., Brewer, W., & McGorry, P. D. (2002). Non-reduction in hippocampal volume is associated with higher risk of psychosis. *Schizophrenia Research, 58*(2-3), 145-158.

219. Pierpaoli, C., Barnett, A., Pajevic, S., Chen, R., Penix, L. R., Virta, A., & Basser, P. (2001). Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *Neuroimage, 13*, 1174-1185.

220. Poulin, J., Daoust, A. M., Forest, G., Stip, E., & Godbout, R. (2003). Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. *Schizophrenia Research, 62*(1-2), 147-153.

221. Pritchett, D., Wulff, K., Oliver, P. L., Bannerman, D. M., Davies, K. E., Harrison, P. J., Peirson, S. N., & Foster, R. G. (2012). Evaluating the links between schizophrenia and sleep and circadian rhythm disruption. *Journal of Neural Transmission, 119*(10), 1061-1075.

222. Rajarethinam, R., Sahni, S., Rosenberg, D. R., & Keshavan, M. S. (2004). Reduced superior temporal gyrus volume in young offspring of patients with schizophrenia. *The American Journal of Psychiatry, 161*(6), 1121-1124.

223. Rees, S. & Inder, T. (2005). Fetal and neonatal origins of altered brain development. *Early Human Development, 81*(9), 753-761.

224. Reichenberg, A. & Harvey, P. D. (2007). Neuropsychological impairments in schizophrenia: integrations of performance-based and brain imaging findings. *Psychological Bulletin, 133,* 833-858.

225. Riemann, D., Hohagen, F., Krieger, S., Gann, H., Muller, W. E., Olbrich, R., Wark, H. J., Bohus, M., Low, H., & Berger, M. (1994). Cholinergic REM induction test: muscarinic supersensitivity underlies polysomnographic findings in both depression and schizophrenia. *Journal of Psychiatric Research, 28*(3), 195-210.

226. Ritsner, M., Kurs, R., Ponizovsky, A., & Hadjez, J. (2004). Perceived quality of life in schizophrenia: relationships to sleep quality. *Quality of life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, 13*(4), 783-791.

227. Ritter, R. S., Marx, C., Lewtschenko, N., Pfeiffer, S., Leopold, K., Bauer, M., & Pfennig, A. (2012). The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. *Journal of Neural Transmission, 119,* 1173-1184.

228. Rosen, J. L., Miller, T. J., D'Andrea, J. T., McGlashan, T. H., & Woods, S. W. (2006). Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. *Schizophrenia Research, 85*(1-3), 124-131.

229. Rosen, J. L., Woods, S. W., Miller, T. J., & McGlashan, T. H. (2002). Prospective observations of emerging psychosis. *The Journal of Nervous and Mental Disease, 190*(3), 133-141.

230. Rotenberg, V. S., Hadjez, J., Indursky, P., Martin, T., Barak, Y., & Gutman, Y. (1997). Eye movement density in positive and negative schizophrenia. *Homeostasis, 38*, 97-102.

231. Royuela, A., Macias, J. A., Gil-Verona, J. A., Pastor, J. F., Maniega, M. A., Alonso, J., Roman, J. M., De Paz, F., Barbosa, M., Rami-Gonzalez, L., & Boget, T. (2009). Sleep in schizophrenia: a preliminary study using the Pittsburgh Sleep Quality Index. *Neurobiology of Sleep-Wakefulness Cycle, 2*(2), 37-39.

232. Sachdev, P. S. & Brodaty, H. (1999). Mid-sagittal anatomy in late-onset schizophrenia. *Psychological Medicine, 29*(4), 963-970.

233. Sadeh, A., Sharkey, K. M., & Carskadon, M. A. (1994). Activity-based sleep-wake identification: an empirical test of methodological issues. *Sleep, 17*(3), 201-207.

234. Salin-Pascual, R. J., Herrera-Estrella, M., Galicia-Polo, L., Rosas, M., & Brunner, E. (2004). Low delta sleep predicted a good clinical response to olanzapine administration

in schizophrenic patients. *Revista de Investigacion Clinica; Organo del Hospital de Enfermedades de la Nutricion, 56*(3), 345-350.

235. Salokangas, R. K., Ruhrmann, S., von Reventlow, H. G., Heinimaa, M., Svirskis, T., From, T., Luutonen, S., Juckel, G., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Schultze-Lutter, F., & Klosterkotter, J. (2012). Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. *Schizophrenia Research, 138*(2-3), 192-197.

236. Schmithorst, V. J., Wilke, M., Dardzinski, B. J., & Holland, S. K. (2002). Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. *Radiology, 222*(1), 212-218.

237. Schmitt, A., Fendt, M., Zink, M., Ebert, U., Starke, M., Berthold, M., Herb, A., Petroianu, G., Falkai, P., & Henn, F. A. (2007). Altered NMDA receptor expression and behavior following postnatal hypoxia: potential relevance to schizophrenia. *Journal of Neural Transmission, 114*(2), 239-248.

238. Schreiber, H., Baur-Seack, K., Kornhuber, H. H., Wallner, B., Friedrich, J. M., De Winter, I. M., & Born, J. (1999). Brain morphology in adolescents at genetic risk for schizophrenia assessed by qualitative and quantitative magnetic resonance imaging. *Schizophrenia Research, 40*(1), 81-84.

239. Segal, D. L., Coolidge, F. L., Cahill, B. S., & O'Riley, A. A. (2008). Psychometric properties of the Beck Depression Inventory II (BDI-II) among community-dwelling older adults. *Behavior Modification, 32*(1), 3-20.

240. Sekimoto, M., Kato, M., Watanabe, T., Kajimura, N., & Takahashi, K. (2011). Cortical regional differences of delta waves during all-night sleep in schizophrenia. *Schizophrenia Research, 126*(1-3), 284-290.

241. Serretti, A., Mandelli, L., Lattuada, E., & Smeraldi, E. (2004). Depressive syndrome in major psychoses: a study on 1351 subjects. *Psychiatry Research, 127*(1-2), 85-99.

242. Shimazoe, T., Morita, M., Ogiwara, S., Kojiya, T., Goto, J., Kamakura, M., Moriya, T., Shinohara, K., Takiguchi, S., Kono, A., Miyasaka, K., Funakoshi, A., & Ikeda, M. (2008). Cholecystokinin-A receptors regulate photic input pathways to the circadian clock. *Federation of American Societies for Experimental Biology, 22*(5), 1479-1490.

243. Shimizu, M., Fujiwara, H., Hirao, K., Namiki, C., Fukuyama, H., Hayashi, T., & Murai, T. (2008). Structural abnormalities of the adhesio interthalamica and mediodorsal nuclei of the thalamus in schizophrenia. *Schizophrenia Research, 101*(1-3), 331-338.

244. Shioiri, T., Shinada, K., Kuwabara, H., & Someya, T. (2007). Early prodromal symptoms and diagnoses before first psychotic episode in 219 inpatients with schizophrenia. *Psychiatry and Clinical Neurosciences, 61*(4), 348-354.

245. Siegel, J. M. (2004). The neurotransmitters of sleep. *The Journal of Clinical Psychiatry, 65 Supplement 16*, 4-7.

246. Sisk, C. L. & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature Neuroscience, 7,* 1040-1047.

247. Sismanlar, S. G., Anik, Y., Coskun, A., Agaoglu, B., Karakaya, I., & Yavuz, C. I. (2010). The volumetric differences of the fronto-temporal region in young offspring of schizophrenic patients. *European Child & Adolescent Psychiatry, 19*(2), 151-157.

248. Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505.

249. Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23 Supplement 1*, S208-219.

250. Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage, 20*(3), 1714-1722.

251. Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage, 17*(3), 1429-1436.

252. Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6*(3), 309-315.

253. Spear, L. P. (2004). Adolescent brain development and animal models. *Annals of New York Academy of Science, 1021*, 23-26.

254. Srinivasan, V., Smits, M., Spence, W., Lowe, A. D., Pandi-Perumal, S. R., Parry, B., & Cardinali, D. P. (2006). Melatonin in mood disorders. *The World Journal of Biological Psychiatry, 7,* 138-151.

255. Stickgold, R. & Walker, M. P. (2005). Memory consolidation and reconsolidation: what is the role of sleep? *Trends in Neurosciences, 28*(8), 408-415.

256. Stiller, J. W. & Postolache, T. T. (2005). Sleep-wake and other biological rhythms: functional neuroanatomy. *Clinics in Sports Medicine, 24*(2), 205-235.

257. Stone, J. M., Bramon, E., Pauls, A., Sumich, A., & McGuire, P. K. (2010). Thalamic neurochemical abnormalities in individuals with prodromal symptoms of schizophrenia - relationship to auditory event-related potentials. *Psychiatry Research, 183*(2), 174-176.

258. Stone, J. M., Day, F., Tsagaraki, H., Valli, I., McLean, M. A., Lythgoe, D. J., O'Gorman, R. L., Barker, G. J., & McGuire, P. K. (2009). Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. *Biological Psychiatry, 66*(6), 533-539.

259. Svirskis, T., Korkeila, J., Heinimaa, M., Huttunen, J., Ilonen, T., Ristkari, T., McGlashan, T., & Salokangas, R. K. (2005). Axis-I disorders and vulnerability to psychosis. *Schizophrenia Research, 75*(2-3), 439-446.

260. Szentkirályi, A., Madarász, C. Z., & Novák, M. (2009). Sleep disorders: impact on daytime functioning and quality of life. *Expert Review of Pharmacoeconomics and Outcomes Research, 9,* 49-64.

261. Taber, K. H. & Hurley, R. A. (2006). Functional neuroanatomy of sleep and sleep deprivation. *The Journal of Neuropsychiatry and Clinical Neurosciences, 18*(1), 1-5.

262. Takahashi, T., Wood, S. J., Yung, A. R., Soulsby, B., McGorry, P. D., Suzuki, M., Kawasaki, Y., Phillips, L. J., Velakoulis, D., & Pantelis, C. (2009). Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. *Archives of General Psychiatry, 66*(4), 366-376.

263. Takahashi, T., Wood, S. J., Yung, A. R., Walterfang, M., Phillips, L. J., Soulsby, B., Kawasaki, Y., McGorry, P. D., Suzuki, M., Velakoulis, D., & Pantelis, C. (2010). Superior temporal gyrus volume in antipsychotic-naive people at risk of psychosis. *The British Journal of Psychiatry: The Journal of Mental Science, 196*(3), 206-211.

264. Tan, H. Y. & Ang, Y. G. (2001). First-episode psychosis in the military: a comparative study of prodromal symptoms. *The Australian and New Zealand Journal of Psychiatry, 35*(4), 512-519.

265. Tandon, R., DeQuardo, J. R., Taylor, S. F., McGrath, M., Jibson, M., Eiser, A., & Goldman, M. (2000). Phasic and enduring negative symptoms in schizophrenia: biological markers and relationship to outcome. *Schizophrenia Research, 45*(3), 191-201.

266. Tandon, R., Lewis, C., Taylor, S. F., Shipley, J. E., DeQuardo, J. R., Jibson, M., & Goldman, M. (1996). Relationship between DST nonsuppression and shortened REM latency in schizophrenia. *Biological Psychiatry, 40*(7), 660-663.

267. Tandon, R., Shipley, J. E., Eiser, A. S., & Greden, J. F. (1988). Association between abnormal REM sleep and negative symptoms in schizophrenia. *Psychiatry Research, 27*, 359-361.

268. Tandon, R., Shipley, J. E., Taylor, S., Greden, J. F., Eiser, A., DeQuardo, J., & Goodson, J. (1992). Electroencephalographic sleep abnormalities in schizophrenia. Relationship to positive/negative symptoms and prior neuroleptic treatment. *Archives of General Psychiatry, 49*(3), 185-194.

269. Taylor, S. F., Tandon, R., Shipley, J. E., & Eiser, A. S. (1991). Effect of neuroleptic treatment on polysomnographic measures in schizophrenia. *Biological Psychiatry, 30*(9), 904-912.

270. Taylor, S. F., Tandon, R., Shipley, J. E., Eiser, A. S., & Goodson, J. (1991). Sleep onset REM periods in schizophrenic patients. *Biological Psychiatry, 30*(2), 205-209.

271. Tekell, J. L., Hoffmann, R., Hendrickse, W., Greene, R. W., Rush, A. J., & Armitage, R. (2005). High frequency EEG activity during sleep: characteristics in schizophrenia and depression. *Clinical EEG and Neuroscience: Official Journal of the EEG and Clinical Neuroscience Society, 36*(1), 25-35.

272. Thaker, G. K., Wagman, A. M., & Tamminga, C. A. (1990). Sleep polygraphy in schizophrenia: methodological issues. *Biological Psychiatry, 28*(3), 240-246.

273. Tibbo, P., Hanstock, C., Valiakalayil, A., & Allen, P. (2004). 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. *The American Journal of Psychiatry, 161*(6), 1116-1118.

274. Unger, M. M., Belke, M., Menzler, K., Heverhagen, J. T., Keil, B., Stiasny-Kolster, K., Rosenow, F., Diederich, N. J., Mayer, G., Moller, J. C., Oertel, W. H., & Knake, S. (2010). Diffusion tensor imaging in idiopathic REM sleep behavior disorder reveals microstructural changes in the brainstem, substantia nigra, olfactory region, and other brain regions. *Sleep, 33,* 767-773.

275. Vacic, V., McCarthy, S., Malhotra, D., Murray, F., Chou, H. H., Peoples, A., Makarov, V., Yoon, S., Bhandari, A., Corominas, R., Iakoucheva, L. M., Krastoshevsky, O., Krause, V., Larach-Walters, V., Welsh, D. K., Craig, D., Kelsoe, J. R., Gershon, E. S., Leal, S. M., Dell Aquila, M., Morris, D. W., Gill, M., Corvin, A., Insel, P. A., McClellan, J., King, M. C., Karayiorgou, M., Levy, D. L., DeLisi, L. E., & Sebat, J. (2011). Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature 471*, 499-503.

276. Van Cauter, E., Linkowski, P., Kerkhofs, M., Hubain, P., L'Hermite-Baleriaux, M., Leclercq, R., Brasseur, M., Copinschi, G., & Mendlewicz, J. (1991). Circadian and sleep-related endocrine rhythms in schizophrenia. *Archives of General Psychiatry, 48*(4), 348-356.

277. van Kammen, D. P., van Kammen, W. B., Peters, J., Goetz, K., & Neylan, T. (1988). Decreased slow-wave sleep and enlarged lateral ventricles in schizophrenia. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 1*(4), 265-271.

278. van Os, J. & Selten, J. P. (1998). Prenatal exposure to maternal stress and subsequent schizophrenia. The May 1940 invasion of The Netherlands. *The British Journal of Psychiatry, 172*, 324-326.

279. Verdoux, H., Pauillac, P., Fournet, O., Bergey, C., Liraud, F., Gonzalez, B., Assens, F., Abalan, F., Beaussier, J. P., Gaussares, C., Etchegaray, B., & Bourgeois, M. (1998). [Childhood antecedents of psychotic disorders. Diagnostic specificity and association with age of onset]. *Annales Medico-Psychologiques, 156*(10), 659-667.

280. Verma, A., Anand, V., & Verma, N. P. (2007). Sleep disorders in chronic traumatic brain injury. *Journal of Clinical Sleep Medicine, 3*(4), 357-362.

281. Vita, A., De Peri, L., Silenzi, C., & Dieci, M. (2006). Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. *Schizophrenia Research, 82*(1), 75-88.

282. Vukadinovic, Z. (2011). Sleep abnormalities in schizophrenia may suggest impaired trans-thalamic cortico-cortical communication: towards a dynamic model of the illness. *The European Journal of Neuroscience, 34*(7), 1031-1039.

283. Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., & Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage, 36*(3), 630-644.

284. Walker, E. & Diforio, D. (1997). Schizophrenia: a neural diathesis-stress model. *Psychological Review, 104*(4), 667-85.

285. Walker, E., Mittal, V., & Tessner, K. (2008). Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. *Annual Review of Clinical Psychology, 4*, 189-216.

286. Walker, E. F., Savoie, T., & Davis, D. (1994). Neuromotor precursors of schizophrenia. *Schizophrenia Bulletin, 20,* 441-451.

287. Wamsley, E. J., Tucker, M. A., Shinn, A. K., Ono, K. E., McKinley, S. K., Ely, A. V., Goff, D. C., Stickgold, R., & Manoach, D. S. (2012). Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? *Biological Psychiatry, 71*(2), 154-161.

288. Waters, F. & Manoach, D. S. (2012). Sleep dysfunctions in schizophrenia: a practical review. *Open Journal of Psychiatry, 2,* 384-392.

289. Weinstock, M. (2001). Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Progress in Neurobiology, 65*(5), 427-451.

290. White, T., Anjum, A., & Schulz, S. C. (2006). The schizophrenia prodrome. *American Journal of Psychiatry, 163*(3), 376-380.

291. Williams, R. L., Karacan, I., & Hursch, C. J. (1974). *Electroencephalography (EEG) of human sleep: clinical applications.* New York: John Wiley.

292. Williams, R. L., Karacan, I., Hursch, C. J., & Davis, C. E. (1972). Sleep patterns of pubertal males. *Pediatric Research, 6*(8), 643-648.

293. Witthaus, H., Brune, M., Kaufmann, C., Bohner, G., Ozgurdal, S., Gudlowski, Y., Heinz, A., Klingbiel, R., & Juckel, G. (2008). White matter abnormalities in subjects at ultra high-risk for schizophrenia and first-episode schizophrenic patients. *Schizophrenia Research, 102*(1-3), 141-149.

294. Witthaus, H., Kaufmann, C., Bohner, G., Ozgurdal, S., Gudlowski, Y., Gallinat, J., Ruhrmann, S., Brune, M., Heinz, A., Klingebiel, R., & Juckel, G. (2009). Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. *Psychiatry Research, 173*(3), 163-169.

295. Witthaus, H., Mendes, U., Brune, M., Ozgurdal, S., Bohner, G., Gudlowski, Y., Kalus, P., Andreasen, N., Heinz, A., Klingebiel, R., & Juckel, G. (2010). Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia. *Journal of Psychiatry & Neuroscience, 35*(1), 33-40.

296. Wolfson, A. R. & Carskadon, M. A. (1998). Sleep schedules and daytime functioning in adolescents. *Child Development, 69,* 875–887.

297. Wolfson, A. R. & Carskadon, M.A. (2003). Understanding adolescents' sleep patterns and school performance: a critical appraisal. *Sleep Medicine Reviews, 7,* 491–506.

298. Wood, S. J., Berger, G., Velakoulis, D., Phillips, L. J., McGorry, P. D., Yung, A. R., Desmond, P., & Pantelis, C. (2003). Proton magnetic resonance spectroscopy in first episode psychosis and ultra high-risk individuals. *Schizophrenia Bulletin, 29*(4), 831-843.

299. Wood, S. J., Kennedy, D., Phillips, L. J., Seal, M. L., Yucel, M., Nelson, B., Yung, A. R., Jackson, G., McGorry, P. D., Velakoulis, D., & Pantelis, C. (2010). Hippocampal pathology in individuals at ultra-high risk for psychosis: a multi-modal magnetic resonance study. *Neuroimage, 52*(1), 62-68.

300. Woods, S. W., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., & McGlashan, T. H. (2009). Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophrenia Bulletin, 35*(5), 894-908.

301. Woods, S. W., Breier, A., Zipursky, R. B., Perkins, D. O., Addington, J., Miller, T. J., Hawkins, K. A., Marquez, E., Lindborg, S. R., Tohen, M., & McGlashan, T. H. (2003). Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. *Biological Psychiatry, 54*(4), 453-464.

302. Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W., David, A. S., Murray, R. M., & Bullmore, E. T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *The American Journal of Psychiatry, 157*(1), 16-25.

303. Wu, E. Q., Birnbaum, H. G., Shi, L., Ball, D. E., Kessler, R. C., Moulis, M., & Aggarwal, J. (2005). The economic burden of schizophrenia in the United States in 2002. *Journal of Clinical Psychiatry, 66*(9), 1122-1129.

304. Wulff, K., Dijk, D., Middleton, B., Foster, R. G., & Joyce. (2012). Sleep and circadian rhythm disruption in schizophrenia. *The British Journal of Psychiatry, 200,* 308-316.

305. Xiang, Y. T., Weng, Y. Z., Leung, C. M., Tang, W. K., Lai, K. Y., & Ungvari, G. S. (2009). Prevalence and correlates of insomnia and its impact on quality of life in Chinese schizophrenia patients. *Sleep, 32*(1), 105-109.

306. Yang, C. & Winkelman, J. W. (2006). Clinical significance of sleep EEG abnormalities in chronic schizophrenia. *Schizophrenia Research, 82*(2-3), 251-260.

307. Youngstrom, E., Meyers, O., Youngstrom, J. K., Calabrese, J. R., & Findling, R. L. (2006). Diagnostic and measurement issues in the assessment of pediatric bipolar disorder: implications for understanding mood disorder across the life cycle. *Development and Psychopathology, 18*(4), 989-1021.

308. Youngstrom, E. A., Findling, R. L., Danielson, C. K., & Calabrese, J. R. (2001). Discriminative validity of parent report of hypomanic and depressive symptoms on the General Behavior Inventory. *Psychological Assessment, 13*(2), 267-276.

309. Youngstrom, E. A., Frazier, T. W., Demeter, C., Calabrese, J. R., & Findling, R. L. (2008). Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. *The Journal of Clinical Psychiatry, 69*(5), 831-839.

310. Yung, A. R. & McGorry, P. D. (1996a). The initial prodrome in psychosis: descriptive and qualitative aspects. *The Australian and New Zealand Journal of Psychiatry, 30*(5), 587-599.

311. Yung, A. R. & McGorry, P. D. (1996b). The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophrenia Bulletin, 22*(2), 353-370.

312. Yung, A. R., McGorry, P. D., McFarlane, C. A., Jackson, H. J., Patton, G. C., & Rakkar, A. (1996). Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin, 22*(2), 283-303.

313. Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S. M., McFarlane, C. A., Hallgren, M., & McGorry, P. D. (2003). Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophrenia Research, 60*(1), 21-32.

314. Yung, A. R., Phillips, L. J., Yuen, H. P. & McGorry, P. D. (2004). Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophrenia Research 67*(2-3), 131-42.Zakzanis, K. K., Poulin, P., Hansen, K. T., & Jolic, D. (2000). Searching the schizophrenic brain for temporal lobe deficits: a systematic review and meta-analysis. *Psychological Medicine, 30*(3), 491-504.

315. Zanarini, M. C. & Frankenburg, F. R. (2001). Attainment and maintenance of reliability of axis I and II disorders over the course of a longitudinal study. *Comprehensive Psychiatry, 42*(5), 369-374.

316. Zanarini, M. C., Skodol, A. E., Bender, D., Dolan, R., Sanislow, C., Schaefer, E., Morey, L. C., Grilo, C. M., Shea, M. T., McGlashan, T. H., & Gunderson, J. G. (2000). The Collaborative Longitudinal Personality Disorders Study: reliability of axis I and II diagnoses. *Journal of Personality Disorders, 14*(4), 291-299.

317. Zarcone, V. P. & Benson, K. L. (1997). BPRS symptom factors and sleep variables in schizophrenia. *Psychiatry Research, 66*(2-3), 111-120.

318. Zhang, Q. & Sachdev, P. S. (2003). Psychotic disorder and traumatic brain injury. *Current Psychiatry Reports, 5*(3), 197-201.

319. Ziermans, T. B., Durston, S., Sprong, M., Nederveen, H., van Haren, N. E., Schnack, H. G., Lahuis, B. E., Schothorst, P. F., & van Engeland, H. (2009). No evidence for structural brain changes in young adolescents at ultra high risk for psychosis. *Schizophrenia Research, 112*(1-3), 1-6.

320. Ziermans, T. B., Schothorst, P. F., Schnack, H. G., Koolschijn, P. C., Kahn, R. S., van Engeland, H., & Durston, S. (2012). Progressive structural brain changes during development of psychosis. *Schizophrenia Bulletin, 38*(3), 519-530.

321. Zito, J. M., Safer, D. J., DosReis, S., Gardner, J. F., Magder, L., Soeken, K., Boles, M., Lynch, F., & Riddle, M. A. (2003). Psychotropic practice patterns for youth: a 10-year perspective. *Archives of Pediatrics and Adolescent Medicine, 157*(1), 17-25.

Appendix A. ECSSii Actigraphy Questioning Form

ECSSii Actigraphy Questioning Form

Date: ___________ Reviewer's initials:________ Questioned by initials:______

Questions: Note all appropriate times (e.g., diary lights-out time, minutes to fall asleep, rise time) on the actigraph printout.

Answers: Please be clear!!! Find out what the child was doing during the time in question. Record their answer in detail. Record if they don't know the answer to a question (note if they thought they were awake or asleep).

Nighttime Awakening Reason Codes:

1) noise
2) bathroom
3) bed or room partner
4) pet
5) bad dream
6) sick
7) too hot/too cold
8) you wet the bed
9) other______________________

Date / Time	Description of Issue / Question	Answers
	High activity ____ min B4 reported rise time. Did child wake before you? Low activity from _________ to _________. Fall Asleep? What doing? High activity from _________ to _________. Awake? Why?	Yes No DK Yes No DK Yes No DK Awakening Reason(s): ____
	High activity ____ min B4 reported rise time. Did child wake before you? Low activity from _________ to _________. Fall Asleep? What doing? High activity from _________ to _________. Awake? Why?	Yes No DK Yes No DK Yes No DK Awakening Reason(s): ____
	High activity ____ min B4 reported rise time. Did child wake before you? Low activity from _________ to _________. Fall Asleep? What doing? High activity from _________ to _________. Awake? Why?	Yes No DK Yes No DK Yes No DK Awakening Reason(s): ____
	High activity ____ min B4 reported rise time. Did child wake before you? Low activity from _________ to _________. Fall Asleep? What doing? High activity from _________ to _________. Awake? Why?	Yes No DK Yes No DK Yes No DK Awakening Reason(s): ____
	High activity ____ min B4 reported rise time. Did child wake before you? Low activity from _________ to _________. Fall Asleep? What doing? High activity from _________ to _________. Awake? Why?	Yes No DK Yes No DK Yes No DK Awakening Reason(s): ____

Did child ever fall asleep while watch was off? Yes No
If Yes, details (day/date, duration, etc): ____

Appendix B. Sleep/Activity Log

SLEEP ACTIVITY LOG

Sleep is an important part of your health. Some people sleep a lot during the day and some people sleep a little; however, it is important that you should get roughly 8 hours of sleep everyday in order to remain healthy and alert during the day. In order to get a complete picture of your sleep health and your activity during the day, we are going to ask you to wear a small bracelet with an activity monitor for 5 days and keep a log of your activity. This monitor records the motion of your arm as you move it as well as the amount of light around you.
We ask that you to keep this bracelet and monitor on your wrist all day and all night except for a few activities.

Please do NOT wear the monitor

-When you shower
- If you go to the swimming pool or swim in a lake, river, pond.
-If you ever feel uncomfortable wearing the monitor, please feel free to take it off and keep it in a safe place until you are ready to wear it again.

You can also decide not to wear the bracelet at all. Your participation in this part of the study is completely your choice. If at any time you decide that you do not want to wear the monitor anymore or if the 5 days of recording are completed, then please mail the monitor and the log back to ADAPT in the addressed envelope we gave you.
If you have any questions, please call ADAPT at 303.492.4616

In order to help us with the study, we would very much appreciate it if you keep a log of your activity. Please try your best to record the things listed below. You can also call ADAPT to help you or ask a family member/significant other to help you.

Please maintain your daily routine. If wearing the monitor disrupts your day or prevents you from sleeping, please call ADAPT and we will try to help you.

Things that you should record:

1) The time you get into bed and are ready to fall asleep.
2) The time you get out of bed after sleeping.
3) The time when you decide to take a nap and the time you wake up from your nap. Please leave the monitor on your wrist when you take a nap.
4) The time you remove the monitor to take a shower, bath, or go swimming and the time you put the monitor back on after showering, taking a bath, or going swimming.
5) The time when you remove the monitor for any other reason and the time you put it back on

Day # ___:

Date: _____

Please circle the day of the week: **Mon Tues Wed Thurs Fri Sat Sun**

I WOKE UP AT_____ (AM/PM)

Did you go to school today?

If yes: From _____ To_____ (AM or PM?)

Did you have any physical illness today such as a cold or the flu?

If yes: From _____ To_____ (AM or PM?)

Please record the times you **took the bracelet off** today:

From _____ To_____ AM or PM (circle)

From _____ To_____ AM or PM (circle)

From _____ To_____ AM or PM (circle)

From _____ To_____ AM or PM (circle)

Please record any **naps** today:

From _____ To_____ AM or PM (circle)

From _____ To_____ AM or PM (circle)

Were you **MORE/LESS** active today than most days? YES / NO (Circle)

Please list below the activities you did today:

I WENT TO BED AT_____ (AM/PM)

Appendix C. The Pittsburgh Sleep Quality Index

Name _____ ID # _____ Date _____ Age _____

Instructions:

The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME _____
2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?
   NUMBER OF MINUTES _____
3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME _____
4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you...

(a) Cannot get to sleep within 30 minutes

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(b) Wake up in the middle of the night or early morning

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(c) Have to get up to use the bathroom

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(d) Cannot breathe comfortably

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(e) Cough or snore loudly

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(f) Feel too cold

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(g) Feel too hot

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(h) Had bad dreams

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(i) Have pain

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(j) Other reason(s), please describe _____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

6. During the past month, how would you rate your sleep quality overall?

Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or roommate?

No bed partner or roommate _____
Partner/roommate in other room _____
Partner in same room, but not same bed _____
Partner in same bed _____

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

(a) Loud snoring

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(b) Long pauses between breaths while asleep

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(c) Legs twitching or jerking while you sleep

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(d) Episodes of disorientation or confusion during sleep

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

(e) Other restlessness while you sleep; please describe _____

_____

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____

Appendix D. Scoring of the Pittsburgh Sleep Quality Index

SCORING PSQI DOMAINS

DURATION OF SLEEP

IF Q4 ≥ 7, THEN set value to 0
IF Q4 < 7 and ≥ 6, THEN set value to 1
IF Q4 < 6 and ≥ 5, THEN set value to 2
IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

SLEEP DISTURBANCE

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) ≥ 1 and ≤ 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and ≤ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

SLEEP LATENCY

First, recode Q2 into Q2new thusly:
IF Q2 ≥ 0 and ≤ 15, THEN set value of Q2new to 0
IF Q2 > 15 and ≤ 30, THEN set value of Q2new to 1
IF Q2 > 30 and ≤ 60, THEN set value of Q2new to 2
IF Q2 > 60, THEN set value of Q2new to 3
Next
IF Q5a + Q2new = 0, THEN set value to 0
IF Q5a + Q2new ≥ 1 and ≤ 2, THEN set value to 1
IF Q5a + Q2new ≥ 3 and ≤ 4, THEN set value to 2
IF Q5a + Q2new ≥ 5 and ≤ 6, THEN set value to 3

Minimum Score = 0 (better); Maximum Score = 3 (worse)

DAY DYSFUNCTION DUE TO SLEEPINESS

IF Q8 + Q9 = 0, THEN set value to 0
IF Q8 + Q9 ≥ 1 and ≤ 2, THEN set value to 1

IF Q8 + Q9 ≥ 3 and ≤ 4, THEN set value to 2
IF Q8 + Q9 ≥ 5 and ≤ 6, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

SLEEP EFFICIENCY

Diffsec = Difference in seconds between day and time of day Q1 and day Q3
Diffhour = Absolute value of diffsec / 3600
Newtib = IF diffhour > 24, then newtib = diffhour – 24
IF diffhour ≤ 24, THEN newtib = diffhour
(NOTE, THE ABOVE JUST CALCULATES THE HOURS BETWEEN GNT (Q1) AND GMT (Q3))
tmphse = (Q4 / newtib) * 100

IF tmphse ≥ 85, THEN set value to 0
IF tmphse < 85 and ≥ 75, THEN set value to 1
IF tmphse < 75 and ≥ 65, THEN set value to 2
IF tmphse < 65, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

OVERALL SLEEP QUALITY

Q6
Minimum Score = 0 (better); Maximum Score = 3 (worse)

NEED MEDS TO SLEEP

Q7
Minimum Score = 0 (better); Maximum Score = 3 (worse)

TOTAL

DURATION + DISTBURBANCES + LATENCY + DAYTIME DYSFUNCTION + EFFICIENCY + SLEEP QUALITY + MEDS
Minimum Score = 0 (better); Maximum Score = 21 (worse)
Interpretation: TOTAL ≤ 5 associated with good sleep quality
TOTAL > 5 associated with poor sleep quality

Reference: Buysse D.J., Reynolds C.F., Monk T.H., Berman S.R., & Kupfer D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research 28,* 193-213.