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THE ROLE OF SLEEP ON INHIBITORY CONTROL IN YOUNG CHILDREN WITH ATTENTION- DEFICIT/HYPERACTIVITY DISORDER (ADHD)

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THE ROLE OF SLEEP ON INHIBITORY CONTROL IN YOUNG CHILDREN WITH
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

A Dissertation Presented

by

AMANDA CREMONE

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

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Neuroscience and Behavior Program

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ABSTRACT

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Alongside the hallmark symptoms of hyperactivity and inattention, children with attention-deficit/hyperactivity disorder (ADHD) often report having sleep problems. Although sleep deficits are consistently found when evaluated subjectively, impairments in sleep physiology are inconsistent. Compared to typically developing (TD) children, children with ADHD have greater spectral power in the delta (0.5 to 4 Hz) and theta frequency bands (4 to 7 Hz). Moreover, activity in these bands is differentially related to cognitive outcomes in ADHD and TD populations. As such, this dissertation sought to examine relations between sleep physiology and inhibitory control, a primary deficit of ADHD, in young children with and without ADHD. In the first study, children completed a Go/No-Go task before and after polysomnography-monitored overnight sleep. Inhibitory control was improved with overnight sleep in TD children but not in children with ADHD. Morning inhibitory control was positively correlated with rapid eye movement (REM) theta activity in TD children. Although theta activity was greater in the ADHD group, it was not associated with subsequent behavior. In the second study, separate groups of children, with and without ADHD, participated in a sleep-based intervention to determine whether extending overnight sleep duration would reduce theta

activity and, in turn, improve inhibitory control. Again, inhibitory control was gauged via a Go/No-Go task and overnight sleep physiology measured with polysomnography. The results of this second study indicate that children with and without ADHD were able to extend overnight sleep duration when bedtime was advanced. In the ADHD group, inhibitory control was improved only when sleep duration was extended. Inhibitory control was improved following overnight sleep in the TD group (regardless of sleep extension), consistent with the results of the first study. In contrast to the results of the first study, however, morning inhibitory control was associated with SWA but not theta activity (recorded during sleep or wake). Specifically, less SWA was related to greater morning inhibitory control in children with ADHD when overnight sleep duration was extended. Collectively, the results of this dissertation suggest that markers of sleep physiology are uniquely related to inhibitory functioning in children with and without ADHD.

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CHAPTER 1

BACKGROUND AND SIGNIFICANCE

1.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a commonly diagnosed neurobehavioral condition, affecting an estimated 7.2% (approximately 129 million) of children 18 years of age and younger (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). The prevalence of childhood ADHD has increased nearly three-fold from 1977 to 2013. Importantly, symptoms of ADHD that manifest during childhood persist throughout adolescence and adulthood, and are linked to heightened risk for maladaptive outcomes throughout development (Harpin, 2005; Wilens, Faraone, & Biederman, 2004). For example, ADHD symptomology is associated with academic underachievement in adolescents. In adulthood, ADHD impedes personal relationships, as evidenced by higher rates of separation and divorce, as well as delayed professional development. Given the widespread prevalence and severity of problems associated with ADHD, opportunities for early diagnosis and intervention are needed.

1.2 Deficits Associated with ADHD

According to the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), ADHD symptoms are grouped into two distinct domains: hyperactivity/impulsivity and inattention. Subtypes of ADHD are determined by the categorization of each individual's symptoms and are used to inform treatment strategies. If an individual presents with six symptoms of excessive activity, particularly motor activity, he or she is assigned the Hyperactive Impulsive subtype. Conversely, the Inattentive subtype is characterized by the presence of six symptoms that

reflect an inability to sustain or modulate attention. If symptoms span both the hyperactive/impulsive and inattentive domains, the individual is classified as having the Combined subtype. Because symptoms of inattention do not typically emerge until the school years, the Inattentive and Combined subtypes are not common in young children (Applegate et al., 1997; Barkley, 1997). Symptoms of hyperactivity/impulsivity, on the other hand, manifest during early childhood.

Theoretical models of ADHD suggest that symptoms, particularly those reflecting the Hyperactive Impulsive subtype, emerge as a consequence of primary deficits in inhibitory control (Barkley, 1997; Doyle, 2006; Nigg, 2000; Oosterlaan, Logan, & Sergeant, 1998). Inhibitory control is defined as the ability to voluntarily withhold a prepotent response (Cavanagh & Frank, 2014; Durston et al., 2002). Inhibitory deficits are associated with secondary cognitive impairments in self-regulation, working memory, abstract thinking, and creativity (Barkley, 1997). Not surprisingly, relative to typically developing (TD) children, children with ADHD have impaired inhibitory control (Castellanos et al., 2000; Doyle, 2006; Durston et al., 2003; Oosterlaan, Logan, & Sergeant, 1998; Schachar, Tannock, Marriott, & Logan, 1995; Yong-Liang et al., 2000). Taken together, these findings suggest that treatments targeting inhibitory deficits may improve symptoms and cognitive outcomes in ADHD children.

In addition to inhibitory deficits, many children with ADHD have insufficient sleep. Both subjective (i.e., caregiver report) and objective (i.e., actigraphy) assessments of sleep indicate that children with ADHD have longer sleep latency, reduced sleep duration, and lower sleep efficiency than TD children (Weiss, Craig, Davies, Schibuk, & Stein, 2015; Yoon, Jain, & Shapiro, 2012). Despite these reported differences in sleep

timing, studies utilizing polysomnography, the gold standard of human sleep measurement, indicate no consistent difference in sleep macrostructure (the proportion of time spent in distinct sleep stages; Cohen-Zion & Ancoli-Israel, 2004; Herman, 2015; Sadeh, Pergamin, & Bar-Haim, 2006). However, recent evidence shows that sleep microstructure (the dynamic characteristics of the sleep electroencephalography) differs between ADHD and TD children (Ringli, Souissi, Kurth, Brandeis, Jenni, & Huber, 2013; Saletin, Coon, & Carskadon, 2016).

Slow wave activity (SWA; the spectral power of the delta frequency band) and theta activity (the spectral power of the theta frequency band) are two components of sleep microstructure that differ between children with and without symptoms of ADHD. Compared to TD children, SWA is greater in children with ADHD (Ringli et al., 2013). Preliminary evidence suggests that theta activity is likewise elevated in ADHD children during sleep (Saletin, Coon, & Carskadon, 2016). Wake theta activity is also greater in individuals with ADHD (Barry, Clarke, & Johnston, 2003; Hermens, Soei, Clarke, Kohn, Gordon, & Williams, 2005; Snyder & Hall, 2006).

Both SWA and theta activity have been linked to cognitive functioning in TD populations. For example, SWA is positively correlated with emotional attention (Cremone, Kurdziel, Fraticelli-Torres, McDermott, & Spencer, 2016) and memory consolidation (e.g., Benedict, Scheller, Rose-John, Born, & Marshall, 2009; Prehn-Kristensen, Munz, Molzow, Wilhelm, Wiesner, & Baving, 2013; Walker, 2009). Theta activity is also associated with memory consolidation (e.g., Hutchinson & Rathore, 2015; Nishida, Pearsall, Buckner, & Walker, 2009; Schrenier, Lehmann, & Rasch, 2015) as

well as decision-making (Seeley, Smith, MacDonald, & Beninger, 2016) and cognitive control (Cavanagh & Frank, 2014).

Although these data highlight connections between sleep microstructure and cognition in TD populations, these relations are understudied in individuals with ADHD. Recent evidence indicates that low frequency SWA (< 1 Hz) is positively correlated with declarative memory consolidation in TD children but not in children with ADHD (Prehn-Kristensen et al., 2011). Similarly, relations between theta activity, recorded during rapid eye movement (REM) sleep, and cognition differ in ADHD and TD children. Greater REM theta activity is associated with enhanced emotional memory consolidation in TD children but poorer memory in children with ADHD (Prehn-Kristensen, Munz, Molzow, Wilhelm, Wiesner, & Baving, 2013). In sum, these data indicate that SWA and theta activity are differentially related to cognitive outcomes in TD children and children with ADHD. As SWA and theta activity are altered in children with ADHD, differences in these sleep components may exacerbate cognitive impairments and ADHD symptomology.

1.3 Developmental Trajectories of Inhibitory Control and Sleep

Electroencephalography (EEG)

From 5 to 7 years of age, significant maturation of the frontal lobe supports the development of executive functions, including inhibitory control (Tao, Wang, Fan, & Gao, 2015). By approximately 7 years of age, maturation of the executive attention network (e.g., prefrontal cortex and cingulate) supports efficient inhibitory control (Anderson, 2002). Imaging data indicate that activity in this network predicts performance on inhibitory tasks such as the Go/No-Go task (Durstun et al., 2002).

Similarly, caregiver's subjective assessments of their child's self-control (e.g., impulsivity, distractibility, persistence), improve significantly between 5 and 6 years of age (Tao, Wang, Fan, & Gao, 2015).

The developmental trajectory of inhibitory functioning coincides with a shift in sleep EEG activity. Longitudinal data indicate both SWA and theta activity decline during childhood and adolescence (Campbell & Feinberg, 2009). Specifically, there is a steady, linear decline in SWA from birth until approximately 6 years of age. Levels of SWA plateau thereafter until adolescence. Theta activity, on the other hand, declines significantly between 6 and 11 years of age. As SWA and theta activity are strongly associated with neural development (Campbell & Feinberg, 2009), it is important to understand relations between SWA and theta activity and inhibitory control in children with ADHD, particularly during early childhood when inhibitory control develops and changes in sleep EEG occur.

1.4 Relations between Inhibitory Control and Sleep in Typically Developing Children

Evidence in TD children indicates that inhibitory control is compromised by sleep loss. In a sample of 7- to 11-year-old children, teachers reported that child impulsivity was greater when overnight sleep was shortened by one hour for one week (Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012). Likewise, 9- to 12-year-old children committed more errors on a Continuous Performance Task, a task used to gauge attention and inhibition, following three days of experimental sleep restriction (Sadeh, Gruber, & Raviv, 2003). In TD children, insufficient sleep is also linked to secondary cognitive impairments associated with reduced inhibitory control (Barkley, 1997). Specifically, self-regulation (Dahl, 1996; Miller, Seifer, Crossin, & LeBourgeois, 2014) and working

memory (Kopasz, Loessl, Hornyak, Reimann, Nissen, Piosczyk, & Voderholzer, 2010; Sadeh, Gruber, & Raviv, 2003; Steenari, Vuontela, Paavonen, Carlson, Fjallberg, & Aronen, 2003) are compromised by sleep loss in TD children. As these cognitive impairments stem from both impaired inhibitory control and insufficient sleep, improving inhibitory control via sleep-targeted interventions should result in reduction of these deficits.

In TD children, experimental interventions that extend sleep length improve cognitive functioning (Gruber et al., 2012; Sadeh, Gruber, & Raviv, 2003; Vriend et al., 2013). For example, a 27-minute increase of overnight sleep duration was associated with reduced daytime sleepiness, emotional lability, and restless/impulsive behaviors in 7- to 11-year-old children (Gruber et al., 2012). Similarly, a 28-minute increase in sleep duration was associated with improved emotional regulation, attention, and working memory in 8- to 12-year-old children (Vriend et al., 2013). Although this growing body of literature indicates that sleep extension improves cognitive functioning in TD children, the effects of sleep extension on cognitive outcomes in children with ADHD remain unexplored.

1.5 Overarching Goal of Dissertation Research

The overarching goal of this dissertation was to determine whether sleep contributes to inhibitory control in children with ADHD. Three studies were designed to test the hypothesis that sleep-related processes are altered in children with ADHD and, in turn, exacerbate inhibitory deficits in this population. The aims of these studies were as follows:

1. Determine whether there was sleep-dependent enhancement of inhibitory control in TD children and children with ADHD symptoms (Chapter 2)
2. Determine if a sleep-targeted intervention (i.e., sleep extension) improved inhibitory control in children with and without ADHD (Chapter 3)
3. Determine whether levels of theta activity were similar across sleep and wake in children with and without ADHD and whether inhibitory control was better predicted by theta activity during sleep or wake (Chapter 4)

CHAPTER 2

REM THETA ACTIVITY ENHANCES INHIBITORY CONTROL IN TYPICALLY DEVELOPING CHILDREN BUT NOT CHILDREN WITH ADHD SYMPTOMS

The aim of this study was to determine whether differences in sleep physiology were related to inhibitory control in typically developing children and children with symptoms of attention-deficit/hyperactivity disorder (ADHD). To test this, children with and without symptoms of ADHD completed a Go/No-Go task to gauge inhibitory control before and after overnight sleep (monitored with polysomnography). The results of this study are published in *Experimental Brain Research*. The publication is provided below.

2.1 Introduction

Inhibitory control, the ability to suppress prepotent responses, is compromised by sleep deficits (Chuah et al. 2006; Drummond et al. 2006; Goel et al. 2009). Individuals with attention-deficit/hyperactivity disorder (ADHD) have impaired inhibitory control (Schachar et al. 1995; Oosterlaan et al. 1998; Castellanos et al. 2000; Yong-Liang et al. 2000; Durston et al. 2003) and commonly experience sleep disturbances (Cohen-Zion and Ancoli-Israel 2004; Owens 2005; Yoon et al. 2012). However, it is unknown whether sleep disturbances are related to cognitive impairments in this population. If so, sleep may be a target for early diagnosis and treatment of ADHD.

Individuals with ADHD have longer sleep latency and reduced sleep duration and efficiency relative to typically developing (TD) controls (Yoon et al. 2012; Weiss et al. 2015). Studies utilizing polysomnography indicate no consistent differences in sleep macrostructure (i.e., sleep stages; Cohen-Zion and Ancoli-Israel 2004; Sadeh et al. 2006; Herman 2015). However, sleep microstructure differs between children with ADHD and

TD children: slow wave activity (SWA; the spectral power of the delta frequency band) is reported to be greater in children with ADHD (Ringli et al. 2013). Preliminary evidence indicates that theta activity (the spectral power of the theta frequency band) is marginally greater during non-rapid eye movement sleep (nREM) in ADHD children 10-12 years of age (Saletin et al. 2016). During wakefulness, theta activity is likewise elevated in young adults with ADHD compared to TD young adults (Barry et al. 2003; Hermens et al. 2005; Snyder and Hall 2006). Whether theta activity differs in early childhood when most ADHD symptoms emerge (Applegate et al. 1997; American Academy of Pediatrics 2011) is unknown.

Slow wave and theta activity decline across childhood into adolescence (Campbell and Feinberg 2009). Developmental changes in SWA and theta activity reflect changes in cortical plasticity and brain maturation (Cajochen et al. 1999; Kurth et al. 2010; Leemburg et al. 2010; Ringli et al. 2013). Supporting this pattern, the rates of decline for SWA and theta activity across development parallel the rate of cortical thinning (Shaw et al. 2008; Campbell and Feinberg 2009). Slow wave and theta activity are both associated with cognitive functioning. For example, consolidation of memories over an interval of sleep correlates with SWA (Benedict et al. 2009; Walker 2009) and theta activity (Nishida et al. 2009; Prehn-Kristensen et al. 2013; Hutchinson and Rathore 2015; Schreiner et al. 2015) in the sleep bout. Prefrontal rapid eye movement (REM) sleep theta activity is also positively correlated with decision-making in young adults (Seeley et al. 2016). Likewise, wake theta activity is linked to inhibitory control in TD populations (Cavanagh and Frank 2014).

These studies pose the hypothesis that differences in sleep microstructure may contribute to reduced inhibitory control, a core deficit in individuals with ADHD. To test this hypothesis, children completed a Go/No-Go task (see Figure 2.1) to gauge inhibitory control and sustained attention before (baseline session) and after (morning session) overnight sleep. High-density polysomnography was used to measure sleep macro- and microstructure. We hypothesized that TD children would exhibit sleep-dependent enhancement of inhibitory control and sustained attention whereas children with ADHD symptoms would not. Moreover, we hypothesized that group differences in inhibitory control and sustained attention, observed after sleep, would be associated with sleep microstructure, specifically SWA and theta activity.

2.2 Methods

2.2.1 Participants

Children, 4-8 years of age, were recruited through community advertisements and the Child Studies Database at the University of Massachusetts Amherst. Caregivers completed a pre-screening phone interview to determine their child's eligibility and group placement (ADHD or TD control) using the ADHD section of the Diagnostic Interview Schedule for Children IV (DISC-IV; Shaffer et al. 2000). The DISC-IV is a structured, diagnostic interview used to assess pediatric psychiatric disorders in children 4 years of age and older (Shaffer et al. 2000; Rolon-Arroyo et al. 2016). The ADHD section of the DISC-IV has adequate test-retest reliability ($Kappa = 0.79$). As Oppositional Defiant Disorder (ODD) is highly comorbid with childhood ADHD (Waschbusch 2002), the ODD scale of the DISC-IV was used to determine whether symptoms of ODD contributed to behavioral outcomes in our sample. All interviews

were conducted by a masters-level graduate student (C.I. Lugo-Candelas), supervised by a licensed clinician (E.A. Harvey).

Exclusion criteria included a current diagnosis or history of intellectual disabilities, hearing or visual disabilities, receptive language delay, cerebral palsy, epilepsy, autism, or psychosis. Children (both ADHD and TD) with a current diagnosis or history of sleep disorders (i.e., sleep apnea, sleep disordered breathing, or restless leg syndrome) were not included in this study as these disorders may confound results. The ADHD group was composed of children who had at least six symptoms of hyperactivity/impulsivity, at least three of which were present in two settings, listed in the ADHD section of the DISC-IV. Hyperactive/impulsive symptoms and not inattentive symptoms were used to determine ADHD status because the presentation of predominately inattentive symptoms typically has later age of onset and is thought to be distinct from presentations involving hyperactivity/impulsivity (Applegate et al. 1997). As ADHD is not typically diagnosed until children enroll in formal schooling, children in this sample were not required to have a physician's formal diagnosis of the disorder (Applegate et al. 1997; American Academy of Pediatrics 2011). Importantly, accumulating evidence indicates that an ADHD diagnosis can be reliably assigned during the preschool years (Rolon-Arroyo et al. 2016). Typically developing controls were defined as having three or fewer symptoms on the ADHD section of DISC-IV.

Thirty-three children (9 F; $M_{age} = 6.71$, $SD = 0.91$ years) were tested. Eighteen children (5 F; $M_{age} = 6.70$, $SD = 1.07$ years) were placed in the ADHD group. Fifteen children (4 F; $M_{age} = 6.73$, $SD = 0.71$ years) were classified as TD controls.

Seven children in the ADHD group (0 F; $M_{age} = 6.79$, $SD = 1$ year) had a prior diagnosis of ADHD whereas 10 (5 F; $M_{age} = 6.61$, $SD = 1.23$ years) did not (diagnosis data missing from 1 child). Only two enrolled children were taking medication for ADHD (1 Tenex, 1 Adderall). As these medications may alter sleep physiology, participants were asked to abstain from using them 48 hours prior to the overnight visit (Konofal et al. 2010). Statistical outcomes (i.e., behavior and sleep physiology) did not differ when the two children with a history of medication use were excluded from analyses.

According to caregiver report, 72.7% of the children tested were white/Caucasian, 6.1% were Latino/Hispanic, 3.0% were black/African American, 3.0% were Asian, and 15.2% were biracial/mixed race. Of the caregivers for enrolled children, 12.1% earned a high school diploma, 6.1% earned an Associate's Degree, 27.3% earned a Bachelor's Degree, 48.5% earned a Master's Degree, and 6.1% earned a Doctorate.

2.2.2 Sleep Physiology

Polysomnography recordings of overnight sleep were obtained using customized high-density polysomnography electrode caps (EasyCap). These caps had 24 EEG electrodes assigned to O₁, O₂, C₃, C₄, CP₁, CP₂, CP₅, CP₆, F₃, F₄, F_z, FC_z, FC₁, FC₂, FC₅, FC₆, F₇, F₈, P₃, P₄, P₇, P₈, P_z, and PO_z. The montage also included two electrooculogram leads and two electromyogram leads (affixed to the chin). Data were recorded relative to mid-forehead ground placed at FP_z. EEG data were recorded referenced to Cz and contralateral mastoids (A1 and A2).

Polysomnography was scored according to the revised American Academy of Sleep Medicine manual (American Academy of Sleep Medicine 2007) by a trained

researcher. Scoring was confirmed against a second trained researcher, who was unaware of the participant's group status (ADHD versus TD). On average, 84% of the sleep stages scored were the same between the two scorers (ranging from 80% to 93%). Importantly, inter-rater reliability did not differ for groups. As such, results are based on staging from the initial scorer.

Spectral analysis was conducted using Brain Analyzer 2 software (Version 2.4; Brain Products). Previous studies have identified links between frontal theta activity and inhibitory control (Cavanagh and Frank 2014). Consistent with these studies and others, spectral power was drawn from F₄ (Mann et al. 1992). Spectral power is reported in power density ($\mu V^2/Hz$). Slow wave activity was characterized as activity between 0.5 and 4 Hz (delta) recorded during slow wave sleep (SWS) and nREM stage 2 and SWS combined (Benedict et al. 2009; Prehn-Kristensen et al. 2013). Theta activity is defined as activity between 4 and 7 Hz recorded during REM and nREM sleep (Nishida et al. 2009; Prehn-Kristensen et al. 2013). Analysis of sleep stages and spectral power was averaged across all participants within each group.

2.2.3 Behavioral Measures

To assess inhibitory control and sustained attention, children completed a Go/No-Go task. The Go/No-Go task is a valid and reliable measure of inhibition and attention in young children (Kindlon et al. 1995; Bezdjian et al. 2009). Stimuli used in the Go/No-Go task were 10 images of animals. Go trials (75% of trials) featured images of various animals (e.g., giraffe, elephant, panda). In remaining trials, No-Go trials (25% of trials), a chimpanzee was presented (see Figure 2.1). The order of No-Go and Go trials varied with the exception that No-Go trials were separated by 0, 2, or 4 Go trials (to prevent children

from learning this pattern of trial presentation). Displayed images were 3 inches in height and 4 inches in length; each centered on a 14-inch computer screen positioned approximately 15 inches from the child.

Each trial began with the presentation of an animal image for 700 ms. Children were instructed to respond, via a button press on a mouse, for all of the animals (Go trials), except for the chimpanzee for which they were to inhibit their response (No-Go trials). A blank screen was presented for 500 ms between trials. Two pseudo-random trial orders were used for all participants (for baseline and morning sessions, trial order counterbalanced across participants).

2.2.4 Procedure

Procedures were approved by the Institutional Review Board at the University of Massachusetts Amherst. Caregivers consented to their child's participation and child verbal assent was obtained before commencing with experimental procedures. Children followed a self-selected sleep schedule prior to the experimental procedures performed in the lab.

Caregivers and children were scheduled to arrive at the sleep lab approximately 1 hour before the child's typical bedtime. After acclimating to the sleep lab, children completed the Go/No-Go task (baseline session). To begin, children were given 12 practice trials to ensure that they understood task instructions. Subsequently, children were presented with test trials in 2 blocks of 60 trials each (total of 120 test trials). The task took approximately 10 minutes to complete.

Following completion of the task and prior to bedtime, children were fitted with a polysomnography cap. Children and caregivers slept in separate beds within the same

room overnight. The following morning, the cap was removed. Approximately 30 minutes after wake onset (to mitigate sleep inertia), children completed the Go/No-Go task once more (morning session). Caregivers were provided monetary compensation and children were given an age-appropriate prize for their participation.

2.3 Results

Demographic information is presented in Table 2.1. Child age ($t(31) = -0.08, p = 0.937$), gender ($X^2(1, N = 33) = 0.01, p = 0.943$), average sleep duration (from caregiver report; $t(30) = 0.91, p = 0.372$; data missing from 1 child), and ethnicity ($X^2(4, N = 33) = 6.25, p = 0.182$) were not significantly different between groups.

2.3.1 REM theta activity is greater in children with ADHD symptoms

Four children in the ADHD group were omitted from sleep physiology analyses due to recording error ($n = 3$) and noncompliance ($n = 1$).¹ Thus, results pertaining to sleep physiology are presented for 14 children in the ADHD group (4 F; $M_{age} = 6.77, SD = 1.05$ years), with 7.29 symptoms of hyperactivity ($SD = 0.91$) and 6.29 symptoms of inattention ($SD = 1.73$) on average, and 15 TD controls (4 F; $M_{age} = 6.73, SD = 0.71$ years).

Independent samples t -tests were used compare sleep microstructure between groups. Theta activity recorded during REM was significantly greater in the ADHD group compared to the TD group (Table 2.2). Theta activity recorded during nREM sleep did not differ between groups, supporting REM-specific elevation of theta activity in the ADHD group. To determine the specificity of REM theta elevation in this sample, full power curves were evaluated (see Figure 2.5). In addition to REM theta activity, SWA

¹ Results were unchanged when the children without usable sleep physiology data ($n = 4$) were omitted from analyses.

recorded during REM sleep was elevated in ADHD children. However, nREM SWA and SWS-specific SWA did not differ between groups. Collectively, these findings indicate that low frequency spectral activity (SWA and theta activity) was significantly elevated in ADHD children during REM but not nREM sleep.

Exploratory independent samples *t*-tests were used to confirm that sleep macrostructure (sleep stages) did not differ between groups. Consistent with prior studies (Cohen-Zion and Ancoli-Israel 2004; Sadeh et al. 2006; Herman 2015), there were no group differences in sleep macrostructure (Table 2.2).² Sleep physiology did not differ between children with or without a prior diagnosis of ADHD (*ps* > 0.133), with the exception that children with a prior diagnosis had less nREM stage 1 ($M = 7.13$, $SD = 2.15$) than those who were not diagnosed ($M = 11.32$, $SD = 3.80$; $t(11) = -2.50$, $p = 0.030$, 95% CI [-7.88, -0.50]).

Given the significant difference in REM theta activity at the *a priori* chosen frontal electrode site (F₄; Table 2.2), we examined whether there were region-specific differences in theta activity between the ADHD and TD groups. In addition to F₄, theta activity was greater in the ADHD group at F₈ ($t(25) = 2.19$, $p = 0.038$) and marginally greater at central electrodes C₃ ($t(26) = 2.02$, $p = 0.054$) and C₄ ($t(26) = 1.82$, $p = 0.081$; Figure 2.2), indicating region-specific enhancement.

2.3.2 Inhibitory Control and Sustained Attention are Improved Following Sleep in TD Children

Whether inhibitory control and sustained attention are modified by sleep in TD children is unknown. To assess the effect of sleep on these measures, we computed

² Group differences in sleep physiology were not different when ODD symptoms were controlled for.

accuracy (% correct) for No-Go and Go trials. Greater accuracy on No-Go trials reflects greater inhibitory control whereas greater accuracy on Go trials corresponds to greater sustained attention (O'Connell et al. 2009; McDermott et al. 2012). Paired samples *t*-tests were used to assess within-group changes in inhibitory control and sustained attention between the baseline (before sleep) and morning (after overnight sleep) sessions.

Inhibitory control improved in the morning relative to baseline ($t(14) = -3.57, p = 0.003$, 95% CI [-0.16, -0.04]), such that morning performance was significantly greater than baseline performance (Figure 2.3). Similarly, sustained attention was significantly greater in the morning, relative to baseline ($t(14) = -3.25, p = 0.026$, 95% CI [-0.18, -0.01]).³

Improved inhibitory control and sustained attention following sleep could reflect circadian variation in performance or practice effects that are independent of sleep *per se*. Alternatively, changes in performance may reflect sleep-specific mechanisms. Partial correlations (controlling for baseline scores) between morning inhibitory control and total sleep time ($r = 0.33, p = 0.255$) and morning sustained attention and total sleep time ($r = -0.13, p = 0.664$) were not significant. Morning inhibitory control was significantly positively associated with REM theta activity at frontal electrode site F₄ ($r = 0.61, p = 0.021$; Figure 2.4), whereas sustained attention was not ($r = -0.10, p = 0.727$). Consistent with this finding, morning inhibitory control was significantly positively correlated with average frontal REM theta activity recorded at F₃, F₄, and F_Z combined ($r = 0.65, p = 0.013$), indicating that these relations are bilateral. Moreover, baseline inhibitory control was not associated with REM theta activity ($r = -0.01, p = 0.971$), supporting this sleep-dependent effect. Neither morning inhibitory control nor sustained attention were

³ Behavioral findings were unchanged when controlling for ODD symptoms.

associated with nREM SWA (r s between -0.29 and -0.09, p s ≥ 0.322). Although SWA recorded during REM sleep was elevated in ADHD children (see Figure 2.5), it was functionally insignificant; unlike REM theta activity, REM SWA was not correlated with morning inhibitory control in TD children ($r = 0.03$, $p = 0.909$). Moreover, morning inhibitory control was not associated with the percentage of time spent in nREM stage 2, SWS, or REM sleep (r s between -0.01 and 0.18, p s ≥ 0.534), supporting a theta-specific enhancement of inhibitory control for the TD children.

To determine whether variables other than REM theta activity contributed to morning inhibitory control, a linear regression model was used. Baseline inhibitory control, child age and gender, hyperactive and inattentive symptoms, total sleep time, and REM theta activity (F_4) were simultaneously entered as predictor variables in a model evaluating morning inhibitory control in TD children. Consistent with the results of the correlation, theta activity significantly predicted morning inhibitory control in TD children ($\beta = 0.01$, $p = 0.034$). All other variables were not significant (p s ≥ 0.124).

2.3.3 Inhibitory Control and Sustained Attention are Unchanged Following Sleep in Children with ADHD Symptoms

In contrast to results in TD children, neither inhibitory control ($t(17) = -0.89$, $p = 0.386$) nor sustained attention ($t(17) = 0.71$, $p = 0.488$) changed in the morning compared to baseline in the ADHD group (Figure 2.3).⁴ These null findings are unlikely due to low power in the ADHD group given the high power observed in the TD group (achieved power = 0.905). Moreover, inhibitory control and sustained attention did not differ for

⁴ Behavioral findings were unchanged when controlling for ODD symptoms.

ADHD children with or without a prior diagnosis of the disorder during the baseline or morning testing sessions ($ps \geq 0.655$).

Partial correlations indicated that morning inhibitory control ($r = -0.15, p = 0.617$) and sustained attention ($r = -0.32, p = 0.282$) were not associated with total sleep time. Interestingly, although children with ADHD symptoms had greater theta activity, neither morning inhibitory control ($r = -0.21, p = 0.489$; Figure 2.4) nor sustained attention ($r = -0.31, p = 0.310$) were associated with REM theta activity in this group. Similarly, the correlation between morning inhibitory control and average REM theta activity recorded at F₃, F₄, and F_z (combined) was not significant ($r = -0.40, p = 0.182$). Baseline inhibitory control was not associated with REM theta activity in this group ($r = -0.22, p = 0.457$). Relations between these behaviors and nREM SWA were also not significant (rs between -0.07 and $0.05, ps \geq 0.828$). REM SWA was also not associated with morning inhibitory control in the ADHD group ($r = -0.29, p = 0.362$). Likewise, morning inhibitory control was not associated with the percentage of time spent in nREM stage 2, SWS, or REM sleep (rs between -0.25 and $0.15, ps \geq 0.409$).

Theta activity did not significantly predict morning inhibitory control ($\beta = -0.01, p = 0.456$) in a linear regression model, suggesting that the mechanism underlying enhanced morning inhibitory control in TD children is absent in ADHD children. Baseline inhibitory control, child age and gender, hyperactive and inattentive symptoms, and total sleep time did not predict morning inhibitory control ($ps \geq 0.294$), consistent with findings in TD children.

A Fisher r -to- z -transformation was used to compare the difference between correlation coefficients (morning inhibitory control and REM theta activity) in the TD

and ADHD groups. The results of this analysis indicate that the correlation between morning inhibitory control and REM theta activity in the TD group ($r = 0.61$) was marginally greater than that of the ADHD group ($r = -0.21$; $z = -1.89$, $p = 0.058$).

2.4 Discussion

We report evidence that differences in REM sleep microstructure contribute to impairments in daytime inhibition in children with symptoms of ADHD. Typically developing children had overnight enhancement of inhibitory control and sustained attention. Moreover, REM theta activity was positively associated with morning inhibitory control in TD children but not in children with ADHD in spite of overall greater REM theta activity in the ADHD group.

Inhibitory control was improved following overnight sleep in TD children. Although circadian processes influence inhibitory control (Sagaspe et al. 2012), our data support an active role of sleep in improving inhibition. Morning inhibitory control was specifically associated with REM theta activity during the overnight sleep bout, suggesting overnight improvement is likely a REM theta-dependent process. The non-significant associations between baseline inhibitory control and REM theta activity in the TD and ADHD groups further qualified this sleep-dependent effect. Additionally, the results of linear regression analyses suggest that REM theta activity predicts morning inhibitory control in TD children, even when accounting for child age, gender, symptomology, and total sleep time.

Not surprisingly, inhibitory control was lower overall in ADHD children (Schacher et al. 1995; Barkley 1997; Oosterlaan et al. 1998; Castellanos et al. 2000; Yong-Liang et al. 2000; Durston et al. 2003). Strikingly, however, inhibitory control was

unchanged following overnight sleep in the ADHD group. Here too, a circadian explanation is unlikely. ADHD is associated with a shortening of the circadian cycle (Baird et al. 2012), which would predict performance improvements in the morning relative to the evening. To the contrary, performance was unchanged. Rather, we posit that the REM theta-dependent process that supports improvements in inhibitory control in TD children is altered in ADHD. Even in the presence of elevated REM theta activity, a significant correlation between REM theta and behavior, which was observed in TD children, was not present in the ADHD group. As the difference between correlation coefficients in the TD and ADHD groups was only marginally significant, this interpretation should be taken with caution. We speculate that differential associations between REM theta and behavior may reflect impairments in theta modulation in individuals with ADHD (Hermens et al. 2005). To a certain point, theta activity may increase inhibitory control; however, past this point, elevated theta activity may impair inhibitory control. This concept is consistent with work in young adults where both low and high levels of cortical activity are indicative of performance difficulties (see Haier et al, 1988). Similarly, having low or high levels of REM theta activity may be detrimental to subsequent inhibitory processes.

Work in primates suggests that wake theta activity coordinates neural interactions between structures responsible for cognitive control (for review, see Womelsdorf et al. 2011). Specifically, theta oscillations in the anterior cingulate cortex modulate excitation of post-synaptic neuronal groups in other structures in the cognitive control network (e.g., hippocampus, frontal and sensory cortices). These interactions are phase-locked to task-related events that require cognitive control, including inhibition. We posit that this same

mechanism may underlie REM theta-dependent enhancement of inhibitory control: REM theta activity may enhance communication between neural structures that support inhibitory control. Provided that children with ADHD have increased REM theta activity, these structures may be over stimulated and, consequently, less efficient during subsequent assessments of inhibition. Additional studies utilizing neuroimaging techniques are needed to test this hypothesis directly.

Elevated REM theta activity in the ADHD group may also reflect a maturational lag in this population compared to the TD group. Topographic assessment of theta activity supports this hypothesis: the greatest difference in theta activity between groups was found in frontal and central regions, areas that lag in the posterior-anterior trajectory of cortical development (Shaw et al. 2008). Theta activity during REM may be a particularly important marker for identifying developmental delays, as REM sleep processes direct brain maturation throughout early development (Marks et al. 1995). As such, although individuals with ADHD have more theta activity than TD controls, these children may require additional theta activity to facilitate sleep-dependent enhancement of inhibitory processes. Alternatively, elevated REM theta may reflect an increased sleep need for ADHD children compared to TD controls. Theta activity is known to increase with sleep deprivation as has been shown in both animal and human paradigms (Borbely et al. 1984; Cajochen et al. 1999). Thus, elevated REM theta activity in the ADHD group, in the absence of a difference in total sleep time on the experimental night (see Table 2.2) or average sleep duration (assessed via caregiver report), may suggest a greater sleep need for children with ADHD. Additional studies targeting theta activity in children with ADHD are needed to explore both hypotheses further. Given that children with ADHD

commonly experience sleep disruptions (Cohen-Zion and Ancoli-Israel 2004; Owens 2005; Yoon et al. 2012), future studies take into account the prior sleep history of TD and ADHD children and assess sleep physiology following an optimized or stabilized sleep schedule.

Counter to Ringli and colleagues (2013), we did not find group differences in nREM SWA. In a cross-sectional study, Campbell and Feinberg (2009) reported that SWA decline is not evident until late childhood (9-12 years of age). Theta decline, on the other hand, is evident earlier in development (6-9 years of age). As such, the lack of group differences in SWA in the present study may reflect the fact that children were 4-8 years of age, younger than those tested in previous studies (Ringli et al. 2013).

Longitudinal assessments of sleep EEG trajectories are needed to better understand developmental differences in the trajectories of SWA and theta decline in children with ADHD. Alternatively, differences between EEG measures in Ringli's study and our own may have contributed to differences in SWA findings. Ringli and colleagues (2013) normalized spectral power in order to compare topographical differences in SWA in TD and ADHD children. As the primary aim of this study was to assess group differences in spectral power in frontal regions associated with inhibitory control, non-normalized power density was compared between the TD and ADHD groups.

Notably, sustained attention was also improved following overnight sleep in TD children but not children with ADHD symptoms. However, morning sustained attention in TD children was not associated with increases in REM theta activity or any other aspect of sleep physiology. Sustained attention did not correlate with inhibitory control during the baseline or morning assessments, suggesting these processes are independent

($p_s \geq 0.292$; Schachar et al. 1995). Importantly, consistent with our baseline measures, sustained attention is not a core deficit in ADHD (Castellanos et al. 2006). In fact, the ADHD group tended to do better than the TD group at baseline leaving less room for overnight change in performance in the ADHD group compared to the TD group. As hyperactive/impulsive children were sampled in the current study, additional research assessing the role of sleep on behavior in children with the predominantly inattentive symptoms are needed.

In summary, these results suggest that increased REM theta activity may be functionally related to ADHD symptomology, providing a target for intervention. Identifying and treating symptoms in early childhood is particularly important given that symptoms typically persist throughout development and are related to maladaptive outcomes such as poor academic performance and interpersonal skills (Ingram et al. 1999). Regarding treatment, sleep extension and sleep hygiene interventions could be implemented as a means of enhancing sleep quality and, in turn, alleviating symptoms (Hiscock et al. 2015).

Table 2.1. Participant demographics and behaviors.

	ADHD	TD	<i>p</i>-value
	Mean (SD)	Mean (SD)	
<u>Participant Demographics</u>			
Age (years)	6.70 (1.07)	6.73 (0.71)	0.937
Gender (Females: Males)	5:13	4:11	0.943
Hyperactive Symptoms	7.28 (1.02)	0.27 (0.80)	< 0.001
Inattentive Symptoms	6.06 (2.13)	0.67 (1.59)	< 0.001
ODD Symptoms	4.33 (2.09)	1.47 (1.96)	< 0.001
Average Sleep Duration (Hours)	10.59 (0.81)	10.28 (1.09)	0.372
Average Bedtime	8:46 PM (38.24 min)	8:18 PM (43.35 min)	0.254
<u>Behaviors (%)</u>			
Baseline Inhibitory Control	70.74 (16.39)	74.44 (10.44)	0.456
Morning Inhibitory Control	74.63 (15.04)	84.44 (8.79)	0.033
Baseline Sustained Attention	77.84 (16.88)	70.74 (21.15)	0.292
Morning Sustained Attention	76.67 (17.05)	80.52 (14.42)	0.494

Note: In the ADHD group, n = 18. In the TD group, n = 15.

Table 2.2. Sleep macrostructure and microstructure (F₄).

	ADHD	TD	<i>p</i>-value
	Mean (SD)	Mean (SD)	
<u>Macrostructure</u>			
TST (minutes)	554.71 (70.28)	552.62 (53.82)	0.929
SOL (minutes)	52.93 (44.89)	49.33 (22.32)	0.785
WASO (minutes)	13.59 (10.52)	21.45 (20.44)	0.209
Sleep efficiency (%)	97.36 (1.88)	94.80 (5.20)	0.094
nREM stage 1 (%)	9.06 (3.47)	10.66 (3.59)	0.233
nREM stage 2 (%)	52.58 (10.67)	49.06 (8.64)	0.336
SWS (%)	22.03 (6.80)	22.92 (4.14)	0.671
REM (%)	16.33 (7.13)	17.32 (7.56)	0.720
<u>Microstructure</u> ($\mu\text{V}^2/\text{Hz}$)			
SWA (SWS)	503.70 (110.38)	447.76 (146.35)	0.258
SWA (nREM)	277.21 (77.51)	239.13 (89.01)	0.231
Theta (REM)	24.75 (9.06)	17.44 (5.55)	0.014
Theta (nREM)	28.49 (9.08)	29.27 (11.54)	0.842

Note: TST = total sleep time; SOL = sleep onset latency; WASO = wake after sleep onset; nREM = non-rapid eye movement sleep; SWS = slow wave sleep; REM = rapid eye movement; SWA = slow wave activity; SWA and theta activity recorded from frontal electrode (F₄).

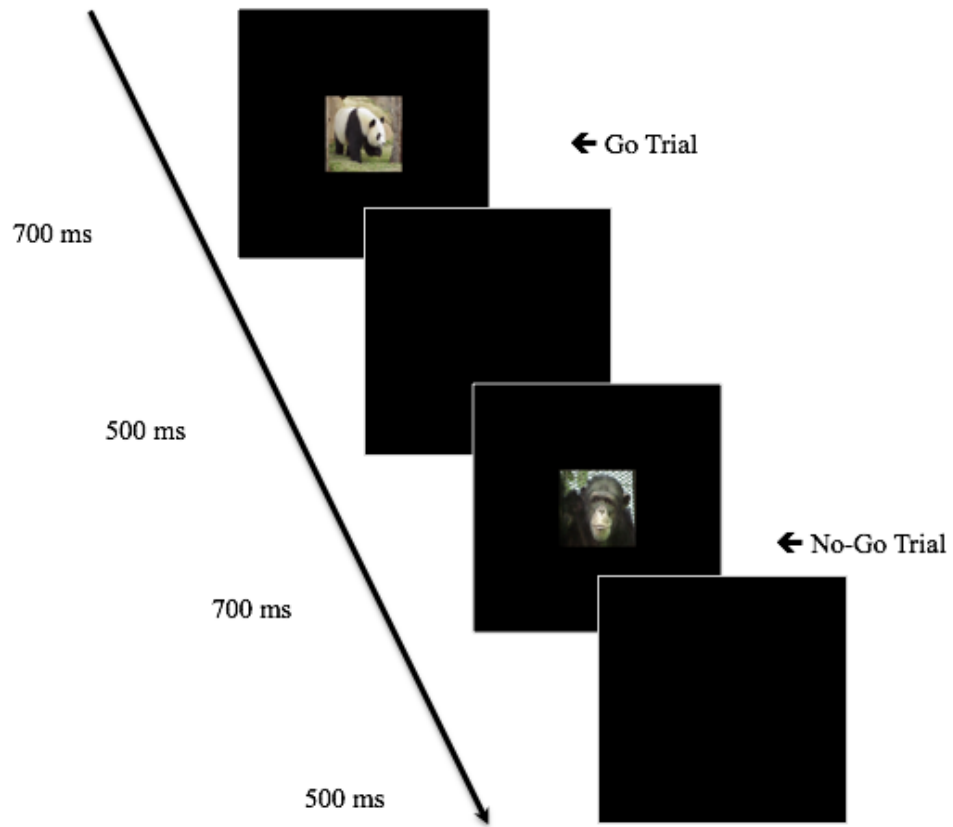


Figure 2.1. Order of stimulus presentation during the Go/No-Go task. Go trials were those in which images of animals including a giraffe, elephant, and panda (shown above) were presented. No-Go trials were those in which an image of a chimpanzee (shown above) was presented.

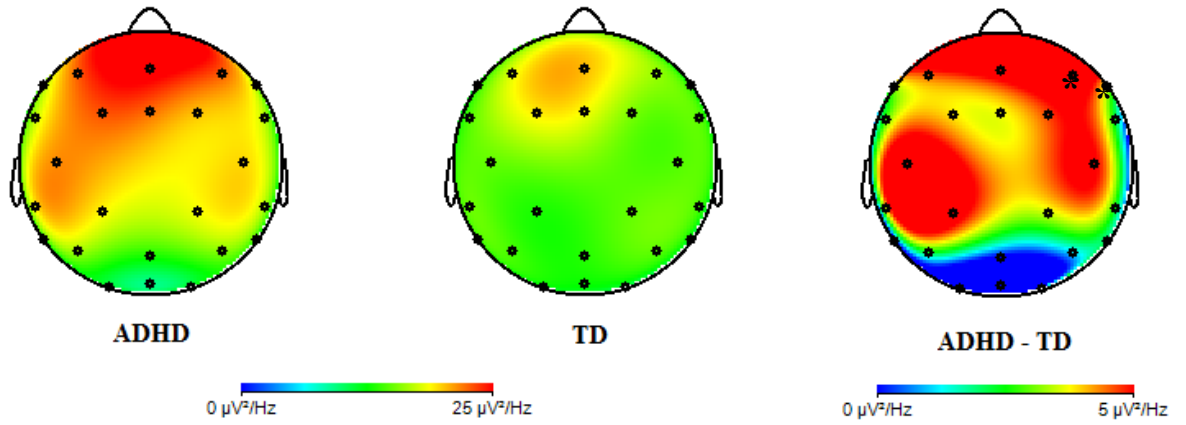


Figure 2.2. Topographic distributions of REM theta activity for ADHD (left) and TD children (middle). Group difference in theta activity (ADHD minus TD) plotted on the right. Note: Electrodes where group differences are statically significant are marked; $*p < 0.05$.

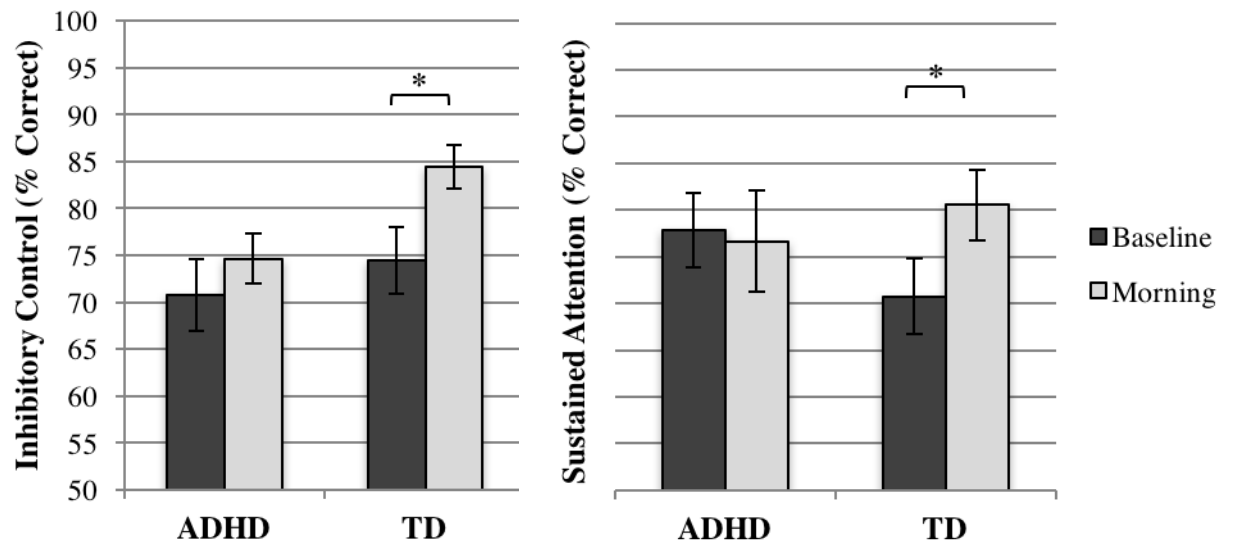


Figure 2.3. Group differences in inhibitory control and sustained attention. Note: Means represent those from paired samples *t*-tests; Error bars represent standard error; * $p \leq 0.05$.

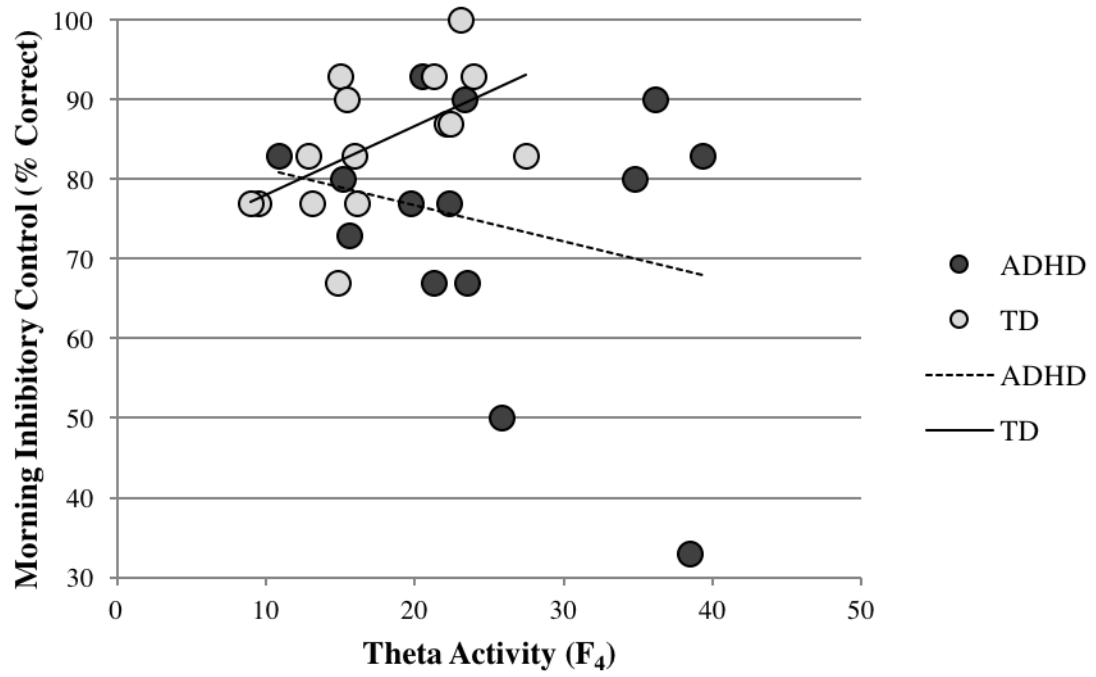


Figure 2.4. Correlations between frontal theta activity (F₄; in $\mu\text{V}^2/\text{Hz}$) and morning inhibitory control.

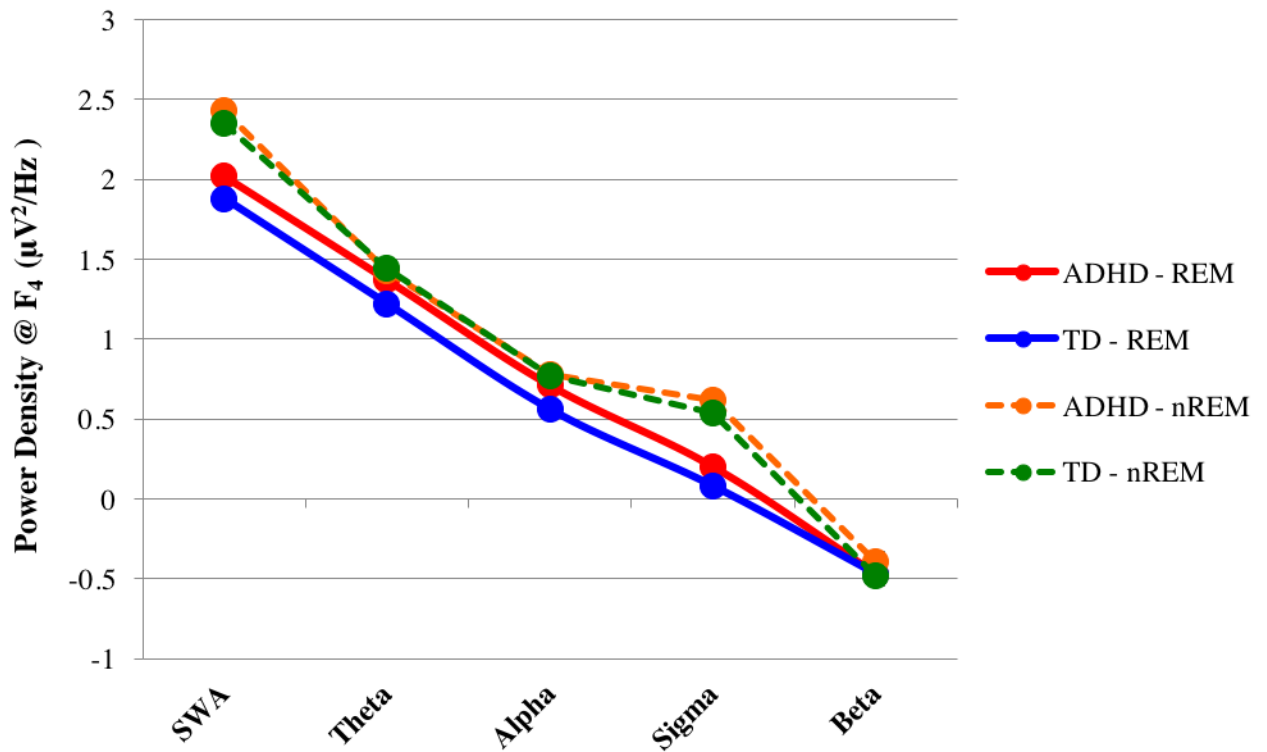


Figure 2.5. Full power curves for REM and nREM sleep at frontal electrode F₄. Raw values were used in statistical analyses; however, log-transformed values are displayed in this figure to aid in interpretation of group differences in activity across REM and nREM sleep.

CHAPTER 3

EFFECTS OF SLEEP EXTENSION ON INHIBITORY CONTROL AND SLEEP PHYSIOLOGY IN CHILDREN WITH AND WITHOUT ADHD

3.1 Introduction

As reviewed in Chapters 1 and 2, children with ADHD are reported to have deficits in inhibitory control (Barkley, 1997) and insufficient sleep (Weiss, Craig, Davies, Schibuk, & Stein, 2015; Yoon, Jain, & Shapiro, 2012). Provided evidence highlighting the positive association between inhibitory control and sleep in TD children (Chapter 2), the aim of the current study was to determine whether extending sleep duration would improve inhibitory control in children with ADHD.

Insufficient sleep is associated with a variety of cognitive deficits in TD children (Astill, Van der Heijden, Van IJzendoorn, & Van Someren, 2012; Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Randazzo, Muehlback, Schweitzer, & Walsh, 1998; Sadeh, Gruber, & Raviv, 2003; Vriend, Davidson, Corkum, Rusak, Chambers, & McLaughlin, 2013) as well as children with ADHD (Gruber, Wiebe, Montecalvo, Brunetti, Amsel, & Carrier, 2011). In TD children, impulsivity and inattention are heightened when sleep is restricted (e.g., Gruber, Cassoff, Frenette, Wiebe, & Carrier, 2012; Sadeh, Gruber, & Raviv, 2003). Recent data suggest that sleep restriction is also related to cognitive impairments in children with ADHD. When instructed to delay their bedtime by one hour for six consecutive nights, children with ADHD subsequently experienced reduced vigilance and attention (Gruber et al., 2011).

In TD populations, sleep-targeted interventions improve cognition (e.g., Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Sadeh, Gruber, & Raviv, 2003). Specifically,

the extension of nocturnal sleep duration was associated with reduced daytime sleepiness, emotional lability, and impulsivity in 7- to 11-year-old children (Gruber et al., 2012). In chronically sleep-deprived adolescents, sleep extension lead to earlier sleep onset, increased time spent in bed, increased sleep duration, and, importantly, improved cognitive functioning (Dewald-Kaufmann, Oort & Meijer, 2014). However, despite this recent work in TD populations, no experimental study has evaluated the effect of sleep extension on cognition in young children with ADHD – a population consistently reported to have insufficient sleep and cognitive deficits (e.g., Barkley, 1997; Owens, 2005; Weiss, Craig, Davies, Schibuk, & Stein, 2015; Yoon et al., 2012).

Moreover, the physiological mechanism supporting the cognitive benefits of sleep extension in young children, with or without ADHD symptoms, is unknown. Theta activity (the spectral power of the theta frequency band) and slow wave activity (SWA; the spectral power in the delta frequency band) are physiological markers of sleep pressure (Campbell & Feinberg, 2009) that are heightened after extended wakefulness and sleep loss (Borbely, Tobler, & Hanagasioglu, 1984; Dijk, Brunner & Borbely, 1990). Studies in adults indicate that extending sleep duration reduces sleep pressure (Arnal et al., 2015). As such, extending sleep duration may also reduce sleep pressure, and the physiological correlates of sleep pressure such as theta activity, in young children. Consequently, cognitive outcomes may be improved, particularly among children with ADHD who have greater SWA and theta activity (Ringli et al., 2013; Saletin et al., 2016; Chapter 2).

Cognitive outcomes are altered when these sleep components are manipulated. For example, when REM theta activity is inhibited, memory was impaired in mice

(Boyce, Glasgow, Williams, & Adamantidis, 2016). Similarly, experimentally increasing SWA improved memory consolidation in healthy adults (Benedict, Scheller, Rose-John, Born, & Marshall, 2009; Marshall, Helgadottir, Molle, & Born, 2006). As sleep pressure is reduced by sleep extension (Arnal et al., 2015), it is likely that changes in theta and SWA are associated with improved cognition.

The aim of this study was to determine whether sleep extension improved inhibitory control in young children with and without ADHD. Based on data in TD children (Gruber et al., 2012), it was hypothesized that inhibitory control would be improved by nocturnal sleep extension. A second aim of this study was to understand the mechanism through which sleep extension supports cognitive enhancement in young children. Provided the positive correlation between inhibitory control and REM theta activity in TD children (Chapter 2), it was predicted that decreasing theta activity, by extending nocturnal sleep duration, would enhance subsequent inhibitory control. As SWA is strongly linked to cognitive outcomes in young children with and without ADHD, it was also hypothesized that improved inhibitory control could be associated with SWA.

3.2 Methods

3.2.1 Participants

Participants were 12 children with ADHD (2 F; $M_{age} = 8.17$, $SD = 1.11$ years; Table 1) and 15 TD children (5 F; $M_{age} = 8.23$ years, $SD = 1.10$ years) between 6 and 9 years of age. Children were recruited from the previous study (Chapter 2, $n = 7$), the University of Massachusetts Amherst's Child Studies Database (IRB protocol #2010-0029), advertisements in child-oriented establishments (e.g., pediatrician offices and schools), and active recruitment during community events.

Children were eligible to participate if they slept less than or equal to 10 hours (on average weeknights) and had a bedtime after 8 PM (on average weeknights). The National Sleep Foundation recommends that 6- to 13-year-old children obtain 9 to 11 hours of sleep per night (Hirshkowitz et al., 2015). Provided this recommendation, it is likely that children sleeping more than 10 hours a night, on average, would have difficulty extending sleep duration further. However, it was expected that children sleeping 10 hours or less would have the ability to extend to the 11 hour sleep duration. As experimental manipulations targeted bedtime (see Protocol), the requirement for children to have a bedtime after 8 PM was intended to prevent the sleep extension manipulation from interfering with evening activities (e.g., dinner time).

Children in the ADHD group were required to have a current diagnosis of ADHD. A current diagnosis was required to confirm that eligible children were formally screened and diagnosed with the disorder. Caregivers were asked who diagnosed their child (e.g., pediatrician) and when that diagnosis was assigned (Table 3.2). Information regarding medication use was also collected (Table 3.2). Diagnosis was confirmed by evaluating ADHD symptomology and impairment rating using the ADHD Rating Scale (Barkley & Murphy, 2006). Exclusion criteria for both groups included: (1) current diagnosis or history of intellectual disabilities or developmental delay, (2) current diagnosis or history of a sleep disorder such as sleep apnea, sleep disordered breathing, or restless leg syndrome, and (3) hearing or visual impairments.

Preliminary data from TD children were used to estimate the sample size needed to measure the effect of sleep extension on theta activity and inhibitory control in children with ADHD. A two-tailed power analysis comparing theta activity between the

baseline and extension conditions in 8 TD children (power set at 0.8, alpha set at 0.05, and an effect size of 0.94) indicated that the estimated sample size for this study was 11 participants. Likewise, an estimated sample of 11 participants was derived when comparing inhibitory control between the baseline and extension conditions in 10 TD children from the same dataset (power of 0.8, alpha of 0.05, and effect size of 0.4). Due to the higher prevalence of ADHD in males (e.g., Boyle et al., 2011), a greater male to female ratio was expected. However, recruitment efforts were not limited to males, or by race or ethnicity.

3.5.1 Sleep Measures

Actigraphy. An Actiwatch Spectrum (Spectrum 2; Philips Respironics, Bend, OR), a wrist-worn device with off-wrist detection and triaxial accelerometer, was used to measure sleep and wake onset times and assure the experimental protocol was followed (Acebo et al., 2005). Enrolled children were instructed to wear the Actiwatch on their non-dominant wrist continuously for the 10-day testing period.

The Actiwatch samples activity at 32 Hz, with a sensitivity of <0.01g. Activity was stored in 15-second epochs. Actigraphy is a reliable index of time spent at rest, asleep, and awake in developmental populations, with 94% agreement with videosomnography (sensitivity = 97%; Sitnick, Goodlin-Jones, & Anders, 2008).

Polysomnography (PSG). Sleep physiology was measured via PSG.

Polysomnography was obtained using customized, high-density PSG electrode caps (EasyCap). These caps had 24 EEG electrodes assigned to O₁, O₂, C₃, C₄, CP₁, CP₂, CP₅, CP₆, F₃, F₄, F_Z, FC_Z, FC₁, FC₂, FC₅, FC₆, F₇, F₈, P₃, P₄, P₇, P₈, P_Z, and PO_Z. The montage also included two electrooculogram leads and two electromyogram leads (affixed to the

chin). Data were referenced to Cz and the contralateral mastoids (A1 and A2). All channels were recorded relative to ground, placed at FPz.

Sleep Diary. During the 10-day testing period, caregivers recorded their child's sleep patterns in a daily sleep diary, logging overnight sleep latency, sleep onset time, and morning wake onset time each day. These logs were used to validate scoring of actigraphy data.

Questionnaires. The Child Sleep Habits Questionnaire (CSHQ) was used to assess each child's normative sleep habits and sleep health. This assessment is reliable ($\alpha = 0.88$) and validated for detecting disordered sleep in young children (Goodlin-Jones, Sitnick, Tang, Liu & Anders, 2008; Owens, Spirito & McGuinn, 2000).

Bedtime routines are associated with improved sleep quality in young children (Mindell, Li, Sadeh, Kwon, & Goh, 2015). As such, the Bedtime Routines Questionnaire (BRQ) was used to quantify (1) the types of activities performed prior to nocturnal sleep and (2) the consistency of bedtime routine performance on weekdays and weekends. The BRQ is a reliable assessment of bedtime routines ($\alpha = 0.69$ to 0.90) in children 2 to 8 years of age (Henderson & Jordan, 2010).

3.5.2 Behavior

Go/No-Go Task. A Go/No-Go task was used to assess inhibitory control. In Go trials (75% of trials), images of various animals (e.g., giraffe, elephant, panda) were presented. In the remaining trials, No-Go trials (25% of trials), a chimpanzee was presented (Figure 3.1). Displayed images were 3 inches in height and 4 inches in length; each centered on a 14-inch computer screen that was positioned approximately 15 inches from participants.

Each trial began with the presentation of an animal image for 500 ms. Children were instructed to respond, via a button press on a mouse, for all of the animals (Go trials), except for the chimpanzee for which they were to inhibit their response (No-Go trials). A blank screen was presented for 500 ms between trials. Children were given 12 practice trials to ensure that they understand task instructions. Subsequently, test trials were presented in 2 blocks of 60 trials each (total of 120 test trials). Two pseudo-random trial orders were used for all participants (for evening and morning sessions). Trial order was counterbalanced across sessions (morning and evening), conditions (baseline and extension), and participants.

Youth Balloon Analog Risk Task (BART-Y). The BART-Y is a valid and reliable assessment of impulsivity in young children (Lejuez et al., 2007; Lahat et al., 2012). The task used was purchased from www.millisecond.com and administered with Inquisit software. In the BART-Y, children were instructed to inflate computer-generated balloons without popping them in order to earn points. Children accumulated points for each pump, but if a balloon exploded then all points accrued for that balloon were lost. Children were informed that they had ability to stop pumping the balloon at any time, prior to explosion, to collect all points earned.

Questionnaires. The ADHD Rating Scale (parent-report) is a valid and reliable assessment of ADHD symptomology in school-aged children (internal consistency: $\alpha = 0.86$ to 0.92 , test-retest reliability $r = 0.49$ to 0.61 ; Pelham, Fabiano, & Massetti, 2005) and was used to evaluate symptomology in the ADHD and TD groups (Barkley & Murphy, 2006). This scale was scored in accordance with the Disruptive Behavior Rating Scales (DBRS; Barkley & Murphy, 2006). The Impairment Scale, also adapted from the

DBRS, was used to determine whether ADHD symptomology interfered with daily functioning in the ADHD group. As Oppositional Defiant Disorder (ODD) is highly comorbid with childhood ADHD (Waschbusch, 2002), the ODD scale of the DBRS was used to evaluate ODD in the ADHD group. In addition to assessing symptomology within the last six months, caregivers of children in the ADHD group completed these scales at the end of both the baseline and extension conditions to determine if subjective assessments of child symptomology changed between conditions.

The Child Behavior Checklist (6-18 years of age) was used as a general assessment of childhood behavior (Achenbach & Rescorla, 2001). The CBCL/6-18 is a widely used, validated, and reliable (test-retest, $\alpha = 0.63$ to 0.97) assessment of behavior problems in school-aged children (Achenbach & Rescorla, 2001). The Child Behavior Questionnaire (CBQ) Short Form was used to assess emotional reactivity. The CBQ is a reliable assessment of emotional reactivity in young children, 3 to 8 years of age, and provides reliable measures of temperament (Putnam & Rothbart, 2006). It is recommended that The Temperament in Middle Childhood Questionnaire (TMCQ) be used for children older than 8 years of age (<https://research.bowdoin.edu/rothbart-temperament-questionnaires/frequently-asked-questions/>). As such, CBQ outcomes in the older children in this sample should be interpreted with caution.

An in-house Health and Demographics form was used to acquire information regarding children's age, gender, race/ethnicity, health, and home life as well as the caregiver's education, employment status, socioeconomic status, and sleep health. An in-house Post-Study Questionnaire was used to assess techniques and strategies that caregivers used to help children adhere to the study protocol (particularly sleep

extension). Caregivers were asked to indicate whether they noticed any changes to their child's behavior following sleep extension. Children were also asked to provide feedback regarding their experience participating in the study.

3.5.3 Procedure

Participants were recruited through the means described above. After screening children for inclusion and exclusion criteria, the researcher scheduled an in-home visit with the caregivers of eligible children to discuss and complete the consent form. During this initial visit, the sleep diary and questionnaire packet (used to assess the child's normative sleep patterns, temperament, and behavior) were given to the caregiver. After obtaining the child's assent, the Actiwatch was fitted to the child's non-dominant wrist. The child and caregiver were shown how to use the Actiwatch and an instruction sheet was provided for future reference. The caregiver was asked to oversee the child's use of the Actiwatch and complete the sleep diary, as accurately as possible, each day of the 10-day testing period (instructions provided). The caregiver was asked to return the sleep diary and questionnaire packet by the end of the 10-day testing period. The Actiwatch was collected at the end of each 5-day testing period (see Procedure).

Researchers provided the caregiver their contact information. Caregivers were encouraged to contact the researchers if they had any questions or concerns. If the Actiwatch was malfunctioning, the caregiver was asked to contact the researcher as soon as possible so that the device could be replaced. The caregiver was also informed that the researcher would be contacting them (via phone or email) each day of the both the baseline and extension conditions to assure the Actiwatch was working properly and that all experimental procedures were being followed.

The study protocol is outlined in Figure 3.2. Five days of the study were considered the baseline condition while the other five days were the extension condition. During the baseline condition, the child followed their normal bedtime schedule for five consecutive nights. On the last night of the baseline condition, the child, accompanied by a caregiver, participated in an in-lab overnight visit in the Cognition & Action Lab's sleep facility (the Life Sciences Laboratory, UMass Amherst) to have inhibitory control and nocturnal sleep physiology measured. During the extension condition, the child was asked to advance their bedtime 90 minutes earlier for five consecutive nights. That is, if the child's bedtime was normally 9 PM (baseline bedtime), he or she was instructed to go to sleep at 7:30 PM each night of the extension condition. The extension paradigm targeted bedtime, rather than wake time, as a child's wake time is often constrained by bus schedules and school start times (<https://sleepfoundation.org/sleep-news/eight-major-obstacles-delaying-school-start-times>). Similarly, a nap intervention would likely be unsuccessful as naps are uncommon in this age group (Iglowstein, Jenni, Molinari, & Largo, 2003).

On the last night of the extension condition, the child participated in a second in-lab overnight visit in the sleep facility. The caregiver was provided a list of tips for helping their child fall asleep earlier during the extension condition (see Appendix). There was approximately 1 week with no experimental manipulations or restrictions between the baseline and extension conditions, and the order of conditions was counterbalanced across participants.

Although napping is uncommon in this age group (Iglowstein et al., 2003), children were instructed to abstain from napping during the two 5-day testing periods.

As expected, the children in this sample did not nap regularly ($M_{naps} = 0$ according to caregiver report).⁵

Additionally, the caregiver and child were instructed that the child must maintain a consistent rise time (e.g., wake time) across the two 5-day testing periods. Maintaining a consistent wake time was intended to ensure that sleep extension was a product of earlier sleep onset time and not delayed wake onset time. Actigraphy data indicate that this protocol was enforced, however, average wake time was significantly earlier during the extension, relative to the baseline, condition for children in both the ADHD ($t(10) = 2.29, p = 0.045, 95\% \text{ CI } [0.46, 34.60]$) and TD groups ($t(13) = 2.21, p = 0.045, 95\% \text{ CI } [0.32, 26.16]$; Table 3.3).

During the overnight visits, participants were asked to arrive at the sleep lab approximately 1 hour before their habitual (baseline condition) or extended (extension condition) bedtime. After settling in, the child was asked to complete a baseline assessment of the Go/No-Go task (~5 minutes). Following completion of the Go/No-Go task, children in the ADHD group were then asked to complete the BART-Y to gauge impulsivity, as impulsivity is prevalent in ADHD and strongly correlated with inhibitory control (~5 minutes). The BART-Y was only administered in the ADHD group as the task was added to the protocol after most of the TD children were tested. The child was then fitted with the polysomnography (PSG) cap (~30 minutes), which recorded sleep physiology during the entire nocturnal sleep bout.

The following morning, the child woke up at their normal rise time. The sleep monitoring equipment was removed and the child was given time to complete their

⁵ Data available from 6/11 children in the ADHD group and 4/15 children in the TD group.

normal morning routine (e.g., breakfast, bath/shower, etc.). Following their morning activities (~20 minutes), the child completed the morning assessments of the Go/No-Go (~5 minutes) and BART-Y (~5 minutes; ADHD group only).

During the overnight visits, caregivers of children in the ADHD group were asked to complete the ADHD, ODD, and Impairment Scales to evaluate their perceived change in their child's behavior between the experimental conditions. Thus, these assessments gauged the child's behavior for the previous 5 days when sleep was manipulated (as opposed to child's normative behaviors expressed in the past six months). The Actiwatch worn for the previous 5-day testing period was collected. This concluded the overnight visit.

At the end of the two 5-day testing periods, the sleep diaries and questionnaires were collected. The caregiver and child completed the Post-Study Questionnaire to gauge feasibility of the sleep intervention and index the strategies used to extend sleep. The caregiver was provided monetary compensation for their time and the child chose an age-appropriate prize. Participants (both the child and their caregiver) could withdraw from the study at any time.

3.3 Statistical Analyses

3.3.1 Sleep

Actigraphy data was evaluated to determine whether experimental manipulations were followed. A repeated-measures ANOVA was used to compare sleep timing variables between the baseline and extension conditions across groups. In these models, sleep timing variables were independently entered as outcomes variables. Condition (baseline and extension) was entered as a within-subjects factor and group (ADHD and

TD) was entered as a between-subjects factor.

To determine whether sleep quality differed between the baseline and extension conditions, repeated-measures ANOVAs were used to compare PSG outcome variables (i.e., total sleep time, time spent in distinct sleep stages, spectral power of REM theta activity and SWS SWA) between conditions and groups. In these models, PSG measures were independently entered as outcomes variables, condition (baseline and extension) was entered as a within-subjects factor, and group (ADHD and TD) was entered as a between-subjects factor.

3.3.2 Behavior

To determine whether sleep extension improved inhibitory control in children with and without ADHD, a repeated-measures ANOVA was used to compare inhibitory control following the baseline and extension conditions in each group (ADHD and TD). In these models, inhibitory control (as measured by accuracy (% correct) on No-Go trials) was entered as the outcome variable. Condition (baseline and extension) and time (evening and morning) were entered as within-subject factors and group (ADHD and TD) was entered as a between-subjects factor. Repeated-measures ANOVAs were then run independently for each group to assess group specific changes in inhibitory control following the sleep manipulation.

Provided relations between impulsivity and inhibitory control (Logan, Schachar, & Tannock, 1997), performance on the BART-Y was compared before and after overnight sleep and between the baseline and extension conditions, to assess the role of sleep and sleep extension on impulsivity in the ADHD group. In accordance with previous studies (Lahat et al., 2012), the dependent measure in this analysis was the adjusted average

number of pumps. The adjusted number of pumps reflects performance that is not constrained by the explosion point of the balloon (randomized across trials). That is, a balloon that pops only after a few pumps is not weighted as heavily as a balloon that pops after dozens of pumps, as riskiness in the former trial is constrained by the low number of pumps until explosion (Lejuez et al., 2007). With this adjustment, a greater value in this measure reflects a greater level of impulsivity, on average.

Finally, paired-samples *t*-tests were used to compare caregiver ratings on the ADHD, ODD, and Impairment Scales following the baseline and extension conditions to determine if the sleep manipulation altered the caregiver's subjective assessment of their child's behavior. This measure was collected only in the ADHD group.

3.3.3 Sleep and Behavior

Partial correlations (controlling for evening inhibitory control) between morning inhibitory control and REM theta activity were run to determine whether changes in inhibitory control were associated with REM theta activity following the baseline and extension conditions in each group (ADHD and TD). As inhibitory control was not associated with theta activity, relations between inhibitory control and SWA were assessed in the same manner.

3.4 Results

At the group level, children in both the TD and ADHD groups met formal screening criteria, as they slept less than 10 hours on average and had bedtimes after 8 PM (Table 3.1). Children in the ADHD group had significantly more symptoms of ADHD than children in the TD group ($t(24) = 7.03, p \leq 0.001, 95\% \text{ CI } [16.47, 30.17]$). Child age ($t(24) = 0.11, p = 0.917$) and gender ($X^2(1, N = 26) = 0.74, p = 0.390$) did not

differ between groups.

One child was excluded from statistical analyses in the ADHD group as this child became ill during the first overnight sleep visit and did not complete the testing protocol. Thus, results are presented for 11 children with ADHD (2 F; $M_{age} = 8.27$, $SD = 1.10$ years) who had complete datasets.

Due to recording error, five participants in the TD group did not have usable PSG data. Consequently, data for sleep architecture and physiology is presented for 10 TD children (2 F, $M_{age} = 7.95$ years, $SD = 0.96$ years). Additionally, data could not be retrieved from one participant's Actiwatch. As such, actigraphy data in the TD group is averaged across 14 TD children (5 F; $M_{age} = 8.18$, $SD = 1.13$ years).

3.4.1 Sleep

In the repeated-measures ANOVA comparing sleep onset time (measured by actigraphy) between conditions and groups, the main effect of condition was significant ($F(1,23) = 258.71$, $p \leq 0.001$, $\eta_p^2 = 0.918$; Table 3.3) such that children advanced sleep onset time from 9:11PM to 8:36PM during the extension condition, on average. The main effect of group and condition by group interaction were not significant (p 's ≥ 0.180).

When comparing total sleep time (measured by actigraphy), the main effect of condition was again significant: children slept 52 minutes longer during the extension condition relative to the baseline condition, on average ($F(1,23) = 59.76$, $p \leq 0.001$, $\eta_p^2 = 0.722$; Table 3.3). Here too, the main effect of group and condition by group interaction were not significant (p 's ≥ 0.336).

An exploratory repeated-measures ANOVA was run to determine whether there were significant differences in total sleep time between days of the experimental

manipulations between the TD and ADHD groups. In this model, the main effect of condition was significant such that total sleep time was longer during the extension condition relative to the baseline condition, overall ($F(1,21) = 55.87, p \leq 0.001, \eta_p^2 = 0.727$; Figure 3.3). The main effect of group was not significant ($F(1,21) = 0.69, p = 0.416$). The main effect of day was significant ($F(4,84) = 2.89, p = 0.027, \eta_p^2 = 0.121$). Interactions between condition, day, and group were not significant (p 's ≥ 0.124).

Follow up paired samples t -tests indicated that, within the ADHD group, total sleep time increased marginally between Days 2 and 5 during the extension condition ($t(10) = -2.01, p = 0.072, 95\% \text{ CI } [-40.16, 2.09]$; Figure 3.3A). Differences in total sleep time between other days during the manipulations were not significant (p 's ≥ 0.094). In the TD group, total sleep time was reduced between Days 1 and 2 ($t(13) = 2.87, p = 0.013, 95\% \text{ CI } [4.85, 34.24]$) and between Days 1 and 3 ($t(13) = 3.11, p = 0.008, 95\% \text{ CI } [7.61, 42.28]$; Figure 3.3B) during the extension condition. All other differences were not significant (p 's ≥ 0.100). These data indicate that, among TD children, total sleep time is reduced during the initial stages of sleep extension (between Days 1 and 3, Figure 3.3B). Children with ADHD, on the other hand, tended to have increased sleep duration toward the end of the 5-day extension manipulation (between Days 2 and 5), although these findings were not significant (Figure 3.3A).

Data from PSG indicate that total sleep time was significantly longer on the extension experimental overnight as compared to the baseline experimental night across all children (main effect of condition: $F(1,19) = 17.26, p = 0.001, \eta_p^2 = 0.476$; Table 3.4). Sleep efficiency was reduced during the extension overnight across both groups ($F(1,19) = 4.98, p = 0.038, \eta_p^2 = 0.208$; Table 3.4). The main effect of group and condition by

group interaction were not significant in either analysis (p 's ≥ 0.117).

The time spent in Stages 1 and 2 did not significantly differ between the baseline and extension experimental nights or between the ADHD and TD groups (p 's ≥ 0.175 ; Table 3.4). Overall, children with ADHD had more SWS than TD children (main effect of group: $F(1,19) = 5.10$, $p = 0.036$, $\eta_p^2 = 0.212$; Table 3.4). The main effect of condition was not significant ($F(1,19) = 0.65$, $p = 0.431$). Time spent in REM sleep did not differ between conditions or groups (p 's ≥ 0.420 ; Table 3.4). The condition by group interactions were not significant (p 's ≥ 0.126).

Theta activity recorded during REM sleep also did not differ between conditions or groups (p 's ≥ 0.429 ; Table 3.4). The condition by group interaction was also not significant ($F(1,19) = 0.40$, $p = 0.537$). SWA recorded during SWS also did not differ between conditions (main effect of condition: $F(1,19) = 0.05$, $p = 0.818$; Table 3.4). However, children with ADHD had more SWA than TD children (main effect of group: $F(1,19) = 6.48$, $p = 0.020$, $\eta_p^2 = 0.254$; Table 3.4). The condition by group interaction was not significant ($F(1,19) = 0.51$, $p = 0.484$).⁶ Collectively, these findings suggest that although total sleep time differed between conditions, sleep physiology was unchanged by sleep extension in either group.

To determine whether there were topographical differences in spectral activity between conditions and groups, an exploratory repeated-measures ANOVA was run with condition and electrode entered as within-subjects factors and group as a between-subjects factor. In the model assessing differences in theta activity, the main effects of

⁶ Results were unchanged when child age was entered as a covariate in this model. The main effect of age and interactions with age were also not significant (p 's ≥ 0.339).

condition and group were not significant (p 's ≥ 0.407). The main effect of electrode ($F(23, 322) = 25.72, p \leq 0.001, \eta_p^2 = 0.648$) and the interaction between condition and electrode ($F(23, 322) = 2.72, p \leq 0.001, \eta_p^2 = 0.163$) were significant. In the model assessing differences in SWA, the main effects of condition and group were not significant (p 's ≥ 0.512). Here too, the main effect of electrode was significant ($F(23, 322) = 4.57, p \leq 0.001, \eta_p^2 = 0.246$). All other interactions in these models (for both theta and SWA) were not significant (p 's ≤ 0.100). To follow up on significant main effects and interactions, separate exploratory ANOVAs comparing spectral activity at each electrode (1) between conditions and (2) between groups are included below.

Exploratory whole brain analyses indicate that, consistent with results at the *a priori* chosen frontal electrode site (F4), REM theta activity did not differ between conditions at any other electrode in the ADHD group (p 's ≥ 0.100). In the TD group, however, REM theta activity was greater during the baseline condition relative to the extension condition at frontal sites FC1 and FC5, central site C3, central parietal site CP5, and parietal sites P3 and P7 (p 's ≤ 0.04). SWA did not significantly differ between conditions at any electrode in either group (p 's ≥ 0.075). These data indicate that REM theta activity was reduced with sleep extension in the TD but not the ADHD group.

Although REM theta activity did not differ between groups at the *a priori* chosen frontal electrode site (F4), exploratory whole brain analyses indicated that, collapsed across conditions, theta activity was significantly greater in the ADHD group relative to the TD group at frontal site F8, central parietal sites CP1, CP5 and CP6, parietal sites P3 and P4, and occipital sites O1 and O2 (p 's ≤ 0.05 ; Figure 3.4A). In addition to frontal site F4, SWA was greater in the ADHD group relative to the TD group at frontal site FCz

($t(15) = 2.52, p = 0.024, 95\% \text{ CI } [10.87, 129.87]$; Figure 3.4B) when collapsed across conditions. Taken together, these data indicate that low frequency EEG is elevated in children with ADHD.

3.4.2 Behavior

A repeated-measures ANOVA was used to compare sleep-dependent changes in inhibitory control between the ADHD and TD groups. Expectedly, inhibitory control was greater in TD children overall (main effect of group: $F(1,24) = 4.32, p = 0.048, \eta_p^2 = 0.153$; Table 3.5 and Figure 3.5). The main effect of time was also significant, such that inhibitory control was greater in the morning relative to the evening ($F(1,24) = 8.39, p = 0.008, \eta_p^2 = 0.259$). The main effect of condition was not significant ($F(1,24) = 2.78, p = 0.109$). The two-way interaction between condition and group was significant ($F(1,24) = 9.23, p = 0.006, \eta_p^2 = 0.278$). Similarly, the two-way interaction between time and group was significant ($F(1,24) = 5.75, p = 0.025, \eta_p^2 = 0.193$). The two-way interaction between condition and time was not significant ($F(1,24) = 1.61, p = 0.216$). The three-way interaction between condition, time, and group was also not significant ($F(1,24) = 0.25, p = 0.620$).⁷ Taken together, the results of this omnibus ANOVA indicate that inhibitory control is improved by sleep in all children. Follow-up ANOVAs were used to assess interactions within each group.

To determine whether order effects influenced outcomes in this task, the model was re-run with condition order entered as a between-subjects factor. The main effect of group remained significant when controlling for the order of conditions ($F(1,22) = 5.05, p$

⁷ When child age was entered as a covariate in this model, the main effect of time was no longer significant ($F(1,23) = 0.002, p = 0.926$). All other results were unchanged. The main effect of age and interactions with age were not significant (p 's ≥ 0.209).

= 0.035, $\eta_p^2 = 0.187$). The main effect of time also remained significant ($F(1,22) = 7.66$, $p = 0.011$, $\eta_p^2 = 0.258$). The main effect of condition became marginally significant, such that performance during the extension condition was greater than performance during the baseline condition ($F(1,22) = 3.46$, $p = 0.076$, $\eta_p^2 = 0.136$). The two-way interaction between condition and group remained significant ($F(1,22) = 12.39$, $p = 0.002$, $\eta_p^2 = 0.360$). Similarly, the two-way interaction between time and group remained significant ($F(1,22) = 5.24$, $p = 0.032$, $\eta_p^2 = 0.192$). The two-way interaction between condition and time was not significant ($F(1,22) = 2.02$, $p = 0.169$). The three-way interaction between condition, time, and group was also not significant ($F(1,22) = 0.56$, $p = 0.461$).

The main effect of order was not significant ($F(1,22) = 2.62$, $p = 0.120$). The two-way interactions between condition and order, time and order, and group and order were also not significant (p 's ≥ 0.254). The three-way interaction between condition, group and order was significant ($F(1,22) = 6.68$, $p = 0.017$, $\eta_p^2 = 0.233$). The three-way interactions between time, group and order, and condition, time, and order were not significant (p 's ≥ 0.925). The four-way interaction between condition, time, group, and order was significant ($F(1,22) = 6.55$, $p = 0.018$, $\eta_p^2 = 0.229$). To understand the significant interactions with order, order effects were evaluated independently for each group in subsequent follow-up analyses.

Behavior in the ADHD Group

To assess the significant two-way interactions reported in the omnibus ANOVA, separate repeated-measures ANOVAs were run for each group, independently. In the ADHD group, the main effect of condition was significant: children with ADHD had greater inhibitory control during the extension condition ($F(1,10) = 7.20$, $p = 0.023$, $\eta_p^2 =$

0.419; Table 3.5 and Figure 3.5). Consistent with the results of Chapter 2, the main effect of time was not significant, suggesting that inhibitory control was comparable during the pre- (evening) and post-sleep (morning) assessments ($F(1,10) = 0.105, p = 0.752$). The condition by time interaction was also not significant ($F(1,10) = 2.79, p = 0.126$).

Consistent with the omnibus ANOVA, order effects were also assessed in the separated repeated-measures ANOVAs run for each group. Among the ADHD group, the main effect of condition remained significant when controlling for order effects ($F(1,9) = 8.80, p = 0.016, \eta_p^2 = 0.494$). The main effect of time was still not significant ($F(1,9) = 0.10, p = 0.764$). However, the condition by time interaction became significant ($F(1,9) = 6.58, p = 0.030, \eta_p^2 = 0.422$), such that morning inhibitory control was greater than evening inhibitory control during the extension condition. The three-way interaction between time, condition, and order was also significant ($F(1,9) = 9.83, p = 0.012, \eta_p^2 = 0.522$), suggesting that morning inhibitory control was greatest during the extension condition when the extension condition occurred first (prior to the baseline condition). The main effect of order and other interactions with order were not significant (p 's ≥ 0.146).

Children with ADHD also completed the BART-Y to assess change in impulsivity between conditions. In the repeated-measures ANOVA used to compare sleep-dependent changes in impulsivity (as measured by performance on the BART-Y), the main effects of condition ($F(1,10) = 1.27, p = 0.286$) and time ($F(1,10) = 0.13, p = 0.723$) were not significant (Table 3.5). Similarly, the condition by time interaction was not significant ($F(1,10) = 0.13, p = 0.728$). These results were unchanged when controlling for order effects. Moreover, the main effect of order and interactions with order were not

significant (p 's ≥ 0.080).⁸

In the ADHD group, caregiver's subjective assessments of their child's ADHD and ODD symptoms did not differ between the baseline and extension conditions (p 's ≥ 0.395 ; Table 3.5). Likewise, the caregiver's subjective assessments of their child's impairment did not differ between conditions ($t(10) = 0.62, p = 0.549$).

Behavior in the TD Group

In the TD group, the main effect of condition was not significant ($F(1,14) = 1.46, p = 0.247$; Table 3.5 and Figure 3.5). Consistent with the results of Chapter 2, however, the main effect of time was significant such that, inhibitory control was significantly greater in the morning, relative to the evening, during both the baseline and extension conditions ($F(1,14) = 16.80, p = 0.001, \eta_p^2 = 0.546$). The condition by time interaction was not significant ($F(1,14) = 0.26, p = 0.621$).

The main effect of condition was still not significant when controlling for order effects ($F(1,13) = 2.31, p = 0.152$). The main effect of time remained significant ($F(1,13) = 15.56, p = 0.002, \eta_p^2 = 0.545$). The condition by time interaction was still not significant ($F(1,13) = 0.18, p = 0.678$). However, the two-way interaction between condition and order was significant ($F(1,13) = 5.08, p = 0.042, \eta_p^2 = 0.281$), such that inhibitory control was greater during the extension condition if the baseline condition

⁸ When child age was entered as a covariate, the main effects of condition and time were still not significant (p 's ≥ 0.663). However, the two-way interaction between condition and time became significant ($F(1,9) = 4.89, p = 0.054, \eta_p^2 = 0.352$) such that performance was improved following overnight sleep, particularly during the baseline condition. The main effect of age was marginally significant ($F(1,9) = 3.84, p = 0.082, \eta_p^2 = 0.299$) suggesting that older children had better performance, overall. The three-way interaction between condition, time, and age was also significant ($F(1,9) = 5.22, p = 0.048, \eta_p^2 = 0.367$). All other interactions with age were not significant (p 's ≥ 0.692).

occurred first (prior to the extension condition). The main effect of order and other interactions with order were not significant (p 's ≥ 0.143).

3.4.3 Sleep and Behavior

In the ADHD group, REM theta activity was not significantly related to subsequent morning inhibitory control (controlling for evening inhibitory control) during either the baseline ($r = 0.347, p = 0.326$) or extension conditions ($r = -0.255, p = 0.477$; Figure 3.6A).⁹ Similarly, REM theta activity was also not related to morning inhibitory control during either the baseline ($r = 0.336, p = 0.337$) or extension conditions ($r = -0.199, p = 0.607$) in the TD group (Figure 3.6B).¹⁰

SWA recorded during SWS was significantly, positively related to subsequent morning inhibitory control (controlling for evening inhibitory control) during the baseline condition ($r = 0.731, p = 0.016$; Figure 3.7A) in the ADHD group. This finding was no longer significant when three outliers were removed ($n = 8, r = 0.546, p = 0.205$; Figure 3.5C). During the extension condition, SWA was not related to morning inhibitory control ($r = -0.133, p = 0.715$; Figure 3.7A). However, SWA was significantly, negatively associated with subsequent morning inhibitory control (controlling for evening inhibitory control) during the extension condition when the outliers were removed ($n = 8, r = -0.812, p = 0.027$; Figure 3.7C). This result suggests that when children with ADHD sleep more than usual, lower amounts of SWA are associated with greater subsequent inhibitory control. Additionally, SWA was not significantly correlated with evening inhibitory control during either condition with or without outlier removed (r 's $\leq -0.299, p$'s ≥ 0.473), supporting this sleep-dependent effect. In the TD group, SWA was not

⁹ Results were unchanged when outliers were removed (p 's ≥ 0.182).

¹⁰ Results were unchanged when outliers were removed (p 's ≥ 0.633).

related to subsequent morning inhibitory control during either the baseline ($r = -0.415, p = 0.267$) or the extension conditions ($r = -0.275, p = 0.475$; Figure 3.7B).¹¹

Because SWA was differentially associated with inhibitory control during the baseline and extension conditions in the ADHD group, relations between the change in SWA and the change in inhibitory control (collapsed across evening and morning assessments) between conditions were evaluated. When the outliers in SWA were removed, this relationship was not significant ($n = 8, r = -0.405, p = 0.320$). To determine whether the change in inhibitory control was related to the change in total sleep time rather than sleep physiology, relations between the change in total sleep time (as measured by PSG) and inhibitory control were also assessed. This relationship was also not significant in either the ADHD ($n = 11, r = 0.413, p = 0.207$) or TD groups ($n = 10, r = -0.221, p = 0.539$; Figure 3.8).

3.4.4 Trait-Like Differences in Sleep and Behavior

Partial correlations were used to determine whether trait-like differences may have influenced relations between sleep-dependent changes in behavior in each group (ADHD and TD). Correlations between morning inhibitory control and outcomes on the ADHD Rating Scale, CBCL, CBQ, and CSHQ (controlling for evening inhibitory control) were not significant in the ADHD group (p 's ≥ 0.152). In the TD group, higher scores on the ADHD Rating Scale were associated with lower morning inhibitory control (as measured by the CBQ) during the baseline condition ($r = -0.557, p = 0.038$). All other correlations in the TD group were not significant (p 's ≥ 0.172).

3.5 Discussion

¹¹ Results were unchanged when outliers were removed (p 's ≥ 0.456 ; Figure 3.7D).

This chapter examined the effect of sleep extension on inhibitory control in children with and without ADHD. Both children with and without ADHD were able to extend overnight sleep duration. Inhibitory control improved more than 13% from baseline when children with ADHD extended overnight sleep duration. Inhibitory control was not improved by sleep extension in the TD group. However, morning inhibitory control was 10% greater than evening inhibitory control in the TD group, consistent with the results of Chapter 2. Improvement in inhibitory control was not associated with REM theta activity as hypothesized. Rather, decreased SWA was associated with improved inhibition following sleep extension in children with ADHD.

3.5.1 Changes in Sleep Timing and Physiology with Sleep Extension

Consistent with data from TD children in this sample and other studies (e.g., Gruber et al., 2012), this study was the first to successfully demonstrate sleep extension in children with ADHD – a population consistently reported to have reduced sleep duration and bedtime resistance (Owens, Maxim, Nobile, McGuinn, & Msall, 2000; Weiss et al., 2015). Specifically, when instructed to advance their bedtime by 1.5 hours, children with ADHD extended overnight sleep duration by approximately 48 minutes, on average.

Although sleep duration was extended, theta and SWA did not differ between conditions, counter to the primary hypotheses. PSG was collected only on the last night of each condition. As such, it is possible that physiological changes in sleep EEG occurred earlier during the extension condition (Days 1-4), when children were transitioning into the new sleep schedule. If such is the case, physiological changes in EEG may not have been as prominent by Day 5.

Relatedly, the lack of change in sleep physiology may also have been a consequence of the magnitude of sleep extension throughout the experimental manipulation. Among children with ADHD, the greatest change in total sleep time occurred during the last few days sleep extension (Figure 3.3A). In contrast, total sleep time was reduced during the first few days of sleep extension in the TD sample (Figure 3.3B). Additionally, the ADHD group had greater variability in the change in total sleep time across both conditions. Taken together, these findings suggest that response to sleep extension varies both between and within groups. As sleep physiology changes with sleep duration (Arnal et al., 2015; Dewald-Kaufmann, Oort & Meijer, 2014), the variability in total sleep time across conditions may have contributed to the non-significant differences in sleep physiology between conditions. Prolonged periods of sleep extension may be needed to facilitate stabilization of total sleep time in order to detect significant differences in sleep physiology after extension.

Although sleep physiology did not differ between conditions, theta and SWA differed between groups. An exploratory whole brain analysis indicated that theta activity was elevated among ADHD children, relative to TD children, at central, parietal, and occipital sites (Figure 3.4A). Additionally, frontal SWA was greater in the ADHD group (at F4 and FCz; Figure 3.4B) regardless of condition. Collectively, these results indicate that low frequency EEG is elevated in children with ADHD. As heightened theta and SWA are associated with the accumulation of sleep pressure, these data support the hypothesis that sleep pressure is greater in children with ADHD as compared to TD children.

3.5.2 Changes in Behavior with Sleep Extension

ADHD is associated with a shortening of the circadian cycle (Baird et al. 2012), which predicts performance improvements in the morning relative to the evening. However, inhibitory control was not improved by overnight sleep in this group, consistent with the results from Chapter 2. As such, it is unlikely that group differences in circadian rhythmicity contributed to behavioral differences in this study. Rather, inhibitory control was improved more than 13% when children with ADHD extended their overnight sleep duration.

In contrast to the findings in the ADHD group, sleep extension did not alter behavior in TD children. In accordance with the data reported in Chapter 2, inhibitory control was improved 10% following overnight sleep regardless of sleep duration. Taken together, these results indicate that sleep extension improved inhibitory control in children with ADHD but not in TD children.

Deficits in inhibitory control contribute to primary symptoms of ADHD (Barkley, 1997; Doyle, 2006; Nigg, 2000; Oosterlaan, Logan, & Sergeant, 1998) as well as secondary cognitive impairments in self-regulation and working memory (Barkley, 1997). Provided that inhibitory control was improved with extended sleep duration in the ADHD group, these findings suggest that extending sleep duration may improve symptoms and cognitive outcomes in this population. Importantly, these effects were achieved by targeting bedtime, as opposed to wake time. Altering bedtime is more practical than adjusting wake time, as work/school start times and morning bus schedules are often inflexible. Although many caregivers reported that the earlier bedtime made them feel “rushed” in the evening, these data suggest that earlier bedtimes may benefit clinical outcomes in this population. Notably, the beneficial effect of sleep extension on

inhibition was robust and the effect size comparable to those of many stimulants used to treat ADHD (effect size approximately 0.7; Faraone, Biederman, Spencer, & Aleardi, 2006), suggesting that sleep-based interventions may be an effective means of symptom management. Importantly, this intervention assessed changes in inhibitory control after only five days of experimental manipulation. As many interventions with this population span several weeks (e.g., Herbert, Harvey, Roberts, Wichowski, and Lugo-Candelas, 2012), it is important to assess prolonged changes to behavior in future studies.

Inhibitory control is highly correlated with impulsivity (Logan, Schachar, & Tannock, 1997). As such, the effects of sleep extension on impulsivity were evaluated in the ADHD group using the BART-Y. Although inhibitory control and impulsivity were highly correlated (CBQ subscales: $r = -0.718$, $p = 0.013$), sleep extension did not improve impulsivity in children with ADHD. This finding contrasts work in TD children, who were rated as being less impulsive following 5-days of sleep extension, relative to an equivalent period of sleep restriction (Gruber et al., 2012). These contrasting findings may have been a consequence of the difference in control conditions (sleep restriction versus normal sleep) or the task used to gauge impulsivity (caregiver report versus objective, task-based measurement).

In the BART-Y, children were awarded “points” based on their performance. Children were told that the points earned would be used to dictate the size of the prize the child would receive when they completed the study (note: children were allowed to pick any size prize they wanted at the conclusion of the study). As this task was not constrained by time and required children to utilize reward-based decision-making, children may have deliberately engaged inhibitory control when making responses in an

effort to gain more points. Therefore, the outcomes derived from this task may have been less sensitive to effects of sleep and, consequently, sleep extension. Responses to the Go/No-Go task, on the other hand, were time sensitive: children were required to make a response as soon as the stimuli appeared on the screen. Thus, inhibition in this sense was automatic and may have been more sensitive to sleep-related benefits.

In the ADHD group, caregiver-report of child symptomology also did not differ between conditions. The lack of statistical differences in symptomology was likely a consequence of the measurement tool used. The ADHD Rating Scale is subjective and has limited range (Likert scale items ranged from 0-3). Consequently, this scale does not provide much room for caregivers to change their ratings between conditions.

3.5.3 Relations between Sleep Physiology and Behavior During Sleep Extension

Counter to the primary hypothesis, inhibitory control was not associated with REM theta activity in the samples tested.¹² An alternative mechanism through which sleep physiology may have impacted subsequent inhibition was via reduction in sleep pressure, as measured by SWA. This hypothesis was supported in the ADHD group but not in the TD group. During the extension condition, a reduction in SWA was associated with improved morning inhibitory control among children with ADHD. The non-significant associations between SWA and evening inhibitory control further qualified this sleep-dependent effect. Collectively, these data suggest that lengthening sleep time reduces sleep pressure, via a reduction in SWA, in children with ADHD. SWA reflects synaptic downscaling or depotentiation (Tononi & Cirelli, 2014). As SWA is elevated in children with ADHD, neural networks may be over stimulated and thus, less efficient.

¹² For discussion of these findings relative to those reported in Chapter 2, please see the General Discussion.

When sleep pressure is reduced, however, these networks may be more rested and subsequent functions such as inhibitory control may be improved as a consequence.

Although this finding presents a possible mechanism through which sleep extension may improve inhibitory control in children with ADHD, there are notable limitations to be discussed. First, correlations between SWA and morning inhibitory control were sensitive to outliers in the ADHD sample tested ($n = 3$). Including these outliers in analyses eliminated the aforementioned correlation during the extension condition and contributed to a significant, positive correlation between SWA and morning inhibitory control during the baseline condition. Second, the effect sizes of other correlations, such as those with REM theta activity and the change in total sleep time, were large although not significant. As such, data targeting the mechanism underlying the beneficial effect of sleep extension on behavior in children with ADHD is inconclusive. Additional data collection and replication is needed to strengthen the interpretation of results related to physiology.

Second, relations between inhibitory control and SWA were detected although SWA did not differ between the baseline and extension conditions. As discussed previously, differences in sleep physiology may have been reduced by the end of the testing periods when PSG was collected. Thus, future studies should evaluate incremental changes in sleep physiology during the course of the sleep extension period to better understand how sleep EEG changes in response to extended periods of prolonged sleep duration.

3.5.4 Conclusions

In summary, the results of this chapter indicate that children with and without

ADHD are capable of significantly extending their overnight sleep duration when instructed to advance their bedtime. In children with ADHD, the extension of overnight sleep duration improved inhibitory control – a primary deficit in this population that is strongly associated with symptom severity. Conversely, inhibitory control was improved by overnight sleep, regardless of sleep duration, in TD children. Collectively, these findings suggest that targeting sleep improves behavioral outcomes in young children with and without ADHD.

Table 3.1. Participant demographics.

	ADHD Mean (SD)	TD Mean (SD)	<i>p</i> -value
<u>Participant Demographics</u>			
Age (years)	8.17 (1.11)	8.23 (1.10)	0.917
Gender (Females: Males)	(2:10)	(5:10)	0.390
Hyperactive symptoms	15.09 (6.70)	3.13 (3.80)	≤ 0.001
Inattentive symptoms	13.36 (5.33)	2.00 (2.70)	≤ 0.001
ODD symptoms	2.18 (2.35)	-	-
Average sleep duration (hours)	9.21 (1.10)	9.98 (0.80)	0.161
Average bedtime (caregiver report; PM)	8:50 (37.99 minutes)	8:32 (28.27 minutes)	0.044

Note: In the ADHD group, n = 12 with the exception of ADHD symptomology ratings in which n = 11. In the TD group, n = 15.

Table 3.2. Information about ADHD diagnoses.

	Mean (SD)
<u>Information about Diagnoses</u>	
Diagnosis assigned by pediatrician (%)	50%
Diagnosis assigned by psychiatrist (%)	16.67%
Diagnosis assigned by psychologist (%)	16.67%
Diagnosis assigned by “other” (%)	16.67%
Diagnosed within 3 years of testing (%)	33.33%
Diagnosed within 2 years of testing (%)	25%
Diagnosed within 1 year of testing (%)	41.67%
<u>Information about ADHD Medications</u>	
Participants not taking medication (%)	33.33%
Participants taking stimulants (%)	50%
Participants taking other medications (%)	16.67%

Note: n = 12.

Table 3.3. Differences in sleep between conditions and groups (actigraphy).

	ADHD Mean (SD)	TD Mean (SD)	<i>p</i> -value (Condition)
Total sleep time (minutes)			
Baseline	579.57 (46.02)	588.94 (26.02)	
Extension	627.53 (46.46)	644.51 (30.48)	≤ 0.001
<i>p</i> -value (Group)		0.336	
Sleep onset time (PM)			
Baseline	9:21 (39.05 minutes)	9:01 (33.60 minutes)	
Extension	8:15 (55.49 minutes)	7:52 (30.06 minutes)	≤ 0.001
<i>p</i> -value (Group)		0.180	
Wake onset time (AM)			
Baseline	7:06 (54.00 minutes)	6:50 (25.35 minutes)	
Extension	6:43 (45.03 minutes)	6:37 (20.73 minutes)	0.004
<i>p</i> -value (Group)		0.570	

Note: In ADHD group, n = 11. In TD group, n = 14.

Table 3.4. Differences in sleep between conditions and groups (PSG).

	ADHD Mean (SD)	TD Mean (SD)	<i>p</i> -value (Condition)
Total sleep time (minutes)			
Baseline	547.83 (41.40)	581.80 (32.99)	
Extension	601.92 (63.50)	610.44 (36.17)	0.001
<i>p</i> -value (Group)		0.233	
Sleep efficiency (%)			
Baseline	93.78 (3.04)	96.02 (5.00)	
Extension	90.80 (5.12)	94.57 (5.63)	0.038
<i>p</i> -value (Group)		0.117	
nREM Stage 1 (%)			
Baseline	11.39 (4.79)	13.50 (7.58)	
Extension	9.26 (2.65)	12.82 (7.66)	0.404
<i>p</i> -value (Group)		0.175	
nREM Stage 2 (%)			
Baseline	52.33 (4.41)	55.13 (6.37)	
Extension	53.31 (4.98)	55.52 (7.49)	0.712
<i>p</i> -value (Group)		0.184	
SWS (%)			
Baseline	21.11 (4.52)	18.52 (3.63)	
Extension	21.69 (5.09)	16.76 (2.89)	0.431
<i>p</i> -value (Group)		0.036	
REM (%)			
Baseline	15.16 (4.72)	12.87 (5.27)	
Extension	15.74 (4.09)	14.89 (6.01)	0.256
<i>p</i> -value (Group)		0.420	
Theta Activity ($\mu\text{V}^2/\text{Hz}$)			
Baseline	17.25 (7.19)	15.77 (5.60)	
Extension	17.77 (5.34)	15.08 (6.85)	0.926
<i>p</i> -value (Group)		0.429	
SWA ($\mu\text{V}^2/\text{Hz}$)			
Baseline	590.20 (119.99)	473.26 (155.34)	
Extension	571.07 (131.81)	510.98 (48.81)	0.818
<i>p</i> -value (Group)		0.020	

Note: In ADHD group, n = 11. In TD group n = 10.

Table 3.5. Differences in behavior between conditions and groups.

	ADHD Mean (SD)	TD Mean (SD)	<i>p</i> -value (Condition)
Inhibitory Control (% Correct No-Go Trials)			
Baseline			
Evening	59.09 (16.61)	71.33 (13.26)	
Morning	56.67 (19.03)	79.56 (15.78)	
Extension			
Evening	69.09 (14.76)	66.00 (12.49)	
Morning	73.33 (15.06)	77.11 (10.07)	0.109
<i>p</i> -value (Group)		0.048	
<i>p</i> -value (Time)		0.008	
Impulsivity (Adjusted Average Pump Count)*			
Baseline			
Evening	24.39 (8.99)	-	
Morning	26.58 (9.85)	-	
Extension			
Evening	28.90 (13.35)	-	
Morning	29.25 (9.94)	-	0.723
<i>p</i> -value (Time)		0.286	
Caregiver Report of Symptoms*			
ADHD symptoms			
Baseline	20.00 (9.71)	-	
Extension	18.91 (11.62)	-	0.694
ODD symptoms			
Baseline	0.91 (1.51)	-	
Extension	1.36 (2.25)	-	0.395
Impairment rating			
Baseline	7.91 (4.85)	-	
Extension	7.09 (4.44)	-	0.549

*Notes: In ADHD, n = 11. In TD group, n = 15. *Data from ADHD group only.*

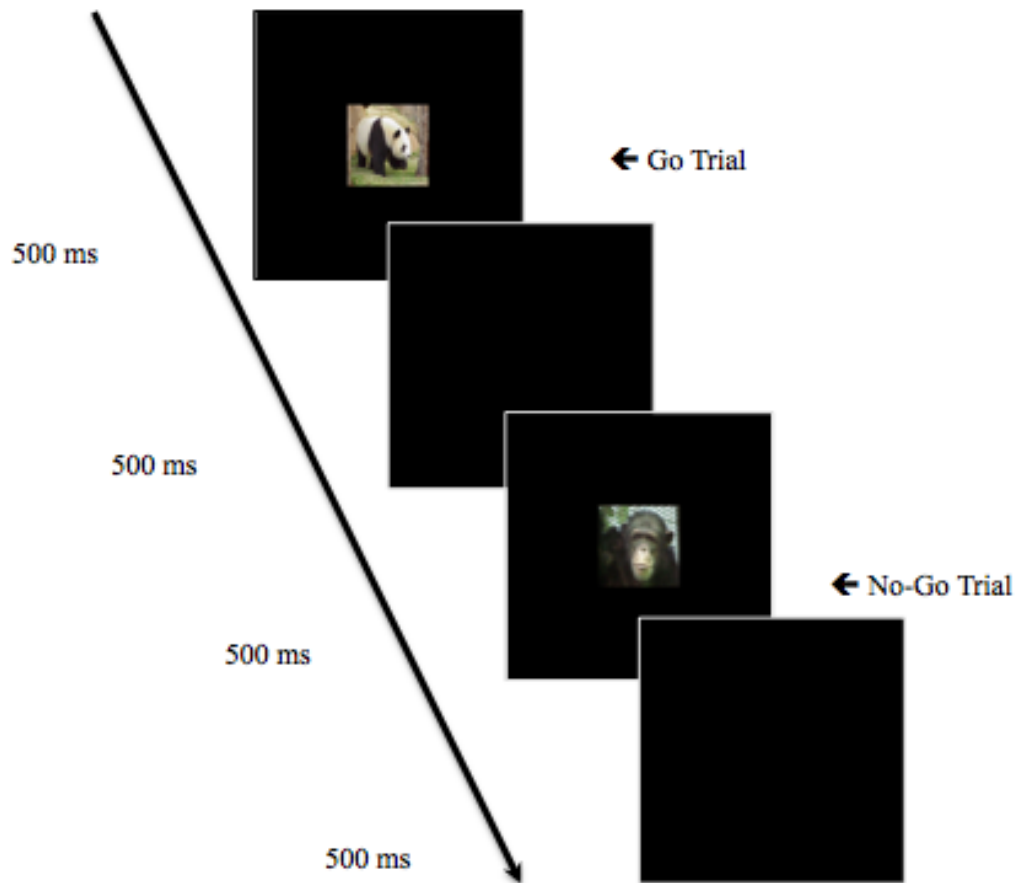


Figure 3.1. Order of stimulus presentation during the Go/No-Go task. Go trials are those in which images of animals including a giraffe, elephant, and panda (shown above) were presented. No-Go trials are those in which an image of a chimpanzee (shown above) was presented.

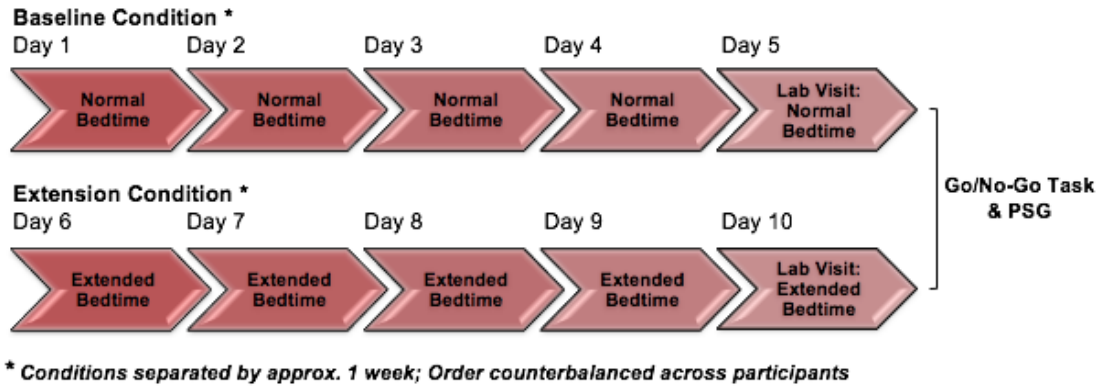


Figure 3.2. Outline of study protocol. Each child completed a 5-day baseline condition and a 5-day extension condition. At the end of each condition, each child participated in an in-lab overnight visit. The order of conditions was counterbalanced across participants.

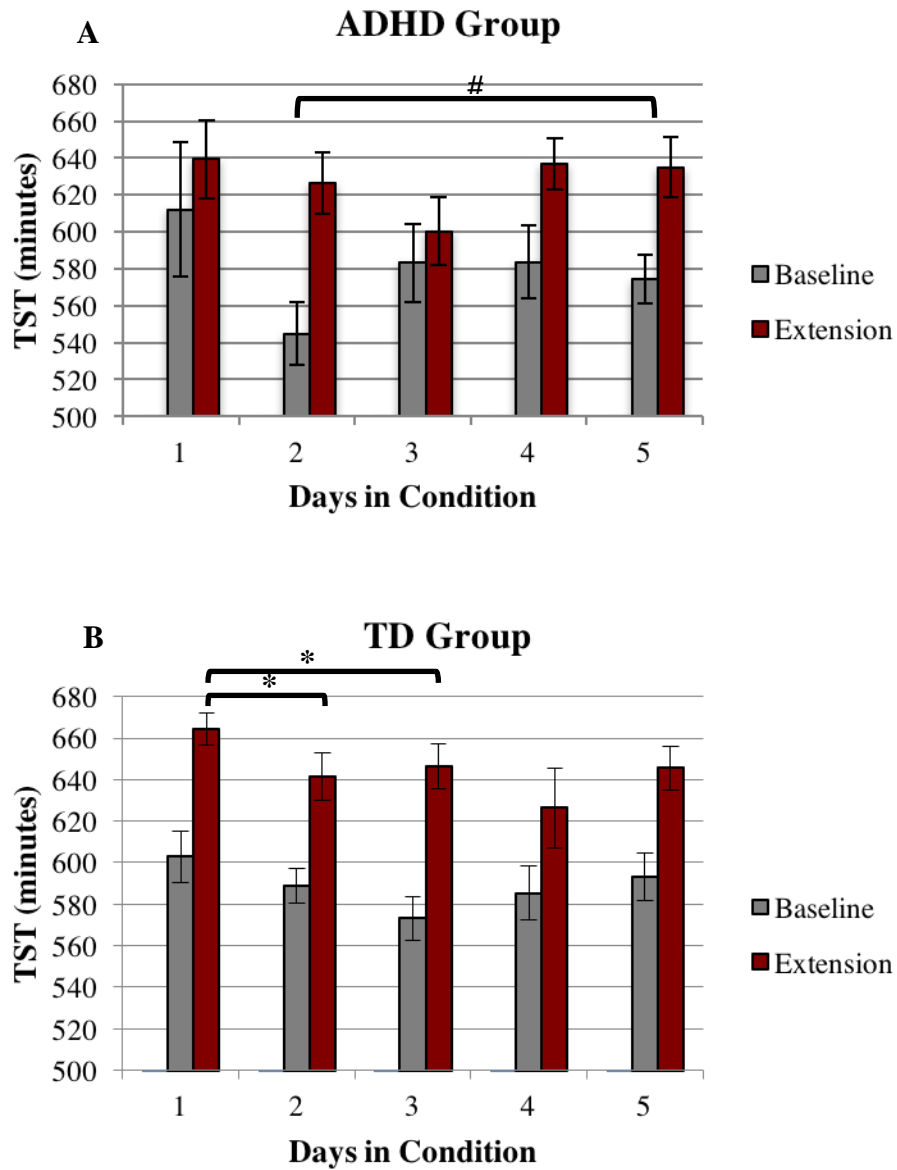


Figure 3.3. Day-by-day plot of change in total sleep time between conditions in the (A) ADHD and (B) TD groups. Note: Error bars represent standard error; * p 's ≤ 0.05 , # $p \leq 0.08$.

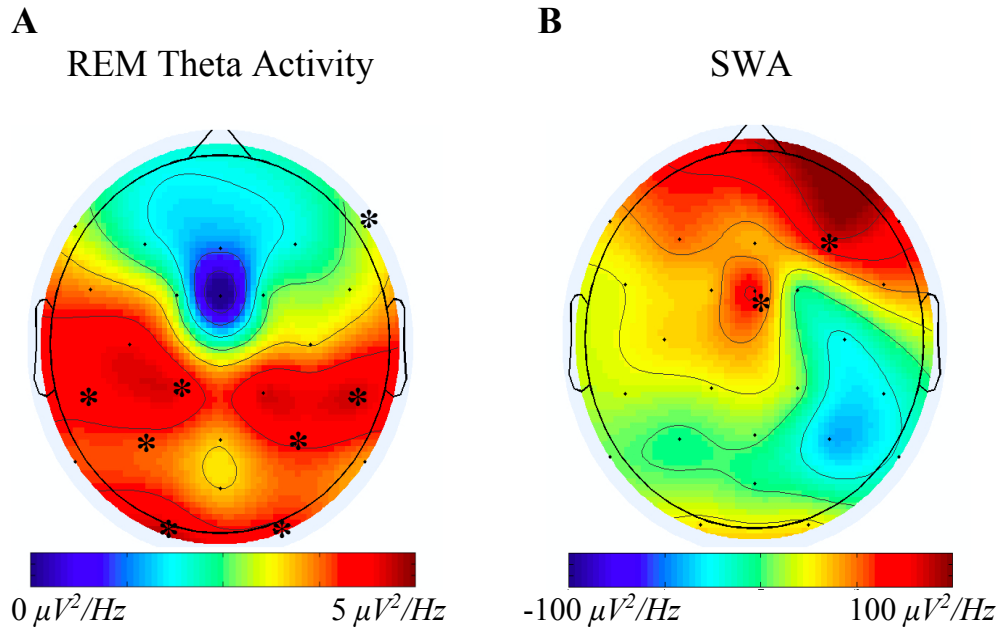


Figure 3.4. Topographic group differences (ADHD minus TD) in (A) REM theta activity and (B) SWS SWA. Note: Analyses collapsed across the baseline and extension conditions; * p 's ≤ 0.05 .

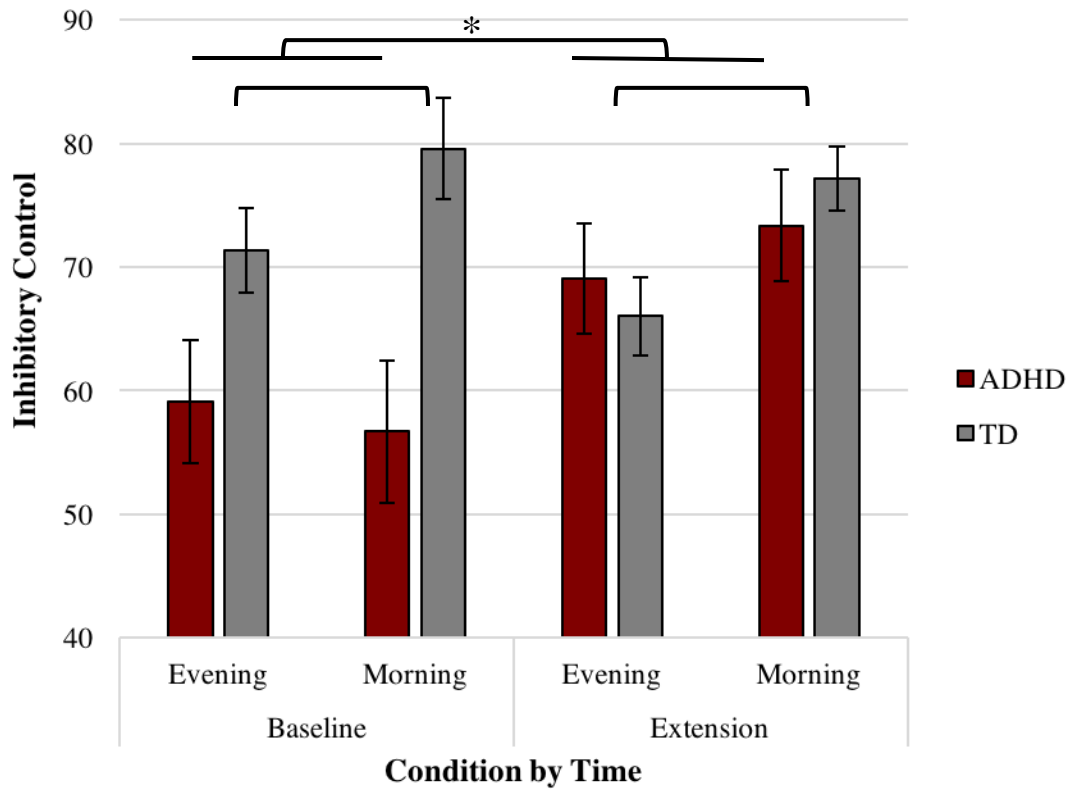


Figure 3.5. Difference in inhibitory control between conditions and groups. Note: Error bars represent standard error; * p 's ≤ 0.05 .

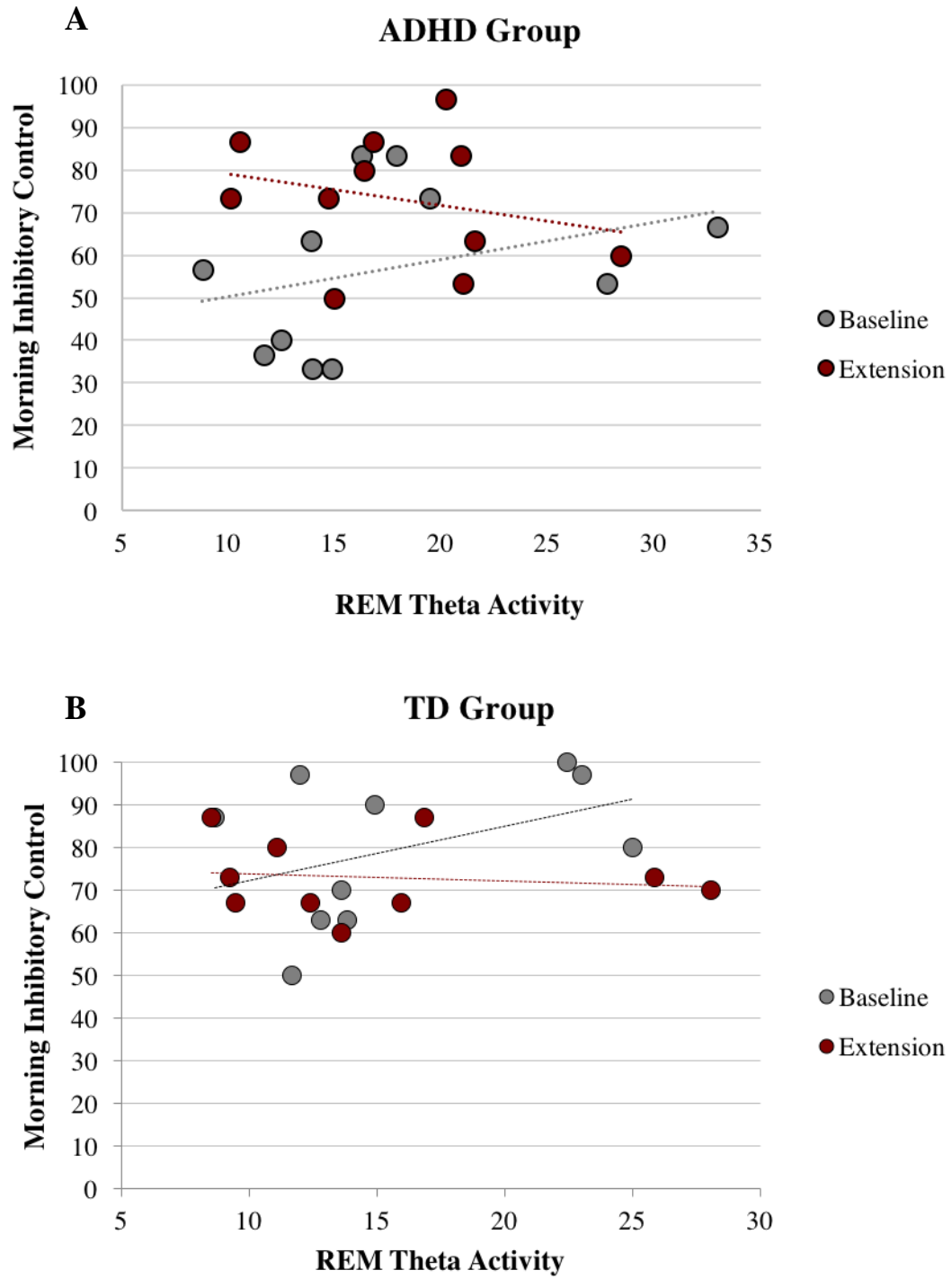


Figure 3.6. Correlations between frontal theta activity (F_4 ; in $\mu V^2/Hz$) and morning inhibitory control during each condition in the (A) ADHD and (B) TD groups.

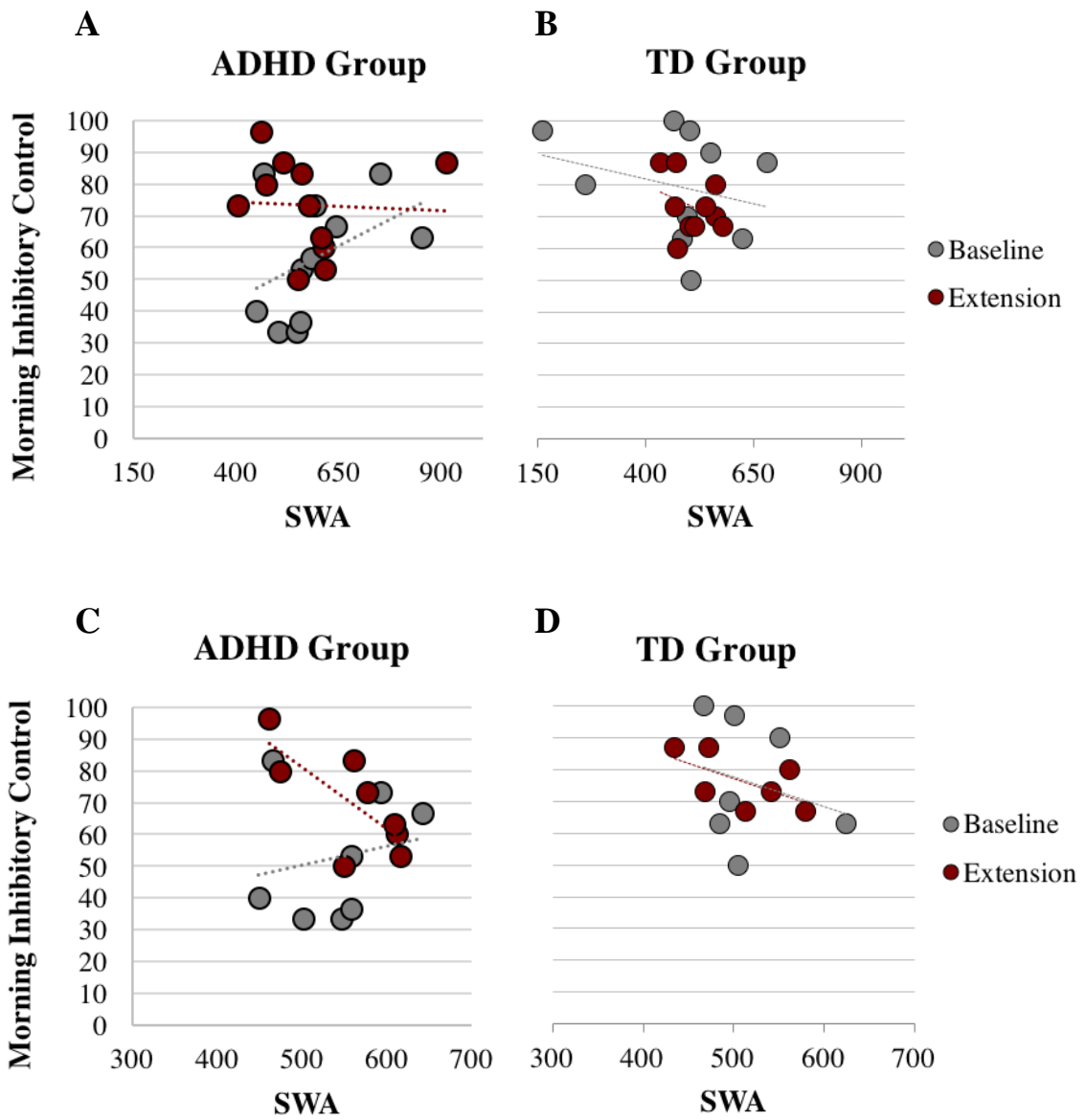


Figure 3.7. Correlations between frontal SWA (F_4 ; in $\mu V^2/Hz$) and morning inhibitory control during each condition in the (A) ADHD and (B) TD groups. Data is also presented with outliers removed for the (C) ADHD and (D) TD groups.

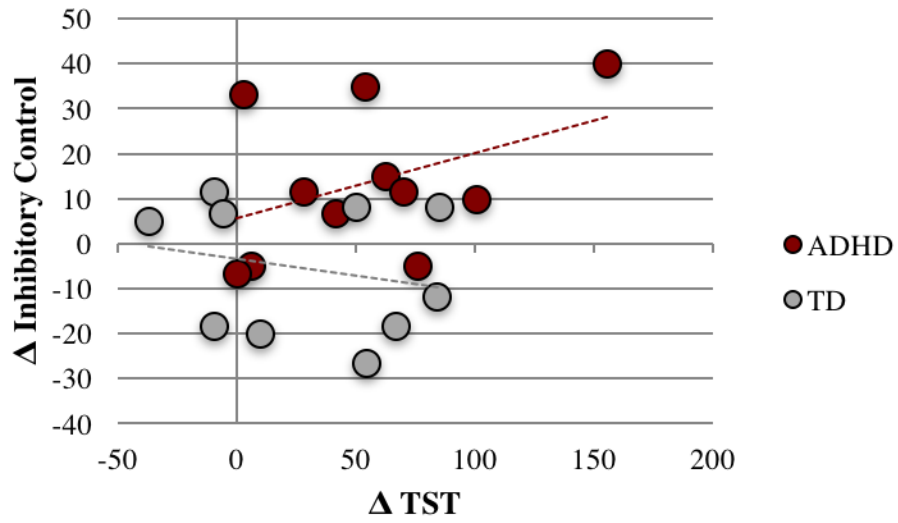


Figure 3.8. Correlations between the change in total sleep time (extension – baseline; as measured by PSG) and the change in inhibitory control (extension – baseline) in each group.

CHAPTER 4

THETA ACTIVITY IN CHILDREN WITH AND WITHOUT ADHD ACROSS WAKE AND SLEEP

4.1 Introduction

Compared to TD controls, individuals with ADHD are reported to have elevated theta activity (neural activity in the 4 to 7 Hz frequency range) during wake and sleep. A meta-analysis assessing quantitative EEG during wake reported a 32% increase in theta activity in individuals with ADHD, 6 to 42 years of age (Snyder & Hall, 2006). Wake theta activity is particularly greater among children and adolescents with ADHD compared to TD individuals (Hermens et al., 2005). Preliminary evidence indicates that theta activity is also elevated in children with ADHD during sleep (Saletin, Coon, & Carskadon, 2016), consistent with the findings reported in Chapter 2.

Theta activity, recorded during sleep and wake, is associated with a variety of cognitive functions in TD populations. Accumulating evidence highlights the beneficial role that sleep theta activity has on memory in school-aged children and young adults (Benedict, Scheller, Rose-John, Born, & Marshall, 2009; Prehn-Kristensen, Munz, Molzow, Wilhelm, Wiesner, & Baving, 2013; Walker, 2009). Sleep theta activity is also positively associated with decision-making in young adults (Seeley, Smith, MacDonald, & Beninger, 2016). Similarly, data from Chapter 2 indicate a positive association between REM theta activity and inhibitory control in TD children 4 to 8 years of age.

Prior to the study described in Chapter 2, inhibitory control was predominately associated with wake theta activity (Cavanagh & Frank, 2014). Specifically, EEG components that index inhibitory control (e.g., N2) are strongly correlated with frontal

theta activity recorded during wakefulness in children, adolescents, and adults (Cavanagh & Frank, 2014; Liu, Woltering, & Lewis, 2014). Wake theta activity also predicts symptom severity in children and adolescents with ADHD (Hermens et al., 2005). As these results attribute inhibitory control to theta activity recorded during both sleep and wake, additional studies are needed to determine whether state-dependent characteristics of EEG better predict inhibitory deficits in children with and without ADHD. A better understanding of relations between inhibitory control and theta activity (during sleep versus wake) may create opportunities for intervention in populations with inhibitory deficits.

The goal of this study was two-fold. The first aim of this study was to compare theta activity between wake and sleep in young children with and without ADHD. Provided evidence that EEG is similar between wake and REM sleep in middle-aged adults (Benca et al., 1999), it was hypothesized that the differences in sleep and wake theta activity would be small (less than 0.3 standard deviations, representing a small-to-medium effect size) in both groups. This null hypothesis was tested by evaluating the effect size of the difference in theta activity recorded during sleep and wake for both TD and ADHD children. If the difference between sleep and wake theta activity was less than 0.3 standard deviations within each group (ADHD and TD), the null hypothesis would not be rejected and it would be determined that wake and sleep theta activity were similar across states (see Streiner, 2003).

The second aim of this study was to determine whether wake or sleep theta activity better predicted inhibitory control in these populations. Based on the prevalence of sleep problems in children with ADHD (e.g., Weiss, Craig, Davies, Schibuk, & Stein,

2015; Yoon, Jain, & Shapiro, 2012) and the positive association between REM theta activity and inhibitory control in TD children (Chapter 2), it was hypothesized that sleep theta activity would account for more variability in inhibitory control than wake theta activity. Alternatively, if variance in morning inhibitory control were better predicted by (or equally predicted by) wake theta activity, the data would suggest that theta activity underlies inhibitory control in young children, regardless of state (i.e., wake versus sleep).

4.2 Methods

4.2.1 Participants

Participants were those described in Chapter 3.

4.2.2 Measures

Theta activity was recorded via EEG electrodes in the PSG cap montage (see Chapter 3).

4.2.3 Procedure

During data collection for the sleep extension paradigm (see Chapter 3), ten minutes of wake EEG was recorded prior to nocturnal sleep onset. Children with ADHD (particularly those with hyperactive/impulsive symptoms) may find the standard resting paradigm especially challenging, as these children characteristically ‘fidget/squirm’ and have ‘difficulty sitting quietly’ (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). To reduce these confounds, ten minutes of wake EEG was recorded while the child quietly read a book (or was read to by a caregiver). Typically, 2-3 minutes of EEG is used to gauge waking neural activity (e.g., Thompson, Woodruff Carr, White-Schwoch, Tierney, Nicol, & Kraus, 2016). A 10-minute recording was used to assure enough

artifact-free data was obtained for statistical analyses. The beginning and end of this recording period was noted on the participant's datasheet and marked in the polysomnogram using digital event markers. Events that may have disrupted the EEG recording (e.g., excessive movement or talking) were noted and omitted from analyses.

Following the wake EEG recording, the lights were turned out and the child was encouraged to go to sleep. Sleep theta activity was computed from EEG recorded during the nocturnal sleep bout (see Chapter 3). Specifically, sleep theta activity was sampled from epochs characterized as REM sleep, as theta activity is prominent during this sleep stage (Hobson & Pace-Schott, 2002). In the ADHD group, ten minutes of wake EEG was also collected the morning following overnight sleep to explore homeostatic differences in wake theta activity.

4.3 Statistical Analyses

4.3.1 Wake Versus Sleep Theta Activity

Paired samples *t*-tests were used to compare average wake theta activity against average sleep theta activity recorded during REM sleep within each group (ADHD and TD). To test the difference in sleep and wake theta activity, the effect size of the difference in theta activity recorded during sleep and wake was evaluated in terms of standard deviations, independently for each group.

In accordance with the *a priori* hypothesis, the null hypothesis would not be rejected if the difference between sleep and wake theta activity was less than 0.3 standard deviations (see Streiner, 2003). If the difference between sleep and wake theta activity was less than 0.3 standard deviations, this would indicate that wake and sleep theta activity were similar in children with and without ADHD. Average wake theta activity

was also compared against random 10-minute samples of REM theta activity to control for differences in wake and sleep EEG recording times.

Finally, an exploratory paired samples *t*-test was used to compare morning theta activity to evening theta activity to assess homeostatic differences in theta activity in children with ADHD.

4.3.2 Theta Activity and Inhibitory Control

To determine whether wake or sleep theta activity better predicted inhibitory control in children with and without ADHD, linear regression models were used. In these models, average morning inhibitory control (collapsed across baseline and extension conditions) was entered as the outcome variable. Group (ADHD and TD) and average wake and sleep theta activity were entered as predictor variables, simultaneously.

4.4 Results

Consistent with the data comparing sleep theta activity in Chapter 3, evening wake theta activity did not differ between conditions in either group ($F(1,18) = 2.27, p = 0.149$; Table 4.1). As such, measurements sampled during the baseline and extension conditions were collapsed into average measures to be used in subsequent analyses. Evening wake theta activity was marginally greater in the ADHD group overall ($F(1,18) = 3.87, p = 0.065, \eta_p^2 = 0.177$; Table 4.1). The two-way interaction between condition and group was not significant ($F(1,18) = 0.06, p = 0.803$).

4.4.1 Wake Versus Sleep Theta Activity

Although positively related to one another, average sleep and wake theta activity were not significantly correlated in either TD or ADHD children (r 's $\leq 0.291, p$'s ≥ 0.415). In children with ADHD, the paired samples *t*-test used to compare average wake

theta activity against average sleep theta activity indicated that theta activity was not statistically different across wake and sleep ($t(10) = -0.44, p = 0.672$; Table 4.1). The mean difference in theta activity between wake and sleep ($-1.11 \mu\text{V}^2/\text{Hz}$) and the standard error of the mean difference ($2.54 \mu\text{V}^2/\text{Hz}$) were then used to calculate a 95% confidence interval for this group (lower bound = -6.19 , upper bound = 3.97). The effect size of the difference between wake and sleep theta activity was computed as 0.3 standard deviations of the pooled standard deviation for wake and sleep theta activity ($(5.83 + 6.57) / 2 = 6.2$; $6.2 * 0.3 = 1.86$). This effect size was not significantly smaller than a small-to-medium effect size, as it fell within our 95% confidence interval. The effect size of difference was also smaller than a large effect size ($3.97 / 1.86 = 2.13$). Thus, the null hypothesis was not rejected.¹³

These findings were similar in TD children, as average wake theta activity did not statistically differ from average sleep theta activity ($t(9) = 1.05, p = 0.319$; Table 4.1). Here too, the mean difference ($2.11 \mu\text{V}^2/\text{Hz}$) and the standard error of the mean difference ($2.00 \mu\text{V}^2/\text{Hz}$) were used to compute a 95% confidence interval for the TD group (lower bound = -1.89 , upper bound = 6.11). The effect size of the difference was computed as described above (1.56) but was not significantly smaller than a small-to-medium effect size.¹⁴

¹³ Results were unchanged when wake theta activity was compared against random 10-minute samples of REM theta activity ($p = 0.568$, 95% confidence interval $[-7.09, 3.87]$, effect size of difference = 1.88).

¹⁴ Wake theta activity was significantly greater than the 10-minute segment of theta activity randomly sampled from REM sleep ($t(5) = -4.40, p = 0.007$, 95% CI $[-1.35, -0.35]$). The effect size of difference was small (1.46), but was outside of the 95% confidence interval computed for this group $[-1.23, -0.47]$. These data should be interpreted with caution, as complete wake theta datasets were only available for 6 TD children.

In the ADHD group, an exploratory paired samples *t*-test revealed that, collapsed across conditions, wake theta activity measured prior to overnight sleep ($M = 18.62$, $SD = 6.57 \mu\text{V}^2/\text{Hz}$) was significantly greater than wake theta activity measured following overnight sleep ($M = 14.07$, $SD = 2.49 \mu\text{V}^2/\text{Hz}$; $t(10) = 3.26$, $p = 0.009$, 95% CI [1.44, 7.65]). This finding suggests that there may be homeostatic differences in theta activity in children with ADHD.

4.4.2 Theta Activity and Inhibitory Control

Consistent with the results of Chapter 3, the linear regression model indicated that neither wake ($B = -0.001$, $p = 0.767$) nor sleep ($B = 0.005$, $p = 0.307$) theta activity predicted morning inhibitory control. The main effect of group also did not significantly predict morning inhibitory control ($B = 0.116$, $p = 0.062$). Controlling for evening inhibitory control, age, and symptomology did not alter these statistical outcomes in either group (p 's ≥ 0.210).

4.5 Discussion

The primary aim of this chapter was to examine whether levels of theta activity were similar across intervals of sleep and wake in children with and without ADHD. Sleep and wake theta activity did not statistically differ in either group. However, the effect size of the difference between activity recorded during wake and sleep was too small to conclude activity was statistically similar across states. The secondary aim of this chapter was to determine whether inhibitory control was better predicted by theta activity during sleep or wake in children with or without ADHD. Neither sleep nor wake theta activity significantly predicted morning inhibitory control in either group.

4.5.1 Differences in Wake and Sleep Theta Activity

Although inconclusive, data from this chapter suggest that cortical activity in the theta frequency band is similar across sleep and wake in young children with and without ADHD. These results support the hypothesis that EEG is trait-like (Benca et al., 1999; Tarokh, Carskadon, & Achermann, 2011) and stable across sleep and wake. If such is the case, endophenotypes evident during sleep may also be identified during resting wakefulness.

4.5.2 Relations between Theta Activity and Inhibitory Control

The results of this chapter also suggest that theta activity, recorded during sleep or wake, was not functionally related to inhibitory control in children with or without ADHD. As morning inhibitory control was associated with SWA in children with ADHD (see Chapter 3), this finding is unsurprising. However, REM theta activity was positively associated with inhibitory control in TD children in Chapter 2. As such, additional studies are needed to better understand the contributions of theta activity to inhibitory functioning during typical development.

4.5.3 Homeostatic Differences in Theta Activity in Children with ADHD

Exploratory analyses suggest that theta activity recorded prior to overnight sleep was greater than that recorded following overnight sleep. This finding is consistent with work in animal models which suggests that theta activity is elevated following prolonged wakefulness and reduced after sleep (Leemburg, Vyazovskiy, Olcese, Bassetti, Tononi, & Cirelli, 2010). Data from these animal studies also indicate that theta activity recorded during wake predicts SWA recorded during subsequent sleep. As ADHD children had elevated wake theta activity in the evening and more SWA than TD children, the results of this dissertation suggest that children with ADHD need more sleep in order to

sufficiently reduce sleep pressure. Unfortunately, data from this dissertation do not support this hypothesis.¹⁵

4.5.4 Conclusions

Taken together, the results of this chapter suggest that cortical activity in the theta frequency band may be stable across sleep and wake, consistent with the notion that EEG is trait-like (Benca et al., 1999; Tarokh, Carskadon, & Achermann, 2011). However, as the confidence intervals were large, these data should be interpreted with caution.

Exploratory analysis of differences in wake theta activity before and after overnight sleep indicate that, among children with ADHD, theta activity is higher in the evening than in the morning. This finding supports animal studies which show that theta activity is elevated following prolonged wakefulness and reduced after sleep (Leemburg et al., 2010). Finally, neither wake nor sleep theta activity were found to predict variability in subsequent assessments of inhibitory control among children with or without ADHD. Data from the TD sample tested in Chapter 2 indicate that inhibitory control was related to sleep theta activity, suggesting that the functional significance of sleep, and potentially wake, theta activity may differ between typically and atypically developing children.

¹⁵ An exploratory linear regression was used to determine whether evening wake theta activity (Chapter 4) and SWA (Chapter 3) interacted to predict morning inhibitory control in the ADHD group. The interaction term did not significantly predict morning inhibitory control during either the baseline or extension condition (p 's = 0.926 and 0.124, respectively).

Table 4.1. Differences in wake and sleep theta activity ($\mu\text{V}^2/\text{Hz}$) in each group.

	ADHD	TD
	Mean (SD)	Mean (SD)
Baseline condition		
Wake		
Evening	18.24 (6.41)	12.96 (4.42)
Morning	14.08 (3.87)	-
Sleep	17.25 (7.19)	15.77 (5.60)
Extension condition		
Wake		
Evening	18.99 (7.13)	13.79 (4.78)
Morning	14.06 (2.99)	-
Sleep	17.77 (5.34)	15.08 (6.85)

Note: In ADHD group, n = 15. In TD group, n = 10.

CHAPTER 5

GENERAL DISCUSSION

The aim of this dissertation was to examine the role of sleep on inhibitory control in young children with ADHD. To assess these relations, children with and without ADHD participated in overnight sleep studies in which sleep physiology was monitored with PSG and inhibitory control gauged via a Go/No-Go task. Collectively, the results of this dissertation indicate that inhibitory control is enhanced by overnight sleep in TD children but not in children with ADHD. However, when children with ADHD were instructed to advance their bedtime in an effort to extend the amount of time they slept at night, inhibitory control was improved. Moreover, the physiological mechanisms underlying the benefits of sleep on inhibitory control differed between TD children and children with ADHD, suggesting that the developmental trajectory of sleep EEG may be altered in atypical development.

5.1 Sleep and Inhibitory Control

The role of sleep on inhibitory control differed between TD and ADHD children. As presented in Chapters 2 and 3, TD children had sleep-dependent enhancement of inhibitory control whereas children with ADHD did not. Specifically, inhibitory control was improved following overnight sleep in TD children but not in children with ADHD. Although average sleep duration did not differ between these groups, the results of Chapter 3 indicate that lengthening sleep duration improves inhibitory control in ADHD children. Given that inhibitory control is a primary deficit in ADHD, and is strongly associated with core symptoms such as hyperactivity and impulsivity (Barkley, 1997), the data from the current set of studies suggest that sleep-related interventions should be

strongly considered to improve outcomes in this population. Relative to pharmacological treatments, sleep-based interventions are cost-effective and have not been linked to adverse side effects.

5.2 Relations between Sleep Physiology and Inhibitory Control

The mechanisms underlying the benefits of sleep on subsequent inhibitory control also differed between TD children and children with ADHD. Enhancement of inhibitory control was positively associated with theta activity recorded during REM sleep in TD children (Chapter 2). Although REM theta activity was elevated in children with ADHD, it was not associated with inhibitory functioning in this group (Chapter 2). Rather, enhanced inhibitory control was associated with reduced SWA, when sleep duration was extended, in children with ADHD (Chapter 3).

Dissimilarities in the neural mechanisms supporting inhibitory control in children with and without ADHD are likely a consequence of developmental differences in EEG trajectories. Longitudinal data indicate both SWA and theta activity decline during childhood, and are strongly associated with neural development (Campbell & Feinberg, 2009). Specifically, SWA declines linearly from birth until approximately 6 years of age. Levels of SWA plateau thereafter until adolescence. Theta activity, on the other hand, declines significantly between 6 and 11 years of age. As changes in SWA (birth to 6 years of age) occur earlier than changes in theta activity (6 to 11 years of age) in TD children, these findings suggest that the developmental trajectories of sleep EEG in children with ADHD are delayed.

Correlations with behavioral outcomes support the hypothesis that children with ADHD have delayed cortical development (Rubia, 2007), as theta activity was related to

inhibitory control in TD children (Chapter 2) and SWA associated with the same outcome in children with ADHD (Chapter 3). However, longitudinal studies of sleep EEG trajectories are needed to directly test this hypothesis.

In addition to potential differences in EEG trajectories, the samples tested in each study differed in age. The children tested in Chapter 2 (4 to 8 years of age; $M_{age} = 6.7$ years) were younger than those tested in Chapter 3 (6 to 9 years of age; $M_{age} = 8.3$ years). Although the children in Chapter 2 met the clinical criteria necessary to diagnosis ADHD, the children in this sample were not required to have a physician's formal diagnosis of the disorder. ADHD is not typically diagnosed until 7 years of age (Applegate et al., 1997). Thus, the age range for children recruited in Chapter 3 was extended to include older children. As EEG trajectories change across early development, age-related differences may have contributed to the mechanistic differences reported between groups in Chapters 2 and 3. Similarly, the inconsistent correlations between inhibitory control and sleep physiology (specifically, REM theta activity in the TD groups and SWA in the ADHD groups) may have been a consequence of age differences.

5.3 Differences in Sleep and Wake Theta Activity

Although theta activity was not associated with inhibitory functioning in children with ADHD, accumulating evidence suggests that theta activity is elevated during both wake (Snyder and Hall, 2006) and sleep (Chapter 2; Saletin et al., 2016) and is functionally related to cognitive outcomes in this population. Thus, the aim of the final study in this dissertation was to determine whether theta activity was stable across states and better understand the role of sleep and wake theta activity in inhibitory control in

children with and without ADHD. Consistent with data suggesting that EEG is trait-like (Benca et al., 1999; Tarokh, Carskadon, & Achermann, 2011), theta activity recorded during sleep and wake was not statistically different. However, the data collected to assess stability across states was inconclusive, as the effect size of the difference between the two measures was small in both groups. Furthermore, neither sleep nor wake theta activity were functionally related to inhibitory control in children with or without ADHD. Given that theta activity was not associated with inhibitory control among the ADHD children tested (in Chapters 2 or 3), this finding is unsurprising. However, as REM theta activity was positively associated with inhibitory control in TD children (Chapter 2), additional studies are needed to better understand the contributions of theta activity to inhibitory functioning during typical development.

Exploratory analyses indicate that wake theta activity was elevated in the evening, relative to the morning, in the ADHD group. Animal studies suggest that greater wake theta activity predicts greater sleep pressure (Leemburg et al., 2010), suggesting that theta and SWA may interact to predict subsequent performance. However, when the data from Chapters 3 and 4 were evaluated together, the interaction between evening wake theta activity and sleep SWA did not predict variability in morning inhibitory control during either condition. Importantly, this data was drawn from a small sample. Additional data collection may be needed to support this hypothesis.

5.4 Summary

Overall, the results of this dissertation support the widespread hypothesis that children with ADHD have insufficient sleep. The current studies also indicate that the developmental trajectory of low frequency sleep EEG is delayed in this population,

relative to TD controls. As such, sleep EEG may be used to index cortical development and identify children at risk for ADHD (Chapters 2 and 3). Similarly, endophenotypes in sleep EEG may be used to predict response to the sleep-based intervention associated with improved inhibitory function in this sample (Chapter 3).

5.5 Future Directions

Based on the results of current studies, future research into the role of sleep and inhibitory control is needed to inform treatment strategies in atypical development. Although the behavioral findings in this dissertation were robust, the sample tested in Chapters 3 and 4 was small. As such, additional data collection is needed to infer generalizability and increase the statistical power needed to detect significant correlations between physiology and behavior. Additional studies are also needed to evaluate incremental changes in sleep physiology with changes in sleep duration (see Discussion of Chapter 3). As sleep quality is associated with cognitive functioning, it is particularly important to better understand how short- and long-term changes to sleep physiology affect outcomes in young children both with and without ADHD.

APPENDIX

TIPS TO HELP YOUR CHILD FALL ASLEEP

- Avoid caffeine (e.g., chocolate, ice tea, and other caffeinated beverages) within 1 hour of bedtime.
- Avoid heavy meals and fluids within 1 hour of bedtime.
- Avoid stimulating activities (e.g., physical activity and scary stories) 1 hour before bedtime.
- Avoid bright light (e.g., TV screen, cell phones, tablets) 1 hour before bedtime.
- Inform your child when bedtime is approaching so they can prepare to wind down.
- Create a sleep-promoting environment: Your child's clothes and blankets should not restrict their movement. The bedroom temperature shouldn't be too warm or too cold. The room should be dark. If you use a nightlight, it should be out of their direct line of vision.
- Learning a new sleep schedule may be challenging so you may need to revert back to some techniques we tend to use in very young children as they learn to sleep. Consider using soothing techniques (e.g., read bedtime stories, rub child's back) to help your child fall asleep on nights when the child's bedtime is advanced.

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