The role of sleep quality and quantity in moderating the effectiveness of medication in the treatment of children with ADHD

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Abstract

There is strong empirical evidence that stimulant medications, such as methylphenidate hydrochloride (MPH), are effective in reducing ADHD symptoms (Ritchers et al., 1995); however, these medications can also cause sleep problems (Corkum et al., 2008). Furthermore, poor sleep has been documented to result in performance deficits in memory, attention and academic performance (Gruber et al., 2011). This study examined: 1) whether stimulant medication is effective in improving performance on measures of memory, attention and academic productivity, and 2) if sleep impacts the relationship between medication and performance. Participants were 21 children (mean age = 9.1 years) with ADHD, who participated in a four week randomized controlled trial of long lasting MPH (2 weeks of medication and 2 weeks of placebo). Participants underwent assessments of sleep (polysomnography and actigraphy) and of cognitive performance. We predicted that there would be a relationship between sleep quantity (duration) and quality (efficiency) medication effects on cognitive performance. Our findings supported stimulant medication as an effective treatment for enhancing alerting attention, executive attention, working memory, and academic productivity performance in children with ADHD. Bivariate correlations between cognitive performance and sleep revealed a significant relationship between sleep duration and executive attention accuracy during incongruent trials of the ANT-I, r= .456, p= .025. A one-way ANOVA was used to compare the good sleep group and poor sleep group (above and below the mean sleep duration, respectively) on executive attention incongruent accuracy. Statistical analysis revealed that children performed significantly different on executive attention incongruent accuracy depending on baseline sleep, $F(1, 19)= 6.859$, p= .017. Findings are discussed in terms of implications for clinical practice and future research.

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Chapter 1: Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent childhood mental health disorders, affecting approximately 5-10% of school-aged children (American Psychological Association, 2000). Core symptoms of ADHD include: inattention, hyperactivity, and impulsivity. Children with ADHD have been shown to display performance deficits in cognitive tasks, such as attention (Mullane, Corkum, Klein, McLaughlin, & Lawrence, 2011), memory (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), and academic productivity (Loe & Feldman, 2007). Children with ADHD are also much more likely than their peers to experience sleep problems (Corkum & Coulombe, In Press), consequently there has been growing interest in sleep problems associated with ADHD (Cortese, Faraone, Konofal, & Lecendreux, 2009; Jan, Yang, & Huang, 2011).

Disturbances in sleep, such as decreased quantity and/or quality may worsen symptoms associated with ADHD, and, in some instances sleep deprivation can mimic ADHD symptoms leading to misdiagnosis of the disorder in clinical practice (Owens, 2009). Furthermore, stimulant medications, which are the most commonly used medication to treat ADHD, may also result in sleep problems, such as difficulty initiating sleep and potentially change circadian phase (Corkum, Moldofsky, Hogg-Johnson, Humphries, & Tannock, 1999; Corkum, Panton, Ironside, MacPherson, & Williams, 2008; Ironside, Davidson, & Corkum, 2010; Mick, Biederman, Jetton, & Faraone, 2000; Stein, 1999). These relationships have important implications for the assessment and treatment of children with ADHD, and as such the following study focused on the association between stimulant medication, sleep quantity and quality, and cognitive functioning of school aged children with ADHD.

Stimulant medication, such as methylphenidate hydrochloride (MPH; widely known as Ritalin®) and Dextroamphetamine (DEX; widely known as Dexedrine®) are the most common treatment for ADHD. In fact, 70-90% of children with ADHD are treated at some point in time with stimulant medications, either alone or in combination with psycho-social interventions (Jensen et al., 2007). Research on stimulant medication treatment has consistently shown these medications to effectively reduce the core symptoms of ADHD, for as long as the medication is continued (Antshel & Barkey, 2008; Stein et al., 2003). Treatment with stimulant medication has also been found to reduce the deficits in attention, memory, and academic productivity (Wigal et al., 2011). For instance, stimulant medication has been found to improve attention networks by speeding up reaction time (Oberlin, Alford, & Marrocco, 2005), improving sustained attention, and attention performance that requires inhibition (Konrad, Gunther, Hanish, & Herpertz-Dahlmann, 2004). For children with ADHD, stimulant medication has also been found to improve performance on working memory tasks such as the widely used finger windows task (Bedard & Tannock, 2008), and increase subjective accounts (i.e., teacher ratings) and objective measures of academic productivity and accuracy (Raggi & Chronis, 2006).

Despite its strong empirical support in the treatment of ADHD, stimulant medications have a range of potential side effects including decreased appetite, headaches, and sleep disruption (Greenhill, Beyer, & Finkleson, 2002). Side effects associated with sleep (i.e., insomnia) are often the reason given when parents choose to discontinue the medication (Charach, Volpe, Boydell, & Gearing, 2008). Sleep loss is highly associated with poor emotional and behavioural functioning. Moreover, reduced sleep duration is also known to lead to observable cognitive performance deficits in attention and memory, as well as poorer academic

outcomes (Sadeh, 2007; Muto et al., 2012). Accordingly, sleep problems have been suggested as the more detrimental side effect of MPH treatment (Corkum et al., 2008).

Very little research has investigated the role that sleep might play in the effectiveness of stimulant medication in reducing cognitive impairments. The majority of research that is available addressing this issue focuses on the use of stimulant medications in healthy adults for the purpose of neuro-enhancement (improving cognitive, emotional and motivational functions; Repantis, Schlattmann, Laisney, & Heuser, 2010). The findings from this small body of literature have shown that stimulant medication is most effective at enhancing performance outcomes in healthy adults when individuals are sleep deprived (Bonnet et al., 2005). To our knowledge, only one study has examined the moderating influence of sleep on the performance enhancing effects of stimulant medication in children with ADHD (Gruber et al., 2007). Specifically, Gruber et al. (2007) collected sleep data through nightly actigraphy recording during a double-blind, placebo-controlled, clinical trial of MPH. Participants were 37 children aged 6-12, who were diagnosed with ADHD. The sample was divided into 2 groups (Poor Sleep Group vs. Good Sleep Group) based on the mean sleep efficiency score during the placebo condition. Consistent with healthy adult studies, the results indicated that children with ADHD and poor sleep efficiency (below the mean) prior to the administration of stimulant medication had better attention outcomes on the Conner's Continuous Performance Task (CPT; Gruber et al., 2007).

There remains a substantial gap in child focused literature that examines the performance-enhancing effects of stimulant medication when accounting for sleep quality and quantity. Moreover, research investigating this relationship in children with ADHD must account for changes in dosage recommendations (TID and long lasting formulas). For instance, Gruber et al. (2007) utilized the BID regime (short acting medication given twice daily) in their study.

However, based on current clinical practice, it is far more likely that school-aged children commencing stimulant medication for ADHD will be prescribed long acting formulas (Swanson & Volkow, 2009). In response to this change in medication formulation and dosing schedule, as well as the inconsistencies and extreme lack of research surrounding the impact of long-acting stimulant medications on sleep, Corkum and colleagues designed a randomized controlled trial (RCT) of 30 newly diagnosed and medication naïve children with ADHD who were being treated with Biphentin®, a long acting stimulant. The current study is a secondary data analysis of this larger study, but distinct from Corkum's original study, which investigated the acute and long-term impact of stimulant medication on sleep quality and quantity. The current study focused on whether sleep quality and quantity impacts the enhancing effects of stimulant medication on cognitive functioning (attention, memory, and academic productivity).

The first objective of the present study was to replicate and extend the previously demonstrated effects of stimulant medication on the cognitive performance and sleep of children with ADHD. Based on previous literature, it was hypothesized that MPH would increase attention and memory performance, as well as academic productivity in school-aged children with ADHD compared to the placebo. More specifically, it was predicted that children would perform better on attention tasks (i.e., faster reaction time, better accuracy), memory tasks (i.e., more correct responses), and complete more math problems (i.e., indicating a higher rate of academic productivity), when taking stimulant medication compared to a placebo. The second objective of this study was to examine whether sleep quantity (i.e., sleep duration) and/or sleep quality (i.e., sleep efficiency) has an impact on the relationship between stimulant medication and attention, memory, and academic productivity in children with ADHD. The researchers of this study expected that sleep duration and efficiency will impact the relationship between

medication effectiveness and performance on memory, attention and academic productivity tasks. In line with Gruber et al (2007), as well as the adult literature on the enhancing effects of stimulant medication, it was predicted that children with poorer sleep would evidence more cognitive improvement when taking stimulant medication compared to placebo.

Chapter 2: Literature Review

Attention Deficit Hyperactivity Disorder (ADHD)

At least one child in every classroom is affected by Attention-Deficit/Hyperactivity Disorder (ADHD; American Psychological Association, 2000). ADHD is a childhood neuropsychiatric disorder, which typically manifests as a difficulty with focusing and sustaining attention, regulating impulses, and behaviour inhibition (APA, 2000). The core symptoms of ADHD impair many areas required for typical daily functioning including cognitive processes of memory and attention (Owens, 2005). Children affected by this pervasive disorder are at a higher risk for low academic achievement and performance, problematic behaviour, and difficultly with interpersonal relationships (Mash & Barkley, 2003; Raggi & Chronis, 2006). Moreover, the disorder has high rates of comorbidity with other psychological disorders and/or problems such as anxiety, depression, conduct disorders, substance use (Aflano & Gamble, 2009) and sleep disturbances (Corkum, Tannock, & Moldofsky, 1998). Although ADHD is referred to as a childhood disorder, ADHD can continue to impact and impair functioning into adolescence and adulthood (Barkley, 2006). Given the high occurrence, the negative consequences associated with ADHD, as well as its persistent effect on an individual into adulthood (Faraone, Biederman, & Mick, 2006), research surrounding the successful treatment of the disorder is particularly pertinent to society.

ADHD and stimulant medication

One theory used to describe the cause of ADHD is the optimal stimulation theory, which suggests that hyperactivity serves to cope with or adapt to low levels of arousal (Zentall, 1985; as cited in Barkley, 1997). Therefore, hyperactivity is thought to be an adaptive and homeostatic

mechanism which aids in bringing arousal levels up to a higher level of functioning. Consistent with this theory, ADHD is most frequently treated with stimulant medications, such as Detroamphetamine (DEX; Dexedrine®) and Methylphenidate Hydrochloride (MPH; Ritalin®), (see Greenhill, Halpherin, & Abikoff, 1999). Psychostimulants are thought to enhance the levels of arousal in the central nervous system (CNS) and autonomic nervous system (ANS) of individuals with ADHD (Durston & Konrad, 2007). Psychostimulants have been shown to effectively reduce ADHD symptomology in both the short and long term for as long as the treatment regime is followed (Jensen et al., 2007; Stein et al., 2003; Ritchers et al., 1995). For instance, stimulants are believed to enhance aspects of cognitive processing, such as working memory and attention, as well as, increase the academic productivity (Steenari et al. 2003; Wigal et al., 2011).

Consistently, research on ADHD, including the largest treatment trial of children's mental health disorders (Multimodal Treatment of ADHD study; Ritchers et al., 1995) has found that stimulant medications provide immediate and pronounced reductions in ADHD symptoms (i.e., core and associated symptoms). Despite its strong empirical support in the treatment of ADHD, stimulant medications have a wide range of potential side effects including decreased appetite, stomach-aches, and headaches (Greenhill et al., 2002). Stimulants (immediate and extended release) have also been found to negatively affect sleep (Charach, Ickowicz, & Schachar, 2004**;** Schachlar, Tannock, Cunningham, & Corkum, 1997; Stein et al., 2003). The negative impact of stimulant medication on sleep is particularly imperative, since unwanted side effects have been found to interfere with treatment adherence (see Charach, Volpe, Boydell, & Gearing, 2008; Schachlar et al., 1997). For instance, it is one of the most commonly cited side effects associated with parents choosing to discontinue their child's medication (see Charach,

Volpe, Boydell, & Gearing, 2008; Schachlar et al., 1997). Few studies have objectively measured the association between stimulant medications and sleep disturbances. Of those studies that have, it has been reported that medication significantly increased sleep onset latency (Corkum, Panton, Ironside, MacPherson, & Williams, 2008; Tirosh et al., 1993), and reduced total sleep time compared to placebo (Stein et al., 1996; Tirosh, Sadeh, Munvez, & Lavie, 1993).

Psychostimulants are low protein binding, and demonstrate rapid absorption and metabolism (Greenhill et al., 1999). Therefore, in the past multiple doses were required to maintain the therapeutic effect over the school day. Historically, common practice was for professionals to prescribe stimulant medication on a twice-a-day (BID) dosing regimen (i.e., administration in the morning and at noon). Over the past decade, ADHD has gone from being primarily viewed as a school disorder to a 24 hour disorder. This shift in thinking has lead to a shift in treatment practice, to address core symptoms at home, as well as at school (Greenhill et al., 1999). Consequently, the addition of a third dose (i.e., three times daily; TID) became common in clinical practice, in which the child receives an added dose after school (Corkum et al., 2008). Unfortunately, the little research that does investigate sleep disturbances and stimulant medication in adults and children with ADHD has used the BID dosing pattern, and as such there is limited information about the impact of TID dosing. In view of the fact that BID administration can lead to sleep disturbances one could hypothesize that receiving a third dose close to bedtime would interfere with arousal patterns and have a profound effect on sleep (Corkum et al., 2008; Stein et al., 2003).

Corkum et al. (2008) designed one of the few studies aimed at determining the impact of immediate release MPH-TID on children (6-12 years) who were newly diagnosed with ADHD and medication-naïve. Analyses of actigraphy data and sleep diaries (medication vs. no

medication condition) indicated statistically and clinically significant alterations in the children's sleep duration (i.e., decreased total sleep time) and sleep onset latency (i.e., longer time needed to fall asleep), but not in sleep quality (e.g., sleep efficiency). Children in the medication condition slept approximately 57 minutes less per night. These findings are consistent with those presented by Sangal et al. (2006), who found that children taking TID MPH took 69 minutes to fall asleep, rather than the 30 minutes that was found at baseline. Changes in sleep duration of this magnitude are important as recent research has established that even reductions as small as 1 hour less in sleep duration can be harmful to daytime functioning (Gruber et al., 2011).

Even across the few studies examining the impact of TID dosing, there are inconsistent findings on the impact of late-afternoon stimulant administration on sleep. For example, one study found that administering a third dose of MPH after school hours, did not alter sleep latencies (Kent, Blader, Koplewicz, Abikoff, & Foley, 1995). The findings of the Kent et al. (1995) study may have been a result of the sample they chose. For instance, the inpatient setting is not particularly generalizable to children with ADHD outside of inpatient care, who do not always have strictly scheduled sleep and wake times. Kent et al. (1995) indicate that their sample size (N=12) may not have been sensitive enough to find altered sleep latencies, obscuring the true effect of a third dose. Lastly, the subjective nature in which they measured sleep (i.e., nurse observations) and failure to address medication status (i.e., half of the samples had been on medication prior to the study) may have confounded the results. Stein and colleagues also investigated the differences between BID and TID dosing regimes in the treatment of ADHD. Stein et al. (2003) found that although there was not a significant difference between BID-MPH and TID-MPH for in regard to sleep duration, there was a considerable difference relative to placebo, with TID-MPH appearing to slightly reduce sleep duration more than BID (relative to

placebo) according to both subjective (parental accounts) and objective (actigraphy) assessment of sleep.

Corkum and colleagues (2008) urged physicians, parents, and researchers to monitor and take into account the quantity and quality of children's sleep when choosing stimulant medication for treatment of ADHD. This is particularly important since there has been a further shift in clinical practice to the use of long acting stimulant medications such as Concerta® and Biphentin® (see Swanson & Volkow, 2009 for review). These medications can be active in a child's system for more than 10-14 hours, depending on metabolism. The changes in dosing patterns and the lack of research into the influence these dosage regimes have on sleep, underscores the need for further research.

ADHD and cognitive functioning

Attention. Difficulty with attention is one of the predominant symptoms in children with ADHD, and this symptom typically persists into adolescence and adulthood (Beiderman, Mick, & Faraone, 2000). Attention is a cognitive process that allows us to actively process relevant information in the environment, while ignoring irrelevant stimuli. One model of attention identifies three networks including alerting, orienting and executive attention (Fan, McCandliss, Sommer, Raz, & Posner, 2002). Alerting can be defined as achieving and maintaining an alert state, whereas the orienting network is responsible for selecting relevant information from sensory input. Finally, executive control is involved in resolving conflict among competing responses (i.e., cognitive conflict; Fan et al., 2002). Evaluation of attention deficits in individuals with ADHD have been extensively investigated using a variety of cognitive tasks. Recently, the *Attention Network Task – Interaction* (ANT-I; Callejas, Lupianez, & Jesus-Funes, 2005) has

become one of the most frequently used tasks to examine attention deficits in children with ADHD.

Using the ANT-I, Johnson et al. (2008) noted that when comparing the attention ability in typically developing (TD) children and children with ADHD, those with ADHD preformed considerably worse (i.e., producing significantly slower reaction times). Specifically, children with ADHD had difficulty with incongruent trials which presented a cognitive conflict (e.g., incongruent planker arrows surrounding the target), and were therefore slower and more prone to errors during these trials (Johnson et al., 2008). In a study examining the three attention networks, Mullane et al. (2011) found children with ADHD had significantly weaker alerting and executive attention than TD children on the ANT-I, yet did not differ in orienting ability. The results of this study were supportive of the Berger and Posner (2000) hypothesis that children with ADHD have deficits in alerting and executive attention in particular.

Sustained-release formulations of stimulant medications commonly used with the treatment of ADHD, such as MPH and DEX, have proven to effectively increase performance on attention tasks for up to 9 hours following administration (Pelham et al., 1990). For instance, Wigal et al. (2011), examined the efficacy of Osmotic-Release Oral System (OROS) MPH on a wide range of academic, behavioural, and cognitive variables including attention, as objectively measured by the Test of Variables of Attention (TOVA). When compared to placebo, OROS-MPH has been found to be significantly effective in approving RT and RT-variability on the computerized TOVA measure of attention (Wigal et al., 2011). Pharmacological studies have shown that the stimulant medications increase the availability of neurotransmitters such as dopamine and norepinephrine, which are associated with executive and alerting attention, respectively (Durston & Konrad, 2007). To our knowledge, there have yet to be any studies

evaluating the effect of stimulant medication on attention in children with ADHD using the ANT or ANT-I tasks.

Memory. When examining memory, researchers often look at both short-term and working memory. Short term memory is the capacity for holding information in an active and readily available state for a short period of time (Baddeley, 1992) .Working memory is a cognitive system that allows us to temporarily store and manipulate information (Baddeley, 1992). Martinussen, Hayden, Hogg-Johnson, & Tannock (2005) found that children with ADHD tend to have more difficulty with memory tasks when they are required to manipulate information (i.e., working memory tasks). This finding is consistent with Bedard and Tannock (2008), who found that treatment with stimulant medication leads to increased working memory performance. Bedard and Tannock (2008) noted that improvements in working memory performance were greater for visual processing (i.e., finger windows backwards task) and that slight increases in performance were also seen in short-term memory (i.e., finger windows forwards task). For school-aged children, meeting academic demands is highly dependent on the ability to attend to relevant information, and having intact functioning of working memory (Steenari et al., 2003).

Academics. Academic problems are often the first indentified when a child is brought to clinical attention (Loe & Feldman, 2007). Despite the fact that children with ADHD have a normal to average level of intelligence, the experience of academic difficulty is very common in this population (Loe & Feldman, 2007; Mash & Barkley, 2003). The core behavioural symptoms of ADHD (inattention, impulsivity, and hyperactivity) are significant contributing factors to the academic difficulties seen in children with the disorder. Research has demonstrated that compared to controls children with ADHD have increased off-task behavior; decreased work

productivity; more errors on tasks over time; frequent distractions from assigned tasks; less attention to the rules governing a task; and decreased ability to shift attention across tasks flexibly (see Raggi & Chronis, 2006 for review). Symptoms of hyperactivity (excessive verbal and motor activity) also have implications for academic functioning of children with ADHD, including excessive fidgeting and difficultly remaining seated, which in turn may lead to lower levels of task completion and academic productivity (Mash & Barkley, 2003). Finally, symptoms of impulsivity, the child's difficulty in withholding active responses, typically result in academic errors because the child fails to wait long enough to consider alternative information, consequences, or responses (Raggi & Chronis, 2006; Zentall, 1993). The academic difficulties experienced by individuals with ADHD are also consistent with deficits in executive functioning processes such as behavioural inhibition, working memory, and attention (Barkley, 1997; see Raggi & Chronis, 2006 for review). Thus, both the core behavioural symptoms and deficits in executive functioning processes have direct implications for the development and maintenance of academic problems in children with ADHD (Raggi & Chronis, 2006).

A big debate in the treatment of ADHD surrounds the efficacy of stimulant medication on learning. Stimulant medication has been found to increase academic productivity (i.e., task completion) and academic accuracy in the short-term within classroom analogous settings (Evans et al., 2001; Pelham et al., 1985). Studies have shown that methylphenidate improves a child's functioning in the classroom setting (e.g., decreasing disruptive behaviour and task-irrelevant activities), thereby increasing academic productivity (Hectman et al., 2004; Pelham et al., 1990). Despite these therapeutic gains, it is important to note the distinction between academic functioning (e.g., productivity, and improvements in accuracy) and long term academic achievement (e.g., standardized test scores, grades, ultimate educational attainment; Loe &

Feldman, 2007). The following study focused on the effect of medication on acute academic productivity and accuracy.

In summary, children with ADHD are known to have deficits in attention, memory, and academic productivity. Stimulant medication has been found to be effective in improving cognitive performance on tasks requiring attention, memory, and academic productivity, yet more research is essential to comprehending this relationship in its entirety (Swanson, Baler, & Volkow, 2011). For that reason, it is necessary to understand the mechanisms by which stimulant medications are influencing cognitive outcomes in children with ADHD, after accounting for the possible moderating impact of other factors such as sleep.

ADHD and sleep disturbances

In addition to the core symptoms of ADHD (i.e., inattention, hyperactivity, and impulsiveness), children with ADHD are five times more likely than their typically developing peers to suffer from sleep disturbances (particularly initiating and maintaining sleep; Corkum et al., 1998; Hart, Palermo, & Rosen, 2005). Therefore, poor sleep is another symptom strongly associated with the disorder. Interestingly, sleep disturbances were once included as criteria in the 3rd Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III; APA, 1980). Although, sleep disturbances are no longer considered criteria for ADHD diagnosis it still continues to hold clinical significance. Despite the fact that there has been a number of systematic literature reviews on the sleep characteristics of children with ADHD, the relationship between ADHD, sleep, and daily functioning remains unclear (Owens, 2009).

Many argue that inconsistencies in research are largely due to differences in methodology, inadequate sample sizes, less than rigorous diagnostic criteria, and not controlling

for medication history or medication status (Corkum et al., 2008). For example, parental reports (subjective measures) of sleep disturbances (e.g., delayed sleep onset) are not always found to be analogous with objective measures of sleep such as *polysomnography (PSG)* or *actigraphy* (Sadeh, 2008). PSG is an objective measure of sleep, in which multiple physiologic variables are recorded during an overnight sleep study. PSG is considered to be the gold standard of sleep measurement. Actigraphy uses an accelerometer-based device resembling a wristwatch to measure motor activity and this activity data is then used to determine sleep versus wake. Actigraphy has been found to be a good estimate of sleep when compared to PSG (Sadeh, 2008).

Cortese, Faraone, Konofal, and Lecendreux (2009) performed a meta-analysis of subjective and objective studies (1987-2008) comparing sleep in children with ADHD to their typically developing peers. Subjective items revealed that children with ADHD had significantly higher bedtime resistance, more difficulties with sleep onset, significantly more night awakenings, and higher levels of daytime sleepiness. In regard to objective sleep measures, the meta-analysis showed that compared to controls children with ADHD had significantly higher sleep onset latency (actigraphy).

Importance of sleep

Human beings spend a significant portion of their lives sleeping, thus practically one could surely propose sleep has a large adaptive role for human survival and well-being. From infancy to adolescence, human beings must have sleep for healthy and optimal development and functioning (Owens, 2005). For instance, sleep not only has a restorative purpose, but also plays a large role in brain maintenance functions including memory consolidation, information processing and learning (Sadeh, 2007). Although the importance of sleep may be clinically

apparent, the current understanding of childhood sleep disturbances and their interactions with development is still less than comprehensive (Sadeh, Gruber, & Raviv, 2003). The research that does exist, suggests that poor sleep, both in terms of sleep quantity and sleep quality, puts children at great risk for a variety of acute and chronic impairments (Bruni, 2010).

Acute sleep deprivation and resulting daytime sleepiness can lead to observable cognitive performance deficits such as decreased attention, memory impairments and poor academic performance (Owens, 2005; Randazzo et al., 1998). Acute sleep restriction has been found to increase teacher and experimenter ratings of inattention (Fallone, Acebo, Arnedt, Seifer, & Carskadon, 2001; Fallone, Acebo, Seifer, & Carskadon, 2005). Gruber et al. (2011) investigated the cumulative impact of one hour sleep restriction over the course of six nights, and found that even this moderate amount of sleep restriction leads to detectable and clinically significant negative impacts of neurobehavioral functioning (NBF), including sustained attention and vigilance). Steenari et al. (2003) found that sleep quality and quantity significantly affects performance on working memory tasks in school-age children aged 6-13 years. Acute sleep loss has also been shown to impede of overall academic performance such as the ability to plan, organize, and problem solve (Owens, 2005).

Stimulant medication, sleep, and performance

Studies of the performance enhancing effects of stimulant medication, especially those that have specifically made use of attention tasks, have found that an individual's basal level of arousal has a large impact on the effectiveness of stimulant medication on cognitive outcomes (Bishops et al., 1997). Although, there is a tremendous lack of studies in this area involving children there have been a handful of studies with adult samples. Previous research in healthy adults with

normal sleep patterns found that the performance enhancing effects of methylphenidate and amphetamine were dependent on prior sleep deprivation (Bishop, Roehrs, Rosenthal, & Roth, 1997; Roehrs, Papineau, Rosenthal, & Roth, 1999). One explanation is that stimulant medications are effective in improving cognitive performance (such as attention) only to a moderate level of arousal. This would be consistent with the optimal stimulation theory of ADHD which proposes that manifestations of the disorder are a compensatory response to hypoarousal (Zentall, 1985; as cited in Barkley, 1997).

To our knowledge, Gruber and colleagues (2007) have been the first researchers to examine the moderating influence of sleep on the effectiveness of medication on improving cognition in children with ADHD. Gruber et al. (2007) examined whether the level of sleep efficiency in children with ADHD moderates their performance on a neuropsychological task called the Conner's Continuous Performance Task (CPT), while receiving a placebo and MPH. Gruber et al. (2007) used a within subjects (crossover) design in which children were divided into two groups based on the mean sleep efficiency score (based on actigraphy) during the week of placebo. The researchers found a Sleep group by medication interaction for one of the CPT factors, indicating that the score of children in the poor sleep group significantly improved when they received MPH compared to placebo, whereas it deteriorated for children that were in the good sleep group (Gruber et al., 2007). Although not directly comparable, these results are consistent with research with healthy adults (Bishop et al., 1997; Roehrs et al., 1999). These findings not only highlight the complex relationship between ADHD, pharmacological treatment and sleepiness, but demonstrate the necessity to construct a more comprehensive account of these interactions in order to adequately treat and support children with ADHD.

There remains a substantial gap in child focused literature that examines the performance-enhancing effects of stimulant medication when accounting for sleep quality and quantity. Moreover, future research investigating this relationship in children with ADHD must account for changes in dosage recommendations (TID and long lasting formulas). For instance, et al. (2007) utilized the BID regime in their study, however, based on today's recommendations, it is far more likely that school-aged children commencing stimulant medication for ADHD will be prescribed long acting formulas. In response to this dosage trend, the inconsistencies and lack of research surrounding the impact of long-acting stimulant medications on sleep, Corkum and colleagues have designed a randomized controlled trial (RCT) of 30 newly diagnosed and medication naïve children with ADHD. The current study is a secondary data analysis of this sample, but distinct from the goal of Corkum's original study (investigating the acute and long-term impact of stimulant medication on sleep quality and quantity). The following investigation concerned itself with whether sleep (quality and quantity) affects the performance enhancing effects of stimulant medication on cognitive functioning (attention, memory, and academic productivity).

It is imperative to understand how sleep problems may impact stimulant medication treatment, given that a significant number of children with ADHD are being treated with stimulant medication, the undeniable importance of sleep in neurocognitive outcomes, the negative impact stimulant medication has on sleep, and the possible role sleep may play in stimulant effectiveness. Moreover, enhancing our knowledge about this relationship is necessary, in order to guarantee children with ADHD are receiving a treatment that minimizes its risks including side effects (i.e., sleep disturbances). Finding that sleep has a role in stimulant

medication effectiveness may indicate a need to assess and independently treat sleep disturbances in children with ADHD who are being treated with stimulants.

Chapter 3: Methods

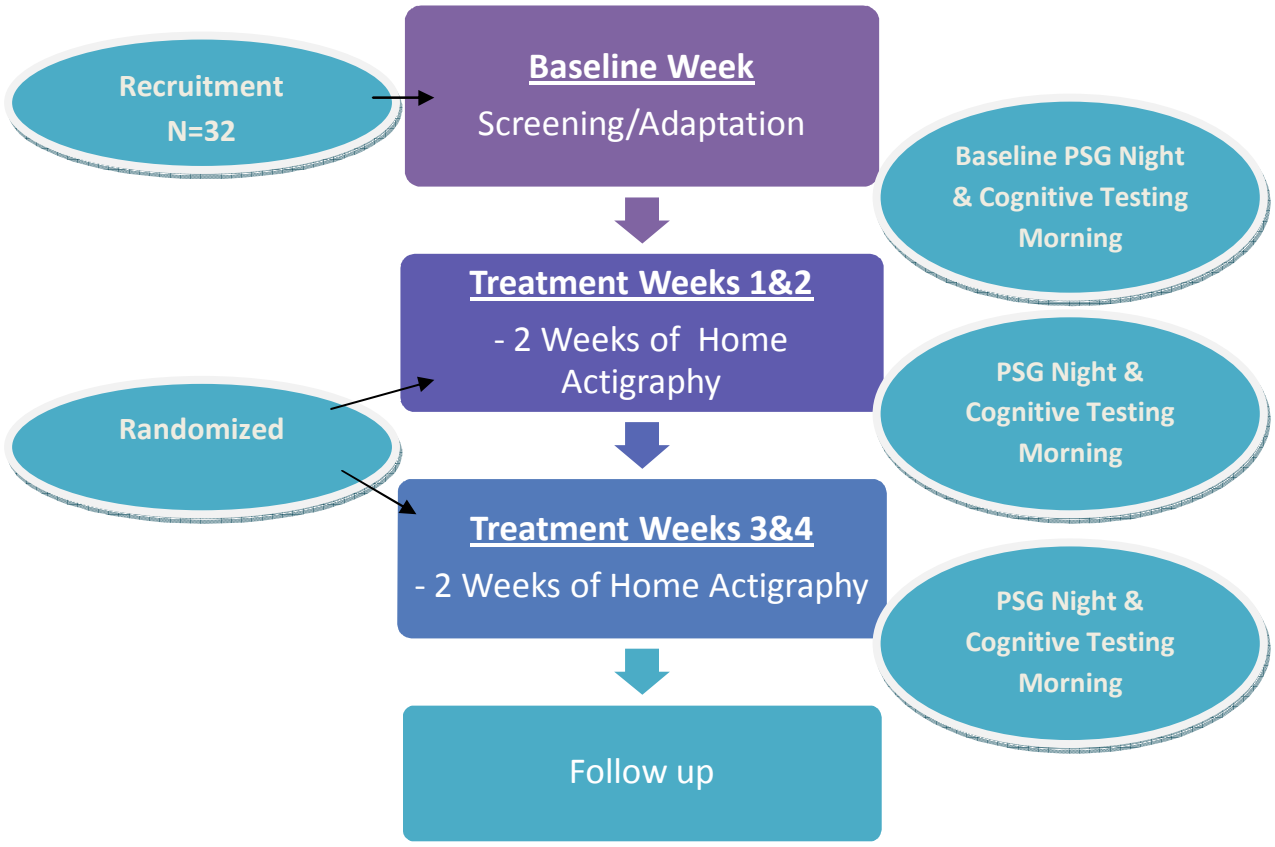
Participants

The current study used data collected from a clinical sample of 30 school-aged children (6-12 years old) who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; 2000) criteria for a diagnosis of ADHD, all of whom were medication naïve. The following research project is part of a larger project under the direction of Penny Corkum, Ph.D., referred to as the *PSG-ADHD Sleep study,* which evaluated the impact of stimulant medication on the sleep of school-aged children with ADHD (see Figure 1). Ethics approval for the current study has been granted from the IWK Health Centre's Research Ethics Board and Mount Saint Vincent University's Research Ethics Board. Children (n=32) were originally recruited into the larger PSG-ADHD Sleep study from two sites: 1) the Colchester East Hants ADHD Clinic in Truro, Nova Scotia and 2) a private psychological practice in Halifax, Nova Scotia, which specializes in children with ADHD. Children with ADHD who had another mental health disorder considered primary to their ADHD were excluded from the study. Children were also excluded if they had ever been treated (e.g., pharmacological or behavioural) for sleep problems and/or were ever diagnosed with a primary sleep disorder (e.g., sleep apnea or restless leg syndrome). Evidence of a significant cognitive impairment, neurological or genetic disorder, metabolic disorder, and/or seizure disorder also led to exclusion from the study. All children received PSG screening to rule out the presence of intrinsic sleep disorders.

From the original sample of recruited participants (n=32), two children and their families did not complete their participation. One chose to end participation due to the child's negative response to sleep recording procedures and the other family was withdrawn due to seizure

activity found during the sleep recording and subsequent diagnosis of epilepsy by a pediatric neurologist. Nine participants had to be removed from analysis due to missing data and the remaining 21 (with full data sets) were examined.

Figure 1



Measures

Polysomnography (PSG). PSG is considered to be the gold standard for sleep evaluation. PSG measures a number of physiological and behavioural variables during an overnight sleep study, which include: electroencephalogram (EEG), electroculogram (EOG), and electromyogram (EMG). Scoring of the sleep study was completed by a registered PSG technologist, based on standard criteria set forth by Rechtschaffen and Kales (1968). The PSG

technologist was supervised by a board certified sleep physician. From the PSG data, sleep was evaluated by both sleep quality (i.e., sleep efficiency) and quantity (i.e., sleep duration). Sleep efficiency (SE) is a ratio of minutes scored as sleep to time in bed. Sleep duration (SD) is the total sleep minutes from onset to final morning waking.

Actigraphy. Actigraphy uses an accelerometer-based device (resembling a wrist watch) to measure motor activity. Based on an acceleration sensor, the actigraph provides continuous monitoring of activity level, which is then translated into a numeric representation of sleep-wake periods (Sadeh, Hauri, Kripke, & Lavie, 1995). Actigraphy has become an increasingly useful tool for assessing sleep in infants, children and adults for both research and clinical practice (Sadeh, 2008). Actigraphy is considered a valid and reliable evaluation of sleep (Sadeh, 2008). Not only does actigraphy provide an ecologically sound representation of sleep in a child's natural setting, but has been found to have good validity compared to PSG (e.g., ~90% night-wake scoring agreement; Sadeh, 2008). Octagonal Basic Motionlogger Actigraphs (AMI) with 2 MB of memory were used, allowing up to two months of data collection. All actigraphy data were scored using Action W (v2.6) Software (AMI). From the actigraphy data, sleep was evaluated by both sleep quality (i.e., sleep efficiency) and quantity (i.e., sleep duration). Actigraphy data based on multiple nights of assessment therefore actigraphy sleep variables were based on an average of all week nights (minus weekends). Each participant had one sleep duration and sleep efficiency score (as measured by actigraphy) for the baseline, medication, and placebo weeks.

Attention. To measure attention, the Attention Network Task – Interaction (ANT-I*;* Callejas, Lupianez, & Jesus-Funes, 2005) was used. The ANT-I is a computerized task designed to evaluate the alerting, orienting, and executive attention networks using simple reaction time

(RT) responses (Callejas et al., 2005). The ANT-I is an adaptation of the original ANT (Fan, McCandliss, Sommer, Raz, & Posner, 2002). Although, the psychometric properties of the ANT-I are only starting to emerge, the original ANT has good test-retest reliability, and has been validated for child assessment (Fan et al., 2002). The little research that does exist has found that the ANT-I actually has greater reliability for the network scores, compared to the ANT (Ishigami & Klein, 2010). Network scores from the ANT-I have also been found to be robust against practice effects (Ishigami & Klein, 2010). The ANT-I consisted of a mixture of congruent and incongruent trials. For instance, when all five arrows point in the same direction of the target arrow is presented in the spatial location congruent with the direction to which it points (e.g., arrow presented on left side of fixation and points left), trials were considered 'congruent'. Incongruent trials occurred when either the target arrow points in the opposite direction of the flanking arrows or when the spatial location is incongruent with the direction to which the target arrow points (e.g., arrow presented on right side and points left). In addition to congruency, trials included various cues such as tones and visual cues (i.e., an asterisk) to direct ones attention to a specific area.

Each trial began with a central fixation point (i.e., a cross). An auditory tone was presented on half of the trials, following a variable duration, 400-1600 milliseconds (ms). On two thirds of the trials, an asterisk was presented following 400 ms; 50 ms later the target arrow was presented either on the same (i.e., valid) or opposite (i.e., invalid) side. The presentation of flanker arrows (two arrows on each side of the target arrow) occur on half of the trials. The arrow(s) remained on the computer screen until the participant responds or until 3000 ms have elapsed. The alerting network is measured by comparing the reaction time and/or accuracy on trials with and without a tone preceding the target. The executive network is assessed by

examining the difference in reaction time and/or accuracy between congruent trials and incongruent trials. The researchers chose to exclude the orienting network from analysis, since it has not been found to be problematic for children with ADHD (Berger & Posner, 2000). See Appendix A for visual representation of the ANT-I.

Reaction times and accuracy scores from the alerting and executive networks were examined as dependant variables. Reaction times were measured in milliseconds (ms.), with lower RTs indicating quicker performance. The highest possible score for accuracy was six. Since, the aim was to examine attention performance in as much detail as possible, a decision was made to analyze ANT-I RT and accuracy for both networks separately, instead of using scores that were based on the participant's network efficiency (i.e., difference scores). As such, four dependant variables were created from the alerting network trials: With tone RT, Without tone RT, With tone accuracy, and Without tone accuracy. Four dependant variables were also created from the executive network trials: Congruent RT, Incongruent RT, Congruent accuracy, and Incongruent accuracy.

Memory. To measure memory, participants preformed two brief tasks that required them to remember and reproduce a sequence of either verbal or visual information. The *Digit Span (DS)* task from the *Wechsler Intelligence Scale for Children, Fourth Edition* (WISC-IV; Wechsler, 2003), was used as a measure of verbal memory. The child was orally presented numerical digits and had to repeat these in either forward or reverse order. The DS task has been found to have good reliability (.78-.91) in children aged 6-16 years (Wechsler, 2003). The *Finger Windows (FW)* task from the *Wide Range Assessment of Memory and Learning, Second Edition* (WRAML2; Sheslow & Adams, 2003), was used to assess visual memory. For this test, the child was visually presented with a sequence of spatial locations and had to replicate this sequence

either in forward or backward order. The FW task has been found to have good internal consistency (.81-.83) for children aged 6-13 years (Sheslow & Adams, 2003).

Both tasks started easy (e.g., repeating two digit or two spatial location sequences) and became increasingly difficult (i.e., longer sequences to reproduce). Each sequence length had two trials, and the child received 1 point for replicating one of the trials correct, and 2 points for two correct trials. The tasks were discontinued if the child got both of the trials within a sequence length incorrect. From the raw data, total scores were produced for DS-forward, DS-backward, FW-forward, FW-backward. The majority of literature surrounding memory performance in children with ADHD has conceptualized memory in terms of short-term and working memory, rather than examining visual or verbal components of memory (Baddeley, 2012; Steenari et al., 2003). Therefore, composite scores were calculated for both short-term and working memory by collapsing across verbal and visual stimuli. As such, the total raw score for forward digit span and forward finger windows tasks were summed to calculate a short term memory score. The total raw score for backward digit span and backward finger windows tasks were summed to calculate a working memory score. Every day sensory perception involves multisensory information (Baddeley, 2012), and rarely only involves one modality (visual or verbal), possibly making the combination of the scores from the digit span(verbal) and finger windows (visual) an more ecologically valid approach. This method has been used in similar research studies and is in line with well known theoretical accounts of memory (Baddeley, 2012).

Academic productivity. The *math fluency test,* from the *Woodcock Johnston III* (WJ-III; Woodcock, McGrew, & Mather, 2001), was used to measure academic productivity. The math fluency test is a series of pages of age appropriate math problems with a time limit of two minutes. The WJ-III is well known for its strong standardization and psychometric properties

(Cizek, 2003; Sandoval, 2003). The reliability and construct validity of the WJ-III is extensively documented (Woodcock & Johnson, 1989; Woodcock et al., 2001). Academic productivity scores were based on the total number of accurate problems completed.

Procedures

Parental consent and child assent was gained from all participants. To collect a representation of baseline sleep, a one-week baseline period was arranged. The baseline week also allowed the children to become acclimatized to all sleep measurement procedures and cognitive tasks. This was done to ensure that the medication trial weeks are not confounded by any first night effects. During the baseline, sleep at home was measured using actigraphy, questionnaires, and sleep diaries, and at the sleep lab it was measured by PSG. The first stay in the sleep lab also allowed for a screening PSG sleep study to rule out primary sleep disorders.

All families and children who consented to participate in the medication trial met with a pediatrician for a pre-medication consultation, and then received their medication from the study's pharmacist. Children and families were in contact with the study pediatrician, throughout the study for medication evaluation. Following the baseline week, the medication trial lasted four weeks. Specifically, the trial involved two consecutive weeks of Pill A, followed by two consecutive weeks of Pill B. Pill A and Pill B were randomly assigned to the stimulant medication or placebo condition. Each week of the medication trial had a Sunday start and concluded on Saturday evening. As with the baseline week, the participants were required to wear the actigraph device during every night of the medication trial. The PSG was conducted at the end of the first week of each medication condition.

Actigraphy was used to measure sleep while at home therefore, with their parents help, children were instructed to wear their actigraph on their non-dominant wrist, every night throughout the study period. All participants were asked to follow their typical sleep schedules (sleep and wake times). They were able to remove the actigraph after waking for the day, and followed the same routine for the entire length of the study (i.e., six weeks).

During PSG studies, children came to the Chronobiology Laboratory at the Queen Elizabeth II Health Sciences Centre (QEII-HSC) in Halifax, NS for an overnight stay. Directed by Dr. Rusak, the laboratory is a two-bedroom research facility equipped with a Sandman® Polysomnography system. One of the bedrooms was prepared as a child-friendly room for the participants (e.g., colourful pictures and bedding). The second room was prepared for the parents, who also had the option of sleeping on a cot in their child's room. Upon arrival, the research assistant (RA) gave the family a tour of the sleep laboratory. At this time the child was introduced to his/her room and informed what would take place. The child and RA would typically play a game, while the parent/guardian filled out paperwork, including the measures involved with the larger PSG-ADHD study. Children were then able to watch a movie and have a bedtime snack while the RA completed the PSG hook up procedures. The child then went about their nightly routine (e.g., brushed teeth, spend time with parent, and got into bed). Before lights out, the RA did a short testing session of bio-calibrations to ensure that the equipment was recording properly.

Children slept in a sound-proof, darkened room with an ambient temperature of 24°C. The children's room was equipped with an infrared camera and a speaker/microphone system so that the RA could ensure the safety and comfort of the child, as well as detect snoring and monitor body position. Bed and wake times were set based on parental reports, in order to

stimulate a typical school night's sleep. Reimbursement for transportation and accommodations was provided; families were offered a honourarium for each assessment period in appreciation of their time.

On the morning following each PSG overnight sleep study, children completed two testing sessions (i.e., one before medication and the other session one hour after medication administration). These testing sessions were designed to measure various cognitive, emotional, and behavioural outcomes. For the current study, three cognitive constructs were examined: 1) the forward portion of the Digit Span task and Finger Windows task to assess short term and the backward portion of these tests to assess working memory, 2) the Attention Network Task-Interactive to measure two types of attention (alerting and executive), and 3) a Math Fluency test to measure academic productivity. Testing Session 1(which occurred prior to medication administration) and Testing Session 2 (which occurred one hour after medication administration) were used as the "No Medication" and "Medication" conditions for the purpose of this study. Data collected during Placebo weeks of the Medication Trial were used to examine any possible practice effects between testing sessions.

The Digit Span task was administered approximately 15 - 20 minutes into the test battery and the RA told the child that he/she was going to say some numbers. The child was asked to listen carefully and repeat the numbers after the RA finished. The RA then moved on to the backwards version of the task and the child was told to repeat the numbers in reverse sequence (See Appendix B). For the Finger Windows task (WRAML2), the RA utilized a small upright board apparatus to administer the task. The RA poked his/her finger through a sequence of windows, which were cut out of the small wooden apparatus. Like the Digit Span task, children preformed this task both in a forward and backwards sequence. The Fingers Windows test

followed the Digit Span test. Together the Digit Span and Finger Windows tasks took on average approximately 10 minutes to complete.

The ANT-I (Callejas et al., 2005) was administered approximately 30 minutes into the test battery. First, participants were asked to complete one practice block, followed by an experimental block of the ANT-I on a laptop computer. The participant was instructed to focus his/her attention on the computer screen and to press the left arrow key if the target stimulus (i.e., an arrow) pointed left and the right arrow key if the arrow pointed right (keys c and m on the keyboard were re-labelled with arrows).The task included one block of 24 practice trials and two blocks of 96 experimental trials. The experimental trials were separated by a 5 min break. The task typically lasted 20-30 minutes.

For the Academic Productivity portion of the testing session, participants were given a math sheet and were instructed to do as many problems as they could in a three minute period. They were instructed to complete questions in the order that they were arranged on the page, rather than jumping around. If the child finished the first math sheet, they were given another and so on until the three minutes elapsed (See Appendix E).

There was an hour in between each testing session, in which children took their pill and went for breakfast. The testing procedure was the same for the first and second session. Both sessions took approximately one hour. Upon completing both testing sessions and prior to going home the children were able to choose a toy in appreciation of their hard work.

Data Analyses

Data was analyzed using SPSS version 17.0 software. In order to test whether medication had an effect on cognitive performance, a repeated measures Multivariate Analysis of Variance (MANOVA) involving medication status (medication vs. no medication) as the repeated measure

and performance on the cognitive tasks as dependant variables was conducted. There were 11 dependent variables included in this analysis (8 for ANT-I, 1 for WM, 1 for STM, and 1 for academic productivity). Secondly, to examine what effect medication had on sleep, a repeated measures MANOVA was used, with medication status as the repeated measure and two actigraphy sleep variables (SD and SE) and two PSG sleep variables (SD and SE) as dependant variables. Lastly, to determine whether a significant relationship existed between sleep and the effect of medication of cognitive performance, bivariate correlations were conducted between cognitive performance (i.e., difference in performance on and off medication), and PSG sleep variables (SD and SE) at baseline. For significant correlations, groups were formed based on mean split and then differences compared using one-way ANOVAs.

Chapter 4: Results

Demographics

Participants ranged in age from 77.30 to 149.50 in months (6.4 to 12.5 years), with a mean age of 108.90 months (9.1 years). Of the 21 participants, there were 4 females and 17 males. In regard to ADHD subtype, 1 child in this sample was predominantly hyperactive-impulsive, 4 were classified as predominantly inattentive, and the remaining 16 were classified as combined type. Two children had been diagnosed with Oppositional Defiance Disorder (ODD), one of which was also diagnosed with Conduct Disorder (CD). Ten participants were found to have or be at high risk for a learning disability (LD). In regard to socioeconomic status (SES), Nam-Powers-Boyd scale (Boyd-NP; Highest score; Boyd, 2008) was used and indicated that the participants came from households where the highest Boyd score ranged from 28 to 98 (M=70.24, SD=22.77). Three of the children in the sample came from single parent homes (14.3%). The household income of this sample ranged from less than $20,000 to greater than $100,000. Specifically, one family reported living on less $20,000 annually (4.8%), 23.8% had a household income between $21,000- $30,000 (n=5), 4.8% had a household income between $31,000- $40,000 (n=1), 9.5% had a household income between $41,000- $50,000 (n=2), 14.3% had a household income between $81,000- $90,000 (n=3), 9.5% had a household income between $90,000- $100,000 (n=2), and 28.6% of this sample reported a annual household income greater than $100, 000 (n=6). Note that household income data for one family was missing. The ethnicity of the sample was 90.5% Caucasian (n=19), 4.8% Aboriginal (n=1), and 4.8% Latin American (n=1).

Medication Effects: Cognitive Variables

A repeated measures Multivariate Analysis of Variance (MANOVA) involving medication status (medication vs. no medication) as the repeated measure and performance on the cognitive tasks as dependant variables was conducted. Four dependant variables were used to examine alerting attention: With Tone RT, Without Tone RT, With Tone Accuracy, and Without Tone Accuracy. As well, four dependant variables were used to examine executive attention: Congruent RT, Incongruent RT, Congruent Accuracy, and Incongruent Accuracy. Further dependant variables included Short-term Memory, Working Memory, and Academic Productivity. Descriptive statistics are displayed in Table 1.

Table 1

Means and Standard Deviations of Cognitive Performance Measures in Medication vs. No Medication Conditions

Variable (n=21)	No Medication	Medication	F	df	*p*
	M(SD)	M(SD)			
Alerting (ANT-I)					
With Tone (RT)	6048.88(1723.87)	5210.46(1693.55)	11.316	20	.003*
Without Tone (RT)	6856.21(1769.10)	5793.53(1789.68)	20.948	20	.000*
With Tone (Acc)	5.65(.78)	5.73(.73)	4.706	20	.042*
Without Tone (Acc)	5.52(.87)	5.81(.38)	5.832	20	.035*
Executive (ANT-I)					
Congruent (RT)	5956.24(1561.62)	5050.51(1651.39)	17.479	20	.000*
Incongruent (RT)	6880.10(1888.82)	5953.48(1856.50)	12.960	20	.002*
Congruent (Acc)	5.69(.64)	5.89(.38)	7.146	20	.015*

Incongruent (Acc)	5.48(1.03)	5.65(.73)	4.048	20	.058~
Memory					
Short term	16.9048(6.52)	16.6667(7.00)	.066	20	.800
Working	11.1905 (6.58)	12.8571(6.48)	5.335	20	.032*
Academic Productivity					
Total Accurate	29.0(25.56)	32.81(28.96)	5.276	20	.033*

Note: ANT-I = Attention Network Task-Interactive. RT = Reaction Time in ms. Acc = Accuracy; possible score out of 6. DS= Digit Span Task. FW= Finger Windows Task. Short-term memory = composite of forward DS and FW (possible score out of 30). Working memory = composite of backward DS and FW (possible score out of 32). Score based on the Math Fluency Task, with scores ranging from 0-96.

Results of the MANOVA showed that there were significant effects of medication on performance for many of the measures of cognitive performance, $F(11,10)= 7.458$, $p= .002$. As such, examination of the univariate analyses was conducted. In regard to the ANT-I alerting network, medication significantly decreased RT during trials with a tone, $F(1,20)=11.316$, $p= .003$, and without a tone, $F(1, 20)= 20.948$, $p < .001$. Medication was also found to significantly improve accuracy during trials with a tone, $F(1, 20)= 4.706$, $p= .042$, and without a tone, $F(1,20)= 5.832$, $p=.025$. With reference to the ANT-I executive network, medication significantly decreased RT during congruent trials, $F(1, 20)= 17.479$, $p < .001$, and incongruent trials, $F(1,20)= 12.960$, $p=.002$. Accuracy was significantly enhanced by medication during congruent trials, $F(1, 20)= 7.146$, $p= .015$. Although, there were no significant effect of medication on accuracy during incongruent trials there was a very strong trend, $F(1, 20)= 4.048$, $p=.058$. In regard to memory, there was a significant effect of stimulant medication on working memory performance, $F(1, 20)= 5.335$, $p=.032$, but not short-term memory, $F(20)= 0.066$, $p=.800$. Medication was also found to significantly affect performance on academic productivity, $F(1,20)= 5.276$, $p= .033$. Our findings revealed that there was no significant effect of medication on short-term memory; therefore this variable was excluded from further analyses.

Medication Effects: Sleep

Descriptive statistics for the sleep variables during medication and placebo weeks can be found in Table 2. Analysis of sleep data through a repeated measures MANOVA, with medication status as the repeated measure and two actigraphy sleep variables (SD and SE) and two PSG sleep variables (SD and SE) as dependant variables revealed a significant effect of medication on sleep, $F(4, 14)= 3.676$, $p= .030$. Univariate statistics revealed significant differences between medication and placebo on sleep duration for actigraphy, $F(17)= 4.524$, $p= .048$. On average, children's sleep duration was 21 minutes less while on medication compared to placebo. There were no significant effects of medication found on sleep efficiency for actigraphy, $F(17)= 2.003$, $p= .175$. Statistical analysis indicated that PSG sleep duration, $F(17)= 12.82$, $p = .002$ was significantly different between medication and placebo weeks. Children were sleeping on average 40 minutes less while taking medication. There were no significant effects of medication found on sleep efficiency for the PSG data, $F(17)=1.493$, $p=.238$. Given that two participants were excluded due to missing actigraphy data, an analysis of PSG only was conducted and the results were found to be very similar. Furthermore, all further analyses involved PSG data (rather than PSG and actigraphy data) for the following reasons: 1) the findings were the same across actigraphy and PSG in terms of the impact of medication on sleep, 2) PSG is considered the gold standard of sleep assessment, and 3) there were a greater amount of participants with full cognitive and PSG data than there were with full cognitive and actigraphy data.

Table 2
Means and Standard Deviations for Sleep Variables in No Medication vs. Medication Conditions

	No Medication	Medication			
	M(SD)	M(SD)	F	df	*p*
Actigraphy (n=18)					
SD	551.92(63.79)	530.65(57.55)	4.524	17	.048*
SE	82.81(11.73)	78.83(7.50)	2.003	17	.175
PSG (n=21)					
SD	550.51(48.56)	510.47 (66.88)	18.194	20	0.00*
SE	87.51(7.00)	83.67(10.21)	2.605	20	.122

Note. SD= Sleep Duration. SE= Sleep Efficiency. PSG=Polysomnography.

Medication, sleep, and cognitive performance

Preliminary Analyses. To ensure that any results found were not due to practice effects, data from the placebo week was analyzed. A MANOVA involving testing session 1 and 2 (prior placebo administration vs. post placebo administration) as the repeated measure and performance on the cognitive tasks as dependant variables was used. There were no significant practice effects on any of the cognitive variables, $F(11,8)= 2.300$, $p= .123$. Given that there were no practice effects from session 1 to session 2 when the children were taking placebo, it was decided that there was no further need to control for practice effects in the primary analyses. Table 3 displays these results.

Table 3
Practice Effects on Cognitive Performance

	Placebo S1	Placebo S2			
	M(SD)	M(SD)	F	df	Sig
Alerting (ANT-I; n=19)					
With Tone (RT)	6150.29(1881.51)	5916.44(1750.04)	.640	18	.434
Without Tone (RT)	6916.66(1995.46)	6691.40(1838.95)	1.000	18	.331
With Tone	5.48(.80)	5.49(.88)	.010	18	.922

(Acc)					
Without Tone (Acc)	5.49(.80)	5.41(.81)	1.332	18	.264
Executive (ANT-I; n=19)					
Congruent (RT)	6136.32(1873.35)	5914.20(1749.24)	.736	18	.406
Incongruent (RT)	7073.03(1864.32)	6646.83(1864.32)	2.426	18	.137
Congruent (Acc)	5.58(.81)	5.61(.73)	.141	18	.711
Incongruent (Acc)	5.39(.79)	5.29(.94)	1.953	18	.179
Short-term Memory	16.43(6.85)	15.29(6.80)	2.404	20	.138
Working Memory	11.32(6.78)	10.84(6.01)	.341	20	.566
Academic Productivity	28.79(25.78)	29.57(27.82)	.253	20	.621

Note: Analysis was conducted using placebo weeks before (S1) and after (S2) pill administration. ANT-I = Attention Network Task-Interactive

Primary Analyses. To test whether there were any significant relationships between sleep and the effect of medication on cognitive performance, bivariate correlations were conducted between cognitive performance differences (i.e., difference between performance after medication and performance before medication) and PSG sleep variables (SD and SE) during baseline week . Positive differences in performance indicated improvement for attention accuracy, working memory, and academic productivity. Oppositely, improvements in reaction time were indicated by negative differences (i.e., faster RT). Four variables were included to examine alerting attention variables: With Tone RT, Without Tone RT, With Tone Accuracy, and Without Tone Accuracy. Four variables were included to examine executive attention variables: Congruent RT, Incongruent RT, Congruent Accuracy, and Incongruent Accuracy. Further variables were Working Memory and Academic Productivity. One significant correlation was found between difference scores for executive attention incongruent accuracy and PSG sleep

duration during baseline, *r*= .456, *p*= .025. One significant correlation was also found between working memory improvement and baseline PSG sleep efficiency, *r*= -.450, *p*=.041. There were no other significant correlations found between sleep and medication enhanced cognitive performance. Table 4 displays these results.

Table 4

Correlations between performance changes related to stimulant medication and sleep variables

	PSG SD		PSG SE	
	R	*p*	*R*	*p*
Alerting (ANT-I)				
With Tone(RT)	-.072	.756	-.188	.413
Without Tone (RT)	-.098	.673	-.203	.378
With Tone (Acc)	.239	.296	-.136	.557
Without Tone (Acc)	.328	.147	.251	.272
Executive (ANT-I)				
Congruent (RT)	-.150	.517	-.168	.465
Incongruent (RT)	.024	.917	-.175	.448
Congruent (Acc)	.078	.737	.072	.757
Incongruent (Acc)	.486	.025*	.236	.303
Working Memory	.259	.258	-.450*	.041
Academic Productivity	-.238	.298	-.357	.112

Note: Correlations were conducted between sleep and medication related cognitive improvements. Improvement was calculated through difference scores between performance after medication minus performance prior to medication. Polysomnography (PSG) sleep variables at Baseline including: SD= Sleep Duration and SE= Sleep Efficiency. ANT-I= Attention Network Task-Interactive. RT = Reaction Time in ms. Acc = Accuracy.

Groups were formed to examine the significant correlations further. Children whose sleep duration was above the mean at baseline (*M*=508.20) were considered the good sleep group (n=10) and those below the mean were considered the poor sleep group (n=11). A one-way ANOVA was then used to compare the groups on executive attention incongruent accuracy. Statistical analysis revealed that children performed significantly different on executive attention incongruent accuracy depending on baseline sleep, *F*(1, 19)= 6.859, p= .017. The children in the

good sleep group had more improvements in accuracy (*M*= 0.3643, *SD*= 0.4372) compared to children in the poor sleep group (*M*= -0.0152, *SD*=0.1921). Accuracy scores on the ANT-I are out of a possible 6, and the means above are based on difference scores. A one-way ANOVA was also used to compare sleep groups based on baseline sleep efficiency on working memory performance. Children whose sleep duration was above the mean at baseline (*M*=83.05) were considered the good sleep group (n=13) and those below the mean were considered the poor sleep group (n=8). There were no significance differences between these groups for working memory performance, $F(1,19)=2.231$, $p=.152$.

Chapter 5: Discussion

There were two main objectives for the current study: 1) to further knowledge regarding the effects of stimulant medication on cognitive performance, a blinded medication trial of extended release stimulant medication (Biphentin®) was conducted and a range of direct measures of cognitive functioning (i.e., alerting and executive networks of attention, working memory, short-term memory, and academic productivity) were used to assess medication effects on cognition, and 2) to gain more knowledge regarding how this relationship was impacted by baseline sleep quantity and quality. It was found that medication improved performance on the majority of cognitive variables assessed. Moreover, medication reduced sleep duration but did not change sleep efficiency. Most importantly, it was found that sleep duration at baseline was related to the effectiveness of medication for improving executive attention.

Based on previous research, the first hypothesis of this study was that stimulant medication would improve performance on alerting and executive attention, working memory, and academic productivity, but would not significantly improve short-term memory. Statistical analysis confirmed this hypothesis. Our finding that children with ADHD performed better when taking stimulant medication compared to placebo for both the alerting and executive networks (i.e., faster RT and higher accuracy) is consistent with previous research (Gruber et al., 2007; Konrad et al., 2004; Oberlin et al., 2005; Wigal et al., 2011). Children with ADHD are known to have difficulties with inhibition (Barkley, 1997). Therefore, one could speculate that stimulant medication enables children to delay responses (decrease RT) long enough to respond to the correct stimuli, rather than responding to the most salient stimuli (in this case the surrounding flanker arrows) during incongruent trials, which in turn would increase their accuracy. Over the past decade, the ANT has become one of the most widely used tasks (along with the Stop Signal

Task and CPT) to assess the cognitive components of attention and impulsivity in children with ADHD (Swanson, Baler, & Volkow, 2011). To our knowledge, the current study is the first study to have examined the effects of extended release stimulant medication on attention as measured by the ANT-I. Our findings that extended release stimulant medication improves both alerting and executive networks of attention are similar to research that examined the effects of short acting medication on the ANT (Konrad, Gunther, Hanish, & Herpertz-Dahlmann, 2004; Oberlin, Alford, & Marrocco, 2005). For instance, Konrad et al. (2004) noted that acute doses of MPH improve the maintenance of attention, as well as, inhibitory performance.

The finding that children with ADHD performed better on working memory tasks while on stimulant medication, but not for short-term memory tasks, is also consistent with previous research (Bedard & Tannock, 2008; Mehta, Goodyer, & Sahakian, 2004; Wigal et al. 2011). One possible reason for medication being effective for working memory but not short-term memory may be the area of the brain involved with each of these processes. For instance, working memory tasks are said to activate more neural connections in the prefrontal cortex than short-term memory, and this is the area of the brain that has been found to be responsive to stimulant medication (Swanson, Baler, & Volkow, 2011). Another possible reason for medication being effective for working memory but not short-term memory may be due to the influence of attention (active maintenance). For instance, unlike short-term memory, working memory requires sustained attention to ensure information is encoded for future use and manipulation, a task that appears more difficult than simple recall, for children with ADHD (Barkley, 1997). Given that working memory ability is essential for supporting the accumulation of knowledge and information consolidation during childhood development (Barkley, 1997; Steenari et al., 2003), the finding that stimulant medication is effective in enhancing working

memory has significant implications for learning. Memory and attention have been identified as two closely linked components of cognition which are very important for daily functioning (Sadeh et al., 2002); therefore the successful treatment of cognitive processing deficits in children with ADHD is vital.

Stimulant medication was also found to significantly improve academic productivity. Children completed more math problems accurately while on medication than while on placebo. This finding was consistent with previous research that used the math fluency test as an objective measure of academic productivity, as well as studies using other measures of academic productivity (see Raggi & Chronis, 2006 for review). Although improvements in academic productivity do not infer improvements in overall academic achievement, some researchers suggest this medication effect may provide an opportunity for children with ADHD to develop academic skills (Corkum, McGonnell, & Schachar, 2010).

Studies using objective measures of sleep to investigate the effect of long-lasting medication on sleep quantity and quality in children are limited. In regard to sleep efficiency, it was found that medication did not have a significant effect, a finding which is consistent with past literature (Corkum et al., 2008; Gruber et al., 2007). The finding that stimulant medication significantly reduced sleep duration is consistent with studies examining immediate release formulations of stimulant medications (BID or TID; Corkum et al., 2008; Stein et al., 2003). Specifically, we found that based on PSG data children sleep approximately 40 minutes less while on medication. This finding warrants clinical attention, given that moderate sleep restriction has been demonstrated to result in a deterioration of cognitive and behavioural functioning (Gruber et al., 2011; Muto et al., 2011; Sadeh, 2007; Steenari et al., 2003; Vriend et

al., 2012). Furthermore, it highlights the need for additional research to increase our knowledge regarding the complex association between ADHD, sleep, and the stimulant treatment of ADHD.

The most novel aspect of our study was the evaluation of how sleep may be associated with the effectiveness of medication. Our general finding that stimulant medication response is associated with sleep for executive attention accuracy during incongruent trials is consistent with Gruber et al. (2007). However, the direction of our finding (i.e., positive correlation) and sleep variable (SD) involved are not consistent with the Gruber et al. (2007) study. We found that sleep duration, not sleep efficiency was related to performance change. Moreover, we found that children with better (not poorer) sleep had better accuracy outcomes on executive incongruent trials. These discrepancies may be explained by the fact that Gruber et al. (2007) used a different task to assess attention, however both the CPT and the incongruent trials of the Executive Network of the ANT-I involve response inhibition, so this explanation seems unlikely. Several other differences in research design and sample composition may have led to dissimilar findings, including: 1) our study used extended release stimulant medication rather than immediate release given twice daily (BID), 2) our study used PSG rather than actigraphy, as PSG is the gold-standard assessment measure of sleep, 3) the baseline mean sleep efficiency (M=83.05) for our sample was slightly higher than the mean sleep efficiency for their sample (M=80.0), 4) Gruber et al., (2007) did have a larger sample of 37 children with ADHD, compared to our 21 children with ADHD, although ours were more rigorously diagnosed, and lastly 5) our sample was medication naïve prior to starting the study, therefore baseline assessments of sleep were not affected by previous medication experience.

Our finding that children with longer sleep durations have more improvement on executive attention task as a result of medication may provide some insight into underlying

individual differences in treatment response for children with ADHD. Moreover, this finding may assist in the development of more focused research and comprehensive treatment strategies. For instance, future clinical trials examining the effectiveness of MPH and its impact on cognitive performance should account for variation in sleep quantity as they would with demographic variables such as age. Controlling for sleep variables such as duration is warranted especially when tasks require children to use executive control and inhibition of salient responses.

Recommendations and Limitations

When interpreting the results of this study, one must consider a variety of strengths and limitations. A major strength of our study was the application of a randomized blinded medication trial to investigate the effects of stimulant medication. Secondly, the ADHD participants were rigorously diagnosed by registered clinical psychologists, and were medication naïve prior to starting their participation. Furthermore, to our knowledge this study was the first to use both actigraphy and PSG to investigate the relationship between sleep and the effect of extended release MPH on cognitive performance. The sample size of the current study was comparable to those examining similar research questions. This being said, a larger sample size may have allowed more in-depth analysis (i.e., moderator and mediator analyses). Secondly, although the over representation of males has been noted in similar studies (e.g., Gruber et al., 2007), future research may want to investigate gender differences in the interaction between sleep efficiency and stimulant medication response. Finally, this study included a wide range of ages. Participants ranged from approximately 6 years to 12 years old. Future studies should account for age differences to ensure effects are not due to development differences alone.

In terms of future research, it will be necessary to replicate our findings, especially with the ANT-I. Our findings regarding the relationship between sleep, medication response, and cognitive performance were correlational and therefore cannot be interpreted as casual. Future research would benefit from applying a moderator/mediator analysis. Another important area for future research would be to examine how improvements in cognitive processes as a result of treatment with stimulant medication translate into long term academic and functional outcomes. As previously mentioned, the long term academic outcomes of stimulant treatment are inconclusive, with many studies suggesting stimulant medication does not directly translate into long term academic gains (Greenhill, Halperin, & Abikoff, 1999; Pelham, 1986; Raggi & Chronis, 2006).

In summary, the current study is one of very few studies that examined the impact of extended release MPH treatment on cognitive and sleep variables, using objective measures of sleep (actigraphy and PSG). Furthermore, it is the only study to investigate whether extended release medication enhances attention performance by using the Attention Network Task-Interactive (ANT-I; Callejas et al., 2005). Similar to previous research the current study's findings indicate that extended release MPH is effective at improving cognitive performance, but also has negative effects on sleep. Our findings also indicate that sleep duration may influence the effectiveness of stimulant medication for executive attention in school-aged children with ADHD.

The findings of this study have several implications for the training and practice of professionals supporting children, youth, and families. For instance, Child and Youth Care Workers (CYCWs), who are on the frontlines of child and youth care are in a good position to monitor sleep, the daytime effects of sleep loss, as well as, the effects of stimulant medication

treatment. Therefore, child and youth professionals need to be adequately trained in regards to ADHD, sleep, and the effects of stimulant medications. Reporting sleep can be particularly important for children with ADHD starting stimulant medication treatment in care (e.g., group homes) where professionals are taking on the role of caregiver. If educated about the relationship between ADHD, sleep, and stimulant medication, child and youth professionals can then become advocates for children with ADHD to ensure each child receives the treatment which is best suited for them.

Conclusions

Given the high prevalence of children affected by ADHD and the many areas impacted by the disorder (behaviour, learning, social, etc.), effective treatment for ADHD is essential. Prescribing physicians and psychiatrists typically apply a cost-benefit analysis when considering medication as a treatment for ADHD. The goal is to enhance the benefits of the medication (i.e., reducing the core symptoms of ADHD and improving deficits in cognitive functioning) while trying to minimize its side-effects. From our study and others like it, we know that long lasting stimulant medication such as Biphentin® effectively enhances specific cognitive abilities such as alerting and executive attention, working memory and academic productivity. On the other hand, we know that along with these positive effects come negative sleep effects, specifically a reduction in sleep duration. Most importantly, we also found that sleep duration appears to impact the effectiveness of medication on some attention processes. Together with previous research, this study highlights the need for clinicians, parents, teachers, and child and youth professionals to monitor sleep when working with children with ADHD on stimulant medications. It is evident that current treatment practices with stimulant medications are very effective. However, if better sleep duration is associated with better medication response, then it

needs to be determined whether treating sleep problems first may be a more effective treatment for ADHD in school-aged children.

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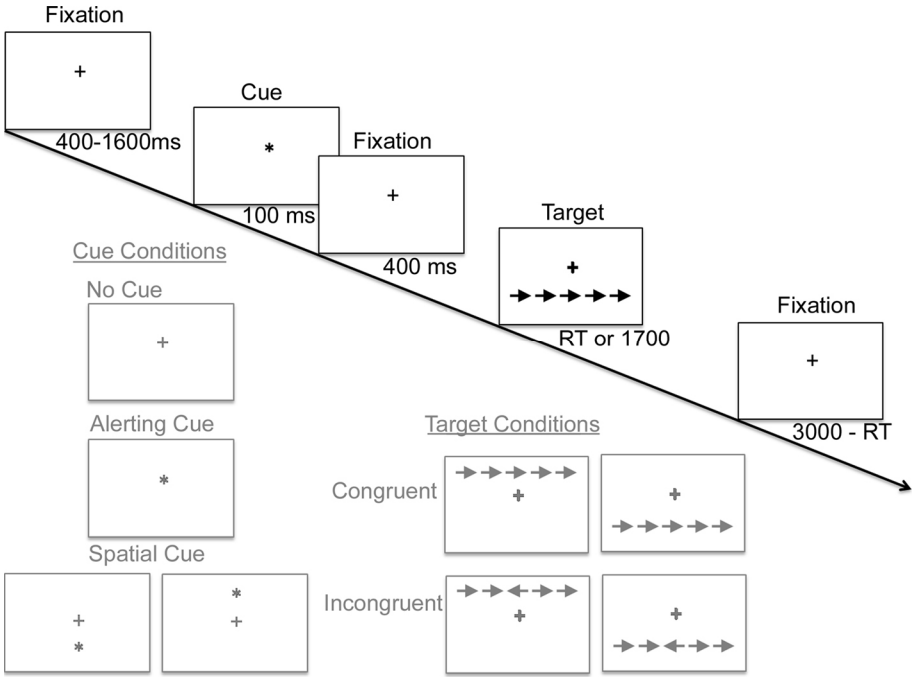
Appendix A
Attention Network Task – Interactive (Callejas et al., 2005)



Appendix B

MEMORY ASSESSMENT – Version 1
Digit Span - Forward

Participant ID: _____ Date: _____

Examiner: _____ Study Week: Med 1, Med 2, F/U Testing Session: 1 2

Instructions: I am going to say some numbers. Listen carefully, and when I am through, you say them right after me.

Start: Item 1 (Administer one per second)

Discontinue: After failure on both trial 1 and 2.

Scoring: 2 points if the child passes both trials, 1 point if passes one trial, 0 points if fails both trials (include in the score items A-C, as well as 1-24 for a possible total of 27)

Trial		Trial Score	Item Score
1	2-9	0 1	0 1 2
	4-6	0 1	
2	3-8-6	0 1	0 1 2
	6-1-2	0 1	
3	3-4-7-1	0 1	0 1 2
	6-1-5-8	0 1	
4	8-4-2-3-9	0 1	0 1 2
	5-2-1-8-6	0 1	
5	3-8-9-1-7-4	0 1	0 1 2
	7-9-6-4-8-3	0 1	
6	5-1-7-4-2-3-8	0 1	0 1 2
	9-8-5-2-1-6-3	0 1	
7	1-6-4-5-9-7-6-3	0 1	0 1 2
	2-9-7-6-3-1-5-4	0 1	
8	5-3-8-7-1-2-4-6-9	0 1	0 1 2
	4-2-6-9-1-7-8-3-5	0 1	
Total Score			

Appendix C

Digit Span - Backward

Participant ID: _____ Date: _____

Examiner: _____ Study Week: Med 1, Med 2, F/U Testing Session: 1 2

Instructions: Now I am going to say some more numbers, but this time when I stop, I want you to say them backward. For example, if I say 8-2, what would you say?

If correct, say "That's right".

If incorrect, say "No, you would say 2-8. I said 8-2, so you say it backward; you would say 2-8.

Now try these numbers. Remember you are to say them backward: 5-6" (give no help on this one whether correct or not)

Start: Item 1 (Administer one per second)
Discontinue: After failure on both trials of one item.
Scoring: 2 points if the child passes both trials, 1 point if passes one trial, 0 points if fails both trials (include in the score items A-C, as well as 1-24 for a possible total of 27)

Trial		Trial Score	Item Score
Sample: 8-2			
5-6			
1	2-5	0 1	0 1 2
	6-3	0 1	
2	5-7-4	0 1	0 1 2
	2-5-9	0 1	
3	7-2-9-6	0 1	0 1 2
	8-4-9-3	0 1	
4	4-1-3-5-7	0 1	0 1 2
	9-7-8-5-2	0 1	
5	1-6-5-2-9-8	0 1	0 1 2
	3-6-7-1-9-4	0 1	
6	8-5-9-2-3-4-2	0 1	0 1 2
	4-5-7-9-2-8-1	0 1	
7	6-9-1-6-3-2-5-8	0 1	0 1 2
	3-1-7-9-5-4-8-2	0 1	
Total Score			

Appendix D

Finger Windows – Forward

Participant ID: _____ Date: _____

Examiner: _____ Study Week: Med 1, Med 2, F/U Testing Session: 1 2

Instructions: This card has holes like windows. I am going to put the end of my pencil into one window and then another. When I am done, I want you to do the same thing with your finger. Let's try one. Wait to I say "Begin" before you start.

Start: Item 1 (Administer one per second)
Discontinue: After 3 consecutive errors
Scoring: One point for each correct sequence

	Forward	Score 0 or 1
A	3	
B	1	
C	7-9	
1	1-7	
2	3-6	
3	7-9-8	
4	3-1-7	
5	6-5-2	
6	1-7-9-3	
7	3-5-4-8	
8	9-5-8-6	
9	8-5-4-7	
10	4-5-2-6	
11	2-4-7-3-1	
12	7-6-8-9-2	
13	7-5-4-8-2	
14	2-8-4-5-7	
15	5-7-2-6-4	
16	1-3-7-4-2	
17	4-5-7-2-8-4	
18	3-6-5-4-1-2	
19	6-5-9-4-3-2	
20	1-9-3-6-7-5	
21	5-4-8-2-8-4-5	
22	9-6-5-8-3-9-1	
23	3-1-6-9-7-3-5-6	
24	3-5-2-9-6-5-8-4	
	Total Score	

Appendix E

Finger Windows - Backward

Participant ID: _____ Date: _____

Examiner: _____ Study Week: Med 1, Med 2, F/U Testing Session: 1 2

Instructions: Now, I am going to put my pencil through some more windows, but this time when I stop, I want you to do them backwards. For example, if I do this (2-4), what would you do? If correct, say "That's right". If incorrect, say "No, you would do this (4-2). I did this (2-4), so you do it backward; you would do this (2-4). Now try these ones. Remember you are to do them backward."

Start: Item 1 (Administer one per second)

Discontinue: After 3 consecutive errors

Scoring: One point for each correct sequence

Backward			Score 0 or 1
		Answer	
A	2-4	4-2	
B	7-9	9-7	
C	1-3	3-1	
1	3-9	9-3	
2	1-5	5-1	
3	1-3-2	2-3-1	
4	9-7-1	1-7-9	
5	7-9-4	4-9-7	
6	5-8-6-2	2-6-8-5	
7	1-6-2-9	9-2-6-1	
8	3-5-4-6	6-4-5-3	
9	7-6-9-4	4-9-6-7	
10	9-5-2-7	7-2-5-9	
11	4-5-3-1-7	7-1-3-5-4	
12	1-6-4-5-2	2-5-4-6-1	
13	9-6-8-7-2	2-7-8-6-9	
14	3-9-4-6-8	8-6-4-9-3	
15	9-8-5-4-6	6-4-5-8-9	
16	7-9-8-6-4	4-6-8-9-7	
17	1-6-8-3-9-5	5-9-3-6-1	
18	1-4-6-8-5-7	7-5-8-6-4-1	
19	7-5-8-1-2-3	3-2-1-8-5-7	
20	3-7-1-5-6-4	4-6-5-1-7-3	
21	6-4-8-1-9-5-4	4-5-9-1-8-4-6	
22	7-5-4-6-9-8-1	1-8-9-6-4-5-7	
23	9-7-6-1-3-5-4-2	2-4-5-3-1-6-7-9	
24	1-6-2-7-8-5-3-9	9-3-5-8-7-2-6-1	
Total Score			

Appendix F

Participant ID: _____ Date: _____

Examiner: _____ Study Week: Med 1, Med 2, F/U Testing Session: 1 2

4 +5	5 +9	3 +3	4 +9	1 + 6	3 +9
1 +2	8 +8	1 +1	6 +6	2 +5	7 +9
4 +6	5 +8	3 +5	6 +8	4 +4	7 +7
1 +5	2 +9	5 +5	4 +7	6 +7	1 +9
8 +9	1 +7	5 +6	4 +8	1 +4	7 +8
1 +3	2 +3	2 +4	5 +7	2 +6	3 +7
3 +6	3 +8	9 +9	2 +2	3 +4	2 +8
6 +9	2 +7	1 +8	2 +6	6 +6	4 +6