IMPACT OF CUMULATIVE SLEEP RESTRICTION ON SLEEP PHYSIOLOGY IN CHILDREN WITH AND WITHOUT ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

by

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Dedication

To the women in my circle – especially my mom, without whom none of this would have been possible.

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Abstract

The impact of reduced sleep duration on sleep physiology has not been extensively studied in children. Children with attention-deficit/hyperactivity disorder (ADHD) may be particularly vulnerable to sleep loss as many of these children have pre-existing sleep problems. Research has yet to establish a physiological basis for these difficulties. The first aim of this dissertation was to examine the impact of cumulative sleep restriction (CSR) on school-age children (aged 6 to 12 years) by exploring sleep physiology. The second and third aims were to compare sleep physiology between TD children and children with ADHD and determine whether the latter are differentially impacted by CSR. An experimental study was conducted where participants' time in bed (TIB) was reduced by one hour per night over six nights (Restricted condition) and compared to six nights of scheduled typical sleep (Typical condition). Sleep was recorded in the laboratory using polysomnography (PSG) at the end of each condition period. The following dissertation consists of two manuscripts based on the PSG data collected. The first manuscript investigated changes in sleep architecture and the power spectrum of sleep electroencephalography (EEG). REM sleep was reduced in both groups at the end of the Restricted condition while there were no changes in slow wave activity (SWA). Trends in the data suggested that TD children had a reduction in N1 and maintenance of N2 while children with ADHD had an increase in these stages and greater sigma power during CSR. The second manuscript looked at sleep spindle activity, finding a trend towards a decrease in slow spindle density during CSR across groups, suggesting a homeostatic response to the decreased sleep opportunity. There were no group differences in spindle activity; however, higher hyperactivity across groups was related to faster mean frequency of fast spindles. While sleep did not differ between TD children and children with ADHD, there was evidence that children with ADHD experienced impairment in their homeostatic response to sleep loss. As there were no changes in SWA and only minor changes in sleep spindles, it is likely that the manipulation protocol was too mild to cause the expected homeostatic changes.

List of Abbreviations Used

ADHD = attention-deficit/hyperactivity disorder

CSR = cumulative sleep restriction

EEG = electroencephalography

ECG = electrocardiogram

EMG = electromyogram

EOG = electrooculogram

FFT = fast-Fourier transformation

IQ = intelligence quotient

M = mean

MSLT = multiple sleep latency test

N; n = sample size

NDD = neurodevelopmental disorder

PSG = polysomnography

SD = standard deviation

SE = sleep efficiency

SOL = sleep onset latency

TD = typically developing

TIB = time in bed

TST = total sleep time

WASO = wake after sleep onset

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Chapter 1: Introduction

It is generally recognized that sleep is an important contributor to overall health and well-being, especially early in life when children's brains are actively developing and sleep is deeper and constitutes a greater proportion of each day (Beebe, 2011; Carskadon & Dement, 2011). There is also an interplay between sleep and cognitive development and several parallels between changes in sleep and changes in brain maturation during this time (Barone, Hawks-Mayer, & Lipton, 2019). While there is a large body of research investigating the impact of inadequate sleep on adults (e.g., Landolt, Sousek, & Holst, 2014), the impact of sleep loss on children has been relatively understudied. From experimental sleep manipulation studies of adults, it is known that acute sleep restriction or total sleep deprivation (much of the night or a full night of no sleep) and chronic sleep restriction (CSR, milder sleep loss over multiple nights) are related to impairment in sustained attention and psychomotor vigilance, an increase in negative mood states, diminished executive functioning and decision-making ability, metabolic changes, and a weakened immune response, among other outcomes (Landolt et al., 2014). Due to differences in sleep need and physiology between children and adults and the limited relevance of severe sleep restriction often used in adult studies, it is important to consider how a chronic but milder degree of sleep loss may impact children (Beebe, 2011). This is especially important given the relationship between sleep and brain development during this time and in light of a decrease in children's sleep duration by about one hour per night over the past century (Matricciani, Olds, &Petkov, 2012).

In the following dissertation I will present the results of two investigations derived from a larger study which used a CSR protocol to experimentally reduce sleep

opportunity in a sample of typically-developing (TD) children and children with attention-deficit/hyperactivity disorder (ADHD; a clinical population with a high proportion of reported sleep problems, Weiss, Craig, Davies, Schibuk, & Stein, 2015). Specifically, these investigations are limited to school-age children (6 to 12 years old) given that sleep need and physiology vary greatly throughout early development and the existing literature is particularly limited for this age range. Prior to presenting the results of these two studies it is first necessary to provide information regarding the measurement of sleep, the basic physiology of sleep, and a broad overview of the physiological regulation of sleep. As much of this information is derived from studies of healthy adults, I have included a subsection which details developmental changes in sleep physiology. I then move into a brief review of the existing literature on correlational and experimental sleep loss in children. Finally, I will provide an overview of what is known about sleep in children with ADHD in comparison to sleep in TD children. I will conclude this chapter by summarizing the rationale for, and outlining the three main objectives of, this dissertation.

The Measurement and Physiology of Sleep

Measurement of sleep. There are a number of measures that are used by both clinicians and researchers to quantify sleep (Landis, 2002). These include both subjective measures (including self-report measures such as sleep diaries and questionnaires) and objective measures (including observations and recordings of body movements, such as with actigraphy, and physiological measures like polysomnography). These measures vary with regard to their cost, level of invasiveness, ease of use (especially over an extended period of time), and the information they provide. Generally, multiple measures

of sleep are employed in both research and clinical settings to provide a comprehensive picture of an individual's sleep physiology as well as their sleep practices and sleep history (Landis, 2002).

One of the most basic and non-invasive methods of measuring sleep in a research context is using subjective self-report measures such as sleep diaries (Landis, 2002). Sleep diaries are completed retrospectively after waking. Individuals are typically asked to record elements of their sleep such as their bedtime, wake time, and how long they believe they took to fall asleep. Sleep diaries are limited by the fact that they are often not completed in real-time (limiting their accuracy) and their reliance on individuals' self-report which means they can be impacted by individuals' inaccurate recall of their sleep (this may be especially true when measuring variables such as the time it took to fall asleep or the number of times an individual woke up throughout the night). In studies of children, sleep diaries are typically completed by caregivers which further impacts their accuracy. However, a benefit of sleep diaries is their ease of use, which makes them an ideal measure to monitor sleep over long periods of time, such as weeks or months. Questionnaires may also be used to gather information on individuals' general sleep patterns. Again, in studies of children, such measures would typically be completed by caregivers.

Actigraphy is a more objective measure and is commonly used to record body movement (or the absence of movement) during sleep (Landis, 2002). Actigraphy uses an actigraph – a small device similar to a watch that is worn on the non-dominant wrist – to measure the frequency of body movements. Periods of sleep correspond with periods of limited movement. Actigraphy is also useful in measuring sleep over long periods of time

and can be easily used in individuals' home environments. Sleep diaries are typically used in conjunction with actigraphy to verify individuals' sleep and wake times. Sleep diaries and actigraphy have been shown to be reliable measures of sleep and wake patterns, both when compared to each other (Usui et al., 1998, 1999; Werner, Molinari, Guyer, & Jenni, 2008) as well as when compared to polysomnography (PSG) which is considered the gold standard of sleep measurement (Rogers, Caruso, & Aldrich, 1993; Sadeh, 2011).

PSG is the most objective measure of sleep and provides information on the physiology of brain and body activity (Landis, 2002). PSG consists of electroencephalography (EEG) which is the measurement of brain waves during sleep, an electrooculogram (EOG) which measures eye movements, electromyogram (EMG) which measures chin and leg muscle movements, and electrocardiogram (ECG) which measures heart rate (Landis, 2002; Malhotra & Avidan, 2014). Measurement of respiration may include (but is not limited to) chest and abdominal bands which record motion effort, nasal airflow measured by an oronasal thermistor, and oxygen saturation measured by pulse oximetry using a finger probe. The organization of sleep (referred to as sleep architecture) is defined by a combination of brainwaves, eye movements, and muscle tone. While PSG is the most objective measure of sleep, it is costly and resource-intensive and typically requires individuals to sleep in a laboratory environment. PSG is therefore not an ideal measure for monitoring sleep within the home environment or over an extended period of time. When PSG is recorded in the laboratory sleep recordings are also subject to "first night" or "adaptation" effects leading to atypical sleep due to the fact

that individuals are in an unfamiliar environment (Bessey, Richards, & Corkum, 2013). Thus, researchers need to take this into account when designing studies using PSG.

Sleep architecture and sleep parameters. Human sleep, as measured by PSG, is comprised of rapid eye movement (REM) and non-REM (NREM) sleep (Carskadon & Dement, 2011). Within REM and NREM, there are various stages of sleep, each of which are characterized by variations in the frequency, amplitude, and morphology of the EEG signal (Carskadon & Dement, 2011; Fuller et al., 2006). Typically, sleep begins with NREM and progresses from lighter to deeper stages of sleep – these stages were previously referred to as stages 1, 2, 3, and 4 but are now referred to as N1, N2, and N3 (previously stages 3 and 4) (Carskadon & Dement, 2011; Malhotra & Avidan, 2014). N1 (sometimes referred to as "transitional" or "light" sleep) is predominated by low-voltage, fast frequency EEG (Malhotra & Avidan, 2014). During this stage, individuals exhibit minimal to no body movement, their breathing becomes shallow, and their eyes begin to roll slowly. They may experience drifting thoughts and are easily awakened. N2 (sometimes referred to as "sigma", "spindle" or "intermediate" sleep) constitutes up to 50 percent of the sleep recording in healthy adults. It is predominated by EEG activity within the theta range (4 to 7 Hz) and is defined by the appearance of K complexes (brief, episodic, and sharp slow waves characterized by a sharp negative peak followed by a slower positive peak) and sleep spindles (brief, episodic bursts of sigma – 11 to 16 Hz – activity). Research has suggested that both sleep spindles and K complexes play a role in the protection and preservation of sleep (e.g., Cote, Epps, & Campbell, 2000; Forget, Morin, & Bastien, 2011). N3 (sometimes referred to as "deep", "slow wave", or "delta" sleep) is predominated by high amplitude slow wave activity (SWA; refers to EEG

activity in the delta band, which is between 0.5 and 4 Hz) and is considered the deepest and most restorative stage of sleep. REM sleep (sometimes referred to as "R", "paradoxical", or "active" sleep) usually begins after 80 minutes of NREM in healthy adults. REM is characterized by low amplitude, mixed frequency EEG. During this stage, the EOG shows bursts of eye movements and there is low muscle tone evident from the EMG signal. REM and NREM sleep cycle throughout the night with cycles typically lasting about 90 to 110 minutes (Carskadon & Dement, 2011). Using PSG, researchers and clinicians are able to derive several variables which can be used to describe an individual's sleep (Landis, 2002). These variables, along with the defining characteristics of each sleep stage, are listed and summarized in Table 1.1.

Developmental changes in sleep physiology. Sleep physiology changes throughout the lifespan, with age being one of the most important variables impacting sleep architecture (Carskadon & Dement, 2011). In newborns, sleep begins with REM (called *active* sleep at this stage) and progresses through cycles of REM-NREM (called *quiet* sleep) more quickly (around 50 minutes). At this age, REM sleep comprises about 50 percent of the sleep period and there is no SWA. Within the first two years of life, REM sleep declines (to about 20 to 25 percent of the sleep period) and slow waves emerge. While the proportion of REM sleep then remains fairly constant throughout the lifespan, the proportion of deeper or "slow wave" sleep (N3) is greatest in early childhood and decreases with age, by about 40 percent in adolescence. In a study which established normative values of PSG variables in 209 children and adolescents between 1 and 18 years of age, Scholle et al. (2011) found significant changes in sleep architecture and various sleep parameters over time. The authors noted an increase in REM latency,

sleep efficiency (SE), N2, cycle duration, and number of stage shifts, and a decrease in total sleep time (TST), wake after sleep onset (WASO), N3, REM, movement, and number of sleep cycles with age. Only sleep onset latency (SOL) and N1 did not differ by age. In children between 6 and 11 years of age (including pubertal development of Tanner stage 1) the mean TST was 512.2 minutes (SD = 61.7), WASO was 5.1 minutes (SD = 5.2), SOL was 21.8 minutes (SD = 23.5), and SE was 94.8 percent (SD = 5.2). The percentage of time spent in each sleep stage was as follows: N1 6.7 percent (SD = 2.8), N2 38.6 percent (SD = 6.8), N3 31.9 percent (SD = 6.7) and REM 21.1 percent (3.7). In children between 9 to 13 years of age (Tanner stage 2) the mean TST was 478.6 minutes (SD = 53.7), WASO was 5.2 minutes (SD = 4.9), SOL was 20.4 minutes (19.6), and SE was 94.9 percent (SD = 5.2) The percentage of time spent in each sleep stage was as follows: N1 6.9 percent (SD = 4.1), N2 42.6 percent (SD = 5.0), N3 28.9 percent (SD = 5.2), and REM 20.3 percent (SD = 4.5). The importance of understanding sleep within a developmental context is underscored by research suggesting an active contribution of sleep to synaptic maturation with correlational studies pointing to negative developmental consequences following from inadequate sleep (Barone et al., 2019).

Physiological regulation of sleep. Much of the literature on the physiological regulation of sleep in humans focuses on adults. From this literature we know that sleep and wake are regulated by a combination of physiological processes (Achermann & Borbély, 2011). First, a homeostatic process – referred to as process S – regulates sleep based on the duration of prior sleep and waking. Second, a circadian process – referred to as process C – regulates sleep independent of sleep and wake history. In mammals, the circadian rhythm of the sleep-wake cycle is established by the circadian clock in the

suprachiasmatic nucleus which is entrained by the light-dark cycle (Fuller, Gooley, & Saper, 2006). Finally, an ultradian process functions during sleep to regulate the cycling of NREM and REM (Achermann & Borbély, 2011). Ultradian rhythms are impacted by sleep and wake history, as well as by variations in neuroendocrine activity and the autonomic nervous system (Achermann & Borbély, 2011; Gronfier, Simon, Piquard, Ehrhart, & Brandenberger, 1999).

When the duration of sleep is curtailed to a large enough degree, compensatory mechanisms will alter sleep architecture and sleep parameters to make up for this change. The mechanisms that are primarily responsible for regulating sleep following deviation from the normal duration are homeostatic in nature. Homeostatic processes increase or decrease sleep propensity. At a basic level, this typically means that when wake is extended, SOL is shorter and WASO is reduced during the next sleep opportunity (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981; Durmer & Dinges, 2005). The intensity or depth of sleep is also regulated by sleep homeostasis and is characterized by the duration of N3 and the predominance of SWA in the EEG (Achermann & Borbély, 2011). SWA, as mentioned above, refers to EEG activity in the delta band, which is between 0.5 and 4 Hz. Research has consistently shown that when sleep duration is reduced in adults, either through acute sleep restriction or total sleep deprivation, there is an increase in the duration of N3 during recovery sleep (or a maintenance of N3 during sleep restriction with a reduction in other stages of sleep). There is also an increase in SWA, the extent of which has been shown to be related to the duration of wake prior to the sleep opportunity (Achermann & Borbély, 2011; Webb & Agnew, 1971). REM sleep in contrast is not prioritized to the same degree as N3; when sleep duration is reduced in

adults, a rebound in REM occurs when N3 pressure has dissipated or when N3 pressure has not been built up to the same degree. While changes in SWA are primarily regulated by homeostatic processes, changes in the duration of REM sleep are impacted by a combination of homeostatic and circadian factors (Achermann & Borbély, 2011; Czeisler, Zimmerman, Ronda, Moore-Ede, & Weitzman, 1980).

With regard to ultradian processes, the development of slow waves is impacted, in part, by the duration of prior wakefulness (Achermann & Borbély, 2011). SWA is present in the highest proportion during the first sleep cycle of the night and declines as the sleep period continues. There is a steeper increase in SWA following prolonged wakefulness, with the rise rate decreasing over the first three sleep cycles (Achermann & Borbély, 2011). The development of slow waves is also impacted by low adrenocorticotropic activity and decreased sympathetic nervous system activity, meaning that the development of slow waves begins when cortisol secretion decreases and there is a decrease in the low-frequency/high-frequency ratio of heart rate variability (Gronfier et al., 1999).

Sleep Loss in Children

As mentioned previously, the majority of data on the physiological regulation of sleep are derived from studies of adults. There is a great deal of research in this area which contributes to an understanding of how sleep physiology changes in response to extended wakefulness and points to a range of negative consequences following from the same. However, these findings cannot be extrapolated to children (Beebe, 2011). Beebe (2011) outlines the importance of considering a developmental context when discussing the impact of insufficient sleep on children. During childhood, neural development is

impacted by genetic and environmental factors, and chronic inadequate sleep can be thought of as a form of exposure to an environmental stressor that negatively impacts the development of normal cognitive, behavioural, and emotional functioning. Beebe highlights that childhood and adolescence are periods wherein key functional skills are developed; therefore, inadequate sleep may impact children's ability to learn and develop these skills leading to disruptions in maturation.

Correlational research with epidemiological samples has pointed to a relationship between children's sleep and daytime sleepiness as well as between sleep and academic performance (Beebe, 2011). Importantly, the relationship between sleep and academic performance appears to be strongest for younger children, with studies that had a greater proportion of boys also noting larger effects. Correlational research in children has also revealed a relationship between poor sleep and daytime consequences such as impaired attention and impulse control, difficulty regulating behaviour (e.g., hyperactivity, conduct problems), depression, and cognitive impairment (Beebe, 2011; O'Brien, 2011). While these studies provide important and clinically-relevant information, as correlational studies do not allow for definitive causal inference, it is also necessary to conduct experimental studies of the impact of inadequate sleep in childhood.

To date, there are 12 known studies that have experimentally investigated the effects of sleep restriction on school-age children specifically (Carskadon, Harvey, & Dement, 1981; Davidson et al., under review; Fallone, Acebo, Seifer, & Carskadon, 2005; Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Gruber et al., 2011; Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012; Kurth et al., 2016; Molfese et al., 2013; Peters et al., 2009; Randazzo, Muehlbach, Schweitzer, & Walsh, 1998; Sadeh, Gruber, & Raviv,

2003; Vriend et al., 2013). These studies have used a variety of sleep restriction (and extension) protocols and have focused on a number of outcomes including physiological, behavioural, and cognitive measures. These studies have used either a within- or between-subjects design to determine the impact of sleep restriction, with most focusing on effects for TD children (one study by Gruber et al., 2011 used a mixed design to determine the impact of cumulative sleep restriction on both TD children and children with ADHD). Overall, these studies have found that restricting sleep in school-age children leads to impaired attention (e.g., slower response times and more lapses during a sustained attention task), impaired academic performance, increased sleepiness (both subjective and objective), poorer emotion regulation, poorer neurocognitive functioning (e.g., impairments in higher cognitive functions such as verbal creativity and abstract thinking), reduced alertness, and impaired working memory. There are some inconsistencies among these studies, specifically with regard to restlessness and impulsivity; where some researchers have found no changes in hyperactivity, impulsivity, or response inhibition ability in response to sleep restriction (Fallone et al., 2001, 2005) other researchers have found that sleep restriction led to a greater degree of restless-impulsive behaviour while extension of sleep led to an improvement in such behaviours (Gruber et al., 2012). These studies form the ground work for future research in this area and more work is needed to confidently answer important questions. Specifically, only two of the aforementioned studies considered changes in sleep physiology following from sleep loss. Such studies are essential to an understanding of how the sleep regulation processes described previously may differ during childhood, a period of time

when sleep duration is longer and slow waves predominate a greater proportion of the night.

Sleep in Children with ADHD

Given that inadequate sleep has been shown to lead to negative consequences in TD children, it is important to consider the impact of poor sleep on children for which sleep is already problematic. One clinical population in which sleep is frequently impacted is attention-deficit/hyperactivity disorder (ADHD), a common neurodevelopmental disorder (NDD) in childhood affecting up to five percent of children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The rates of sleep problems among children with ADHD vary across studies as a function of demographics and the use of objective versus subjective sleep measures (Weiss et al., 2015); estimates of the proportion of children with ADHD for which sleep is problematic range from 25 to 50 percent (Owens, 2005) with some research pointing to sleep problems in up to 70 percent of cases (Weiss et al., 2015). These sleep problems may include difficulty falling asleep and staying asleep and can lead to significantly shortened sleep duration (Owens, 2005). As previously mentioned, research on the effects of sleep loss in children have pointed to an impairment in several cognitive functions which are known to involve the prefrontal cortex (e.g., working memory). Given that executive functions (such as working memory) are impaired in children with ADHD, the relationship between sleep and ADHD would seem to be bidirectional, with sleep problems leading to and/or exacerbating symptoms of ADHD, and behavioural symptoms leading to and/or exacerbating sleep problems (Weiss et al., 2015). Sleep loss is also known to impact mood and therefore symptoms such as irritability may be amplified by sleep problems in

children with ADHD. Additionally, epidemiological research suggests that sleep duration is actually predictive of the development of an ADHD diagnosis (Scott et al., 2013).

Importantly, the impact of sleep problems on children with ADHD may be more problematic than for children without ADHD who are more likely to experience transient issues with sleep (Gruber et al., 2011). For example, Gruber et al. (2011) conducted an experimental CSR study using TD children and children with ADHD and found that, while CSR led to deterioration of neurobehavioural functioning in both groups of children, the functioning of children with ADHD was reduced from a subclinical to clinical level. Therefore, not only is it the case that shortened sleep duration and difficulties with sleep may be related to the development of ADHD or related symptoms (Lundahl et al., 2015; Paavonen et al., 2009; Scott et al., 2013), for children who do meet diagnostic criteria for ADHD, shortened sleep duration seems to lead to more serious consequences when compared to TD children (Kirov & Brand, 2014). With regard to the specific ways in which sleep differs between TD children and children with ADHD, the most consistent findings come from parental reports and include a greater degree of restless sleep, difficulty falling and staying asleep, and shortened sleep duration compared to TD children (Owens, 2005). More objective studies of sleep which used actigraphy also noted differences in sleep in children with ADHD. For example, Gruber, Sadeh, & Raviv (2000) found a greater degree of night-to-night variability in the sleep patterns of these children.

In looking at what may underlie the differences in sleep between these two populations at a physiological level, several studies have investigated sleep in children with ADHD using PSG. Corkum and Coulombe (2013) conducted a review of reviews

within the literature looking at sleep problems in children with ADHD. Overall, the authors noted that the most consistent results across systematic reviews were increased parent-reported sleep problems and more nocturnal movement/periodic limb movements in children with ADHD. Despite this, the sleep architecture of children with ADHD did not show any consistent differences to that of TD children. Corkum and Coulombe also made note of the many confounding variables which impacted group differences, such as age, sex, comorbidity, ADHD subtype/presentation, medication use, diagnostic procedures, and sleep laboratory adaptation. Following from this review of reviews, Speth, Benoit, and Corkum (2014) conducted a study which rigorously controlled for confounding variables by age- and sex-matching TD children and children with ADHD, using children with ADHD who were medication-naïve and who did not have any comorbid psychiatric conditions, and comparing children with different subtypes/presentations of ADHD. In line with previous findings, these authors concluded that there was no specific sleep architecture profile in children with ADHD. They did note that children with ADHD had a longer SOL than TD children. Their results did not differ based on subtype/presentation of ADHD. Overall, research to date has failed to provide an objective, physiological explanation for subjective differences in sleep problems between TD children and children with ADHD. However, the failure to find objective differences in sleep between groups is likely not due to the fact that such differences do not exist, but more likely due to the inadequacy of the methods used to measure them (Weiss et al., 2015). To date, the majority of studies looking at objective differences in sleep have examined sleep architecture which only considers possible differences at a macro-level of analysis while relatively few studies have looked at sleep

physiology at a micro-level (e.g., power spectrum of sleep EEG). Owens (2006) therefore highlights the need for a continued study of sleep in children with ADHD using more detailed analyses.

Rationale and Objectives of the Current Dissertation

Rationale. Despite the large body of research investigating the impact of sleep loss on adults, far fewer studies of experimental sleep loss have been conducted with school-age children. Of the existing studies, only two have considered the impact of sleep loss on sleep physiology. As sleep physiology is qualitatively and quantitatively different in school-age children as compared to adolescents and adults, it is important to develop an understanding of how sleep changes in response to reduced sleep opportunities within this specific age group. Furthering the research literature in this area is especially important when one considers the active brain development that occurs during childhood and the interplay between sleep and cognitive development during this time. Interestingly, many of the consequences following from reduced sleep duration in children seem to mimic symptoms of ADHD and a high proportion of children diagnosed with ADHD experience sleep problems. Given the relationship between sleep and ADHD, it is important to not only establish what physiological differences might underlie these sleep problems but also determine how children with ADHD might uniquely respond to a reduced sleep opportunity.

Objectives. The following dissertation has three main objectives. (1) First, within this dissertation I investigate the impact of experimentally restricted sleep in a sample of healthy school-age children. Specifically, I am concerned with the impact of CSR of one hour less time in bed (TIB) per night for six nights on sleep physiology. I will determine

whether this degree of CSR leads to homeostatic changes in sleep at the level of sleep architecture, the power spectrum of sleep (e.g., SWA), and sleep spindles. Given that childhood is an important period of brain and functional development, it is essential to understand whether and how children's brains adapt to restricted sleep. (2) Second, I aim to investigate potential physiological differences in sleep between TD children and children with ADHD at the level of sleep architecture, the power spectrum of sleep, and sleep spindles, using a sample of rigorously diagnosed, medication-naïve, age- and sex-matched children with ADHD. (3) The third and final objective of this dissertation is to determine whether children with ADHD have the same homeostatic response to CSR compared to their TD peers at the level of sleep physiology. Given that previous studies have failed to find consistent differences in sleep architecture yet report that children with ADHD have more movement during sleep (Corkum & Coulombe, 2013) and take longer to fall asleep (Speth et al., 2014), it is possible that these children do not experience the same homeostatic drive which regulates processes such as the onset to sleep and changes in sleep architecture in response to inadequate sleep. As parent reports suggest that children with ADHD have more problems with sleep under normal conditions, it is also conceivable that they would be more severely impacted by CSR than TD children. This dissertation is derived from a larger study which investigated the impact of CSR in school-age TD children and children with ADHD (CIHR grant 44586).

In the following chapters I will present the findings of three different analyses conducted using PSG recorded during the sleep manipulation. Chapter 2 will look at sleep architecture and the power spectrum of sleep EEG and Chapter 3 will look at sleep spindles in N2 sleep. Chapter 4 will provide an overview of findings, discuss broad

theoretical and methodological concerns related to this field of research, discuss our findings within the context of the broader literature on sleep in children with ADHD, review the strengths and limitations of this dissertation, discuss the clinical implications of the findings, and provide suggestions for future research that should be conducted moving forward.

Table 1.1

Summary and Definitions of Sleep Stages and Sleep Parameters

Sleep Stages	
N1 Sleep (previously called Stage 1)	Sometimes referred to as "transitional" or "light" sleep; predominated by low-voltage, fast frequency EEG; during this stage there is minimal to no body movement, breathing is shallow and eye movements are defined by a rolling pattern; individuals may experience drifting thoughts and are easily awakened.
N2 Sleep (previously called Stage 2)	Sometimes referred to as "sigma", "spindle", or "intermediate" sleep; constitutes up to 50 percent of the sleep recording in healthy adults; predominated by EEG activity within theta range (4 to 7 Hz); defined by appearance of K complexes and sleep spindles.
N3 Sleep (previously Stages 3 and 4)	Sometimes referred to as "deep", "slow wave", or "delta" sleep; predominated by high amplitude slow waves; considered the deepest and most restorative stage of sleep.
REM Sleep	Sometimes referred to as "R", "paradoxical", or "active" sleep; characterized by low amplitude, mixed frequency EEG, eye movements, and low muscle tone.
Sleep Parameters	
Time in Bed (TIB)	The time between lights out (when the individual goes to bed) and lights on (when the individual wakes up or is woken up and gets out of bed).
Sleep Onset Latency (SOL)	The amount of time an individual takes to fall asleep after lights out; typically measured from lights out to the first instance of sleep (either N1 or N2).
Wake After Sleep Onset (WASO)	The amount of time an individual spends awake after they initially fall asleep.
Total Sleep Time (TST)	The amount of time an individual spends in any of the sleep stages during the night, not including WASO.
Sleep Efficiency (SE)	The ratio of TST to TIB, calculated as a percentage.

Chapter 2: Sleep Architecture and Power Spectrum of EEG Following Cumulative Sleep Restriction: A Comparison between Typically-Developing Children and Children with ADHD

This investigation is derived from a larger study broadly investigating the effects of sleep restriction on daytime functioning in children (CIHR grant 44586). The following manuscript describes and discusses the analyses of participants' sleep physiology during CSR. These analyses are focused on sleep architecture and the power spectrum of sleep EEG and compare results between TD children and children with ADHD. Readers are advised that Ms. Tamara Speth, under the supervision of Dr. Penny Corkum, was responsible for reviewing extant literature and formulating the research questions; training and supervising research staff; completing and overseeing data collection; processing data and completing statistical analyses; and all aspects of the writing process. Ms. Speth obtained a travel grant from the Canadian Sleep and Circadian Network to support the cost of travel to Brock University for the purpose of learning, under the supervision of Dr. Kimberly Cote, the data processing methods described in this manuscript. In addition to the above-noted support, Ms. Speth completed this research in consultation with her dissertation committee members (Dr. Benjamin Rusak and Dr. Tara Perrot) from whom she also received editorial feedback. At this time, the following manuscript has not yet been submitted for publication.

Abstract

Background: There are no studies have looked at the effects of cumulative sleep restriction (CSR) on sleep architecture or the power spectrum of sleep electroencephalography (EEG) in school-age children. The current study investigated these measures during CSR in typically-developing (TD) school-age (6 to 12 years old) children and children with attention-deficit/hyperactivity disorder (ADHD).

Method: Participants were 18 TD children and 18 age- and sex-matched children with ADHD. Participants completed a sleep restriction protocol which included a two-week baseline, a Typical condition (six nights of sleep based on baseline sleep schedules), and a Restricted condition (six nights of average baseline time in bed [TIB] reduced by one hour). Polysomnography was recorded in the laboratory at the end of each condition.

Results: Children with ADHD took longer to reach N3, had more WASO and (within the first 5.1 hours of the night) and had more REM sleep than TD children, regardless of condition. Across groups, participants had less REM sleep during CSR (during the full night and the first 5.1 hours). Trends suggested that additional changes in sleep architecture during CSR varied by group, with a longer duration of lighter stages of sleep (N1, N2) in children with ADHD. No significant differences in the power spectrum of sleep EEG were found between groups or conditions.

Conclusions and Implications: One hour of reduced TIB per night for six nights impacts some physiological aspects of sleep but may not be sufficient to cause changes in the power spectrum of sleep EEG. Group by condition interactions suggest that the homeostatic processes in children with ADHD may be impaired during sleep loss compared to their TD peers.

Introduction

Background

In an increasingly fast-paced and technologically-driven world, both children and adults are getting less sleep than ever before. Among children, there has been a decline in sleep duration of approximately one hour per night over the past century (Matricciani, Olds, & Petkov, 2012). While the recommended sleep duration for children between 6 and 13 years of age is 9 to 11 hours per night (Hirshkowitz et al. 2015), data from the 2014 National Sleep Foundation's Sleep in America poll indicate that 61 percent of 6- to 12-year-old children are getting less than 10 hours of sleep on non-school nights while 74 percent are getting less than 10 hours of sleep on school nights (National Sleep Foundation, 2014). The implications of this decline in sleep duration are especially troubling when one considers that sleep in childhood plays a critical role in neurodevelopment, learning, and the development of key functional skills (Beebe, 2011). Particularly during childhood, chronic inadequate sleep can be conceptualized as a form of chronic stress that may be related to a range of neural, emotional, physical, and behavioural issues (Beebe, 2011; Chen, Beydoun, & Wang, 2012; Shochat, Cohen-Zion, & Tzischinsky, 2013).

At present, there is a large body of research on the impact of sleep loss in adults and a growing body of research in children, both pointing to a range of negative consequences. Correlational studies with children have found a relationship between inadequate sleep and daytime sleepiness, difficulties with attention, impulse control and behavioural regulation, and impairments in cognitive functioning and academic performance (Beebe, 2011). There are only 12 experimental studies of sleep restriction in

school-age children (Carskadon, Harvey, & Dement, 1981; Davidson et al., under review; Fallone, Acebo, Seifer, & Carskadon, 2005; Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Gruber et al., 2011; Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012; Kurth et al., 2016; Molfese et al., 2013; Peters et al., 2009; Randazzo, Muehlbach, Schweitzer, & Walsh, 1998; Sadeh, Gruber, & Raviv, 2003; Vriend et al., 2013). While there are inconsistencies, these studies have generally found that sleep loss leads to impaired attention, increased restlessness and impulsivity, impaired academic performance, increased sleepiness (both subjective and objective), poorer emotion regulation, poorer neurocognitive functioning, and reduced alertness, relative to a baseline habitual or imposed 10- or 11-hour time in bed (TIB). The impacts within this population are similar to those documented in the more extensive adult literature (e.g., Banks & Dinges, 2007). These studies are important as they allow for inference of causation; however, additional research is needed to corroborate and expand on these findings.

One area in which research is especially limited is that of the physiological effects of sleep restriction. Given that childhood represents a sensitive period of neural development, it is important to understand the ways in which children's brains adapt (or fail to adapt) to shortened sleep opportunities. Typically, studies looking at the effects of sleep loss on sleep physiology (e.g., sleep architecture, the power spectrum of sleep EEG) have taken two forms – acute sleep restriction or deprivation (much of the night or a full night of no sleep) and chronic sleep restriction (CSR, milder sleep loss over multiple nights). In children, CSR represents a more real-world form of sleep loss (Beebe, 2011). Research on the impact of CSR on sleep physiology in adults is plentiful and points to a

homeostatic response of sleep architecture (i.e., the pattern of sleep stages). This response typically takes the form of a preservation of N3 and a corresponding decrease in other stages of sleep such as N2 and REM (Banks & Dinges, 2007). Studies in this area have also shown that changes in sleep are not adequately captured by sleep architecture alone, with authors noting a dynamic increase in slow wave activity (SWA, activity in the delta band between 0.5 and 4 Hz) across all NREM stages. Some studies suggest that this increase may extend beyond the traditional delta band to include an increase in theta power (Åkerstedt, Kecklund, Ingre, Lekander, & Axelsson, 2009).

To date, three studies have examined the effects of experimental sleep loss on sleep physiology in adolescents (Agostini, Carskadon, Dorrian, Coussens, & Short, 2016; Ong et al., 2016, 2017). In these studies, participants were restricted to five hours TIB for five (Agostini et al., 2016; Ong et al., 2017) or seven (Ong et al., 2016) nights. All three studies noted a reduction in sleep onset latency (SOL) and wake after sleep onset (WASO), and two (Agostini et al., 2016; Ong et al., 2016) found an increase in sleep efficiency (SE), suggesting an increase in sleep propensity due to the reduced sleep opportunity. There was a decrease in total sleep time (TST) as would be expected given the reduced sleep opportunity (Ong et al., 2016, 2017); however, it was noted by Ong et al. (2017) that TST increased across progressive nights of restriction (in line with the reduction in WASO and increased SE) and that SOL progressively decreased (suggesting an accumulation of sleep debt). All three studies also consistently noted a reduction in N1, N2, and REM sleep, with an increase in N3 during particular nights of the restriction protocol (there was no significance difference in the average duration of N3 across nights

compared to baseline). Ong et al. (2016) also found a reduced REM latency across nights during restriction.

Additionally, Ong et al. (2016) looked at the first 5 hours of sleep only (the longest common sleep duration across participants and conditions), as comparing a common temporal window may reveal changes in sleep homeostasis that would otherwise be undetected (this procedure has also been used in adult studies of CSR, e.g., Åkerstedt et al., 2009). They noted a reduction in the duration of N1 (similar to what was found when looking at the full night) and also found an increase in REM and N3 relative to baseline. When Ong et al. looked at changes in SWA from baseline, they found that there was an increase in mean SWA across the full night. However, when SWA during the first 5 hours of the night was compared between CSR and baseline nights, mean SWA was maintained throughout the manipulation period. Therefore, Ong et al. found that changes in sleep architecture were more apparent when comparing common sleep durations and that homeostatic changes in sleep were not fully reflected in sleep architecture alone.

There are currently no known studies that have investigated the effects of CSR in school-age (6-12-year-old) children on sleep architecture or the power spectrum of sleep EEG. Studies in this area have been limited to acute sleep restriction (Carskadon et al., 1981; Kurth et al., 2016). An early study by Carskadon et al. (1981) with children between 11 and 13 years of age looked at the effects of a single night of sleep restriction on subsequent nocturnal sleep patterns, finding similar results to adult studies with a preservation of slow wave stage 4 (now combined with stage 3, and referred to as N3) and a corresponding reduction in stages 1 (now N1), 2 (now N2), 3, and REM. They also

saw a decrease in SOL and latency to stage 4, and no arousals during sleep. They did not find a decrease in REM latency but there was a trend in this direction. A more recent study by Kurth et al. (2016) also looked at how children's brains responded to acute sleep restriction (one night of half their usual sleep duration). These authors did not look at changes in sleep architecture but found that acute sleep restriction altered myelination in the brain and noted an increase in SWA localized to the parieto-occipital region.

Finally, given that all of the aforementioned studies were conducted with healthy children, it is important to consider whether the effects of sleep loss would be greater in children for whom sleep is already problematic. Attention-deficit/hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder (NDD) which is known to be related to sleep problems in up to 70 percent of children who are diagnosed (Weiss, Craig, Davies, Schibuk, & Stein, 2015). The most consistent findings of sleep complaints in children with ADHD come from parent reports (Owens, 2005) while studies using actigraphy have found a greater degree of variability in night-to-night TST and SOL in children with ADHD (Gruber, Sadeh, & Raviv, 2000). In contrast, studies using polysomnography (PSG) have not found consistent differences in sleep between the two populations (Corkum & Coulombe, 2013; Speth, Benoit, & Corkum, 2014). Given the lack of consistent objective differences in sleep, it is possible that differences can be found using a finer grain analysis, such as an examination of the power spectrum of sleep EEG. Findings of baseline differences in the power spectrum of sleep EEG between TD children and children with ADHD are mixed, with some studies finding more SWA in central regions of the brain in children with ADHD (Ringli et al., 2013) and others finding no differences between the two groups (Prehn-Kristensen et al., 2011, 2013).

Rationale

The aforementioned research indicates that there can be a range of pervasive negative effects as a result of sleep loss in school-age children, yet there are currently no published studies that have investigated physiological sleep processes during CSR in this population. Based on the findings presented above, the current study investigated changes in sleep architecture and the power spectrum of sleep EEG as a result of CSR in a sample of school-age children. Looking at CSR (versus acute sleep restriction) is particularly relevant, as the former reflects a more typical pattern of sleep loss among children (Beebe, 2011). Furthermore, the current study compared physiological sleep processes during CSR between TD children and children with ADHD, a common NDD in children that is known to be related to high levels of sleep problems (Weiss et al., 2015). The current investigation is derived from a larger study which investigated the impact of CSR in school-age children on a variety of outcome measures (CIHR grant 44586). The larger study utilized a seven-week repeated-measures protocol which included a two-week baseline period, six nights of typical sleep (based on participants' baseline sleep schedules) and six nights of restricted sleep (wherein TIB was reduced by one hour each night relative to participants' average baseline sleep schedules). There was a one-week break following the baseline period, and Typical and Restricted conditions were counterbalanced and separated by a two-week recovery period.

Research Goals and Hypotheses

The first goal of the current study was (1) to determine how six nights of CSR (as compared to six nights of prescribed typical sleep based on average baseline sleep duration) impacts physiological sleep processes in school-age children, as measured by

sleep architecture and the power spectrum of sleep EEG with PSG recorded in a controlled laboratory environment. Based on previous findings, we predicted a higher degree of sleep propensity as measured by shorter SOL, less WASO, and higher SE during CSR. We hypothesized that there would be a shorter duration of N1, N2, and REM and a preservation of N3 during CSR. We also hypothesized that REM latency would be shorter during CSR. In looking at the first 5.1 hours of the night (the longest common sleep duration across all recordings, including recordings for TD and ADHD participants during both Typical and Restricted conditions), we expected to see a longer duration of REM and N3 sleep. Regarding the power spectrum of sleep, we predicted a greater amount of mean SWA during CSR when looking at NREM sleep across the entire sleep period and a maintenance of SWA when considering only the first 5.1 hours of the night.

Our second and third goals were (2) to compare sleep between TD children and children with ADHD using the measures indicated above, and (3) to determine whether children with ADHD are more severely impacted by CSR when compared to their TD peers. While no previous studies have examined changes in sleep architecture or the power spectrum of sleep EEG during CSR in children with ADHD, given their pre-existing difficulty with sleep, we predicted that children with ADHD would not experience the same degree of homeostatic response as TD children. As the results of studies looking at differences in the power spectrum of sleep EEG between TD children and children with ADHD have had mixed results with regard to SWA (Prehn-Kristensen et al. 2011, 2013; Ringli et al., 2013), it was not possible to hypothesize whether there would be differences in the current study.

Finally, given the evidence suggesting that the homeostatic response to CSR extends beyond the traditional delta band, the fourth and final goal of the current study was (4) to explore changes in the broader power spectrum during CSR in school-age children (i.e., examination of theta, alpha, sigma, and beta bands) both across and between groups. While these analyses were exploratory, we hypothesized possible differences between Restricted and Typical condition nights characterized by an increase in theta activity (consistent with previous findings in adults, e.g., Åkerstedt et al., 2009).

Method

Participants

TD children were recruited from the community using newsletters, web-based advertisements, and through a research database of past research participants. Children in the ADHD group were recruited from a speciality ADHD clinic, two private practices focusing on NDDs, and through a research ADHD clinic, all of which employed the same diagnostic tools, including semi-structured diagnostic parent and teacher interviews, collection of historical information, rating scales, and a psycho-educational assessment (for details see McGonnell et al., 2009). Given that the DSM-V now specifies presentations of ADHD but no longer categorizes children with ADHD into subtypes, the current study included children across all ADHD presentations. All ADHD participants were medication-naïve for treatment of ADHD or any other psychopathology.

Before the study, potential participants were screened using questionnaires to ensure that they met all inclusion criteria and did not meet any of the general exclusion criteria. Inclusion criteria for both groups were that the children must be between 6 and 12 years of age. For the TD group, children could not have been previously diagnosed

with a mental health disorder, whereas for the ADHD group children were required to meet DSM-V diagnostic criteria for ADHD, to not have any comorbid mental health disorders (with the exception of learning disorders), and to be medication naïve. These criteria were assessed through screening questionnaires for the TD group and a comprehensive clinical diagnostic assessment for the ADHD group. General exclusion criteria for the present study stipulated that participants must not have (1) a chronic and impairing medical illness, (2) a history of neurological impairments, (3) a primary sleep disorder (screened during the baseline PSG night in the laboratory), (4) used medication during the past month that is likely to affect sleep, (5) crossed more than two time zones in the last month, (6) regularly sleep less than 8 hours or more than 12 hours nightly, or (7) developed beyond Tanner stage 2 (based on a parent-completed questionnaire).

A total of 33 TD children and 32 children with ADHD between the ages of 6 and 12 met initial screening criteria. Prior to the start of the baseline period, 1 TD child and 5 children with ADHD withdrew or were excluded by researchers[1]. After enrollment in the baseline period, 2 TD children and 4 children with ADHD withdrew or were excluded from the study[2]. Therefore, 30 TD children and 23 children with ADHD completed the study protocol in its entirety. Of the children that completed all study weeks, 7 TD children and 5 children with ADHD were excluded from the final analysis as they did not

[1] One TD participant withdrew because they found the actigraph uncomfortable; 5 children with ADHD withdrew or were excluded for the following reasons: could not make schedule work, did not attend baseline visit, met exclusion criteria, lost actigraph, sick, or did not give a reason.

[2] Two TD participants were excluded because they met exclusion criteria; children with ADHD withdrew or were excluded for the following reasons: epileptic activity found on the PSG, diagnosis of ADHD could not be confirmed, could not make time commitment, or did not give a reason.

meet the sleep restriction criterion. This criterion required the average difference in TIB during the Restricted condition period and TIB during the Typical condition period as measured by actigraphy to be a minimum of 30 minutes less per night. One additional TD child was excluded from analyses due to the diagnosis of a chronic health disorder following completion of the study.

Participants who met all study criteria were then age- and sex-matched, resulting in a final sample of 36 children (18 in each of the TD and ADHD groups). Consistent with the known higher incidence of ADHD among boys (Arnold, 1996), the final sample included 14 boys and 4 girls in each group. No significant differences between groups were found in participants' age, ethnicity, family composition, parental education, or family income as determined by t-tests and Pearson Chi-Squared tests. A t-test indicated a significant difference in estimated full-scale IQ between groups, with TD children having a higher IQ than children with ADHD, but both groups were in the Average range (see Table 2.1). The study was run across several years throughout the school months (between September and June) with neither group being studied exclusively during any particular time of year.

A reduced sample was used for some analyses, as the EEG data for five participants (two boys with ADHD, two TD boys, one TD girl) included a large amount of artifact that made some analyses impossible to complete, including power spectrum analysis. An additional age-matched girl with ADHD was removed from the analyses to ensure even numbers of participants in each group. Therefore, 15 participants (3 girls) remained in each group for these analyses. Sleep architecture analyses that were carried

out using the first 5.1 hours of sleep (the longest common sleep duration among all recordings not including WASO) were also conducted with the reduced sample.

Procedure

During the baseline period, sleep durations were established for each participant over the course of two weeks, during which time they were asked to wear an actigraph (a wrist-worn accelerometer). Participants' parents were also asked to complete a sleep diary during this time in which they recorded various elements of the child's sleep such as bed time, wake time, and number of awakenings during the night. At the end of this two-week period, participants spent a night in the sleep laboratory and had their sleep recorded using PSG. After a one-week break, participants underwent a sleep manipulation protocol. Relative to baseline sleep patterns, participants were asked to go to bed one hour later nightly for one week (Restricted condition); during another week, their sleep scheduled was assigned based on average baseline sleep and wake times (Typical condition). The order of the Restricted condition and Typical condition was counterbalanced and there was a two-week recovery period between condition periods. Participants were also asked to wear an actigraph throughout each of these condition periods to confirm that they had followed the restriction protocol; adherence was confirmed following participation when actigraphy data were extracted and analyzed. Participants then came into the laboratory for an overnight PSG recording at the end of each of the condition periods, wherein sleep was scheduled according to their condition (i.e., they continued to follow their restriction schedule during the Restricted condition night in the laboratory and their typical sleep schedule during the Typical condition night in the laboratory).

On the day following each PSG assessment in the laboratory, participants underwent four daytime multiple sleep latency tests (MSLTs). During the MSLTs participants had opportunities for 20- to 30-minute naps scheduled 2 hours apart (10:00, 12:00, 14:00, and 16:00). Participants also underwent daytime assessments of cognitive and emotional functioning. Between assessments, participants had free time during which they were able to engage in activities such as reading, playing games, and watching movies. Participants had limited exposure to natural sunlight during their time in the sleep laboratory and they were prohibited from consuming caffeine or products that contain caffeine (e.g., chocolate). Results regarding daytime consequences and MSLTs are reported separately (Corkum et al., in preparation; Davidson et al., under review). Descriptive statistics for actigraphy data are also presented separately (Davidson et al., under review).

Polysomnography. PSG assessments were carried out by trained research assistants. Assessments were conducted with a Sandman® PSG system which recorded four electroencephalogram (EEG) channels (C3, C4, O1, O2), left and right electrooculogram (EOG), two submental electromyogram (EMG) channels, and electrocardiogram (ECG). Leg movements were measured using electrodes placed on the left and right anterior tibialis muscles. Respiratory effort was measured using bands on the chest and abdomen and breathing was measured using an oronasal cannula. Oxygen saturation was measured using a finger-probe pulse oximeter. Snoring was identified using a room microphone and participants' body position was recorded using an infrared camera. Sleep stages were scored offline visually in 30-second epochs by a registered sleep technologist (supervised by a physician with a specialization in sleep medicine)

according to American Academy of Sleep Medicine (AASM) guidelines (Iber, Ancoli-Israel, Chesson, & Quan, 2007). The sleep technologist was blind to the condition of PSG recordings. Sleep parameters (e.g., SOL, SE) were calculated using reports generated through Sandman®.

Data processing and signal analysis. PSG files were exported in European Data Format (EDF) and processed using Neuroscan version 4.5 SCAN software (Compumedics Neuroscan, Inc., El Paso). All files were either recorded at a sampling rate of 128 Hz or were down-sampled to that value at the time of export. Using SCAN software, all EEG channels were re-referenced offline to the average of the two mastoid channels (A1/A2) for analysis and signals were band-pass filtered between 1 and 30 Hz. Artifacts were then visually identified and highlighted. Using the reduced sample size (*n* = 15 per group), the average amount of artifact-free data from the Typical condition night was 89.22 percent and 91.47 percent from the Restricted condition night. Data were then exported into Microsoft Excel for calculation of additional variables of interest.

Power spectrum analysis was conducted using fast-Fourier transformation (FFT) with 2 second, 75% overlapped Hanning windows on C3 and C4. FFT was carried out in epochs that contained at least 15 seconds of continuous artifact-free data. Absolute power values in the following bands were obtained: delta (1-4 Hz); theta (4-7 Hz); alpha (8-12 Hz); sigma (13-16 Hz); and beta (16-24 Hz). Data were averaged between the left (C3) and right (C4) hemispheres and across NREM stages for the entire sleep period (i.e., all epochs of NREM that contained at least 15 seconds of continuous artifact-free data for the entire night) as well as for NREM within the first 5.1 hours of sleep (i.e., epochs of NREM from the first 5.1 hours of the EEG recording that contained at least 15 seconds of

continuous artifact-free data). FFT analyses used the smaller sample size as they required a sufficient amount of artifact-free data. Data were logarithmically transformed prior to statistical analyses. In 9 files one channel had poor quality data for a portion of the sleep recording, and data from a single channel were used.

Data Analyses

To determine the impact of CSR on sleep parameters across the entire sleep period, two-way mixed ANOVAs were used to examine the effect of group (TD, ADHD) and experimental manipulation (Typical condition, Restricted condition). Separate ANOVAs were run for TIB, TST, SOL, WASO, and SE. To examine the effect of group and experimental manipulation on sleep architecture two-way mixed ANOVAs were also used. Separate ANOVAs were run for minutes of N1, N2, N3, and REM. ANOVAs were also run to test for differences in sleep architecture using the first 5.1 hours of sleep.

Looking at the power spectrum of sleep EEG, two-way mixed ANOVAs were used to examine the effect of group and experimental manipulation on SWA. Separate ANOVAs were run for NREM across the full night of sleep and NREM within the first 5.1 hours of sleep. Exploratory analyses looking at the full power spectrum of sleep EEG were also conducted using two-way mixed ANOVAs. Separate ANOVAs were run for the full night of sleep and the first 5.1 hours of sleep for each of the bands noted above.

Statistical assumptions were checked prior to running ANOVAs. Outliers were defined as studentized residuals plus or minus three values. For the sleep architecture data, variables that were non-normally distributed, contained significant outliers, and/or violated the assumption of homogeneity of variance were square root transformed. Transformations were applied to 14 out of 16 dependent variables. ANOVAs were run

both prior to transformations being applied and after. As results did not change after applying transformations, results using the raw data are presented below. No further transformations were applied to FFT data as these data were already logarithmically transformed prior to statistical analyses.

Results

Sleep Manipulation

Means, standard deviations and effect sizes for TIB and TST are presented in Table 2.2. There were main condition effects related to the sleep manipulation, such that there was a statistically significant difference in TIB ($F(1, 34) = 49.03$, $p < .001$, partial $\eta^2 = .59$) as well as in TST between conditions ($F(1, 34) = 10.35$, $p < .01$, partial $\eta^2 = .23$) showing that, on average, participants spent 45.39 minutes less in bed and slept 28.37 minutes less during the Restricted condition night in the laboratory compared to the Typical condition night[3]. There was no main effect of group and no condition by group interaction. These findings based on PSG are consistent with those from actigraphy recorded throughout each of the manipulation periods. Actigraphy data showed that during the Restricted condition period, children had less TIB and shorter TST which corresponded to a significantly later bedtime during the Restricted condition period (Davidson et al., under review).

Sleep Parameters and Sleep Architecture Across the Full Sleep Period

Means, standard deviations, and effect sizes for all sleep parameters and sleep architecture variables across the full sleep period are presented in Table 2.2. For all sleep

[3] The 30-minute restriction criterion noted previously was based on the average nightly difference in TIB during the Restricted and Typical condition periods based on actigraphy.

parameters, there were no significant interaction effects. There were no main effects of condition or group on SE or SOL. There was no main effect of condition on WASO but there was a main group effect ($F(1, 34) = 4.54$, $p = .04$, partial $\eta^2 = .118$), such that children with ADHD had 15.21 minutes more WASO than TD children regardless of condition.

With regard to sleep architecture, there were no significant main effects for condition or group or interactions for minutes of N1, N2, or N3. However, there was a trend towards an interaction for minutes of N1 ($F(1, 34) = 3.26$, $p = .08$, partial $\eta^2 = .09$). Based on a visual inspection of the graphed and raw mean data for each group and condition, there appears to have been less N1 during CSR in the TD group, and more N1 during CSR in the ADHD group. There was a significant group difference in latency to N3 sleep ($F(1, 34) = 9.70$, $p = .004$, partial $\eta^2 = .22$), such that children with ADHD took 13.80 minutes longer to reach N3 than TD children regardless of condition. There was no significant main effect of condition nor a significant interaction. There were no group differences in minutes of REM but there was a statistically significant main effect of condition ($F(1, 34) = 5.537$, $p = .025$, partial $\eta^2 = .14$), such that the amount of REM sleep was reduced by 14.94 minutes during restriction when compared to the Typical condition night in both groups. There was no significant interaction effect. There were no significant main effects for REM latency but there was a trend towards a group by condition interaction ($F(1, 34) = 3.917$, p .056, , partial $\eta^2 = .103$). Based on a visual inspection of the graphed and raw mean data for each group and condition, REM latency during CSR appeared longer in the ADHD group and shorter in the TD group.

Sleep Architecture Within the First 5.1 Hours of Sleep

Means, standard deviations and effect sizes for all sleep architecture variables within the first 5.1 hours of sleep are presented in Table 2.2. Within the first 5.1 hours of sleep there were no main effects or interactions in minutes of N1. There were no group differences in the duration of N2 but there was a significant main effect of condition ($F(1, 28) = 4.64$, $p = .04$, partial $\eta^2 = .14$), such that participants spent 11.55 more minutes in N2 during the Restricted condition night compared to the Typical condition night. There was also a trend towards a group by condition interaction ($F(1, 28) = 3.21$, $p = .08$, partial $\eta^2 = .10$). Based on a visual inspection of the graphed and raw mean data for each group and condition, it seems that this condition effect was driven primarily by ADHD children, while there appears to have been very little change in N2 during CSR in TD children. There were no main effects or interactions for duration of N3. Finally, there was a significant main effect of group for REM duration ($F(1, 28) = 4.79$, $p = .04$, partial $\eta^2 = .15$), and a significant main effect of condition ($F(1, 28) = 5.38$, $p = .03$, partial $\eta^2 = .16$), such that both groups had 10.90 fewer minutes of REM sleep during the Restricted condition night than during the Typical condition night and that children with ADHD had 8.96 minutes more REM sleep than TD children regardless of experimental condition. There was no significant interaction effect.

The Power Spectrum of NREM Across the Full Sleep Period

Means, standard deviations, and effect sizes for all power spectrum variables across the full sleep period are presented in Table 2.3. There were no significant main effects or interactions in SWA nor for power in any other bands investigated.

The Power Spectrum of NREM Within the First 5.1 Hours of Sleep

Means, standard deviations, and effect sizes for all power spectrum variables within the first 5.1 hours of sleep are presented in Table 2.3. In looking at the first 5.1 hours of sleep, there were again no significant main effects or interactions in SWA or power in any other bands investigated. There was a trend towards a group by condition interaction for sigma ($F(1, 28) = 3.44$, $p = .07$, partial $\eta^2 = .11$). Based on a visual inspection of the graphed and raw mean data for each group and condition, it appears that there was a greater amount of power in the sigma band during CSR in children with ADHD and less power in the sigma band during CSR in TD children.

Follow-Up Analyses

As there was a high degree of variability between participants in the extent to which their sleep was restricted during the Restricted condition, we sought to determine whether the degree of sleep restriction was related to changes in sleep architecture and the power spectrum of sleep EEG. We therefore calculated the difference between the Typical and Restricted conditions in the cumulative TST from the nights leading up to and including the PSG night based on actigraphy. Cumulative TST could not be obtained for three participants (2 during the Typical condition, 1 during the Restricted condition) as there were no actigraphy data for these children during these manipulation periods (this was either due to non-compliance with study protocol or technical issues with the actigraph). We therefore used Little's MCAR test (Little, 1988) to determine that the cumulative TST values were missing completely at random ($\chi^2 = 1.44$, $p = .49$) and imputed missing data in SPSS using expectation maximization. We also calculated difference scores between Typical and Restricted conditions for each of the PSG sleep parameters (SE, SOL, WASO), sleep architecture variables (minutes of N1, N2, N3,

REM), and power spectrum bands (SWA, theta, alpha, sigma, beta) for the full sleep period as well as the first 5.1 hours of sleep. We then ran simple linear regressions using the cumulative TST difference score to predict changes in sleep architecture and the power spectrum of sleep EEG. Results indicated that the degree of sleep restriction was not predictive of any sleep parameter (SE, $F(1, 35) = 0.02$, $p = .89$; SOL, $F(1, 35) = 0.17$, $p = .68$; WASO, $F(1, 35) = 1.16$, $p = .29$, sleep architecture variable during the full night (minutes of N1, $F(1, 35) = 0.42$, $p = .52$; minutes of N2, $F(1, 35) = 2.92$, $p = .10$; minutes of N3, $F(1, 35) = 1.15$, $p = .29$; minutes of R, $F(1, 35) = 0.02$, $p = .89$; N3 latency, $F(1, 35) = 1.15$, $p = .29$; R latency, $F(1, 35) = 0.32$, $p = .58$) or within the first 5.1 hours of the night (minutes of N1, $F(1, 29) = 0.38$, $p = .54$; minutes of N2, $F(1, 29) = 0.01$, $p = .94$; minutes of N3, $F(1, 29) = 0.31$, $p = .58$; minutes of R, $F(1, 29) = 0.43$, $p = .52$), or power within any frequency band during the full night (SWA, $F(1, 29) = 2.75$, $p = .11$; theta, $F(1, 29) = 2.43$, $p = .13$; alpha, $F(1, 29) = 1.86$, $p = .18$; sigma, $F(1, 29) = 1.73$, $p = .20$; beta, $F(1, 29) = 1.28$, p .27) or within the first 5.1 hours (SWA, $F(1, 29) = 2.06$, $p = .16$; theta, $F(1, 29) = 2.39$, $p = .13$; alpha, $F(1, 29) = 1.85$, $p = .19$; sigma, $F(1, 29) = 1.59$, p .22; beta, $F(1, 29) = 1.27$, $p = .27$).

Discussion

The first goal of the current study was to (1) investigate how school-age children respond to mild CSR with regard to physiological changes in sleep. We noted less TIB and TST during the Restricted condition, with no change between conditions in SOL, SE, or WASO. Regarding sleep stages, there was a main condition effect of a shorter duration of REM during CSR. During the first 5.1 hours of sleep, we again noted a shorter duration of REM as well as a longer duration of N2 during CSR relative to sleep during

the Typical condition. There were no differences in SWA in either analysis. The second and third goals of the current study were (2) to investigate whether there were differences in sleep between TD children and children with ADHD regardless of condition, and (3) to determine whether children with ADHD would be more severely impacted by CSR compared to TD children. Our findings indicated that across conditions, children with ADHD had more WASO and a longer latency to N3, as well as more REM within the first 5.1 hours of the night. There were no differences between groups in SWA or any of the additional frequency bands examined. Trends towards interaction effects suggested that children with ADHD had more minutes of N1 and a longer REM latency during the Restricted condition compared to the Typical condition, while values for TD children appeared to change in the opposite direction (i.e., fewer minutes of N1 and a shorter latency to REM during CSR). Within the first 5.1 hours of the night, we found a trend suggesting that the increase in N2 during CSR was primarily driven by children with ADHD. Similar to TD children, there were no differences in mean SWA during CSR either when looking at the full night or the first 5.1 hours of sleep. The final goal of the current study was to explore changes in the power spectrum of sleep beyond the traditional delta band. We found no differences in power within the theta, alpha, or beta bands either between groups or between conditions. There was a trend towards greater sigma power during CSR in the first 5.1 hours of sleep in the ADHD group with what appeared to be less sigma power in the TD group.

As expected, our study protocol led to a decrease in TST during the Restricted condition night across both groups, indicating that our experimental manipulation on the laboratory night was successful. However, despite strict laboratory conditions, the mean

difference in TST between Typical and Restricted condition nights was only 28 minutes. This is in contrast to TIB which showed that children were in bed for an average of 45 minutes less during the Restricted condition night in the laboratory. Although there were no statistically significant changes in SOL, WASO, or SE (Agostini et al., 2017; Ong et al., 2016, 2017), participants seem to be making up (to some degree) for the shortened TIB with more efficient use of their sleep opportunity. Looking at the raw data for these variables between conditions, the values for SE, SOL, and WASO are changing in the expected direction (i.e., higher SE, shorter SOL, and less WASO during CSR) with effect sizes for the condition effects in the medium range (.04 to .07; Cohen, 1988). It would therefore seem that CSR led to the expected changes in sleep parameters, although these changes were not large enough on the laboratory recording night to result in statistically significant differences between conditions. Our belief that participants were making up for the shortened sleep opportunity is supported by the finding that participants had a shorter SOL and decreased WASO (but no change in SE) during the Restricted condition period leading up to the laboratory night, as measured by actigraphy (Davidson et al., under review).

While our results did not show a maintenance of N3 with a corresponding reduction in all other stages of sleep as was hypothesized, we did note a decrease in REM during CSR. The decrease in REM was also evident when we considered the first 5.1 hours of sleep. This more pronounced deficit in REM is consistent with previous research (Skorucak et al., 2018) but is in contrast to our hypothesis based on the findings of Ong et al. (2016) who noted an increased duration of REM when looking at the longest common sleep duration. The authors suggested that this may have been a result of their

experimental protocol which had participants go to bed two hours later during manipulation nights while aligning the midpoints of these manipulation nights with baseline sleep periods. Due to the circadian influence on REM sleep and therefore increased REM priority in the early morning/latter half of the sleep period, it is likely that the more dramatic delay in bedtime in Ong et al. resulted in a greater proportion of sleep falling within the morning circadian phase, contributing to the increase in REM that was not found in the current study (Czeisler, Zimmerman, Ronda, Moore-Ede, & Weitzman, 1980). Interestingly, when looking at the first 5.1 hours of sleep only we also noted an increase in N2. This finding is in contrast to the findings of Åkerstedt et al. (2009) and Ong et al. (2016) who found an increase in N3 during CSR and a decrease in other stages of sleep. Given that research in adults has shown a robust preservation in N3 and a reduction in N2 and REM following both acute and chronic sleep restriction (e.g., Banks & Dinges, 2007), it is possible that the modest decrease in TST in the current study is what contributed, at least in part, to the maintenance of N2.

The lack of condition effect for N1 and the increase in N2 were both surprising but may be better understood within the context of the additional trends toward group by condition interactions for these variables. These trends suggest that specifically children with ADHD had more N1and N2 during CSR. Therefore, for TD children, a decrease in N1 (full night), a maintenance in N2, and a decrease in REM (full night and first 5.1 hours) is mostly consistent with our hypothesis that N3 sleep would be maintained at the expense of other stages of sleep. It is also worth noting that, while the ANOVA for the duration of N3 within the first 5.1 hours of sleep did not come out as significant in the statistical analysis, the duration of N3 increased marginally (by approximately four

minutes) early in the night in TD children which is consistent with a homeostatic response to sleep restriction, while it decreased by approximately six minutes in children with ADHD. It is therefore unclear why children with ADHD would experience a decrease in N3 and an increase in N1 and N2 sleep during CSR. These findings are consistent with the group effect which showed a longer onset to N3 in children with ADHD and suggest that there is something different about the homeostatic response to sleep restriction and the way in which N3 pressure accumulates in this group.

Given the increase in N2 and decrease in N3 during CSR in children with ADHD, it would seem that there is a prioritization of N2 sleep over N3 in this clinical population. This is consistent with our finding of a trend towards an increase in sigma power within the first 5.1 hours of the night during CSR in children with ADHD. While N2 sleep is predominated by theta activity (4-7 Hz), sleep spindles are a distinguishing feature of this stage and are characterized by EEG activity within the sigma (13-16 Hz) range (Malhotra & Avidan, 2014). With the apparent increase in both N2 and sigma power during CSR in children with ADHD, it would be of interest to look at the impact of CSR on sleep spindles within this population.

These results should also be considered in light of our results for the full sleep period which indicated that irrespective of condition, children with ADHD had more WASO. Although the apparent increase in N2 and decrease in N3 during CSR among children with ADHD (together with the finding that these children had a longer N3 latency and more WASO) may seem to indicate an altered homeostatic response, another possibility is that children with ADHD do experience the same homeostatic sleep processes as TD children but have a greater degree of difficulty reaching N3 sleep. This

could be due to increased WASO interfering with their ability reach this stage (therefore resulting in their increased latency to N3). Thus, the finding that children with ADHD spend more time in N2 sleep during CSR relative to TD children might indicate that while the brain is progressing towards achieving deeper sleep, arousals interrupt the progression from N2 to N3 thus increasing the time spent in N2 without these children reaching N3 as often. This interpretation is in line with the findings of previous researchers who examined sleep instability in children with ADHD by measuring the cyclic alternating pattern (CAP) – a method of coding arousal fluctuations that do not lead to awakenings. The authors noted that children with ADHD had a reduced total A1 index (Akinci et al., 2015; Miano et al., 2006) and longer duration of A1 subtypes (Miano et al., 2006), which are responsible for the build-up and consolidation of slow wave NREM sleep and protecting sleep against disturbances (Parrino & Culebras, 2018). Therefore, under typical sleep conditions, it is possible that children with ADHD are not experiencing the same degree of consolidated deep NREM sleep, which is further exacerbated and made more apparent under conditions of experimental sleep restriction.

This interpretation may also help to explain the trend towards an interaction for REM latency such that REM latency appeared to be increased during CSR in the ADHD group and decreased during CSR in the TD group. Based on previous findings in children (Carskadon et al., 1981; Ong et al., 2016) as well as findings in adult studies (Van Dongen et al., 2003a), we expected to see a decrease in REM latency during CSR. The decrease in REM latency is thought to reflect increased REM pressure accumulating over days of CSR as NREM sleep is prioritized (Brunner et al., 1993; Ong et al., 2016). While both groups were found to have a decrease in REM duration during CSR, given the

finding that REM latency appeared to be increased during CSR in the ADHD group, it would seem that these children are not experiencing the same buildup of REM pressure. It may also be possible that repeatedly interrupted attempts to achieve N3 sleep during CSR resulted in this prolonged latency to REM, as proposed above.

Children with ADHD were also found to have more REM in the first 5.1 hours of the night than TD children regardless of experimental condition. This finding leads one to consider the influence of the dopaminergic system as having an additional impact on sleep in these children. It has been proposed that both sleep problems and ADHD may stem from common aetiologies such as altered dopaminergic pathways in the brain (Kirov & Brand, 2014; Owens, 2005, 2006; Weiss, Craig, Davies, Schibuk, & Stein, 2015). Dopamine has also been implicated as playing a role in the control of the sleep-wake cycle as well as the alternation between NREM and REM sleep, with dopaminergic neurons projecting to zones in the brain that are important for sleep-wake control (Kirov & Brand, 2014; McCarley, 2007) and there is research to suggest that lower levels of dopamine are related to increased REM propensity (Gillin, Pulvirenti, Withers, Golshan, & Koob, 1994). While there is some existing research to suggest that REM sleep is altered in children with ADHD, the direction of this relationship is inconsistent between studies and appears to depend on age and to be modulated by sleep lab adjustment (Kirov & Brand, 2014). The relationship between ADHD, sleep disturbances, and the dopaminergic system is not yet fully understood and merits further research.

Our results did not reveal an increase in SWA during restriction, as would be expected based on previous research in both children and adults (Ong et al., 2016; Banks & Dinges, 2007). Our lack of significant findings regarding SWA are in contrast to those

of Ong et al. (2016) but are consistent with at least one study with adults that failed to establish changes in SWA during CSR (Skorucak et al., 2018). While the participants in Ong et al. (2016) and Ong et al. (2017) reported an average TIB of approximately 6 hours on weeknights, they were required to adhere to a 9-hour sleep schedule for one week prior to the experimental manipulation. The restriction to 5 hours TIB for 5 or 7 nights thus results in a more extreme degree of restriction than was used in the current study, and therefore, similar to Skorucak et al. (2018), it is possible that the manipulation used in the current study was too mild to lead to changes in sleep at the level of the power spectrum of the EEG. While more studies are needed to confirm this finding, it would seem to suggest that a reduction of TIB by about one hour less per night for six nights does not lead to a robust homeostatic response – both with regard to N3 and SWA – in school-age children. This finding highlights the fact that restricting TIB is not the same as restricting sleep, as individuals adapt to make up for some of this loss.

Finally, exploratory analyses of the EEG power spectrum in additional frequency bands yielded non-significant results, with the exception of the trend towards a group by condition interaction for sigma power within the first 5.1 hours of the night, as previously mentioned. Although there were no changes in SWA as was expected, the difference in sigma power does provide some evidence of a homeostatic response in our participants as a reduction in sigma power has been found in other studies of experimental sleep loss (e.g., Jenni, Achermann, & Carskadon, 2005, in a study of adolescents). This reduction is related to the inverse relationship between sigma power and slow waves (Achermann & Borbléy, 2011; De Gennaro & Ferrara, 2003). That there was more sigma power during CSR in children with ADHD provides further evidence of altered or impaired

homeostatic processes in this population. The fact that there were no differences in power within any other bands during CSR (including the delta band) suggests that our manipulation was not powerful enough and/or that our sample size was too small to detect differences that may have occurred. The lack of between-group findings across all bands and across conditions is consistent with previous studies in adults (Philipsen et al., 2005) and some studies in children (Prehn-Kristensen et al. 2011, 2013).

Clinical Implications

We did not find changes in SWA during CSR as we had hypothesized. In considering this result within the context of the broader study, there some daytime consequences for our participants that did not differ between groups (Davidson et al., under review). Support was not found for all hypotheses, however, the differences that were found are noteworthy given the minimal sleep restriction These findings suggest that perhaps one hour less TIB per night over six nights is insufficient to cause major changes both in homeostatic sleep processes as well as in daytime functioning. With that being said, some previous studies have found that a similar amount of CSR led to significant impairments in neurocognitive functioning, with the performance of children with ADHD falling from a subclinical to clinical level (Gruber et al., 2011). Therefore, it is possible that a mild dose of CSR as was used in the current study affects specific areas of daytime functioning, while other areas are only impacted when sleep loss is more severe. In line with this idea, Van Dongen et al. (2003a) used a dose-response sleep restriction protocol to investigate the impact of varying degrees of CSR on sleep and waking neurobehavioural functioning in adults. The authors demonstrated that under

varying degrees of CSR, changes in waking neurobehavioural functioning were dose-dependent and more impacted by CSR than was sleep physiology.

It should also be acknowledged that while there was little impact of the degree of CSR produced in this study, research has shown that children may be more physiologically sensitive to the effects of sleep loss when compared to adults. For example, Carskadon et al. (1981) found (using a single night of sleep restricted to four hours) that SOL during MSLTs decreased and did not recover to baseline values even following a 10-hour recovery sleep. Ong et al. (2016) also noted that TST, N2, and REM remained altered in the sleep restricted group following three nights of 9 hours of TIB opportunity. Given the implications of these findings, it is important to consider interventions that may improve sleep opportunities for children. For example, Ong et al. (2017) also investigated the impact of napping on sleep EEG during CSR and noted that homeostatic pressure was lower in the nap group. This suggests that napping may offset (to some degree) the impact of poor sleep. While the results of the current study suggest that future experiments looking at the impact of sleep restriction in school-age children need to impose a more severe degree of TIB restriction, it is important to acknowledge that our restriction protocol reflected a more typical degree of sleep loss within this age group. Therefore, from a clinical perspective, our results offer important information about the way in which children may adapt to a modestly shortened sleep opportunity for a short period of time. It should be highlighted that CSR in the current study was only imposed for a period of one week. Increasing the duration of this period may have also produced stronger effects.

Therefore, our study suggests that children seem to adapt to a modestly shortened sleep opportunity, but it is unknown whether negative effects would accumulate if restriction was continued. Given that the average TST during the Typical condition was more than one hour below the average amount recommended for this age group (8.67 hours per night for TD children and 8.43 hours for children with ADHD, Hirshkowitz et al. 2015) future studies may wish to examine the impact of the same degree of sleep restriction relative to a control period with a longer imposed sleep opportunity (rather than basing TIB during the Restricted condition off of participants' typical sleep schedules). Finally, as our results indicate that children with ADHD may not experience the same homoeostatic response to sleep loss as TD children or may have difficulty achieving deep sleep when sleep is restricted, the consequences of sleep loss for these children may be more severe. Future studies of experimental sleep restriction in this age group should consider the impact on children with ADHD relative to TD children, as was done by Gruber et al. (2011).

Beebe (2011) highlighted the importance of adding a developmental context to the study of inadequate sleep in children and adolescents. Childhood is a period of dramatic brain development which is influenced by environmental factors; chronic inadequate sleep is one environmental factor which can negatively impact the development of neural connections and therefore influence developmental trajectories. Longitudinal studies have shown an association between inadequate sleep and the development of both internalizing and externalizing problems in the future (e.g., substance use in adolescence; Wong, Brower, & Zucker, 2009). This is of particular importance as according to the National Sleep Foundation (2014), children are getting

less sleep than is recommended. Indeed, we corroborated this finding with the participants in our study, as previously stated. Therefore, an understanding of the effects of CSR in childhood may help in establishing public health initiatives focused on the promotion of adequate sleep and prevention of negative physical and mental health consequences. Finally, given that children are generally sleeping less than the recommended amount each night, it may be useful to look at the effects of both CSR and sleep extension. For example, Vriend et al. (2013) employed a protocol including both sleep restriction and extension and found significant differences in positive affective response, emotion regulation, short-term and working memory, and attention between the two conditions, with improvements in these measures in the extension condition.

Limitations

The current study had limitations which should be acknowledged. First, while the sleep manipulation employed reflected a realistic sleep deficit that may be experienced by school-age children, it is possible that one hour less TIB per night over a period of six nights is not sufficient to demonstrate robust changes in sleep architecture and the power spectrum of sleep. Furthermore, children in the current study were, on average, already sleeping approximately one hour less than the average recommended amount for this age group. It is therefore possible that our participants had already habituated to a reduced sleep duration. It should also be highlighted that the current study had a modest sample size which was reduced further for some analyses. This likely impacted our ability to detect effects and limits confidence in our results. Therefore, the findings presented above should be thought of as hypothesis-generating as they provide preliminary evidence of altered homeostatic processes in children with ADHD and offer possible

directions for future lines of inquiry. Finally, the current study only considered the impact of CSR on medication naïve children with ADHD without any comorbid mental health disorders – this is not representative of many children with ADHD. However, given that this study is the first to investigate the effects of CSR on sleep architecture and the power spectrum of sleep EEG in this population, it was important to establish the impact of CSR using an unmedicated sample with no comorbidities. Future studies may wish to explore the generalizability of these results.

Areas for Future Research

Given that the current study is the first to investigate the effects of CSR on sleep architecture and the power spectrum of sleep EEG in TD school-age children and children with ADHD, future studies should determine dose-response effects of CSR within this population (similar to Van Dongen et al., 2003a). Given the limited findings in our study, it is possible that one hour less TIB per night over six nights is not sufficient for changes to be reflected in sleep physiology (particularly the power spectrum of the EEG). It will be important to determine the dose at which a homeostatic response is detectable and if/how this response changes with varying degrees of restriction. It may also be of interest to look at differences in sleep spindles given that sleep spindles are impacted by sleep loss (Curcio, Ferrara, Pellicciari, Cristiani, & De Gennaro, 2003) and there is some research pointing to differences in sleep spindles/sigma power in sleep EEG between TD children and children with ADHD (Gruber & Wise, 2016; Saletin et al., 2016). It would be particularly interesting to look at changes in sleep spindles in these groups during CSR given the trends suggesting a greater amount of N2 and sigma power in children with ADHD during CSR in the current study. Finally, as previously stated, it

will be important to further study the impact of both sleep restriction as well as extension, especially given that children are getting less sleep at baseline than is recommended.

Conclusions

The current study is the first known study to experimentally investigate the effects of CSR in school-age children on both sleep architecture and the power spectrum of sleep EEG. Our study is also the first to investigate changes in these variables during CSR in children with ADHD, a clinical population known to have difficulty with sleep (Weiss et al., 2015). Results revealed a reduced duration of REM during CSR, with some differential changes in sleep architecture during restriction based on group. There were no significant findings regarding differences in the power spectrum of sleep EEG between groups or changes during CSR, with the exception of a trend towards a group by condition interaction for sigma power. Overall, our results suggest that there may be factors impacting homeostatic sleep processes in children with ADHD. These findings are preliminary, and more research needs to be done to understand the way in which children (both TD and with ADHD) respond to varying degrees of CSR behaviourally and physiologically.

Table 2.1

Participant Demographics by Group

	ADHD (n = 18)	TD (n = 18)		
Variable	M (SD)	M (SD)	t	p
Age (months)	107.67 (18.96)	104.06 (16.43)	0.61	.55
Estimated FSIQ	99.92 (10.86)	107.98 (9.50)	-2.37	.02
Variable			χ^2	p
Ethnicity (n = 32)	15/16 White/Caucasian; 1/16 Multi-Racial	15/16 White/Caucasian; 1/16 Multi-Racial	0.00	1.00
Family Composition (n = 34)	13/17 two parent; 4/17 single parent	16/17 two parent; 1/17 single parent	2.11	.15
Maternal Education (n = 35)	6.00	4.50	4.70	.45
Paternal Education (n = 29)	2.50	4.00	6.48	.26
Annual Family Income (n = 36)	5.00	6.00	4.86	.43

Note: Age in years and months at the time of baseline; M = mean; SD = standard deviation; TD = typically developing; FSIQ = full scale intelligence quotient; Median values presented for maternal and paternal education: 1 = some secondary/high school, 2 = completed secondary/high school, 3 = some community, technical, or CEGEP college; 4 = completed community, technical, or CEGEP college; 5 = some university or teacher's college, 6 = completed university or teacher's college; Median values presented for annual family income: 1 = up to $20,000, 2 = $20,001 to $30,000, 3 = $30,001 to $40,000, 4 = $40,001 to $50,000, 5 = $50,001 to $60,000, 6 = $60,001 to $70,000, 7 = More than $70,000.

Table 2.2

Means, Standard Deviations, and Effect Sizes for Sleep Architecture Variables for The Full Night and the First 5.1 Hours by Group

	Mean (SD)								
	All Participants (n = 36)		ADHD (n = 18)		TD (n = 18)		Effect Size[a]		
Full Night	Typical	Restricted	Typical	Restricted	Typical	Restricted	G	C	GxC
TIB (min)	582.85 (41.06)	537.46 (38.07)	575.15 (37.64)	535.06 (37.75)	590.55 (43.91)	539.87 (39.33)	.02	.59*	.02
TST (min)	512.79 (56.20)	484.42 (47.96)	505.67 (56.09)	473.51 (53.85)	519.91 (57.01)	495.34 (39.78)	.04	.23*	.01
SE (%)	88.03 (7.90)	90.14 (5.60)	87.87 (7.08)	88.41 (6.87)	88.19 (8.86)	91.75 (3.15)	.03	.06	.03
SOL (min)	22.75 (23.84)	16.58 (15.70)	19.94 (15.17)	17.27 (19.63)	25.56 (30.39)	15.89 (11.01)	.004	.07	.02
WASO (min)	43.25 (34.74)	34.60 (26.35)	49.14 (41.28)	43.92 (32.06)	37.36 (26.60)	25.28 (14.76)	.12*	.04	.01
N1 (min)	28.49 (10.91)	28.27 (14.11)	26.74 (10.27)	31.11 (16.87)	30.24 (11.54)	25.43 (10.39)	.003	<.001	.09†
N2 (min)	227.41 (49.94)	223.61 (38.39)	223.77 (57.26)	219.26 (40.92)	231.06 (42.75)	227.97 (36.33)	.01	.01	<.001
N3 (min)	142.59 (42.20)	133.18 (33.50)	140.68 (45.44)	123.97 (39.80)	144.50 (39.94)	142.39 (23.37)	.03	.05	.03
N3 Latency (min)	11.01 (8.72)	12.35 (9.89)	13.67 (11.51)	15.14 (13.01)	8.36 (2.99)	9.56 (3.95)	.22*	.01	<.001
REM (min)	114.30 (25.42)	99.36 (27.21)	114.49 (20.73)	99.18 (30.28)	114.11 (30.02)	99.54 (24.64)	<.001	.14*	<.001
REM Latency (min)	124.78 (47.67)	126.07 (45.42)	119.39 (42.12)	138.61 (43.55)	130.17 (53.32)	113.53 (44.93)	.01	.001	.10†
First 5.1 Hours	All Participants (n = 30)		ADHD (n = 15)		TD (n = 15)				
N1 (min)	9.55 (4.35)	9.85 (5.42)	8.44 (4.03)	10.20 (4.89)	10.67 (4.51)	9.50 (6.05)	.01	.003	.06
N2 (min)	125.06 (31.35)	136.61 (25.13)	119.06 (39.90)	140.23 (39.09)	131.06 (19.18)	133.00 (19.37)	.003	.14*	.10†
N3 (min)	118.58 (29.02)	117.64 (25.85)	118.03 (34.84)	112.37 (31.25)	119.14 (23.04)	122.90 (18.65)	.02	.001	.03
REM (min)	54.80 (21.66)	43.90 (12.50)	62.47 (24.80)	45.20 (8.72)	47.14 (15.20)	42.60 (15.61)	.15*	.16*	.06

Note: M = mean; SD = standard deviation; TD = typically developing; TIB = time in bed; TST = total sleep time; SE = sleep efficiency; SOL = sleep onset latency; WASO = wake after sleep onset; G = group main effect; C = condition main effect; GxC = group by condition interaction.

[a]Effect size reported as partial eta squared.

*=significant at $p < .05$; † = trend at $p > .05$ and $< .10$.

Table 2.3

Means, Standard Deviations, and Effect Sizes for Log Transformed Power Spectrum Values for NREM within the Full Night and the First 5.1 Hours by Group

	Mean (SD)								
	All Participants (n = 30)		ADHD (n = 15)		TD (n = 15)		Effect Size[a]		
Full Night (NREM)	Typical	Restricted	Typical	Restricted	Typical	Restricted	G	C	GxC
Delta (SWA)	3.38 (0.24)	3.42 (0.24)	3.37 (0.25)	3.42 (0.25)	3.40 (0.24)	3.42 (0.25)	.001	.02	.01
Theta	2.35 (0.23)	2.36 (0.29)	2.31 (0.18)	2.37 (0.37)	2.38 (0.28)	2.36 (0.20)	.01	.004	.02
Alpha	1.67 (0.32)	1.69 (0.40)	1.60 (0.20)	1.71 (0.52)	1.73 (0.41)	1.67 (0.27)	.01	.004	.04
Sigma	1.09 (0.40)	1.12 (0.44)	1.00 (0.27)	1.18 (0.56)	1.19 (0.49)	1.06 (0.29)	.004	.003	.09
Beta	0.87 (0.45)	0.87 (0.46)	0.76 (0.20)	0.94 (0.61)	0.98 (0.60)	0.81 (0.26)	.01	<.001	.08
First 5.1 Hours (NREM)									
Delta (SWA)	3.46 (0.26)	3.49 (0.25)	3.43 (0.27)	3.49 (0.24)	3.49 (0.25)	3.49 (0.27)	.004	.01	.01
Theta	2.40 (0.24)	2.40 (0.30)	2.35 (0.19)	2.41 (0.38)	2.44 (0.27)	2.40 (0.21)	.01	<.001	.04
Alpha	1.70 (0.33)	1.72 (0.41)	1.63 (0.21)	1.74 (0.53)	1.77 (0.41)	1.70 (0.27)	.01	.002	.05
Sigma	1.07 (0.40)	1.09 (0.45)	0.97 (0.25)	1.17 (0.58)	1.17 (0.50)	1.02 (0.28)	.001	.002	.11†
Beta	0.86 (0.46)	0.85 (0.48)	0.75 (0.21)	0.92 (0.63)	0.96 (0.60)	0.78 (0.25)	.003	<.001	.08

Note: M = mean; SD = standard deviation; TD = typically developing; G = group main effect; C = condition main effect; GxC = group by condition interaction; SWA = slow-wave activity.

[a]Effect size reported as partial eta squared.

*=significant at $p < .05$; † = trend at $p > .05$ and $< .10$.

Chapter 3: Sleep Spindles During Cumulative Sleep Restriction: A Comparison Between Children with Attention-Deficit/Hyperactivity Disorder and Their Typically-Developing Peers

This investigation is derived from the same larger study described in Chapter 2 which broadly investigated the effects of sleep restriction on daytime functioning in children. Following from Chapter 2, we further explored changes in participants' sleep physiology during a period of CSR by looking at sleep spindles, which are phasic events in the sleep EEG. We again looked at differences between TD children and children with ADHD. Readers are advised that Ms. Tamara Speth, under the supervision of Dr. Penny Corkum, was responsible for reviewing extant literature and formulating the research questions; training and supervising research staff; completing and overseeing data collection; completing statistical analyses; and all aspects of the writing process. Ms. Speth completed this research in consultation with her dissertation committee members (Dr. Benjamin Rusak and Dr. Tara Perrot) from whom she also received editorial feedback. At this time, the following manuscript has not been submitted for publication.

Abstract

Background: Sleep spindles are related to sleep preservation and synaptic plasticity. There is limited understanding of the impact of sleep restriction on sleep spindles in children. There are also few studies of sleep spindles in children with attention-deficit/hyperactivity disorder (ADHD) and existing studies are limited by methodological inconsistencies.

Method: A sample of 16 children with ADHD and 16 typically-developing (TD) children underwent an experimental sleep restriction protocol with a Typical condition where they were asked to maintain their usual sleep schedule for six nights and a Restriction condition where they were asked to reduce their time in bed (TIB) by one hour per night for six nights. Polysomnography was recorded in the laboratory at the end of each of the manipulation periods and sleep spindles were compared between groups and conditions.

Results: Sleep spindles did not differ between experimental conditions or between groups, although there was a trend towards lower slow spindle density during restriction. The extent to which sleep was restricted during the manipulation periods was not predictive of changes in spindle activity; however, ADHD symptoms were related to higher frequency of fast spindles during the Typical condition across groups.

Conclusions and Implications: A reduction of TIB by one hour per night over six nights is insufficient to lead to robust physiological differences in sleep spindles. Our findings also contribute to a small body of research on sleep spindles in children with ADHD and suggest that sleep spindles do not categorically differentiate these children from their TD peers. However, it is possible that more dimensional measures of ADHD symptoms may be related to sleep spindle activity in children.

Introduction

Background

There is a growing interest in the importance of sleep as it relates to human functioning. Over the past decade, sleep spindles have become an area of growing interest as research on both the neurophysiological underpinnings and functions of spindles has advanced. Sleep spindles are transient, oscillatory events that are unique to sleep in human electroencephalography (EEG) (De Gennaro & Ferrara, 2003; Lüthi, 2014). The function of sleep spindles is thought to be multifaceted. Research has pointed to a role of the spindle in inhibiting sensory input during sleep and has shown that individuals with higher spindle rates experience better maintenance of sleep in the face of environmental noise (Cote et al., 2000; Dang-Vu, McKinney, Buxton, Solet, & Ellenbogen, 2010), therefore suggesting that spindles play a sleep-protective role.

Sleep spindles are also related to brain plasticity and the long-term strengthening of synapses in the brain, which is in turn thought to be related to the role they play in learning and memory (Lindemann, Ahlbeck, Bitzenhofer, & Hanganu-Opatz, 2016; Lüthi, 2014; Ulrich, 2016). There is a great deal of research pointing to a positive correlation between various sleep spindle parameters and measures of intelligence in adults (e.g., Fogel & Smith, 2011); however, a recent meta-analysis found that the amplitude of slow and fast spindles was the only variable to be robustly associated with cognitive ability across a range of age groups (Ujma, 2018). Furthermore, another recent study which included a sample of 176 17-year-olds (the largest study on this topic) failed to find any significant associations between spindle variables and cognitive ability (Pesonen, Ujma, Halonen, Räikkönen, & Kuula, 2019), further calling into question this

proposed relationship.

Sleep spindles are typically measured as EEG activity occurring between 11 and 16 Hz (Ray et al., 2015). Studies of sleep spindles have used various approaches to quantify spindle activity; while some studies use visual identification of spindles in EEG recordings, others employ automatic spindle detection algorithms, and still others use spectral analysis to calculate sigma power in the EEG (De Gennaro & Ferrara, 2003). The frequency of spindles changes relative to topography, with slower frequency spindles (approximately 12 Hz) found in anterior/frontal cortical areas and faster frequency spindles (approximately 14 Hz) in central/parietal areas (De Gennaro & Ferrara, 2003; Lüthi, 2014).

There is also greater prevalence of spindles in N2 versus N3 sleep and an increase in sleep spindles over progressive cycles of sleep; this increase is related to the reciprocal relationship between spindles and slow waves, with the latter decreasing as the night continues (Achermann & Borbléy, 2011; De Gennaro & Ferrara, 2003). This reciprocal relationship has been highlighted in studies of sleep deprivation, wherein slow wave sleep (i.e., N3) is increased and spindle density is reduced during recovery sleep (Curcio, Ferrara, Pellicciari, Cristiani, & De Gennaro, 2003), particularly within the high spindle frequency range (Knoblauch, Martens, Wirz-Justice, & Cajochen, 2003). Studies of sleep deprivation in adults also indicate that spindles have a reduction in mean frequency and an increase in amplitude, particularly within the slow spindle frequency range (Knoblauch et al., 2003), and are longer in duration (Dijk, Hayes, Czeisler, 1993). It is thought that these changes are related to a greater degree of synchronization of thalamocortical cells.

Research on sleep spindles and development indicates that sleep spindles appear when children are between six weeks and three months old (Clawson et al., 2016). These early spindles appear primarily in central regions with an increase in distribution to frontotemporal regions by around four months. As children age, spindles become more synchronous between both hemispheres of the brain. Younger children (up to around age 13) have a greater prominence of frontal (slow) spindles while older children (around 13 years and older) have more centro-parietal (fast) spindles (Shinomiya, Nagata, Takahashi, & Masumura, 1999). Overall, there is an increase in the number and frequency of both slow and fast spindles during childhood and adolescence (Campbell & Feinberg, 2016; Purcell et al., 2017), although there do not appear to be major changes in density of spindles, duration of spindles, or the inter-spindle interval (ISI) between the ages of around 5 to 16 (Scholle et al., 2007). The peak frequency of fast spindles increases in a linear fashion across childhood and early adulthood, while for slow spindles there is more of an abrupt increase which occurs during early adolescence (Clawson et al., 2016; De Gennaro & Ferrara, 2003).

The relationship between spindles and intelligence has also been studied in children, with spindle frequency found to be negatively associated with full scale IQ (Geiger et al., 2011) and the perceptual reasoning and working memory subscales of the WISC-IV (Gruber et al., 2013). It has been suggested that this inverse relationship is related to synaptic pruning, such that children with higher IQs have fewer but more efficient synaptic connections (Chatburn et al., 2013). There is also research to suggest that a higher density of slow spindles and lower density and lower power of fast spindles are related to improved consolidation of executive functioning skills in school-age

children (Vermeulen, Van der Heijden, Swaab, & Van Someren, 2019). However, these findings must again be considered in light of the meta-analysis conducted by Ujma (2018) (including 10 studies of children ranging in age from 4 to 13 years old) that did not find an association between intelligence and spindle frequency or density, and the large-scale study with adolescents conducted by Pesonen et al. (2019) which found no associations between intelligence and any spindle parameter after correcting for multiple comparisons.

As previously stated, studies of sleep spindles following sleep loss in adults indicate that sleep loss leads to a reduction in spindle density, an increase in spindle amplitude and duration, and a reduction in mean spindle frequency (Curcio et al., 2003; Dijk et al., 1993; Knoblauch et al., 2003). There are currently no known studies that have experimentally investigated the effects of sleep loss on spindle activity in school-age children; however, a recent study by Reynolds, Gradisar, Coussens, and Short (2018a) looked at this relationship in adolescents. After five nights of either 5, 7.5, or 10 hours sleep opportunity, their findings were somewhat inconsistent with those from adult studies. Reynolds et al. found that fast spindles were longer during the experimental phase and had decreased amplitude (although amplitude was increased relative to baseline in the 7.5-hour condition in females), while there was no change in spindle density. While the finding regarding spindle amplitude was in contrast to adult studies (e.g., Knoblauch et al., 2003) the authors proposed that the decrease in amplitude was related to a decrease in sigma power that has been found in adult studies following sleep loss. They proposed that a reduction in spindle activity following sleep loss is caused by homeostatic processes reducing activation of the thalamocortical circuit. In general,

Reynolds et al. concluded that fast spindle activity seems to be more affected by sleep restriction compared to slow spindle activity. The authors proposed that these changes may be related to daytime cognitive deficits as fast spindle activity specifically has been implied as being related to cognitive ability to a greater extent than slow spindles (Bódizs, Gombos, Ujma, & Kovács, 2014; Reynolds et al., 2018a).

Research has also considered the ways in which spindle characteristics differ in clinical populations, such as in children with delayed neurodevelopment wherein both sleep and cognitive abilities are commonly affected. One such population is children with attention-deficit/hyperactivity disorder (ADHD) – a disorder associated with sleep problems in up to 70 percent of children who are diagnosed (Weiss, Craig, Davies, Schibuk, & Stein, 2015). In a review of sleep spindle characteristics in children with neurodevelopmental disorders (NDDs), Gruber and Wise (2016) highlighted the inconsistent findings regarding sleep spindles in children with ADHD. The authors included three studies that looked specifically at sleep spindle characteristics in children with ADHD compared to typically-developing (TD) children and noted that while one study found no differences in spindle characteristics between children with ADHD and controls (Kiesow & Surwillo, 1987), one study found more spindles in children with ADHD (Poitras, Bylsma, Simeon, & Pivik, 1981) while another study found fewer (Khan & Rechtschaffen, 1978). The authors attributed these inconsistencies in part to methodological differences between studies (e.g., when sleep was measured). An additional study cited by Gruber and Wise looked at memory consolidation in children with ADHD and its relationship to spindle density in N2 sleep (Prehn-Kristensen et al., 2011). These authors found no differences in sleep spindles in children with ADHD

relative to controls and noted a deficit in sleep-related enhancement of declarative memory in this population.

There are two relevant studies that were not included in the review by Gruber and Wise (2016). A study by Saletin et al. (2016) looked at the relationship between spindles and sleep-dependent motor learning in 10- to 13-year-old children with ADHD by examining sigma frequency in the sleep EEG. The researchers found that these children had lower sigma activity (with the greatest difference between groups in the slow spindle range). Additionally, a recent study by Merikanto et al. (2019) looked at subclinical ADHD symptoms in adolescents (as measured by the Adult ADHD Self-Report Scale, ASRS-v1.1) and their relationship to sleep spindles. These authors found that the relationship between sleep spindle features and ADHD symptoms is not unique to children meeting diagnostic criteria for the disorder, noting an association between higher total ADHD symptom scores and lower amplitude and shorter duration of fast spindles. This relationship was the same when the authors used the hyperactivity and inattention subscales of the same measure. Given that parent-reported sleep problems in children with ADHD have not been substantiated by objective differences in sleep as measured by sleep architecture or the power spectrum of sleep EEG broadly (Corkum & Coulombe, 2013; Speth et al., in preparation; Speth, Benoit, & Corkum, 2014), it has been proposed that differences in sleep continuity – which would not be captured by traditional scoring of PSG data – may be related to sleep problems in these children (Cohen-Zion & Ancoli-Israel, 2004). As sleep spindles have been shown to protect the continuity of sleep through sensory gating (Cote et al., 2000; Dang-Vu et al., 2010) altered sleep spindle activity would seem to be a likely mechanism by which sleep may be disturbed in

children with ADHD.

Rationale, Study Goals and Hypotheses

Research suggests that sleep spindles play a role in protecting sleep, strengthening synapses in the brain, and facilitating learning. Studies with adults and one study with adolescents have shown that sleep spindles are reduced (either in density and/or amplitude) following or during sleep loss, with some inconsistencies between adult and adolescent findings. To date, no studies have looked at the impact of experimental sleep restriction on sleep spindle activity in school-age children. We therefore conducted the current investigation as part of a larger experimental sleep restriction study with TD children and children with ADHD (CIHR grant 44586). The study involved six nights of typical sleep (Typical condition) and six nights of time in bed (TIB) restricted by one hour per night (Restricted condition), with sleep recorded in the laboratory using polysomnography (PSG) at the end of each condition period. The larger study also included a variety of daytime and additional nighttime measures that will be examined and reported separately (Corkum et al., in preparation; Davidson et al., under review; Speth et al., in preparation). The primary goal of the current study was to investigate the impact of sleep restriction on sleep spindles in school-age children. Based on the findings above, we predicted that sleep restriction would be related to reduced spindle density and increased ISI, reduced spindle amplitude, increased spindle duration, and reduced spindle frequency. Furthermore, we predicted that sleep restriction would have a greater impact on fast versus slow spindles.

Secondly, as the key areas thought to be affected by spindle activity are those which are known to be impaired in children with NDDs such as ADHD, and sleep

problems are common among these children, it is possible that children with ADHD may be more disposed towards impaired spindle activity and be more vulnerable to the impact of the same (Gruber & Wise, 2016). However, due to limited previous research in this area and methodological issues among existing studies, it is difficult to draw conclusions about spindles within this population. Given the inconsistent results of previous studies examining sleep spindles in children with ADHD, the current study will add to the existing literature by providing an analysis of spindles between TD children and children with ADHD within the context of a rigorously controlled experimental study and determining whether these differences are impacted by sleep restriction.

Method

Participants

TD children were recruited through online advertisements, newsletters, and a laboratory research database. Children with ADHD were recruited through an ADHD clinic and private practices (both of which used the same diagnostic procedures, see McGonnell et all., 2009). To participate in the current study, children were required to be between 6 and 12 years of age. TD children were required to not have been previously diagnosed with a mental health disorder. Children with ADHD were required to meet DSM-5 diagnostic criteria for ADHD, to not have any other comorbid mental health diagnoses (with the exception of learning disorders), and to be medication naïve. Children were excluded from the study if (1) they had a medical illness that was impairing or a history of neurological impairment, (2) they met criteria for a primary sleep disorder, (3) they used medication to fall asleep in the last month, (4) they crossed

more than two time zones in the last month, (5) they regularly slept less than 8 or more than 12 hours per night, or (5) their pubertal development was beyond Tanner stage 2.

In total, 65 children (32 ADHD) met initial screening criteria. Thirteen participants were excluded from the study or dropped out for reasons such as scheduling conflicts, illness, or meeting exclusion criteria. Twelve children were also removed from the study as they did not meet restriction criteria, which required an average reduction of 30 minutes TIB per night during the Restricted condition based on actigraphy. An additional child was removed from analyses as she was given a diagnosis of a chronic health condition after she had completed the study protocol. The remaining participants were then age- and sex-matched resulting in a final sample of 18 TD children (4 girls) and 18 children with ADHD. At the time of analysis, two participants' data were removed as their PSG recording from either the Typical or Restricted condition night included a large amount of artifact which made spindle detection impossible to complete. Two additional participants were removed from spindle analyses due to extreme outlying data as determined by visual examination. This resulted in a final sample of 16 TD children and 16 children with ADHD. See Table 3.1 for a summary of participant demographics (n = 16 per group). Groups did not differ on ethnicity, age, family composition, family income or parental education. Estimated full scale IQ was measured for all children using the Block Design, Matrix Reasoning, Vocabulary, and Similarities subtests of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV). Children with ADHD were administered the WISC-IV as part of their diagnostic assessment, and TD children were administered the WISC-IV during the baseline laboratory day. Children with ADHD were found to have significantly lower IQ scores

compared to TD children (p = .04), although the mean score for both groups was in the Average range.

Procedure

Participants were first screened for eligibility using questionnaires. Eligible participants then completed a two-week at home baseline period. During this time, they were asked to wear an actigraph and parents were asked to complete a daily sleep diary to determine participants' typical sleep schedules. At the end of the baseline period, participants spent a night in the sleep laboratory where their sleep was recorded using PSG. The baseline period was followed by a one week break after which time participants began the sleep manipulation. The sleep manipulation involved six nights of typical sleep (Typical condition) and six nights of time in bed (TIB) restricted by one hour less per night than their typical TIB (Restricted condition). Restriction was achieved by delaying bedtime by one hour. The two conditions were counterbalanced and there was a two-week recovery period between each. Participants again spent a night in the sleep laboratory at the end of each of the sleep manipulation periods. In the day following each of their PSG nights in the laboratory, participants engaged in cognitive and emotional testing and had four multiple sleep latency tests (MSLTs) (these data are reported elsewhere). They were prohibited from consuming caffeine or products that contain caffeine (e.g., chocolate) during this time and had limited exposure to natural sunlight.

Conners Parent Rating Scale – Third Edition (Conners 3-P; Conners, 2008). The Conners 3-P is a 110-item behaviour rating scale designed to evaluate problem behaviours in the home in children aged 6 to 18 years old. This measure was

administered to participants' parents during screening and was used to ensure that children in the TD group did not have clinically elevated symptom levels and to confirm ADHD status in the ADHD group. It has been shown to have excellent internal reliability (Conners, 2008). Higher scores on this measure indicate higher symptom levels. For the current study we also used this measure to determine whether ADHD symptoms were related to sleep spindle activity and looked at the Conners 3-P raw inattention score, raw hyperactivity/impulsivity score, and ADHD combined total score.

Polysomnography. EEG was recorded from four channels (C3, C4, O1, O2). Electromyogram (EMG) was recorded from two submental sites as well as on the left and right anterior tibialis muscles. Electrocardiogram (ECG) and left and right electrooculogram (EOG) were also recorded. Respiration was recorded using bands on the chest and abdomen to measure respiratory effort, an oronasal cannula to measure breathing, a finger-probe pulse oximeter to measure oxygen saturation, and a room microphone to identify snoring. An infrared camera was used to monitor and record participants' body position. All PSG assessments were conducted with a Sandman® PSG system and sleep stages were visually scored offline in 30-second epochs by a registered sleep technician (supervised by a physician with a specialization in sleep medicine) according to American Academy of Sleep Medicine (AASM) guidelines (Iber, Ancoli-Israel, Chesson, & Quan, 2007).

Spindle detection. Following the procedure outlined by Ray and colleagues (Ray et al., 2015), we limited the detection and analysis of spindles only to the C3 channel. In cases where the signal for the C3 channel was poor for the majority of a recording, data

from C4 was substituted.[1] EEG data were band-pass filtered between 0.3-35 Hz prior to applying the algorithm for automatic detection, with all parameters set as default. Activity in the frequency range of 11 to 16 Hz longer than 0.5 s was isolated through band-pass filtering. The resulting signal was then squared, obtaining a profile that reflected how amplitude changed with time, and then finally converted into z-scores so that the same criteria for isolating spindles could be applied across subjects. Spindles were defined as the bouts of signal with corresponding z-scores higher than 2.33 (99th percentile). The length was then adjusted such that the onset/offset corresponded to the first/last points preceding the threshold for which z=0.5, respectively. The spindle amplitude was calculated by considering the maximum peak-to-peak amplitude value in the given time window in microvolts, while mean frequency was calculated as the peak-to-peak mean distance in Hz. The latter feature was used to distinguish between fast and slow spindles, according to whether their mean frequency was above or below 13.5 Hz (slow spindles were defined by frequency between 11 and 13.5 Hz while fast spindles were between 13.5 and 16 Hz). Metrics of interest were then extracted, and included average spindle density, ISI, mean duration, mean amplitude, and mean frequency separately for slow and fast spindles. Variables were analyzed separately for slow and fast spindles given that slow and fast spindles have been shown to be topographically and functionally distinct (Schabus et al., 2007). Spindle density was defined as the number of spindles per minute calculated over 60 second time windows across the entire signal; density across all windows was then averaged. ISI was defined as the time interval

[1] This occurred in 4 out of 64 files.

between the end of a spindle and the onset of the next one.. Analyses were focused on sleep spindles in N2 given the prominence of spindles during this stage.

Data Analyses. To determine the impact of sleep restriction and ADHD diagnosis on spindle variables, two-way mixed ANOVAs were used to examine the effect of group (TD, ADHD) and experimental manipulation (Typical condition, Restricted condition). Separate ANOVAs were run for slow and fast spindle density, ISI, duration, amplitude, and mean frequency. Outliers were defined as studentized residuals plus or minus three. Variables that were non-normally distributed, contained significant outliers, and/or violated the assumption of homogeneity of variance were square root transformed and ANOVAs were run both prior to transformations being applied and after. As results did not change after applying transformations, results using the raw data are presented below. An alpha level of .05 was used to determine the statistical significance of all analyses.

Results

Sleep and Sleep Spindle Characteristics

T-tests were used to compare sleep parameters and sleep architecture between TD children and children with ADHD during the Typical condition night in the laboratory. Results indicated that there were no differences between groups, although there was a trend towards a longer latency to N3 sleep in children with ADHD (p = .08). Means and standard deviations for all sleep parameters and sleep architecture variables are presented in Table 3.2. T-tests were also used to determine that there were no significant differences between male and female participants in any of the spindle variables during either the Typical or Restricted condition nights (see Table 3.3 for means and standard deviations). Bivariate correlations were run between sleep spindle variables and age in

months at baseline as well as IQ, as both of these variables have been shown to be related to spindles in children (see Table 3.4 for correlations). Correlations indicated that age was positively correlated with amplitude of slow spindles on the Typical condition night (r = .42, p = .02) as well as the Restricted condition night (r = .40, p = .02) (consistent with research showing an increase in slow spindle amplitude within this developmental period, Clawson et al., 2016) while IQ was positively correlated with the mean frequency of slow spindles during the Restricted condition night only (r = .35, p = .05). Comparisons of fast and slow spindles indicated that slow spindles had a higher density, smaller ISI, were longer in duration, and had a higher amplitude. Means and standard deviations for sleep spindle variables are presented in Table 3.5.

Group and Condition Effects

ANOVA results indicated that there were no significant condition or group main effects and no condition by group interactions for any of the spindle variables of interest (p > .05 for all). There was a trend towards a condition effect for the density of slow spindles (F(1, 30) = 4.59, p = .07) with participants having a lower spindle density during the Restricted condition night (Mean = 3.69, Standard Deviation = 0.99) compared to the Typical condition night (M = 4.00, SD = 0.70), as was hypothesized[2]. Effect sizes are presented in Table 3.5.

Follow-Up Analyses

[2] As age and IQ were only related to slow spindle amplitude and frequency (for which group and condition effects were null) and given our small samples size, we did not include these variables as covariates in our analyses. Groups were also matched on age and average IQ in both groups was in the Average range. Future studies with a broader age range and a larger sample size may choose to include these variables as covariates in their analyses.

Given the variability in the extent to which sleep restriction was achieved across participants, it was of interest to determine whether the degree to which participants were sleep restricted was related to changes in their spindle activity. To do this, cumulative TST was calculated from the nights leading up to and including the PSG night based on actigraphy. Values for cumulative TST could not be calculated for three participants (2 during the Typical condition, 1 during the Restricted condition) as these participants were missing all nights of actigraphy for these manipulation periods. Little's MCAR test (Little, 1988) was used to determine that the cumulative TST values were missing completely at random ($\chi^2 = 1.44$, $p = .49$) and expectation maximization was then used to generate missing values in SPSS. The degree of sleep restriction was defined as the difference score between the cumulative TST during the Typical condition and the cumulative TST during the Restricted condition. Difference scores were also calculated between Typical and Restricted conditions for each of the five spindle variables, separately for slow and fast spindles. Ten simple linear regressions were run using the cumulative TST difference score to predict changes in spindle activity. Results indicated that the degree of sleep restriction was not predictive of spindle density (slow, $F(1, 31) = 0.47$, $p = .50$; fast, $F(1, 31) = 0.48$, $p = .49$), ISI (slow, $F(1, 31) = 1.71$, $p = .20$; fast, $F(1, 31) = 0.13$, $p = .72$), duration (slow, $F(1, 31) = 0.86$, $p = .36$; fast, $F(1, 31) < .001$, $p = .99$), amplitude (slow, $F(1, 31) = 1.42$, $p = .24$; fast, $F(1, 31) = 0.20$, $p = .66$), or mean frequency (slow, $F(1, 31) = 1.41$, $p = .24$; fast, $F(1, 31) = 0.20$, $p = .66$).

Additionally, ADHD symptoms, rather than ADHD diagnosis, were investigated to determine their relationship to sleep spindles during the Typical condition (similar to Merikanto et al., 2019). Ten standard multiple regressions were run using the Conners 3-

P raw inattention score, raw hyperactivity/impulsivity score, and ADHD combined total score as the independent variables and each of the spindle variables noted above as dependent variables. Results indicated that spindle density (slow, $F(3, 30) = 0.41$, $p = .75$; fast, $F(3, 30) = 1.31$, $p = .29$), ISI (slow, $F(3, 30) = 0.25$, $p = .86$); fast, $F(3, 30) = 1.37$, $p = .27$), duration (slow, $F(3, 30) = 0.82$, $p = .50$; fast, $F(3, 30) = 0.51$, $p = .68$), amplitude (slow, $F(3, 30) = 0.42$, $p = .74$; fast, $F(3, 30) = 0.38$, $p = .77$), and slow spindle mean frequency ($F(3, 30) = 0.99$, $p = .41$) were not predicted by the Conners 3-P scores. However, the multiple regression model for mean fast spindle frequency was significant ($F(3, 30) = 4.17$, $p = .02$)[3]. Only the Conners 3-P raw hyperactivity/impulsivity score added statistical significance to the prediction ($p = .02$) where higher levels of symptoms were predictive of faster fast spindles. There was also a trend towards a contribution of the raw inattention score ($p = .08$). Overall, ADHD symptoms collectively accounted for 31.6% of explained variability in the model.

Discussion

The primary goal of the current study was to determine whether slow and fast sleep spindle variables (density, ISI, duration, amplitude, mean frequency) are impacted by a mild degree of chronic sleep restriction in school-age children. Our results indicated that sleep restriction led to a trend towards a reduction in slow spindle density, in line with our hypotheses. This finding is consistent with previous literature in adults (Curcio et al., 2003) and has been interpreted as being related to the inverse relationship between sleep spindles and slow waves, thus being indicative of a homeostatic response to sleep

[3] The regression model was also tested controlling for the contribution of age given that age tends to impact hyperactivity/impulsivity in children. The model remained significant after controlling for age.

loss (Achermann & Borbléy, 2011; De Gennaro & Ferrara, 2003). In adults, there is some evidence that this reduction in spindle density is exclusive to fast spindles (Knoblauch et al., 2003). In adolescents, sleep restriction has not been found to be related to spindle density, although Reynolds et al. (2018a) did conclude that overall, fast spindle activity appeared to be affected by sleep restriction to a greater degree than slow spindle activity. Therefore, the results of the current study are somewhat consistent with those of previous investigations to the degree that sleep spindles were reduced during sleep restriction across groups (consistent with adult studies of sleep loss but inconsistent with the findings of Reynolds et al.) while our findings diverge from previous research in that density was reduced for slow spindles only (though it should be noted that this was a trend and not statistically significant). This difference could be due to the age group of our participants, as younger children have been shown to have a greater prominence of slow spindles compared to older children (Shinomiya et al, 1999). We did not find any differences in ISI, duration, amplitude, or frequency of spindles, as had been hypothesized. Regression analyses indicated that the degree of sleep restriction achieved did not significantly predict any spindle variables.

The second goal of the current study was to determine whether and how ADHD status impacts sleep spindles, both across conditions and during sleep restriction. Results suggest that ADHD status was also unrelated to spindle activity. We therefore considered the contribution of ADHD symptoms across groups, in line with the investigation by Merikanto et al. (2019) in adolescents (although it should be noted that Merikanto et al. exclusively considered sub-clinical symptoms). No relationship was found between ADHD symptoms and the amplitude or duration of spindles in the current study;

however, it was found that ADHD symptoms (specifically higher hyperactivity/impulsivity scores) were predictive of faster fast spindles. Therefore, while the current study did not replicate the findings of Merikanto et al., the finding that ADHD symptoms were related to mean frequency of fast spindles is consistent with their finding that ADHD symptoms were exclusively related to fast spindles. As the authors did not look specifically at mean frequency in their investigation, this finding unfortunately cannot be directly compared between studies. Overall, our results highlight that despite employing similar metrics to measure spindle activity, findings related to the relationship between sleep spindles and ADHD diagnosis/symptoms are inconsistent (Gruber & Wise, 2016). This inconsistency may be related to methodological issues (see below).

Contributions of the Current Study

Although we did not find that spindle variables were affected by sleep restriction to the extent that we had predicted, the current study contributes to the field in several important ways. First, the current study is the first to examine sleep spindles during experimental sleep restriction in a sample of school-age children. Despite the extensive experimental literature examining the various impacts of sleep loss in adults, this body of literature in children is far more limited. To date, there are only 12 studies of experimental sleep restriction in school-age children, only 2 of which looked at physiological changes in sleep. This is important as childhood is a period of acute neural development and as such, the impact of insufficient sleep may have unique developmental consequences (Beebe, 2011). Second, given the existing state of research on sleep spindles in children with NDDs such as ADHD, the current study contributes to the literature by providing data from a study with rigorous methodological control. In

reviewing the existing literature, Gruber and Wise (2016) suggest that looking at more homogenous groups in terms of age and sex may result in more significant findings. Participants with ADHD in the current study were both age- and sex-matched with their TD peers and the greater number of boys reflected a higher prevalence of ADHD among boys clinically (Arnold, 1996). As the current study included children between 6 and 12 years of age, future studies may wish to recruit participants within a narrower age range to increase the likelihood of obtaining significant results should differences between populations exist (as suggested by Gruber and Wise). This is particularly important as spindles have been shown to change across development with regard to morphology and topography, which is believed to be related to changes in brain structure and function during this period (Clawson et al., 2016). Finally, the current study also controlled for medication status, requiring all participants with ADHD to be stimulant medication naïve, thus removing this as a potential confounding variable (Corkum & Coulombe, 2013).

Methodological Issues and Limitations of the Current Study

The results of the current investigation must be considered within the context of the broader study from which the data were obtained. Examinations of daytime consequences (Davidson et al., under review) as well as sleep architecture and the power spectrum of sleep EEG (Speth et al., in preparation) point to a limited impact of the sleep restriction protocol. Therefore, it is possible that the degree of sleep restriction used in the current study was too mild to cause notable changes in sleep spindles. This conclusion is in line with that of Reynolds et al. (2018a) who found that restricting adolescents' sleep to 7.5 hours (which is approximately 30 minutes less than the recommended amount for

this age group) did not result in any negative impact on spindles. In the current study, while TIB was reduced by approximately 45 minutes during the Restricted condition night in the laboratory, TST differed between conditions by less than 30 minutes.

Two additional methodological issues that may have impacted results are the number of nights of EEG recording used to calculate spindle variables and the choice of spindle detection method. Reynolds et al. (2018b) found that a minimum of two nights of EEG recording is necessary to reliably measure slow spindle duration in adolescents while a minimum of four nights is necessary for measurement of spindle density. Regarding spindle detection, while the automatic detection algorithm used in the current study has been validated in healthy young participants and against two experts each employing a different scoring approach, Ray et al. (2015) acknowledge the need for further validation in clinical populations.

Indeed, researchers highlight the importance of employing automatic detection methods in the measurement of sleep spindles to ensure reproducible analyses between studies and to reliably compare results between different populations (Wallant, Maquet, & Phillips, 2016). However, the use of automatic detection presents new methodological concerns, as research has revealed minimal overlap between some spindle parameters when using different methods (Ujma et al., 2015). In addition to the variability in methodology used to measure sleep spindles, the high degree of variability between studies in the specific spindle variables used makes it difficult to build hypotheses and compare findings between studies (Mantua, 2018). Finally, the reduced sample size of 16 participants per group raises the question of whether our analyses were powered sufficiently to detect the expected effects. In a meta-analysis of 22 studies, Ujma (2018)

found that most previous studies looking at the association between sleep EEG (including spindles) and intelligence have been underpowered to reliably find associations between these variables. On the other hand, large scale comprehensive studies looking at the relationship between sleep characteristics and cognition have failed to replicate many previously reported findings (Achermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2018; Pesonen et al., 2019). This suggests that statistical power may not be the only issue at play in this field of research and calls into question the validity of some of the widely accepted relationships between sleep characteristics and other aspects of cognitive or behavioural functioning.

Future Directions

As this study is the first to investigate sleep spindle activity in school-age TD children and children with ADHD both under typical sleep conditions and during sleep restriction, future research is needed to validate and add to our findings. Additionally, future studies may also wish to look at temporal changes in sleep spindles across the night and across epochs of individual cycles, given that in children and adolescents, variables such as spindle density and frequency change over the course of the night and within NREM cycles (Clawson et al., 2016; McClain et al., 2016; Purcell et al., 2017). In an attempt to understand physiological differences in sleep between TD children and children with ADHD, researchers have started to employ alternative methods for measuring changes in sleep microstructure. For example, Akinci et al. (2015) and Miano et al. (2006) investigated NREM sleep instability in TD children and children with ADHD by looking at the cyclic alternating pattern (CAP) which measures the fluctuation of arousals during sleep. The authors found that children with ADHD had a lower CAP

rate indicating that sleep problems in children with ADHD may stem from a dysregulation of arousal mechanisms. More recently, De Dea, Zanus, Carrozzi, Stecca, and Accardo (2018) looked at the power spectrum of sleep EEG preceding, during, and following sleep spindles in children with ADHD and found that power in almost all frequency bands in the period following spindles was lower in children with ADHD. The authors suggest that this reduced spindle-related activity may be related to impairment in memory consolidation and may explain difficulties with sleep in this population.

Clinical Implications

While the results of the current study did not show differences in sleep spindles between TD children and children with ADHD, hyperactivity/impulsivity was related to spindles when this symptom was looked at across both groups. While we did not replicate the findings of Merikanto et al. (2019) with regard to the amplitude or duration of spindles, our results are in line with their finding that higher ADHD symptoms were exclusively related to fast spindle characteristics (i.e., lower amplitude, shorter duration). As previously stated, the literature looking at sleep spindles in children with ADHD is characterized by mixed results. These studies were likely impacted by similar methodological issues as studies investigating the relationship between sleep spindles and cognitive ability, with these issues accounting, at least in part, for the inconsistencies. In the current study, we also found that IQ was positively correlated with the frequency of slow spindles during the Restricted condition night only. This finding is somewhat in contrast to the results of previous studies which showed a negative relationship between IQ and spindle frequency, although this association was found during a habitual night of sleep (Geiger et al., 2011; Gruber et al., 2013). Again, in light of recent research (e.g.,

Pesonen et al., 2019) and considering the methodological challenges related to the study of sleep spindles and general cognitive ability (Ujma, 2018) these conflicting results are not surprising. It is therefore difficult to draw conclusions about what our results may mean with regard to the cognitive and neurological functioning of our participants.

Generally speaking, the results of the current study as well as those of Merikanto et al. (2019) point to the possibility of altered spindle activity in children and adolescents with a higher degree of ADHD symptomatology. While the results of the current study do not support the idea that altered sleep spindle activity is unique to children who are within a discrete diagnostic category of ADHD, it is possible that an established relationship between sleep spindles and dimensional aspects of ADHD may be helpful in identifying early markers of developmental issues such as hyperactivity (Gruber & Wise, 2016). Researchers should exercise caution when carrying out studies in this area and take the necessary steps to ensure a high degree of methodological control (e.g., using more than one spindle detection method, using methods validated for clinical populations, pooling data from multiple studies for larger sample sizes). If a consistent and reliable relationship between sleep spindles and measures of ADHD symptoms can be established, it is possible that by using markers such as sleep spindles to identify potential difficulties early on (for example, during a routine sleep assessment in young children) health professionals could intervene before these difficulties have a more serious impact on the development of at-risk children.

Conclusions

The current study used an automatic spindle detection algorithm to determine whether fast and slow sleep spindle density, ISI, duration, amplitude, and mean frequency

is impacted by sleep restriction, ADHD diagnosis, and ADHD symptoms (in TD children and in children with ADHD). Our results suggest that there was a reduction in slow spindle density related to sleep restriction. We found no differences in density, ISI, duration, amplitude, or frequency of slow or fast spindles between children with ADHD and their TD peers which did not change when participants were sleep restricted. However, when we considered ADHD symptoms rather than diagnosis, we found that the Conners 3-P raw hyperactivity/impulsivity score was related to faster frequency of fast spindles. Overall, our results are in line with some previous research pointing to reduced sleep spindle activity as a result of sleep loss as well as differential sleep spindle activity as a function of ADHD symptomatology. Given that this is the first study to investigate differences in sleep spindles between these two groups under experimental sleep restriction conditions, future research is needed to corroborate and extend our findings.

Table 3.1

Participant Demographics for the Reduced Sample by Group

	ADHD (n = 16)	TD (n = 16)		
Variable	M (SD)	M (SD)	t	p
Age (months)	105.69 (19.16)	103.44 (17.35)	0.35	.73
Estimated FSIQ	100.16 (11.42)	108.36 (9.67)	-2.19	.04
Variable			χ^2	p
Ethnicity (n = 28)	13/14 White/Caucasian; 1/14 Multi-Racial	13/14 White/Caucasian; 1/14 Multi-Racial	0.00	1.00
Family Composition (n = 30)	12/15 two parent; 3/15 single parent	14/15 two parent; 1/15 single parent	1.15	.60
Maternal Education (n = 31)	6.00	4.50	4.84	.30
Paternal Education (n = 26)	2.00	4.00	8.11	.11
Annual Family Income (n = 32)	6.00	7.00	4.25	.51

Note: Age in years and months at the time of baseline; M = mean; SD = standard deviation; TD = typically developing; FSIQ = full scale intelligence quotient; Median values presented for maternal and paternal education: 1 = some secondary/high school, 2 = completed secondary/high school, 3 = some community, technical, or CEGEP college; 4 = completed community, technical, or CEGEP college; 5 = some university or teacher's college, 6 = completed university or teacher's college; Median values presented for annual family income: 1 = up to $20,000, 2 = $20,001 to $30,000, 3 = $30,001 to $40,000, 4 = $40,001 to $50,000, 5 = $50,001 to $60,000, 6 = $60,001 to $70,000, 7 = More than $70,000.

Table 3.2

Means and SD and Results of T-Tests Comparing Sleep Parameters and Sleep Architecture Variables during the Typical Condition Night Compared between TD Children and Children with ADHD

	Mean (SD)			
Sleep Parameters and Architecture	ADHD (*n* = 16)	TD (*n* = 16)	*t*	*p*
TST (min)	515.74 (50.89)	524.09 (58.97)	-0.43	.67
SE (%)	88.54 (7.22)	87.63 (9.20)	0.31	.76
SOL (min)	20.62 (15.53)	26.92 (31.91)	-0.71	.48
WASO (min)	45.81 (42.72)	39.75 (27.20)	0.48	.64
N1 (min)	25.88 (9.26)	31.43 (11.49)	-1.51	.14
N2 (min)	230.58 (56.97)	233.69 (41.93)	-0.18	.86
N3 (min)	142.54 (47.58)	142.44 (40.27)	0.01	.86
N3 Latency (min)	14.06 (12.20)	8.38 (3.18)	1.81	.08
REM (min)	116.74 (20.21)	116.53 (31.06)	0.02	.98
REM Latency (min)	116.56 (43.93)	135.38 (53.90)	-1.08	.29

Note: TST = total sleep time; SE = sleep efficiency; SOL = sleep onset latency; WASO = wake after sleep onset.

Table 3.3

Means and SD and Results of T-Tests Comparing Sleep Spindle Variables during the Typical Condition Night and the Restricted Condition Night between Boys and Girls

	Mean (SD)			
Typical – Slow (11-13.5 Hz)	Boys (*n* = 24)	Girls (*n* = 8)	*t*	*p*
Density	3.96 (0.76)	4.13 (0.49	-0.57	.57
ISI	14.46 (3.08)	13.92 (1.68)	0.47	.64
Duration	1.08 (0.16)	1.10 (0.09)	-0.46	.65
Amplitude	40.30 (16.24)	43.15 (12.86)	-0.45	.66
Frequency	12.47 (0.26)	12.53 (0.26)	-0.57	.58
Typical – Fast (13.5-16 Hz)				
Density	0.54 (0.27)	0.47 (0.26)	0.61	.55
ISI	16.98 (3.50)	17.76 (3.26)	-0.56	.58
Duration	0.76 (0.09)	0.78 (0.06)	-0.67	.51
Amplitude	33.28 (9.85)	37.00 (9.61)	-0.92	.36
Frequency	14.06 (0.14)	14.00 (0.10)	1.18	.25
Restricted – Slow (11-13.5 Hz)				
Density	3.64 (1.10)	3.85 (0.58)	-0.52	.61
ISI	16.30 (6.33)	13.89 (1.24)	1.06	.30
Duration	1.06 (0.22)	1.09 (0.09)	-0.31	.76
Amplitude	37.05 (19.25)	41.03 (11.80)	-0.55	.59
Frequency	12.50 (0.27)	12.61 (0.29)	-0.98	.34
Restricted – Fast (13.5-16 Hz)				
Density	0.56 (0.30)	0.68 (0.43)	-0.92	.36
ISI	18.20 (5.41)	17.89 (3.92)	0.15	.88
Duration	0.76 (0.10)	0.79 (0.14)	-0.84	.41
Amplitude	30.80 (13.40)	35.44 (10.58)	-0.89	.38
Frequency	14.07 (0.12)	14.00 (0.12)	1.41	.17

Note: ISI = inter-spindle interval.

Table 3.4

Bivariate Correlations Between Age (Months), Estimated FSIQ, and Sleep Spindle Variables During the Typical and Restricted Condition Nights

	Slow (11-13.5 Hz)					Fast (13.5-16 Hz)				
Typical Condition	Density	ISI	Duration	Amplitude	Frequency	Density	ISI	Duration	Amplitude	Frequency
Age (months)	.21	-.15	.31	.42*	.07	-.22	-.05	.29	.11	-.13
Estimated FSIQ	-.28	.27	-.17	-.11	.25	.20	.25	.14	-.06	-.13
Restricted Condition										
Age (months)	.15	-.10	.29	.40*	.20	-.02	-.16	.34	.13	-.13
Estimated FSIQ	-.24	.22	-.24	-.10	.35*	.21	.19	.06	.02	-.16

Note: ISI = inter-spindle interval; FSIQ = full scale intelligence quotient.
*=significant at $p < .05$; † = trend at $p > .05$ and $< .10$.

Table 3.5

Means, Standard Deviations, and Effect Sizes for Sleep Spindle Variables

	Mean (SD)								
	All Participants (n = 32)		ADHD (n = 16)		TD (n = 16)		Effect Size[a]		
Slow (11-13.5 Hz)	Typical	Restricted	Typical	Restricted	Typical	Restricted	G	C	GxC
Density	4.00 (0.70)	3.69 (0.99)	4.08 (0.42)	3.75 (0.95)	3.92 (0.91)	3.63 (0.99)	.01	.11†	<.001
ISI	14.33 (2.78)	15.70 (5.58)	14.10 (1.17)	15.87 (6.65)	14.55 (3.81)	15.52 (4.49)	<.001	.07	.01
Duration	1.08 (0.14)	1.07 (0.19)	1.13 (0.11)	1.11 (0.18)	1.04 (0.17)	1.03 (0.20)	.08	.01	.001
Amplitude	41.01 (15.32)	38.04 (17.59)	42.73 (11.50)	38.95 (15.30)	39.28 (18.61)	37.13 (20.09)	.01	.07	.01
Frequency	12.49 (0.26)	12.53 (0.27)	12.43 (0.28)	12.50 (0.31)	12.54 (0.23)	12.57 (0.24)	.04	.04	.01
Fast (13.5-16 Hz)									
Density	0.46 (0.18)	0.59 (0.33)	0.46 (0.18)	0.53 (0.35)	0.59 (0.32)	0.64 (0.32)	.06	.05	.001
ISI	17.18 (3.41)	18.12 (5.02)	16.87 (2.52)	18.30 (5.89)	17.49 (4.18)	17.94 (4.15)	<.001	.04	.01
Duration	0.76 (0.08)	0.77 (0.11)	0.77 (0.08)	0.78 (0.13)	0.76 (0.09)	0.75 (0.08)	.02	.001	.01
Amplitude	34.20 (9.77)	31.96 (12.75)	36.09 (7.00)	32.93 (11.41)	32.31 (11.86)	30.99 (14.28)	.02	.05	.01
Frequency	14.05 (0.13)	14.05 (0.13)	14.06 (0.15)	14.06 (0.13)	14.03 (0.11)	14.05 (0.12)	.01	.002	.02

Note: ISI = inter-spindle interval.

[a]Effect size reported as partial eta squared.

*=significant at $p < .05$; † = trend at $p > .05$ and $< .10$.

Chapter 4: Discussion

Overview of Findings

There were three main objectives of this dissertation: (1) to determine the impact of CSR of one hour less TIB per night over six nights on sleep architecture, the power spectrum of sleep EEG, and sleep spindles in school-age children, (2) to explore potential differences in sleep physiology in children with ADHD as compared to TD children at a deeper level of analysis than most previous studies, using a sample of rigorously diagnosed, medication-naïve, age- and sex-matched children, and (3) to determine whether children with ADHD have the same homeostatic response to CSR relative to their TD peers as measured by sleep architecture, the power spectrum of sleep EEG, and sleep spindles. In the following sections, I will discuss the results pertaining to each of these objectives in turn. After providing an overview of our findings, broader theoretical and methodological concerns related to this field of research are discussed, along with the ways in which our findings contribute to an understanding of sleep in children with ADHD. Finally, I will review the strengths and limitations of this dissertation, along with the clinical implications of our findings and possible directions for future research.

Objective 1: To determine the impact of CSR of one hour less TIB per night over six nights on sleep architecture, the power spectrum of sleep EEG, and sleep spindles in school-age children. This objective was pursued in light of the limited existing literature on the effects of sleep restriction on sleep physiology in school-age children. Sleep EEG was first investigated at the broadest level of analysis, by comparing sleep architecture during the Typical and Restricted condition nights. This comparison was made using the full night of sleep as well as by using the first 5.1 hours of sleep only,

which was the longest duration of artifact-free sleep that was common to all participants across both condition nights. Overall, there was a TIB difference of 45 minutes between conditions, but only a 28-minute differences in TST as recorded by PSG during the laboratory night. Despite the fact that participants seemed to be making up to some extent for the shortened sleep opportunity (given that the difference in TST is almost 20 minutes less than the difference in TIB), there were no significant changes in SOL, SE, or WASO (although there were differences found using actigraphy, which will be discussed in more detail below). Regarding sleep architecture, there was a reduction in the duration of REM sleep, both across the full night and when looking at the first 5.1 hours of sleep. Additional differences in sleep architecture related to CSR differed by group. Thus, in looking specifically at TD children, we noted a shorter duration of N1 (using the full night), maintenance of N2, and a shorter duration of REM (using the full night and first 5.1 hours) which is mostly in line with the expected homeostatic response based on previous research of CSR in other populations. There was no change in SWA as had been predicted based on previous research in adults (Banks & Dinges, 2007) and adolescents (Ong, Lo, Gooley, & Chee, 2016); however, this was likely due to an insufficient degree of sleep restriction (Skorucak, Arbon, Dijk, & Achermann, 2018). In looking beyond SWA, we found one trend which again differed as a function of group. In TD children only, there appeared to be less power in the EEG in the sigma band during CSR. This finding is in line with previous research which has shown a reduction in sigma activity following from sleep loss (e.g., Jenni, Achermann, & Carskadon, 2005, in a study of adolescents). We did not find any differences in theta activity, as was found by Åkerstedt, Kecklund, Ingre, Lekander, and Axelsson (2009) in adults.

Finally, in Chapter 3 we investigated changes in sleep physiology at the level of phasic events in the EEG. Specifically, sleep spindles were investigated as they have been shown to be affected by sleep loss and are thought to play an important role in protecting sleep, strengthening synapses in the brain, and facilitating learning. The results presented in Chapter 3 indicate that CSR led to a trend towards lower slow spindle density, as was predicted due to the inverse relationship between spindles and slow waves, with sleep loss leading to an increase in slow waves (Achermann & Borbléy, 2011; De Gennaro & Ferrara, 2003). There were no additional changes in sleep spindle variables related to CSR, despite hypothesized increases in ISI and spindle duration, and reductions in spindle amplitude and mean frequency. It is important to note that there are inconsistencies in the results of studies looking at the impact of sleep loss on sleep spindles in adults and adolescents, which makes it difficult to form hypotheses or evaluate our findings in light of previous research. While our failure to replicate many of the results of previous studies is most likely due to the minimal degree of sleep restriction achieved by our study protocol it may also be related to methodological issues tied to the field of sleep spindle research more broadly (see below for a more thorough discussion of this issue). Despite this, the results of this study do seem to suggest that children are affected by sleep loss with regard to sleep spindle activity in a similar way to adults, even under a mild degree of sleep restriction. The results of Chapter 3 converge with those presented in Chapter 2, with both pointing to a homeostatic response of sleep physiology to the reduced sleep duration (at least with regard to TD children). This finding also corresponds to the trend towards lower sigma power found for TD children during CSR in Chapter 2, as spindles (a defining characteristic of N2 sleep) occur within the sigma

range (Malhotra & Avidan, 2014). Interestingly, slow spindle density was found to be lower during CSR across both groups suggesting that this response was not exclusive to TD children, which is in contrast to the findings of Chapter 2 where there appeared to be a differential homeostatic response in children with ADHD. This differential response will be discussed in more detail below, with regard to Objective 3.

Objective 2: To explore potential differences in sleep physiology in children with ADHD as compared to TD children at a deeper level of analysis than most previous studies, using a sample of rigorously diagnosed, medication-naïve, age- and sex-matched children. While sleep problems are common in children with ADHD, existing research has yet to establish the underlying physiological cause of these difficulties (Weiss, Craig, Davies, Schibuk, & Stein, 2015). To date, research has found no consistent differences in sleep architecture between TD children and children with ADHD (Corkum & Coulombe, 2013; Speth, Benoit, & Corkum, 2014). The results of Chapter 2 corroborated those of previous studies finding limited evidence of altered sleep architecture in children with ADHD, with two exceptions. Results indicated that children with ADHD had a prolonged latency to N3 sleep across conditions and more REM sleep when looking at the first 5.1 hours of the night – it is possible that this finding is related to alterations in the dopaminergic system given that this system has been implicated as an underlying mechanism in both sleep problems and ADHD (Kirov & Brand, 2014; Owens, 2005, 2006) and that dopamine has been shown to be related to the regulation of REM sleep (Kirov & Brand, 2014). Studies looking at the relationship of the dopaminergic system to sleep (especially the regulation of REM sleep) and symptomatology in ADHD have produced inconsistent results; however, given that alterations in REM sleep are

among the most commonly reported findings related to sleep in children with ADHD (Kirov & Brand, 2014) this topic merits further investigation. Finally, in looking at sleep parameters, results indicated that children with ADHD had more WASO. This finding will be discussed in greater detail below.

We added to the existing literature by examining differences in the power spectrum of sleep EEG between groups. This has only been done three times before in children with ADHD, with mixed results between these studies (Prehn-Kristensen et al., 2011, 2013; Ringli et al., 2013). Consistent with Prehn-Kristensen et al. (2011, 2013), we found no evidence to suggest that there are differences in sleep physiology between TD children and children with ADHD at the level of the power spectrum of EEG. We then examined differences between groups by comparing sleep spindle activity. This has also been done before in a limited number of previous studies, and the findings of these studies are again extremely variable (Gruber & Wise, 2016). The results of Chapter 3 found no differences between groups with regard to the physiological characteristics of sleep spindles. However, we did note a relationship across groups between higher mean frequency of fast spindles and a higher level of ADHD symptomatology (specifically, higher hyperactivity/impulsivity scores). The implications of this finding will be discussed in greater detail in the following sections, but generally support the notion that while sleep spindles may not categorically differentiate children with ADHD from TD children, sleep spindles may be used to identify specific symptom features across children.

Objective 3: To determine whether children with ADHD have the same homeostatic response to CSR relative to their TD peers as measured by sleep

architecture, the power spectrum of sleep EEG, and sleep spindles. The results discussed above indicate that children demonstrated a mild homeostatic response to the sleep restriction protocol as expected based on literature in adults and adolescents; however, these results must be considered in light of group by condition interactions. These interactions point to a differential response to sleep restriction in children with ADHD which could have potentially serious implications if these results are supported by additional future research. In Chapter 2, children with ADHD were found to have an increase in N1, N2, and sigma power during CSR, which was the opposite of the response for TD children (although TD children were shown to have a maintenance of, rather than a decrease in, N2). In light of the finding that children with ADHD had a longer latency to N3 and more WASO regardless of condition, and given the increase in REM latency during CSR (again, opposite to the change in TD children) we interpreted these findings as being related to *impaired* homeostatic processes (i.e., factors getting in the way of homeostatic processes functioning normally) rather than an alteration in the homeostatic processes themselves. Indeed, one possible explanation for the divergent findings between TD children and children with ADHD in Chapter 2 is that greater instability of sleep in children with ADHD (presenting itself in our study as more WASO) is preventing the progression from lighter to deeper stages of NREM during CSR. While these children may be able to adapt during typical sleep conditions, this greater degree of arousal during sleep may have impaired their ability to reach N3 sleep as often or stay in N3 for as long as TD children during CSR. This interpretation seems promising in light of previous research measuring the cyclic alternating pattern (CAP) in children with ADHD, in which a reduction in sleep features thought to be related to sleep preservation

and the consolidation of slow wave NREM have been found in children with ADHD (Akinci et al., 2015; Miano et al., 2006).

Following from this investigation, we considered whether the results presented in Chapter 2 (i.e., longer duration of N2 and greater sigma power during CSR) might be related to differences in spindle activity. Therefore, in Chapter 3 we again compared the response to CSR both between and within groups and considered the impact on various sleep spindle variables. While we did find a reduction in slow spindle density (consistent with a homeostatic response to the sleep restriction protocol) we did not see an interaction between group and condition as we would have expected given the greater amount of N2 and sigma power during CSR in children with ADHD. This would seem to suggest that children with ADHD are still experiencing a homeostatic response to sleep restriction, to some degree. This finding also highlights the fact that various methods of evaluating spindle activity do not necessarily map onto one another, which presents concerns for this field of research more broadly.

Theoretical and Methodological Concerns

This dissertation adds to a small collection of studies investigating the effects of CSR in school-age children. This body of research is small and relatively new when one considers the extensive experimental research that has been conducted on the effects of sleep loss in adults. With limited existing research in this area, this dissertation highlights several unique theoretical and methodological concerns that do not follow directly from research in adults and therefore should be considered in future research.

Degree of sleep restriction. Given the consistent and robust results of previous studies with adults and adolescents that have shown changes in sleep architecture and the

power spectrum of sleep (e.g., Banks & Dinges, 2007) and sleep spindles (e.g., Curcio, Ferrara, Pellicciari, Cristiani, & De Gennaro, 2003) as a result of CSR, the limited results of the current study suggest that our sleep restriction protocol may have been too mild to lead to significant changes in sleep physiology. For example, Carskadon, Harvey, and Dement (1981) studied children 11 to 13 years old and employed an acute sleep restriction protocol with TIB reduced to four hours on a single night. These authors found a similar impact on sleep parameters and sleep architecture as has been found in studies of adults, including decreased SOL and latency to stage 4, a preservation in the duration of stage 4 sleep, and a corresponding reduction in time spent in stages 1, 2, 3 and REM. Similarly, Kurth et al. (2016) employed a more acute degree of sleep loss (restricting TIB to half of participants' habitual sleep) and noted an increase in SWA specifically in the parieto-occipital region of the brain. Alteration in sleep spindles related to CSR has not been studied in school-age children but has been investigated in adolescents, with researchers finding that fast spindles were longer and had decreased amplitude (Reynolds, Gradisar, Coussens, & Short, 2018a). While the findings presented in this dissertation were in line with previous studies to some extent, there was limited or no evidence to support some hypotheses.

Considering additional findings of the larger study, there is more evidence to suggest that the sleep restriction protocol employed was too mild to produce the effects expected based on previous research. For example, an investigation of the impact of the sleep restriction protocol on daytime functioning found that sleep restriction was related to minimal consequences for participants despite a great deal of research consistently detailing the impact of sleep loss on attention, emotion, and cognition in both children

and adults (Davidson et al., under review). While using a more severe degree of restriction would have likely led to more significant findings, it is also important to consider both the ethical and methodological issues related to doing so. One of the reasons for conducting the larger study was to investigate the effects of sleep restriction in school-age children as childhood is a period of acute neural development and thus, the consequences of sleep restriction in this population are likely more severe compared to adults. In line with this idea, both Carskadon et al. (1981) and Ong et al. (2016) found alterations in sleep architecture and/or sleep propensity which remained even after a recovery night with a 9- or 10-hour sleep opportunity (in Ong et al., these differences remained after three nights of recovery sleep). Therefore, increasing the severity of the sleep restriction protocol would require researchers to consider and account for potential physical and cognitive consequences (e.g., a poor grade in school; Beebe, 2011) that may extend for days beyond the manipulation period. This would require alterations in methodology such as the incorporation of recovery nights (increasing both the cost and length of the study) and more commitment from participants and their families. It is possible in these cases that children may also be more resistant to spending an extended period of time away from home and likewise that parents would be hesitant to leave their children with researchers (Beebe, 2011). One must also consider the ability of young participants to assent to an extended sleep restriction protocol, as these children may not understand how this degree of sleep loss will feel.

Finally, while a more severe degree of sleep restriction may have led to more significant findings, the applicability of results to real-world conditions is questionable. While there are certainly circumstances in which young children would be exposed to

sleep loss greater than one hour per night (e.g., illness) these situations would likely be rare for most children. As such, the consequences following from this degree of restriction would be less clinically relevant. Therefore, while the studies presented in this dissertation failed to find evidence for several hypotheses, the protocol reflects a more typical degree of sleep restriction found among school-age children (Beebe, 2011) and therefore provides important and relevant information. What cannot be determined based on the results presented in this dissertation is whether one hour less TIB would lead to a greater impact on sleep physiology if this degree of sleep restriction was extended for a longer period of time. As research has pointed to a decline in sleep duration among children over the past century by about one hour per night (Matricciani, Olds, & Petkov, 2012) it would be important to consider the potential impact of a more chronic degree of mild sleep loss (see discussion of future directions and clinical implications below).

Measurement issues and methodological considerations. This dissertation also brings to light several issues specifically related to the measures and measurement techniques employed in the field of sleep research. EEG broadly is a time consuming and costly measurement tool (Ujma, 2018). The application of EEG apparatus takes time and requires specialized training of research assistants and cooperation from participants. It is likely that this would be made more difficult in studies involving children, especially under conditions of experimental sleep restriction (which can lead to impaired attention, Lundahl, Kidwell, Van Dyk, & Nelson, 2015) and with clinical populations such as children with ADHD (a disorder defined by attentional and behavioural difficulty). Additionally, when measuring brain activity using EEG there are several potential sources of artifact (Benbadis, 2006; Teplan, 2002). This may have implications for data

processing algorithms or automated data processing techniques, such as fast-Fourier transformation (FFT). Perhaps the most challenging feature of sleep measured within this dissertation was sleep spindles. Researchers have highlighted several issues related to the measurement of sleep spindles such as limited agreement between automated detection methods (Ujma et al., 2015) and variability in spindle metrics employed across studies (Mantua, 2018). Additionally, there are findings to suggest that many previous studies of spindle activity have been statistically underpowered (Ujma, 2018) which may lead to inconsistent results between studies. The results of large-scale comprehensive studies of spindle activity – specifically those looking at the relationship between spindles and cognitive functioning – highlight the possibility that small sample sizes may result in spurious findings, as these studies failed to replicate many of the widely-accepted relationships between these variables (Achermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2018; Pesonen et al., 2019). Indeed, the small sample size in the larger study (and the further reduced sample sizes in both Chapters 2 and 3) are a cause for caution in interpreting our results and additional research with larger sample sizes will be necessary to increase confidence in our results (and findings in the field broadly). The results presented in Chapter 3 provide an example of how findings can diverge from those of previous studies despite employing similar methodologies.

In light of the methodological issues presented above, researchers have proposed a number of approaches to future research that would improve consistency among studies and allow for greater statistical power in analyses involving sleep characteristics, such as sleep spindles (Mantua, 2018; Ujma, 2018). As research in this area moves forward, it will be especially important to look at a standardized set of sleep parameters (including

spindle variables) and establish a consistent method of reporting results which would include all parameters investigated, rather than selectively reporting results which are significant and do not conflict with previous findings or expectations (Mantua, 2018). Furthermore, given the cost-, time- and labour-intensive nature of studies measuring sleep physiology, Ujma (2018) encourages the sharing of PSG and other relevant data to allow for higher powered analyses. This would require ethics applications to include permissions for data sharing and an understanding on the part of individuals serving on ethics boards regarding the importance of sharing appropriately anonymized data among laboratories. Another approach is for researchers to routinely include measures of effect size in their results regardless of the significance of their findings, so that they can more easily be used in meta-analyses.

Additional methodological considerations are related to the field of pediatric sleep research and experimental sleep restriction more broadly. First, in comparing this dissertation to existing experimental studies of sleep restriction in school-age children, the methods used in the larger study were the first to compare a period of sleep restriction to controlled typically sleep over several nights (i.e., in the larger study, sleep schedules during the Typical condition period were prescribed over a period of six nights and based on typical sleep patterns that were measured objectively using actigraphy). All previous studies of experimental sleep restriction in children have compared a period of sleep restriction either to an imposed and optimized TIB (Carskadon et al., 1981; Fallone 2005, 2001; Molfese et al., 2013; Peters et al., 2009; Randazzo, Muehlbach, Schweitzer, & Walsh, 1998), a period of extended sleep (Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012; Vriend et al., 2013), baseline sleep (Gruber 2011; Sadeh, Gruber, & Raviv, 2003),

or a single night of prescribed sleep based on reported bedtimes (Kurth et al., 2016). This makes comparing results between studies difficult. In studies comparing sleep restriction to extended or optimized sleep, it cannot be determined whether the results of these studies are truly related to the impact of sleep loss or if differences between conditions are driven by participants having an enhanced sleep opportunity. Given that the participants in the current study were already sleeping approximately one hour less per night than the average recommended duration for this age group (as noted in Chapter 2, Hirshkowitz et al. 2015), results could have differed if sleep under CSR conditions had been compared to optimized or extended sleep. Therefore, the choice of methodology may impact the significance of results and has important implications for their interpretation.

Sleep in Children with ADHD

Research has consistently reported a high proportion of sleep problems among children with ADHD (Weiss et al., 2015). The most consistent findings regarding sleep problems in this population come from parental reports and include difficulties with restlessness during sleep, falling and staying asleep, and sleeping for a shorter period of time compared to TD children (Owens, 2005). In light of this, a great deal of research has been conducted to establish objective differences in sleep physiology that may underlie the difficulty with sleep reported so frequently within this population. There have been many studies on this topic, with researchers reporting conflicting findings. A review of reviews by Corkum and Coulombe (2013) considered the research in this area collectively and concluded that there were no consistent differences in sleep architecture between TD children and children with ADHD. The authors proposed that one

explanation for the conflicting findings between studies was the moderating impact of variables such as diagnostic procedures, comorbidity, medication use, age, sex, ADHD subtype, and sleep laboratory adaptation. Therefore, this dissertation contributes to the existing literature on sleep in children with ADHD in three ways, each of which will be discussed in turn below.

First, the results corroborate the idea that sleep problems in children with ADHD are not related to differences in sleep architecture, using a well-controlled study with a sample of rigorously-diagnosed, medication-naïve, age- and sex-matched children with ADHD (Corkum & Coulombe, 2013; Speth et al., 2014). Second, this dissertation extends previous research by examining sleep in children with ADHD at a deeper level of analysis. While there are some existing studies that have looked at sleep in children with ADHD at the level of the power spectrum of EEG and sleep spindle activity, these studies are limited in number and impacted by methodological inconsistencies. Within the context of a highly controlled study, we corroborated the results of previous studies that found no differences between groups in the power spectrum of sleep EEG (Prehn-Kristensen et al. 2011, 2013) or sleep spindle activity (Kiesow & Surwillo, 1987; Prehn-Kristensen et al., 2011). Third, this dissertation is only the second study to experimentally restrict sleep in school-age children with ADHD (Gruber et al., 2011) and the first to consider the impact of CSR on sleep physiology in this population. A key difference across previous studies of sleep in children with ADHD relates to study populations, with our study including rigorously-diagnosed children with ADHD (as mentioned above). Although we did not find differences in the power spectrum of sleep EEG or sleep spindles (either during the Typical condition or during CSR) and interaction effects for

sleep architecture were not statistically significant, post-exploration of the data in Chapter 2 suggest that children with ADHD in our study differed from TD children in their homeostatic response to CSR as measured by sleep architecture. This suggests a need for future work with larger samples and a more robust sleep manipulation.

In general, the results presented above can be interpreted in one of two ways. First, it is possible that the relationship between sleep problems and symptoms of ADHD is reciprocal, with each caused by separate underlying factors and interacting to influence and exacerbate the other. For example, given the research on sleep in children with ADHD that has been discussed previously in this dissertation, it is possible that an altered CAP is related to poorer consolidation of deep, restorative sleep, which may lead to children presenting with symptoms of ADHD during the day. These symptoms may lead to issues such as greater bedtime resistance which may then impact factors such as the duration of their sleep opportunity (Owens, 2005). A second possibility is that sleep problems and symptoms of ADHD are both related to a common biological abnormality in brain physiology and development. Barone, Hawks-Mayer and Lipton (2019) discuss the ontogeny of sleep dysfunction and neurodevelopmental disorders (NDD), noting that sleep problems are one of the most highly reported issues for children with NDDs and their families. These authors discuss the possibility of common underlying genetic factors leading to the parallel development and interplay between sleep and synapses in the brain, with abnormal synaptic physiology resulting in the extremely high rate of sleep problems among children with NDDs. While this dissertation cannot provide any direct evidence to corroborate or disconfirm this hypothesis, the results presented herein

provide support for the idea of altered sleep processes in children with ADHD at a physiological level.

Strengths and Limitations

There are several strengths of this dissertation. First, the studies presented within this dissertation are novel, as they are the first to investigate the effects of CSR on physiological changes in sleep with a sample of school-age children. While Carskadon et al. (1981) and Kurth et al. (2016) studied physiological changes in sleep following sleep loss in children between the ages of 11 to 13 and 5 to 12 years respectively, these authors investigated the effects of acute sleep restriction, as previously mentioned. In the current study, we employed a CSR protocol of one hour less TIB over six nights. Additionally, we not only investigated the impact of CSR on physiological changes in sleep in TD children but also considered the impact on children with ADHD. This is significant as many children with ADHD have pre-existing sleep problems and may therefore be more drastically impacted by sleep loss. Only one previous study has investigated the effects of experimental sleep restriction in children with ADHD (Gruber et al., 2011). This dissertation therefore represents an important first step in understanding homeostatic processes following sleep loss in children and how these processes may differ in children with ADHD. A second important strength of this dissertation is the degree of methodological control. As previously mentioned, Corkum and Coulombe (2013) found that a number of variables moderated the differences in sleep architecture between TD children and children with ADHD in previous studies. As such, children in the current study were rigorously diagnosed (using consistent diagnostic procedures), did not have

any comorbid mental health disorders (with the exception of learning disorders), were medication-naïve, and were age- and sex-matched to participants in the TD group.

The study protocol was also well controlled. The protocol included a baseline night in the sleep laboratory, thereby allowing for adaptation and accounting for the first night effect. Sleep laboratory adaptation has been shown to impact sleep in both TD children and children with ADHD but has frequently been overlooked in studies of sleep in these children (Bessey, Richards, & Corkum, 2013; Corkum & Coulombe, 2013; Kirov et al., 2012; Kirov & Brand, 2014). Actigraphy was used to measure habitual sleep patterns and to generate participants' sleep schedules for the Typical and Restricted conditions. Actigraphy was also used to objectively determine whether participants met the sleep restriction criterion rather than relying on sleep diary data. Finally, while the degree of sleep restriction employed was milder than previous studies examining the impact of sleep loss on sleep physiology in school-age children (Carskadon et al., 1981; Kurth et al., 2016) it represents a more typical or real-world degree of sleep loss that would be seen in children of this age (Beebe, 2011). Indeed, going to bed one hour later could be the result of getting home late from a basketball practice or staying up to complete extra homework. This degree of sleep restriction may be especially relevant to children with ADHD as these children have been reported to have a greater degree of bedtime resistance compared to TD children (Corkum, Tannock, Moldofsky, Hogg-Johnson, & Humphries, 2001).

In addition to the strengths of this dissertation, there are also limitations which must be discussed. First, as previously mentioned, while our sleep restriction protocol represents a more real-world degree of sleep loss within the age group studied, it is likely

that one hour less TIB over a period of six nights is too mild to find statistically significant differences in sleep between conditions. Additionally, some analyses in both Chapters 2 and 3 were run with a reduced sample size. This again could have impacted our ability to detect statistically significant differences. Another methodological limitation which has been mentioned briefly but merits further discussion is the number of nights of sleep recording used to establish values for the sleep variables we measured. In the larger study, a single night of sleep was recorded using PSG at the end of the Typical condition and at the end of the Restricted condition. Researchers have noted the importance of using multiple nights of sleep recordings to obtain reliable values for variables such as slow spindle density and duration (Reynolds, Gradisar, & Short, 2018). Additionally, children with ADHD have been shown to have a high degree of night-to-night variability in their sleep as measured by actigraphy (Gruber, Sadeh, & Raviv, 2000) which could have implications for the reliability of a single night of PSG data as this single night may not be representative of average sleep for these children. Differences in sleep between home and laboratory environments may have also contributed to our results, as laboratory PSG recordings do not account for factors that could contribute to sleep problems in the home environment, such as stress or ambient sounds (Owens, 2006; Weiss et al., 2015). This may be especially important when studying things like sleep spindles, which have been shown to contribute to the maintenance of sleep in the face of environmental noise (Cote et al., 2000; Dang-Vu, McKinney, Buxton, Solet, & Ellenbogen, 2010).

Taken together, the night-to-night variability in sleep in children with ADHD and differences between home and laboratory sleep environments may contribute to the high

degree of variability among studies that have examined sleep physiology in this population, as well as to the discordance between subjective and objective measures of sleep problems (Weiss et al., 2015). These limiting factors may also help to explain why, across groups, we failed to find differences between conditions in sleep parameters (i.e., SOL, WASO) using PSG recorded in the laboratory when differences between conditions were found for these variables using actigraphy recorded in the home environment and averaged over six nights (Davidson et al., under review; Owens, 2006; Weiss et al., 2015). Finally, as previously mentioned, research involving EEG recordings of sleep requires both a great deal of time and cooperation from participants. This is made more difficult when participants are young, sleep restricted, and – in the case of participants with ADHD – already face behavioural challenges. In the larger study, bedtimes were sometimes delayed during laboratory PSG nights. Anecdotally, delays in bedtime were sometimes due to challenges related to study protocol and procedures (challenges included but were not limited to, participants showing up late, technical problems, and more difficulty applying PSG apparatus due to participants' behaviour). Delays in bedtime (especially during the Typical condition night in the lab) may have also impacted our results and contributed to inconsistent findings such as those noted between the PSG and actigraphy data above. It should be noted however, that this possibility is speculative and would need to be examined more objectively to determine the degree to which these challenges may have impacted results.

Clinical Implications and Future Directions

As has been highlighted above, the research presented in this dissertation is novel. The wider literature on sleep restriction in children and sleep physiology in children with

ADHD is still in its infancy and compromised by numerous methodological issues; this makes it difficult to form sound clinical recommendations based on the findings to date (including those presented here). However, the results of this dissertation provide direction for future research. If future studies corroborate the results presented in this dissertation – finding that children with ADHD do indeed have an impaired capacity to adapt to sleep loss compared to TD children – the clinical implications would be profound. It has been proposed that ADHD and sleep disorders are derived from the same physiological underpinnings that present separately during the day and during the night (Weiss et al., 2015). If there is indeed an interplay between sleep problems and brain development in children with NDDs, then increased sleep problems (such as an inability to adapt to reduced sleep opportunity) may actively contribute to impaired brain functioning (Barone et al., 2019; Weiss et al., 2015). In addition, some of the psychotropic medications commonly used to treat ADHD have been shown to lead to sleep problems in these children (such as prolonged SOL), which may further exacerbate this problem (Kirov & Brand, 2014; Weiss et al., 2015). This makes sleep problems in and of themselves an important focus for clinical intervention (Barone et al., 2019). As such, clinicians will need to target both sleep problems and symptoms of ADHD to maximize the outcomes for either (Owens, 2006; Weiss et al., 2015).

Barone et al. (2019) also raise the question of whether features of sleep may be useful biomarkers in the identification of NDDs. This idea has also been proposed by Gruber and Wise (2016). While we did not find support for categorical differences in sleep variables between TD children and children with ADHD, our finding that higher levels of hyperactivity were related to a higher frequency of fast spindles suggests that

sleep spindles (or related features of sleep such as the CAP) may be useful in earlier identification of children for whom neurodevelopment may be altered. In light of the methodological issues presented earlier in this dissertation, the most fruitful avenue for future research would be to improve methodology used to measure sleep prior to exploring possible clinical applications of these findings.

Moving forward, another important area for future research would be the use of sleep restriction protocols to examine correlations between physiological changes following or during sleep loss with demographic variables, and causal relationships between these changes and daytime measures of brain activity, clinical variables (such as symptom ratings), and other measures of daytime functioning (such as cognitive and emotional measures) (Beebe, 2011). These types of analyses would not only provide information regarding which aspects of sleep physiology are most important to daytime functioning in children but would also help researchers to determine why certain individuals may experience a greater degree of vulnerability to sleep loss. The use of different sleep restriction protocols could also provide important information about how various degrees of restricted or extended sleep impact sleep physiology, as well as other important aspects of daytime functioning. Finally, it is unclear to what extent sleep physiology in school-age children may be impacted by an accumulation of sleep debt over an extended period of time. While it is likely that the degree of sleep restriction used in the larger study was too mild to lead to some of the expected changes in sleep physiology, it is possible that our results would have been different if this degree of sleep restriction were continued over a longer period of time. In light of the ethical and practical challenges that this would present, one possible solution would be to study

children in a camp setting – not only would this allow researchers to ensure participants' safety while employing a more acute level of restriction and/or restricting children over a longer period of time, it would also allow for a high degree of experimental control (e.g., diet, activity, light exposure).

Conclusions

The investigations presented within this dissertation are highly novel, as they are the first to consider the impact of CSR on the sleep physiology of school-age children. Moreover, the larger study is only the second study to date that has experimentally restricted sleep in children with ADHD. Based on our findings, it appears that TD children experience a similar homeostatic response to CSR as compared to adults and adolescents, even when the degree of CSR is mild. While the results presented above offer preliminary evidence of impaired homeostatic processes in children with ADHD, we view these results as hypothesis-generating and more research is needed in this area to corroborate these findings. If future research were to corroborate these findings, the results would have a profound impact on our understanding of the bidirectional relationship between sleep and ADHD and could lead to unique ways of treating symptoms of ADHD through direct interventions on sleep. This dissertation also highlights some of the methodological challenges inherent in this field of research and provides some direction to help improve future studies in this area. In sum, this dissertation contributes novel data to the field of pediatric sleep research and offers innovative ideas related to how physiological sleep and sleep processes may differ between TD children and children with ADHD.

References

Achermann, P., & Borbély, A. A. (2011). Sleep homeostasis and models of sleep regulation. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (5th ed.). (431-444). St. Louis: Elsevier Saunders.

Agostini, A., Carskadon, M. A., Dorrian, J., Coussens, S., & Short, M. A. (2017). An experimental study of adolescent sleep restriction during a simulated school week: Changes in phase, sleep staging, performance and sleepiness. *Journal of Sleep Research*, *26*, 227-235. doi: 10.1111/jsr.12473

Åkerstedt, T., Kecklund, G., Ingre, M., Lekander, M., & Axelsson, J. (2009). Sleep homeostasis during repeated sleep restriction and recovery: Support from EEG dynamics. *Sleep*, *32*(2), 217-222. https://doiorg.ezproxy.library.dal.ca/10.5665/sleep/32.2.217

Akinci, G., Oztura, I., Hiz, S., Akdogan, O., Karaarslan, D., Ozek, H., & Akay, A. (2015). Sleep structure in children with attention-deficit/hyperactivity disorder. *Journal of Child Neurology*, *30*(11), 1520-1525. doi: 10.1177/0883073815573318

Arnold, L. E. (1996). Sex differences in ADHD: Conference summary. *Journal of Abnormal Child Psychology*. *24*(5), 555-569. Retrieved from: https://link-springer-com.ezproxy.library.dal.ca/article/10.1007/BF01670100

Banks, S., & Dinges, D. F. (2007). Behavioral and physiological consequences of sleep restriction. *Journal of Clinical Sleep Medicine*, *3*(5), 519-528. Retrieved from: http://jcsm.aasm.org/Articles/030513.pdf

Barone, I., Hawks-Mayer, H., & Lipton, J. O. (2019). Mechanisms of sleep and circadian ontogeny through the lens of neurodevelopmental disorders. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2019.01.011

Beebe, D. W. (2011). Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescence. *Pediatric Clinics of North America*, *58*(3), 649-665. doi: 10.1016/j.pcl.2011.03.002

Benbadis, S. R. (2006). Introduction to electroencephalography. In T. Lee-Chiong (Ed.), *Sleep: A comprehensive handbook* (pp. 989-1024). Hoboken, NJ: Wiley & Sons.

Bessey, M., Richards, J., & Corkum, P. (2013). Sleep lab adaptation in children with attention-deficit/hyperactivity disorder and typically developing children. *Sleep Disorders*, *2013*, 1-4. http://dx.doi.org/10.1155/2013/698957

Bódizs, R., Gombos, F., Ujma, P. P., & Kovács, I. (2014). Sleep spindling and fluid intelligence across development: Sex matters. *Frontiers in Human Neuroscience*, *8*, 1-11. https://doi.org/10.3389/fnhum.2014.00952

Borbély, A. A., Baumann, F., Brandeis, D., Strauch, I., & Lehmann, D. (1981). Sleep deprivation: Effect on sleep stages and EEG power density in man. *Electroencephalography and Clinical Neurophysiology*, *51*, 483-493. https://doi.org/10.1016/0013-4694(81)90225-X

Brunner, P., Dijk, D-J., Borbély, A. A. (1993). Repeated partial sleep deprivation progressively changes the EEG during sleep and wakefulness. *Sleep*, *16*, 100-113. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/16.2.100

Cain, N., & Gradisar, M. (2010). Electronic media use and sleep in school-aged children and adolescents: A review. *Sleep Medicine*, *11*, 735-742. https://doi.org/10.1016/j.sleep.2010.02.006

Campbell, I. G., & Feinberg, I. (2016). Maturational patterns of sigma frequency across childhood and adolescence: A longitudinal study. *Sleep*, *39*(1), 193-201. https://doi-org.ezproxy.library.dal.ca/10.5665/sleep.5346

Carskadon, M. A., & Dement, W. C. (2011). Monitoring and staging human sleep. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed.) (pp 16-26). St. Louis: Elsevier Saunders.

Carskadon, M. A., Harvey, K., & Dement, W. C. (1981). Acute restriction of nocturnal sleep in children. *Perceptual and Motor Skills*, *53*, 103-112. https://doi-org.ezproxy.library.dal.ca/10.2466/pms.1981.53.1.103

Chatburn, A., Coussens, S., Lushington, K., Kennedy, D., Baumert, M., & Kohler, M. (2013). Sleep spindle activity and cognitive performance in healthy children. *Sleep*, *36*(2), 237-243. https://doi-org.ezproxy.library.dal.ca/10.5665/sleep.2380

Chen, X., Beydoun, M. A., & Wang, Y. (2008). Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. *Obesity*, *16*(2), 265-274. https://doi-org.ezproxy.library.dal.ca/10.1038/oby.2007.63

Clawson, B. C., Durkin, J., & Aton, S. J. (2016). Form and function of sleep spindles across the lifespan. *Neural Plasticity*, *2016*, 1-16. http://dx.doi.org/10.1155/2016/6936381

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum.

Cohen-Zion, M., & Ancoli-Israel, S. (2004). Sleep in children with attention-deficit hyperactivity disorder (ADHD): A review of naturalistic and stimulant intervention studies. *Sleep Medicine Reviews*, *8*, 379-402. doi: 10.1016/j.smrv.2004.06.002

Conners, C. K. (2008). *Conners 3rd edition*. Toronto, ON: Multi-Health Systems.

Corkum, P. V., & Coulombe, J. A. (2013). Sleep in the context of ADHD: A review of reviews to determine implications for research and clinical practice. In A. R. Wolfson & E. H. Montgomery-Downs (Eds.), *The Oxford handbook of infant, child, and adolescent sleep and behavior* (pp. 286-602). New York, NY: Oxford University Press.

Corkum, P., Tannock, R., Moldofsky, H., Hogg-Johnson, S., & Humphries, T. (2001). Actigraphy and parental ratings of sleep in children with attention-deficit/hyperactivity disorder (ADHD). *Sleep*, *24*(3), 303-312. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/24.3.303

Cote, K. A., Epps, T. M., & Campbell, K. B. (2000). The role of the spindle in human information processing of high-intensity stimuli during sleep. *Journal of Sleep Research*, *9*, 19-26. https://doi-org.ezproxy.library.dal.ca/10.1046/j.1365-2869.2000.00188.x

Curcio, G., Ferrara, M., Pellicciari, M. C., Cristiani, R., & De Gennaro, L. (2003). Effect of total sleep deprivation on the landmarks of stage 2 sleep. *Clinical Neurophysiology*, *114*, 2279-2285. https://doi.org/10.1016/S1388-2457(03)00276-1

Czeisler, C. A., Zimmerman, J. C., Ronda, J. M., Moore-Ede, M. C., & Weitzman, E. D. (1980). Timing of REM sleep is coupled to the circadian rhythm of body temperature. *Sleep*, *2*(3), 329-346. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/2.3.329

Dang-Vu, T. T., McKinney, S. M., Buxton, O. M., Solet, J. M., & Ellenbogen, J. M. (2010). Spontaneous brain rhythms predict sleep stability in the face of noise. *Current Biology*, *20*(15), R626-R627. https://doi.org/10.1016/j.cub.2010.06.032

Davidson, F., Brine, S., Speth, T., Miller, L., Rusak, B., Chambers, C., … Corkum, P. (Under Review). Impact of sleep restriction on attention, emotions, and cognitive functioning in children with ADHD and their typically developing peers. *Research in Developmental Disabilities.*

De Dea, F., Zanus, C., Carrozzi, M., Stecca, M., & Accardo, A. (2018). Characteristics of EEG power spectrum during sleep spindle events in ADHD children. 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (pp. 1456-1459). Honolulu, HI, USA. doi: 10.1109/EMBC.2018.8512486

De Gennaro, L., & Ferrara, M. (2003). Sleep spindles: An overview. *Sleep Medicine*

Reviews, *7*(5), 423-440. doi: 10.1016/S1087-0792(02)00116-8

Dewald, J. F., Meijer, A. M., Oort, F. J., Kerkhof, G. A., & Bögels, S. M. (2010). The influence of sleep quality, sleep duration and sleepiness on school performance in children and adolescents: A meta-analytic review. *Sleep Medicine Reviews*, *14*, 179-189. https://doi.org/10.1016/j.smrv.2009.10.004

Dijk, D-J., Hayes, B., & Czeisler, C. A. (1993). Dynamics of electroencephalographic sleep spindles and slow wave activity in men: Effect of sleep deprivation. *Brain Research*, *626*(1-2), 190-199. https://doi.org/10.1016/0006-8993(93)90579-C

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*, *25*(1), 117-129. doi: 10.1055/s-2005-867080

Fallone, G., Acebo, C., Arnedt, J. T., Seifer, R., & Carskadon, M. A. (2001). Effects of acute sleep restriction on behavior, sustained attention, and response inhibition in children. *Perceptual and Motor Skills*, *93*, 213-229. https://doi-org.ezproxy.library.dal.ca/10.2466/pms.2001.93.1.213

Fallone, G., Acebo, C., Seifer, R., & Carskadon, M. A. (2005). Experimental restriction of sleep opportunity in children: Effects on teacher ratings. *Sleep*, *28*(12), 1561-1567. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/28.12.1561

Fogel, S. M., & Smith, C. T. (2006). Learning-dependent changes in sleep spindles and stage 2 sleep. *Journal of Sleep Research, 15*(3), 250-255. https://doi-org.ezproxy.library.dal.ca/10.1111/j.1365-2869.2006.00522.x

Fogel, S. M., & Smith, C. T. (2011). The function of the sleep spindle: A physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neuroscience and Behavioral Reviews*, *35*, 1154-1165. https://doi.org/10.1016/j.neubiorev.2010.12.003

Forget, D., Morin, C. M., & Bastien, C. H. (2011). The role of the spontaneous and evoked k-complex in good-sleeper controls and in individuals with insomnia. *Sleep*, *34*(9), 1251-1260. https://doi-org.ezproxy.library.dal.ca/10.5665/SLEEP.1250

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. https://doi-org.ezproxy.library.dal.ca/10.1177/0748730406294627

Geiger, A., Huber, R., Kurth, S., Ringli, M., Jenni, O. G., & Achermann, P. (2011). The sleep EEG as a marker of intellectual ability in school age children. *Sleep*, *34*(2), 181-189. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/34.2.181

Gillin, J. C., Pulvirenti, L., Withers, N., Golshan, S., & Koob, G. (1994). The effects of

lisuride on mood and sleep during acute withdrawal in stimulant abusers: A preliminary report. *Biological Psychiatry*, *35*(11), 843-849. https://doi.org/10.1016/0006-3223(94)90019-1

Gronfier, C., Simon, C., Piquard, F., Ehrhart, & Brandenberger, G. (1999). Neuroendocrine processes underlying ultradian sleep regulation in man. *The Journal of Clinical Endocrinology & Metabolism*, *84*(8), 2686-2690. https://doi-org.ezproxy.library.dal.ca/10.1210/jcem.84.8.5893

Gruber, R., Cassoff, J., Frenette, S., Wiebe, S., & Carrier, J. (2012). Impact of sleep extension and restriction on children's emotional lability and impulsivity. *Pediatrics*, *130*(5), e1155-e1161. doi: :10.1542/peds.2012-0564

Gruber, R., Wiebe, S., Montecalvo, L., Brunetti, B., Amsel, R., & Carrier, J. (2011). Impact of sleep restriction on neurobehavioral functioning of children with attention deficit hyperactivity disorder. *Sleep*, *34*(3), 315-323. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/34.3.315

Gruber, R., Sadeh, A., & Raviv, A. (2000). Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *39*(4), 495-501. https://doi.org/10.1097/00004583-200004000-00019

Gruber, R., & Wise, M. S. (2016). Sleep spindle characteristics in children with neurodevelopmental disorders and their relation to cognition. *Neural Plasticity*, *2016*, 1-27. http://dx.doi.org/10.1155/2016/4724792

Gruber, R., Wise, M. S., Frenette, S., Knäauper, B., Boom, A., Fontil, L., & Carrier, J. (2013). The association between sleep spindles and IQ in healthy school-age children. *International Journal of Psychophysiology*, *89*, 229-240. https://doi.org/10.1016/j.ijpsycho.2013.03.018

Hirshkowitz, M., Whiton, K., Albert, S. M., Alessi, C., Bruni, O., DonCarlos, L., … Hillard, A. (2015). National Sleep Foundation's sleep time duration recommendations: Methodology and results summary. *Sleep Health*, *1*, 40-43. https://doi.org/10.1016/j.sleh.2014.12.010

Hoedlmoser, K., Heib, D. P. J., Roell, J., Peigneux, P., Sadeh, A., Gruber, G., & Schabus, M. (2014). Slow sleep spindle activity, declarative memory, and general cognitive abilities in children. *Sleep*, *37*(9), 1501-1512. https://doi-org.ezproxy.library.dal.ca/10.5665/sleep.4000

Iber, C., Ancoli-Israel, S., Chesson, A. L., & Quan, S. F. (2007). The AASM manual for the scoring of sleep and associated events: Rules, terminology, and technical specifications. Westchester, IL: American Academy of Sleep Medicine.

Khan, A., & Rechtshaffen, A. (1978). Sleep patterns and sleep spindles in hyperkinetic

children. *Sleep Research*, *7*, 137-139.

Kiesow, N. A., & Surwillo, W. W. (1987). Sleep spindles in the EEGs of hyperactive children. *Psychological Reports*, *60*(1), 139-144. https://doi-org.ezproxy.library.dal.ca/10.2466/pr0.1987.60.1.139

Kirov, R., & Brand, S. (2014). Sleep problems and their effect in ADHD. *Expert Reviews*, 1-13. https://doi-org.ezproxy.library.dal.ca/10.1586/14737175.2014.885382

Kirov, R., Uebel, H., Albrecht, B., Banaschewski, T., Yordanova, J., & Rothenberger, A. (2012). Attention-deficit/hyperactivity disorder (ADHD) and adaptation night as determinants of sleep patterns in children. *European Child and Adolescent Psychiatry*, *21*, 681-690. doi: 10.1007/s00787-012-0308-3

Knoblauch, V., Martens, W. L. J., Wirz-Justice, A., & Cajochen, C. (2003). Human sleep spindle characteristics after sleep deprivation. *Clinical Neurophysiology*, *114*, 2258-2267. https://doi.org/10.1016/S1388-2457(03)00238-4

Konofal, E., Lecendreux, M., & Cortese, S. (2010). Sleep and ADHD. *Sleep Medicine*, *11*, 652-658. doi: 10.1016/j.sleep.2010.02.012

Kurth, S., Dean III, D. C., Achermann, P., O'Muircheartaigh, J., Huber, R., Deoni, S. C. L., & LeBourgeois, M. K. (2016). Increased sleep depth in developing neural networks: New insights from sleep restriction in children. *Frontiers in Human Neuroscience*, *10*(456), 1-9. doi: 10.3389/fnhum.2016.00456

Landis, C. A. (2002). Sleep and methods of assessment. *Nursing Clinics of North America*, *37*, 583-597. doi: 10.1016/S0029-6465(02)00027-0

Landolt, H-P, Sousek, A., & Holst, S. C. (2014). Physiological basis of sleep: Effects of acute and chronic sleep deprivation. In C. L. Bassetti, Z. Dogaš, & P. Peigneux (Eds.), *ESRS European sleep medicine textbook* (pp. 49-62). Regensburg, Germany: European Sleep Research Society.

Laventure, S., Fogel, S., Lungu, O., Albouy, G., Sévigny-Dupont, P., Vien, C., … Doyon, J. (2016). NREM2 and sleep spindles are instrumental to the consolidation of motor sequence memories. *PLOS Biology*, *14*(3), 1-27. https://doi.org/10.1371/journal.pbio.1002429

Lindemann, C., Ahlbeck, J., Bitzenhofer, S. H., & Hanganu-Opatz, I. L. (2016). Spindle activity orchestrates plasticity during development and sleep. *Neural Plasticity*, *2016*, 1-14. http://dx.doi.org/10.1155/2016/5787423

Lüthi, A. (2014). Sleep spindles: Where they come from, what they do. *The Neuroscientist*, *20*(3), 243-256. doi: 10.1177/1073858413500854

Lycett, K., Mensah, F., Hiscock, H., & Sciberras, E. (2014). A prospective study of sleep problems in children with ADHD. *Sleep Medicine*, *15*(11), 1354-1361. https://doi.org/10.1016/j.sleep.2014.06.004

Malhotra, R. K., & Avidan, A. Y. (2014). Sleep stages and scoring technique. In S. Chokroverty & R. J. Thomas (Eds.), *Atlas of sleep medicine* (2nd ed.) (pp. 77-99). Philadelphia, PA: Elsevier Saunders.

Matricciani, L., Olds, T., & Petkov, J. (2012). In search of lost sleep: Secular trends in the sleep time of school-age children and adolescents. *Sleep Medicine Reviews*, *16*, 203-211. https://doi.org/10.1016/j.smrv.2011.03.005

McCarley, R. W. (2007). Neurobiology of REM and NREM sleep. *Sleep Medicine*, *8*, 302-330. doi: 10.1016/j.sleep.2007.03.005

McClain, I. J., Lustenberger, C., Achermann, P., Lassonde, J. M., Kurth, S., & LeBourgeois, M. K. (2016). Developmental changes in sleep spindle characteristics and sigma power across early childhood. *Neural Plasticity*, *2016*, 1-9. http://dx.doi.org/10.1155/2016/3670951

McGonnell, M., Corkum, P., McKinnon, M., MacPherson, M., Williams, T., Davidson, C., … Stephenson, D. (2009). Doing it right: An interdisciplinary model for the diagnosis of ADHD. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *18*(4), 283-286.

Merikanto, I., Kuula, L., Makkonen, T., Halonen, R., Lahti, J., Heinonen, K., … Pesonen, A-K. (2019). ADHD symptoms are associated with decreased activity of fast spindles and poorer procedural overnight learning during adolescence. *Neurobiology of Learning and Memory*, *157*, 106-113. https://doi.org/10.1016/j.nlm.2018.12.004

Miano, S., Donfrancesco, R., Bruni, O., Ferri, R., Galiffa, S., Pagani, J., … Pia Villa, M. (2006). NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. *Sleep*, *29*(6), 797-803. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/29.6.797

Molfese, D. L., Ivanenko, A., Fonaryova Key, A., Roman, A., Molfese, V. J., O'Brien, L. M., … Hudac, C. M. (2013). A one-hour sleep restriction impacts brain processing in young children across tasks: Evidence from event-related potentials. *Developmental Neuropsychology*, *38*(5), 317-336. https://doi-org.ezproxy.library.dal.ca/10.1080/87565641.2013.799169

National Sleep Foundation. (2014). *2014 Sleep in America® poll: Summary of findings*. Retrieved from https://sleepfoundation.org/sites/default/files/2014-NSF-Sleep-in-America-poll-summary-of findings---FINAL-Updated-3-26-14-.pdf.

National Sleep Foundation. (2018). *Sleep in America® poll 2018: Sleep and effectiveness are linked, but few plan their sleep*. Retrieved from https://www.sleepfoundation.org/sites/default/files/Sleep%20in%20America%202018_prioritizing%20sleep.pdf.

Ong, J. L., Lo, J. C., Gooley, J. J., & Chee, M. W. L. (2016). EEG changes across multiple nights of sleep restriction and recovery in adolescents: The need for sleep study. *Sleep*, *39*(6), 1233-12-40. http://dx.doi.org/10.5665/sleep.5840

Ong, J. L., Lo, J. C., Gooley, J. J., & Chee, M. W. L. (2017). EEG changes accompanying successive cycles of sleep restriction with and without naps in adolescents. *Sleep*, *40*(4), 1-10. http://dx.doi.org/10.1093/sleep/zsx030

Owens, J. A. (2005). The ADHD and sleep conundrum: A review. *Journal of Developmental & Behavioral Pediatrics*, *26*, 312-322. doi: 0196-206X/05/2604-0312

Owens, J. A. (2006). The ADHD and sleep conundrum redux: Moving forward. *Sleep Medicine Reviews*, *10*, 377-379. https://doi.org/10.1016/j.smrv.2006.08.002

Paavonen, E. J., Räikkönen, K., Lahti, J., Komsi, N., Heinonen, K., Pesonen, A-K., … Porkka-Heiskanen, T. (2009). Short sleep duration and behavioral symptoms of attention-deficit/hyperactivity disorder in health 7- to 8-year-old children. *Pediatrics*, *123*(5), e857-e864. doi:10.1542/peds.2008-2164

Parrino, L., & Culebras, A. (2018). Cyclic alternating pattern. *Neurology MedLink*, 1-14. Retrieved from: http://www.medlink.com/scripts/mpdf/print_friendly.php?title=cyclic_alternating_pattern&action=print&channel=public_content&entryid=11856

Pesonen, A-K., Ujma, P., Halonen, R., Räikkönen, K., & Kuula, L. (2019). The associations between spindle characteristics and cognitive ability in a large adolescent birth cohort. *Intelligence*, *72*, 13-19. https://doi.org/10.1016/j.intell.2018.11.004

Peters, J. D., Biggs, S. N., Bauer, K. M. M., Lushington, K., Kennedy, D., Martin, J., & Dorrian, J. (2009). The sensitivity of a PDA-based psychomotor vigilance task to sleep restriction in 10-year-old girls. *Journal of Sleep Research*, *18*, 173-177. doi: 10.1111/j.1365-2869.2008.00716.x

Philipsen, A., Feige, B., Hesslinger, B., Ebert, D., Carl, C., Homyak, M., … Riemann, D. (2005). Sleep in adults with attention-deficit/hyperactivity disorder: A controlled polysomnographic study including spectral analysis of the sleep EEG. *Sleep*, *28*(7), 877-884. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/28.7.877

Poitras, L., Bylsma, F. W., Simeon, J., & Pivik, R. T. (1981). Cortical sleep spindle

activity in hyperkinetic children. *Sleep Research*, *10*, 117.

Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rhode, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *American Journal of Psychiatry*, *164*(6), 942-948. Retrieved from: https://ajp-psychiatryonline-org.ezproxy.library.dal.ca/doi/full/10.1176/ajp.2007.164.6.942

Prehn-Kristensen, A., Göder, R., Fischer, J., Wilhelm, I., Seeck-Hirschner, M., Aldenhoff, J., & Baving, L. (2011). Reduced sleep-associated consolidation of declarative memory in attention-deficit/hyperactivity disorder. *Sleep Medicine*, *12*, 672-679. https://doi.org/10.1016/j.sleep.2010.10.010

Prehn-Kristensen, A., Munz, M., Molzow, I., Wilhelm, I., Wiesner, C. D., & Baving, L. (2013). Sleep promotes consolidation of emotional memory in healthy children but not in children with attention-deficit hyperactivity disorder. *PLOS ONE*, *8*(5), 1-10. https://doi.org/10.1371/journal.pone.0065098

Purcell, S. M., Manoach, D. S., Demanuele, C., Cade, B. E., Mariani, S., Cox, R., … Stickgold, R. (2017). Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. *Nature Communications*, *8*(15930), 1-16. doi: 10.1038/ncomms15930

Randazzo, A. C., Muehlbach, M. J., Schweitzer, P. K., & Walsh, J. K. (1998). Cognitive function following acute sleep restriction in children ages 10-14. *Sleep*, *21*(8), 861-868. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/21.8.861

Ray, L. B., Sockeel, S., Soon, M., Bore, A., Myhr, A., Stojanoski, B., … Fogel, S. M. (2015). Expert and crowd-sourced validation of an individualized sleep spindle detection method employing complex demodulation and individualized normalization. *Frontiers in Human Neuroscience*, *9*(507), 1-16. doi: 10.3389/fnhum.2015.00507

Reynolds, C. M., Gradisar, M., Coussens, S., & Short, M. A. (2018a). Sleep spindles in adolescence: A comparison across sleep restriction and sleep extension. *Sleep Medicine*, *50*, 166-174. https://doi.org/10.1016/j.sleep.2018.05.019

Reynolds, C. M., Gradisar, M., Short, M. A. (2018b). Reliability of sleep spindle measurements in adolescents: How many nights are necessary? *Journal of Sleep Research*, *28*, 1-5. https://doi.org/10.1111/jsr.12698

Ringli, M., Souissi, S., Kurth, S., Brandeis, D., Jenni, O. G., & Huber, R. (2013). Topography of sleep slow wave activity in children with attention-deficit/hyperactivity disorder. *Cortex*, *49*, 340-347. https://doi.org/10.1016/j.cortex.2012.07.007

Rogers, A. E., Caruso, C. C., & Aldrich, M. S. (1993). Reliability of sleep diaries for assessment of sleep/wake patterns. *Nursing Research, 42*(6), 368-372. http://dx.doi.org/10.1097/00006199-199311000-00010

Sadeh, A. (2011). The role and validity of actigraphy in sleep medicine: An update. *Sleep Medicine Reviews*, *15*, 259-267. https://doi.org/10.1016/j.smrv.2010.10.001

Sadeh, A., Gruber, R., & Raviv, A. (2003). The effects of sleep restriction and extension on school-age children: What a difference an hour makes. *Child Development*, *74*(2), 444-455. https://doi-org.ezproxy.library.dal.ca/10.1111/1467-8624.7402008

Saletin, J. M., Coon, W. G., & Carskadon, M. A. (2016). Stage 2 sleep EEG sigma activity and motor learning in childhood ADHD: A pilot study. *Journal of Clinical Child & Adolescent Psychology*, *00*(00), 1-10. doi: 10.1080/15374416.2016.1157756

Schabus, M., Dang-Vu, T. T., Albouy, G., Balteau, E., Boly, E., Carrier, J., … Maquet, P. (2007). Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *PNAS*, *104*(32), 13164-13169. https://doi.org/10.1073/pnas.0703084104

Schabus, M., Hödlmoser, K., Gruber, G., Sauter, C., Anderer, P., Klösch, G., … Zeithofer, J. (2006). Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. *European Journal of Neuroscience*, *23*, 1738-1746. https://doi-org.ezproxy.library.dal.ca/10.1111/j.1460-9568.2006.04694.x

Scholle, S., Beyer, U., Bernhard, M., Eichholz, S., Erler, T., Graneß, P., … Scholle, H. C. (2011). Normative values of polysomnographic parameters in childhood and adolescence: Quantitative sleep parameters. *Sleep Medicine*, *12*(6), 542-549. https://doi.org/10.1016/j.sleep.2010.11.011

Scholle, S., Zwacka, G., & Scholle, H. C. (2007). Sleep spindle evolution from infancy to adolescence. *Clinical Neurophysiology*, *118*, 1525-1531. https://doi.org/10.1016/j.clinph.2007.03.007

Scott, N., Blair, P. S., Emond, A. M., Fleming, P. J., Humphreys, J. S., Henderson, J., & Gringras, P. (2012). Sleep patterns in children with ADHD: A population-based cohort study from birth to 11 years. *Journal of Sleep Research*, *22*(2), 121-128. https://doi-org.ezproxy.library.dal.ca/10.1111/j.1365-2869.2012.01054.x

Shinomiya, S., Nagata, K., Takahashi, K., & Masumura, T. (1999). Development of sleep spindles in young children and adolescents. *Clinical Electroencephalograpy*, *30*(2), 39-43. https://doi-org.ezproxy.library.dal.ca/10.1177/155005949903000203

Shochat, T., Cohen-Zion, M., & Tzischinsky, O. (2014). Functional consequences of inadequate sleep in adolescents: A systematic review. *Sleep Medicine Reviews*, *18*(1), 75-87. https://doi.org/10.1016/j.smrv.2013.03.005

Skorucak, J., Arbon, E. L., Dijk, D-J., & Achermann, P. (2018). Response to chronic sleep restriction, extension, and subsequent total sleep deprivation in humans: Adaptation or preserved sleep homeostasis? *Sleep*, 41(7), 1-17. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/zsy078

Speth, T. A., Benoit, A., & Corkum, P. V. (2014). Sleep parameters and architecture in children with attention-deficit/hyperactivity disorder: A comparison with typically developing peers and across subtypes. *Journal of Sleep Disorders: Treatment & Care*, *4*(1), 1-7. http://dx.doi.org/10.4172/2325-9639.1000149

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement Science Review*, *2*, 1-11. Retrieved from: http://www.edumed.org.br/cursos/neurociencia/MethodsEEGMeasurement.pdf

Ulrich, D. (2016). Sleep spindles as facilitators of memory formation and learning. *Neural Plasticity*, *2016*, 1-7. http://dx.doi.org/10.1155/2016/1796715

Usui, A., Ishizuka, Y., Obinata, I., Okado, T., Fukuzawa, H., & Kanba, S. (1998). Validity of sleep log compared with actigraphic sleep-wake state. *Psychiatry and Clinical Neurosciences*, *52*(2), 161-163. https://doi-org.ezproxy.library.dal.ca/10.1111/j.1440-1819.1998.tb01006.x

Usui, A., Ishizuka, Y., Obinata, I., Okado, T.,Fukuzawa, H., & Kanba, S. (1999). Validity of sleep log compared with actigraphic sleep-wake state II. *Psychiatry and Clinical Neurosciences*, *53*(2), 183-184. https://doi-org.ezproxy.library.dal.ca/10.1046/j.1440-1819.1999.00529.x

Van Dongen, H. P. A., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003a). The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*, *26*(2), 117-126. https://doi-org.ezproxy.library.dal.ca/10.1093/sleep/26.2.117

Van Dongen, H. P. A., Rogers, N. L., & Dinges, D. F. (2003b). Sleep debt: Theoretical and empirical issues. *Sleep and Biological Rhythms*, *1*, 5-13. Retrieved from: https://link-springer-com.ezproxy.library.dal.ca/content/pdf/10.1046%2Fj.1446-9235.2003.00006.x.pdf

Vermeulen, M. C. M., Van der Heijden, K. B., Swaab, H., & Van Someren, E. J. W. (2019). Sleep spindle characteristics and sleep architecture are associated with learning of executive functions in school-age children. *Journal of Sleep Research*, *28*, 1-10. https://doi-org.ezproxy.library.dal.ca/10.1111/jsr.12779

Vriend, J. L., Davidson, F. D., Corkum, P. V., Rusak, B., Chambers, C. T., & McLaughlin, E. N. (2013). Manipulating sleep duration alters emotional functioning and cognitive performance in children. *Journal of Pediatric Psychology*, *38*(10), 1058-1069. https://doi-org.ezproxy.library.dal.ca/10.1093/jpepsy/jst033

Wallant, D. C., Maquet, P., & Phillips, C. (2016). Sleep spindles as an electrographic element: Description and automatic detection methods. *Neural Plasticity*, *2016*, 1-19. http://dx.doi.org/10.1155/2016/6783812

Webb, W. B., & Agnew, H. W. (1971). Stage 4 sleep: Influence of time course variables. *Science*, *174*, 1354-1356. doi: 10.1126/science.174.4016.1354

Weiss, M. D., Craig, S. G., Davies, G., Schibuk, L., & Stein, M. (2015). New research on the complex interaction of sleep and ADHD. *Current Sleep Medicine Reports*, *1*, 114-121. doi: 10.1007/s40675-015-0018-8

Werner, H., Molinari, L., Guyer, C., & Jenni, O. G. (2008). Agreement rates between actigraphy, diary, and questionnaire for children's sleep patterns. *Archives of Pediatrics and Adolescent Medicine*, *162*(4), 350-358. doi: 10.1001/archpedi.162.4.350

Wong, M. M., Brower, K. J., & Zucker, R. A. (2009). Childhood sleep problems, early onset of substance use and behavioral problems in adolescence. *Sleep Medicine*, *10*, 787-796. https://doi.org/10.1016/j.sleep.2008.06.015