Sleep and Pediatric ADHD: Effects of Sleep Restriction on Performance on the Multi-Source Interference Task

By

Gabriela de Queiroz Campos

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Thesis

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Date _____ _____

Mary A. Carskadon, Advisor

Approved by the Department of Cognitive, Linguistic and Psychological Sciences

Date _____ _____

David Badre, Director of Graduate Studies

Preface and Acknowledgements

I took on the role of primary research assistant on the project for which I am submitting this thesis. I was involved in helping with preparation of study materials, data collection, entry, and analysis. My primary responsibility was creating and executing a framework through which to analyze the Multi-Source Interference Task data. My principal intention in conducting this investigation was to further our understanding of attention-deficit/hyperactivity disorder and how it relates to sleep.

I could not have completed this project without the outstanding mentorship of both Dr. Jared Saletin, the principal investigator, and Dr. Mary Carskadon, my thesis advisor. I have both of them to thank for guiding me through this process and for giving me the opportunity to be involved in sleep research. You were both much more than just faculty advisors. I also want to thank the wonderful teams both at the Bradley Sleep Lab and in the CLPS Department, without which this thesis could not have been done.

I also want to acknowledge my friends and family for all their love, support, and encouragement. To the people of Pitman and 341, Danai, the 2019 first-year cohort, Jasdeeb, and the Grill: thank you.

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Introduction

This thesis examines the cognitive consequences of sleep loss in the context of attention-deficit/hyperactivity disorder (ADHD) symptom severity. As suggested by the resemblance of the well-known behavioral signs of obtaining poor sleep (such as difficulty staying on task, forgetfulness, and lowered cognitive performance) and symptoms of ADHD, it is likely that this neuropsychiatric disorder has strong ties to sleep. Further, not only do children with ADHD very often present with sleep difficulties, but there is also strong evidence to suggest that poor sleep might be exacerbating ADHD symptom presentation in children. We sought to probe this association by further exploring how disrupting sleep alters ADHD-relevant cognitive processes. In the present investigation, we used a cognitive interference task in conjunction with an experimental wake extension protocol in order to better parse how exactly differences in sleep might be affecting presentation of ADHD in this domain. Previous studies have shown that children with more severe ADHD do poorly on cognitive interference tasks when compared to typically-developing controls, our goal was to explore the effects of shortened sleep duration on that performance as a function of ADHD symptom severity across children.

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder and is currently one of the most common neuropsychiatric conditions diagnosed in childhood, with over 11% of children in the United States carrying a diagnosis (NIMH, 2016). Children with ADHD are commonly characterized by one of three main disorder subgroups, as defined by their symptoms: hyperactive-impulsive, inattentive, or combined presentation (see below for index of symptoms). Hyperactivity and impulsivity are characterized by behaviors such as interrupting and having difficulty playing quietly, waiting one's turn, and staying in one's seat. Inattention, on the

other hand, is indicated by symptoms such as having trouble listening, forgetfulness, making careless mistakes, and difficulty following instructions. Epidemiological studies in the United States estimate that about 30% of children and adolescents diagnosed with the disorder are of the inattentive subtype, 9% are hyperactive-impulsive, and 60% present with a combined type (ADHD Institute, 2020). While these behaviors that characterize ADHD are common in childhood, they become clinically relevant if they are determined to be severe and frequent enough that they interfere with daily functioning.

The heterogeneous nature of ADHD— arising from not only three diagnostically distinct symptom presentations but also from widely varying severity— is important to highlight. The diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association & American Psychiatric Association, 2013) is evidence of this heterogeneity. According to the DSM-V, individuals under the age of 17 need to show six or more symptoms from a previously determined list to be deemed "inattentive" and six or more symptoms from a different list to be deemed "hyperactive-impulsive" (see below for symptom lists). Another criterion for ADHD on the DSM-V list is that the individual must also have shown inattentive or hyperactive/impulsive symptoms for at least six months before the age of twelve in order to be diagnosed.

Inattentive Symptoms	**Hyperactive-Impulsive Symptoms**
Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.	Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
Often has trouble holding attention on tasks or play activities.	Often leaves seat in situations when remaining seated is expected.
Often does not seem to listen when spoken to directly.	Often fidgets with or taps hands or feet, or squirms in seat.

Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).	Often unable to play or take part in leisure activities quietly.
Often has trouble organizing tasks and activities.	Is often "on the go" acting as if "driven by a motor".
Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).	Often interrupts or intrudes on others (e.g., butts into conversations or games)
Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).	Often blurts out an answer before a question has been completed.
Is often easily distracted	Often has trouble waiting their turn.
Is often forgetful in daily activities.	Often talks excessively.

Table 1: This symptom list is from the DSM-V (American Psychiatric Association & American Psychiatric Association, 2013).

As shown in **Table 1**, the DSM offers an inflexible definition of whether an individual qualifies for diagnosis. Someone who shows only four symptoms from either list would not be considered to have ADHD by these criteria and neither would someone who has missed the twelve-years mark and started presenting symptoms only when they were thirteen years old. Both of these hypothetical children are considered typically-developing in research studies, which we do not believe to be a fair assessment.

While these categorical and fixed classifications may be useful in a clinical context, they show a clear limitation in experimental psychology research where more nuance and a greater specificity in description is required. For example, we would not expect an individual showing all nine inattentive symptoms to have a similar presentation to someone who shows six hyperactive-impulsive symptoms. Yet, in ADHD research, due to a reliance on dichotomous group studies (Lansbergen et al., 2007), it is common practice to group these two individuals together. Individuals in this group are then to be compared to a group of "controls," in which someone

presenting with many but not "enough" symptoms of ADHD— such as someone showing only four inattention symptoms— would be placed. Thus, studies of the disorder that separate participants into groups based on presence of diagnosis or lack thereof, do not reflect the reality of ADHD presentation and are insensitive to the individual, symptomatologic nuances that exist in these populations.

There are alternative ways to conceptualize ADHD in a research framework which we have decided to employ in this investigation. There are several disorder assessment tools that index symptom severity. These include the Child Behavior Checklist Attention Problems Scale, the Vanderbilt ADHD Diagnostic Scale, symptom counts from diagnostic interviews (e.g. the K-SADS-PL), and the Conners Symptom Questionnaire (Gaba & Giordanengo, 2019; Kaufman et al., 1997). Tools like these better reflect the heterogeneity in ADHD presentations by allowing us to assess the disorder on a continuum along both the hyperactive-impulsive and inattentive symptom subgroup axes. Further, scales like the Conners, which we have chosen for this present study, allow researchers to compare research subjects based on standardized, quantified symptom severity scores (Conners, 2011), making it a particularly useful tool to probe the correlates of ADHD severity free of diagnostic boundaries.

ADHD and Cognitive Interference

Although the cognitive profile of attention-deficit/hyperactivity disorder can take many forms, there are some key neurocognitive deficits that individuals with the disorder usually present with. These deficits include, most prominently, problems with working memory (Schreiber et al., 2014), slowed reaction time (Pievsky & McGrath, 2018), tendency to provide wrong responses with perseverance and impairment in response inhibition (Ahmadi et al., 2014). These deficits can

be probed and better understood by using laboratory cognitive-behavioral tasks specifically designed to target each cognitive process (Meier & Kane, 2013).

Literature on ADHD has reflected a particular focus on cognitive interference as a central aspect of the cognitive neuroscience model of the disorder (Mullane et al., 2009). Children with more severe symptom presentations of ADHD have shown difficulty on a variety of cognitive interference tasks (Carter et al., 1995; Kóbor et al., 2015; Mullane et al., 2009; Shin, 2005). These difficulties manifest as slowed reaction time on incongruent trials (Carter et al., 1995), slowed reaction time for accurate responses (Kóbor et al., 2015), increased errors due to interference (Shin, 2005), and lowered interference control measured by performance efficiency (Mullane et al., 2009). Given the hallmark functional deficits that are observed in individuals with the disorder, it follows that they would have more difficulty successfully completing tasks that require inhibitory control and suppression of interference (Kóbor et al., 2015; Shin, 2005; Stins et al., 2005). This deficit in performance supports a view that these children have a difficult time filtering out competing information and consequently suppressing a dominant response in order to successfully complete the task at hand (Mullane et al., 2009). Some authors suggest that indeed the commonly observed deficits in working memory in children with ADHD (Ahmadi et al., 2014; Pievsky & McGrath, 2018; Schreiber et al., 2014) are mediated by limited attentional resources and are therefore driving poor performance in tasks that require solving stimulus incongruence, leading to cognitive interference (Stins et al., 2005). Some commonly administered tasks that probe deficits in these functions include the Stroop task, the Simon task, and the Eriksen Flanker task (Stins et al., 2005).

In all three of these tasks, a participant is presented with stimuli that activate two competing channels of information (Stins et al., 2005). The individual must then resolve that cognitive

competition in order to successfully respond to the tasks' demands. The Stroop task is very commonly used as a cognitive interference task in psychology studies. In this task, participants are asked to name aloud the color in which a stimulus word is printed. Cognitive interference arises from the fact that, in incongruent trials, the stimulus word reads a certain color name that does not match the color it is printed in. The individual must then resolve the competing stimuli of what the word reads and what color it's printed in order to give the correct response. The incongruence between the word/color stimulus leads to increased error rate and reaction times (Stins et al., 2005).

The Eriksen Flanker and Simon tasks also probe the participants' ability to engage interference control (Stins et al., 2005). In the Simon task, participants must identify target items with a left or right keypress, regardless of the object's position on the screen. In this task, cognitive interference is expected from an incongruence between the target's position on the screen and the position of the correct key. The Eriksen Flanker task requires that participants neglect flanking stimuli (usually arrows), regardless of directional congruence with the central target, and focus only on a center object. Both tasks rely on executive functions similar to those needed for the Stroop, but that are often impaired in ADHD (Stins et al., 2005). **Figure 1** below illustrates the stimuli presented in each of these tasks.

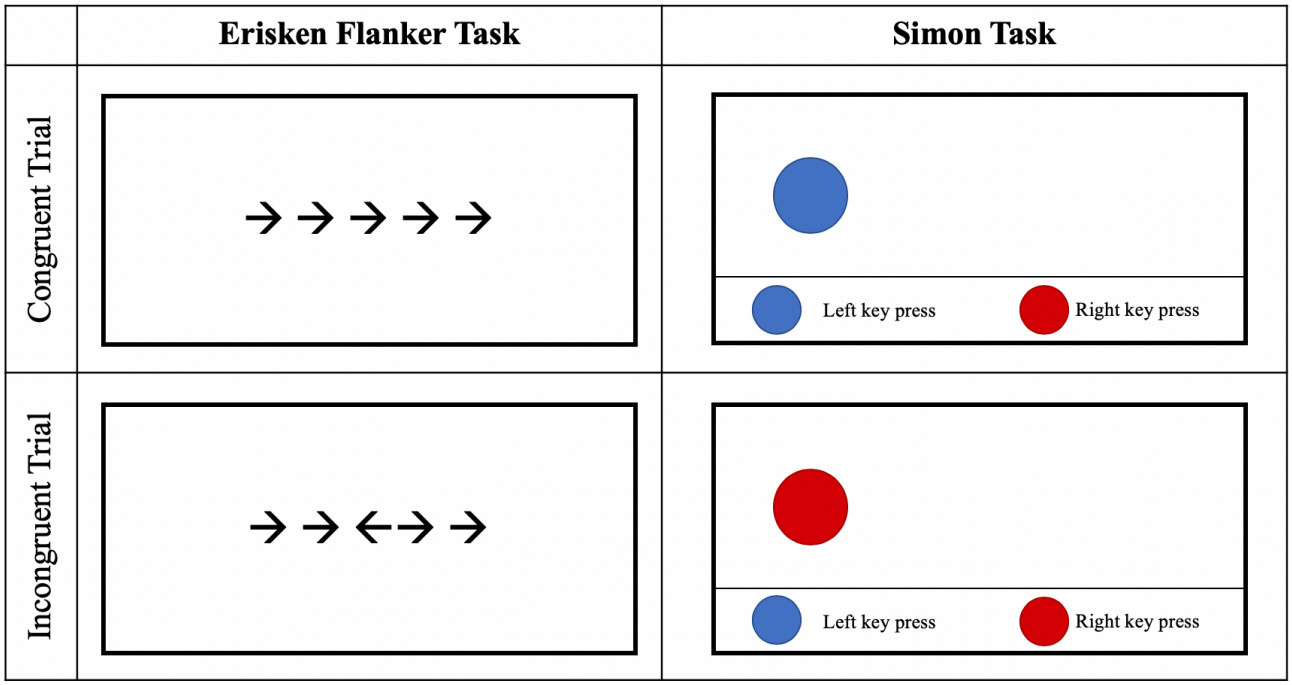

Figure 1: Illustration of common Eriksen Flanker and Simon Task stimuli in both congruent (top row) and incongruent (bottom row) trial types.

It is also important to highlight how performance is quantified in these tasks. Each of these cognitive exercises has one source of interference and gives the researcher a choice of using either reaction time or accuracy as their primary behavioral measure of performance. However, Mullane (2009) argues that considering either in isolation is not a proper way of assessing performance. For example, faster reaction times could be a bad measure as they could mean the subjects are responding faster but making more mistakes. Similarly, lower error rate can also be an equally improper measure of performance efficiency as the participants might be taking very long to respond. The most desirable option, she posits, is to use a measure that combines accuracy and reaction time (Mullane et al., 2009), such as considering reaction times only on accurate trials. By doing so, our results reflect a better sense of the cognitive profile of the participants by being sensitive to performance features like speeding to error or slowing to accuracy. Meta-analyses assessing the performance of children with ADHD on cognitive interference tasks versus typically-developing controls have yielded mixed results in the effect sizes of difference in performance.

The results become clearer— showing decreased performance in the ADHD groups— once frequency outcomes such as accuracy are removed and more nuanced, time-based variables (such as reaction time in accurate trials) are taken into account (Mullane et al., 2009). This was a methodological issue that we took into consideration when designing our experimental approach.

According to current literature, children with ADHD do in fact show poorer performance on these types of cognitive interference tasks —Stroop (Carter et al., 1995; Kóbor et al., 2015; Shin, 2005), Simon and Flanker (Mullane et al., 2009; Stins et al., 2005). For example, in a study conducted in 2015 by Kóbor and colleagues, children with ADHD showed slower reaction times (despite similar accuracy) than typically-developing controls when completing a Stroop task. These increased reaction times, Kóbor suggests, might be a result of increased allocation of effort during early processing phases involved in conflict resolution. They suggest that this is a clear demonstration of impaired information processing, more so than a specific impairment in inhibition of the incorrect response, in symptomatic youth (Kóbor et al., 2015). While this impairment doesn't necessarily manifest in their error rates, it is clear from the reaction times that these individuals are not performing similarly on the Stroop. This increase in reaction time observed in more symptomatic youth is also vulnerable to cognitive interference, meaning that the observed effect is exacerbated in incongruent trials (Kóbor et al., 2015; Shin, 2005). This is likely due to the increased neurocognitive vulnerability of children with ADHD being faced with the more cognitively demanding characteristic of these trials (Stins et al., 2005).

Convergent evidence was reported by Mullane, who conducted a meta-analysis of studies on children with ADHD's performance on Simon and Eriksen Flanker tasks compared to typically-developing controls. In their meta-analysis, Mullane and colleagues found that children with a diagnosis of ADHD showed slower reaction times on these tasks than typically-developing

controls (Mullane et al., 2009). Much like Kóbor, they also found that this effect was exacerbated in incongruent trials, which are designed to cause more cognitive interference, suggesting that children with ADHD are more sensitive to congruence effects as they show "weaker interference control." She concludes that children with ADHD indeed might be showing these deficits in performance due to a failure in recruiting the necessary attentional resources required to resolve interference (Mullane et al., 2009).

Combining Sources of Interference: The Multi-Source Interference Task (MSIT)

The Simon, Eriksen, and Stroop tests described above, are helpful at capturing a single, specific source of interference each– spatial position, flanker effects, and color name, respectively. However, in order to best capture the complex behavior children with ranging severity of ADHD symptom severity, we chose a test which combines multiple sources of interference called the Multi-Source Interference Task, or MSIT. The MSIT, as created by George Bush and colleagues at Harvard Medical School, is a cognitive interference task designed with the intent of targeting goal and novelty detection, motor response selection, and reward signaling (Bush et al., 2003).

The task itself, as it was designed, is quite simple. Subjects are shown groups of three numbers (the identity of which can be 0, 1, 2, or 3) in a line. Two of these are the same and one is different (for example, 131). The person doing the task must answer which number is the different one via a specific button press (in the 131 example the correct answer would be 3, so the subject would press the corresponding button). In congruent trials, the identity of the different number matches its position on the screen. One example of a congruent trial would be 003, where the different number is 3 and it is in the third position. In incongruent trials, however, the different number does not match its position in the order on the screen. An example of an incongruent trial would be 212. In this example, the correct answer would be 1, as it is the number that is different,

but the number is not in the first position, it is in the second position. In other words, in these trials, the identity and position of the target number are incongruent. See illustration of stimuli in **Figure 2** below.

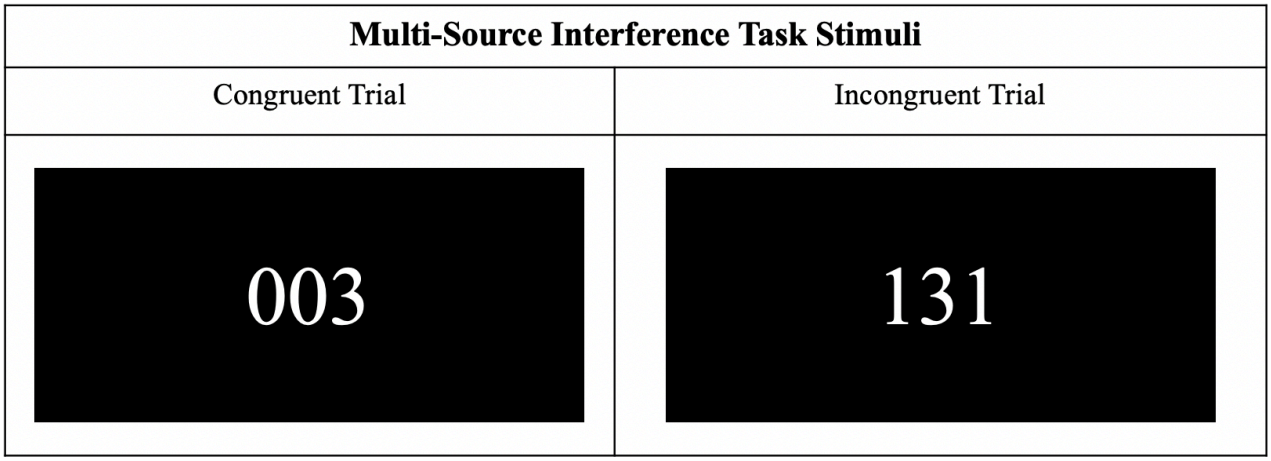

Figure 2: Illustration of MSIT task stimuli in both congruent (left) and incongruent (right) trial types.

The MSIT was originally constructed by combining elements of several of the aforementioned cognitive interference tasks in order to create an even more cognitively taxing exercise that relies on multiple sources of interference. For example, there is a flanker effect in incongruent trials as the numbers that flank the target stimulus are incongruent with the right answer. In these trials, the target number's position on the screen does not match its identity, producing a Stroop effect, nor does it match the position of the target keypress, producing interference like that of the Simon task. As measured by reaction time, the interference effect of the MSIT was shown to be greater than that achieved using classical single-interference paradigms, rendering his goal of making a more robust interference task quite successful (Bush et al., 2003). Specifically, the reaction time interference effect produced by the MSIT was around 200-300ms, compared to averages around 100ms seen in prior work using a Stroop task (Davidson et al., 2003). Bush and his colleagues have established a reliability of the MSIT with stable results within

subjects, according to both neuroimaging and performance data, without needing to rely on group data (Bush & Shin, 2006). They suggest that the MSIT can be a useful tool in the study of human cognition and psycho-pathophysiology.

The MSIT was also explicitly designed as an fMRI task used to probe a specific brain circuit capable of being monitored with neuroimaging. Different component parts of the cingulo-frontal-parietal network (CFP) have been consistently implicated in ADHD (Bush, 2010), and the way in which the task was structured aims to target these specific neural regions. Bush's work has focused the anterior cingulate cortex (ACC) as a central node for cognitive interference in ADHD. More specifically, their work has focused on the dorsal anterior cingulate cortex (dACC)— a key subregion of the ACC— and its role in cognitive interference. The dACC has shown reliable hypoactivation in individuals with ADHD during completion of cognitively demanding tasks (Bush, 2010; Hart et al., 2013). Therefore, the MSIT was designed in a way that would ensure greatest activation of the dACC, as measured through fMRI, when participants were completing the task. By probing this region directly, Bush's team hoped to create a task that would be sensitive to this hypoactivation, therefore, becoming a good indicator of the presence and perhaps the severity of the disorder.

As discussed above, Bush found that subjects show increased reaction times and error rates in the incongruent condition in contrast to the congruent one (Bush, 2010; Bush & Shin, 2006), which is known as a "congruence effect" or an "interference effect." Under F.C. Donders' classic framework, it follows that the incongruent condition requires more mental processing than the congruent one, which makes logical sense and explains the longer reaction times (Donders, 1969). Bush's findings therefore support the conclusion that the MSIT indeed produces cognitive interference in testing subjects. Based on the results of the studies by Mullane and Kóbor, showing

that children with ADHD perform worse on interference tasks, one would therefore expect youth presenting with more severe ADHD symptoms to have decreased performance on the MSIT when compared to typically-developing controls. These results would also be expected to reflect a congruence effect, showing even worse performance on incongruent trials (Kóbor et al., 2015; Mullane et al., 2009).

The imaging data also corroborates the reaction time findings. Indeed, Bush and his team found an association between greater reaction times and greater activation of the dACC, meaning that this region was more active in the more "demanding" trials of the task (Bush, 2008). If individuals with ADHD show a hypoactivation of this region, it would be expected that they would have more difficulty with the incongruent trials of the MSIT as Bush's results suggest that greater activation of the dACC is involved in resolving stimulus incongruence. It is possible that those with more severe symptom presentations would show this effect to an even greater extent if their pathophysiology, like their symptoms, presents with greater magnitude.

There are several advantages to using this task over its predecessors and other cognitive interference protocols. As previously mentioned, the Simon, Eriksen Flanker, and Stroop tasks, all provide a single, distinct source of interference each. Therefore, performance on any one of these tasks cannot predict performance on the others (Stins et al., 2005). Furthermore, no single one of these tasks has reliably and significantly activated the fronto-parietal regions associated with the neuroetiology of ADHD. The MSIT, on the other hand, maximally activated these regions, making it a better probe and more direct probe of the disorder. Indeed, the task was specifically designed to have near-diagnostic replicability in individuals with the disorder, as Bush originally intended for it to be used as a diagnostic tool (Bush, 2008). The MSIT, therefore, is perfectly suited to be used in studies of attention-deficit/hyperactivity disorder.

The Multi-Source Interference Task can also be more widely administered as it is not language-specific (unlike a color Stroop, for example), so it need not be translated if it is to be administered to people of different cultures. It is also easily explained and straightforward enough that people of all ages and cognitive abilities can learn it, making a robust test that can be used to compare a wide variety of populations. The MSIT is also completely standardized, allowing researchers to administer it identically to multiple subjects and easily compare the results (Bush & Shin, 2006).

The nature of the MSIT also offers temporal stability as the task can be repeatedly administered to the same subject without losing its interference effect (Bush & Shin, 2006).Therefore, the MSIT can be administered longitudinally in order to assess a participant's evolution in performance over the course of potential treatment regimens or over more long-term research protocols. There's also value in the MSIT being based on cognitive tasks that are tried and true in psychological experiments. This established and proven set of tasks that serve as the basis for its design— the Stroop, Simon, and Eriksen Flanker Tasks— have been tested and refined over countless trials and experiments (Stins et al., 2005), supporting the reliability of the final product. The MSIT, however, shows an even more robust interference effect than its predecessors (Bush, 2008; Bush & Shin, 2006). The increased effect might make this task more sensitive to the resulting deficits of ADHD symptoms, leading to more nuanced outcomes.

Sleep, ADHD, and the MSIT

Reports of sleep disturbances and difficulties are common in children and young adolescents with psychiatric disorders. In fact, some of the hallmark traits observed in children with attention-deficit/hyperactivity disorder are problems with and surrounding sleep (Baddam et al., 2018). Although sleep problems are not listed as a symptom of ADHD in guides such as the

DSM-V, these children present with an estimated five times as many sleep issues compared to typically-developing controls (Kothare & Kotagal, 2011). These usually manifest as increased sleep onset latency, lowered sleep efficiency, bedtime resistance, daytime sleepiness, and less total sleep time (Baddam et al., 2018; Kothare & Kotagal, 2011).

In a study of elementary school children comparing sleep in those with ADHD with a group of controls, Owens and colleagues (2000) found that children with the disorder had significantly more disturbed sleep on all Sleep Habits Questionnaire subscales, a survey filled out by parents about their children's sleep. The researchers obtained sleep measures through a comprehensive sleep screening battery and used the DSM-IV criteria as a basis for their ADHD neuropsychiatric assessments (Owens et al., 2000). The results of Owens' study are further confirmed by a number of papers across both sleep and ADHD literature: children with ADHD are getting poorer sleep than their typically-developing counterparts (Baddam et al., 2018; Owens et al., 2000).

In my undergraduate honors thesis investigation, we also further explored the dimensions of sleep that are most closely associated with ADHD symptom presentation in youth (Campos et al., 2019). We addressed the lack of long-term studies objectively measuring naturalistic sleep patterns in these individuals by monitoring their sleep-wake patterns over a period of twelve weeks using actigraphy. By taking this approach, we were able to better discern where the differences in sleep were occurring in more symptomatic youth. As a result, we observed that children presenting with more severe hyperactive and impulsive symptoms, as assessed by the Conners-3, showed more irregular sleeping patterns. Moreover, we identified that, indeed, symptom severity was varying monotonically with a dimension of sleep, namely sleep regularity (Campos et al., 2019). These results have two important implications: first, that ADHD is associated with poor sleep; second, as opposed to other studies using dichotomous categorization of ADHD, the Conners-3

proved to be an effective index of symptom severity in a way that varied directly with a measure of sleep.

It is quite clear from this data and those above it that sleep and ADHD symptomatology in children and adolescents are inextricably related. However, what is not clear is a more detailed outline of the dynamics of the interplay between the two. We do not yet know if more severe symptom presentation driving greater changes in sleep or are changes in sleep leading to more severe symptom presentation in these youth. It is also still unclear what the consequences of poor sleep are for children with symptoms. This cannot be discerned from our past analyses. Accordingly, we have designed the current study in order to add another piece to our understanding of how sleep and ADHD are related. One of our goals with the current investigation is to assess whether shortened sleep duration can lead to differences in performance in a cognitive interference task based on symptom severity. The task, the MSIT, specifically targets processes and brain structures associated with the pathophysiology of ADHD. By manipulating sleep duration preceding completion of the task, we can better discern the direct effects of sleep on these processes, giving us greater insight into the behavioral presentation of ADHD in youth.

Sleep restriction has been shown to affect performance on cognitive interference tasks in youth. In a study conducted in 2013 by Molfese and colleagues, the subjects participated in a mild sleep restriction protocol for a whole week which was directly followed by a behavioral task battery. The researchers administered a series of cognitive interference tasks, including a Stroop, while collecting EEG data. They found that, compared to a week of typical sleep, children who had shortened sleep showed decreased EEG amplitude when completing cognitive interference tasks (Molfese et al., 2013). Interestingly, additional studies have found that, although subjects show decreased performance (measured as reaction time) on the Stroop and other cognitive

interference tasks following acute sleep deprivation protocols, the congruence effect does not seem to change based on this manipulation of sleep (Cain et al., 2011; Sagaspe et al., 2006). According to these studies' findings, sleep curtailment does not lead to increased cognitive interference in the incongruent trials of interference tasks. This is an unexpected, yet quite interesting finding. However, these studies' subjects were all typically-developing individuals. These results might not be the same in individuals with increased ADHD symptom severity.

The cognitive consequences of sleep loss— such as difficulty staying on task, forgetfulness, and lowered cognitive performance— look just like the cognitive difficulties seen in ADHD (American Psychiatric Association & American Psychiatric Association, 2013). Prompted by these clear behavioral similarities between sleep deprived individuals and individuals with ADHD, Saletin authored a meta-analysis that uncovered a functional homology between ADHD and sleep deprivation that could further support this point (Saletin et al., 2017). In this systematic review, fMRI data from several studies was compiled and compared to examine the similarities between the brains of acutely sleep deprived individuals and children with ADHD. A common neural signature was found: sleep loss and ADHD were both marked by decreased activity in networks associated with executive functioning and increased activity in networks associated with cognitive lapses. Important information, however, existed also in differences, rather than just the similarities, between these two groups. In the group containing sleep deprived, typically-developing individuals there was greater activation in the same subcortical, thalamic regions that promote arousal and goal-directed behavior that George Bush targeted with the MSIT in response to sleep loss (Bush, 2008). This activation was not observed in individuals with ADHD (Saletin et al., 2017).

We posit that the thalamic activation has a compensatory function to the sleep deprivation, its purpose being to mitigate the lapse-promoting effects of curtailing sleep and counteract the destabilizing of frontal networks (Soehner et al., 2018). This compensatory mechanism might not be present to counteract the hypoactivation of regions like the dACC, which is likely responsible for the task lapses characteristic of the presentation of ADHD (Bush, 2008). In other words, in ADHD patients, lapses are not dampened by compensatory activity in thalamic, arousal-promoting regions. Thus, this renders the cognitive performance of individuals with the disorder more likely to be more sensitive to sleep loss.

Changes in sleep might also exacerbate the severity of ADHD symptom presentation in youth. Important evidence for this is provided by Huang and colleagues in a paper about obstructive sleep apnea (OSA) and ADHD. This study reports that, in children with a comorbid diagnosis of ADHD and mild sleep-disordered breathing, an adenotonsillectomy— a surgical procedure that targets OSA and involves removal of both the adenoids and tonsils— improved some ADHD symptoms more effectively than pharmaceutical treatment with methylphenidate (MPH). By directly improving sleep in these individuals through treatment of their OSA, the authors were able to see significant, positive effects on their ADHD presentation. The ADHD symptoms diminished by treating OSA were most likely due to poor sleep (Huang et al., 2007). Another study also found that children with short sleep duration were at a greater risk for a series of behavioral problems, including increased ADHD symptoms (Pesonen et al., 2010). Therefore, if we conclude that shortened sleep duration is resulting in children being more hyperactive or more inattentive, it is likely that, under these sleep curtailment conditions, they will perform worse on cognitive interference tasks, this includes being more vulnerable to congruence effects.

It is not novel to anyone who has had to go to work after a night of poor sleep that shortened sleep duration can lead to decreased cognitive performance. Indeed, Short and colleagues illustrated that insufficient sleep can directly, negatively impact neurobehavioral functioning (Short & Banks, 2014). Typically-developing and symptomatic youth alike suffer the consequences of not obtaining a full night of sleep. However, it is also evident that the cognitive profile of someone who has not obtained enough sleep presents quite similarly to the hallmark cognitive profile of someone with attention-deficit/hyperactivity disorder. This similarity persists at the neural level, as the brain of an individual with ADHD looks quite similar to that of a sleep deprived, typically-developing control (Saletin et al., 2017). This neural presentation is marked by a possible absence of compensatory mechanisms that counteract sleep loss in individuals with the disorder. Additional to or perhaps because of this, poor sleep exacerbates ADHD symptom presentation in youth (Huang et al., 2007). This is further aggravated by sleep being a clear problem for individuals with ADHD (Baddam et al., 2018; Owens et al., 2000; Sagaspe et al., 2006). This combination of factors might render individuals with ADHD more vulnerable to changes in sleep. The magnitude of this effect is likely indexed by symptom severity, as measured on a continuum, rather than in a categorical manner (Campos et al., 2019). Therefore, we propose to investigate of the ways and the extent to which youth with more severe presentation of ADHD symptoms respond to sleep loss.

Specific Aims

This investigation is primarily concerned with how sleep loss fits into our understanding of the etiology, presentation, and severity of ADHD. As previously discussed, there is strong evidence of an association between this disorder and sleep, but we are trying to uncover more details about that relationship. Therefore, not only do we wish to investigate the relationships

between ADHD symptom severity and performance of youth on the MSIT, but we also examine how sleep curtailment affects their task performance.

The primary aim of this investigation is to use a cognitive interference task— the MSIT— within a sleep restriction protocol in order to assess how short sleep disrupts attention in children with a range of ADHD symptom presentations. Based on our current understanding, children with ADHD show worse performance on cognitive interference tasks than typically-developing controls. It has also been found that youth presenting with ADHD show decreased activity in neural circuitry that is directly involved in cognitive interference tasks. Therefore, we hypothesize that, regardless of sleep manipulation, children with more severe ADHD symptoms will show worse performance on the MSIT, as evidenced by increased reaction times in accurately responded trials.

Through the manipulation of sleep duration on the night preceding the completion of the MSIT, we also aim to better discern the direct effects of sleep on these processes, which will add important insight into our understanding of the causal relationships between sleep and ADHD symptom manifestation. Based on existing literature, people do worse on cognitive interference tasks following shortened sleep. Sleep curtailment can also exacerbate ADHD symptom presentation, and it is possible that individuals with ADHD do not have proper function of the neural systems that counteract the effects of sleep loss. Therefore, we hypothesize that children with more severe symptom presentations will show overall worse performance on the task not only at baseline, but they will also show a greater difference in performance between baseline and shortened sleep, due to their greater vulnerability to sleep loss.

The results of these analyses can have important clinical implications. By better characterizing the effects of sleep loss on the cognitive domain of ADHD, we can begin to consider sleep-based interventions for particular cases of the disorder as an alternative or complement to

pharmaceutical interventions. Attention-deficit/hyperactivity disorder is extremely common in the United States today (NIMH, 2016). By better understanding the condition we can more efficiently design interventions and treatments with the ultimate goal of minimizing its impact on people's daily lives.

Methods

This investigation was approved by the Institutional Review Board of Rhode Island Hospital. All participants' parents signed an informed consent and participants themselves provided an informed assent before enrollment in the study. Participants and their parents were given clear communication that participation was entirely voluntary and that they held the right to withdraw from the study at any point.

Participants

The recruiting process for this investigation occurred in the fall of 2017. Participants were recruited primarily through flyering in Providence, RI, and by reference of past subjects of the Bradley Sleep Lab. Past participants of other studies conducted at the Lab that fit the eligibility criteria were also reached out to as possible subjects. The results reported in this investigation reflect a sample of a total of 13 children of ages 10-13 (7F, 11.7 ± 1.28 years).

Screening

All participants were screened before enrollment in the study and a prior ADHD diagnosis was not required for inclusion. A thorough phone screen with parents for any present psychopathology was done for all participants. Children were excluded if they presented with any

comorbidities to ADHD (with the exception of Oppositional Defiant Disorder, or ODD). Additionally, a trained professional also administered the ADHD subsection of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Life Edition (K-SADS-PL) (Kaufman et al., 1997). The K-SADS is a semi-structured diagnostic interview that includes interviews with both children and parents. This double-interviewing method by a single interviewer allows for questioning of any discrepancies between child and parental report and is based on symptom lists determined by the DSM-V (Kaufman et al., 1997). This interview contains different sections that address different disorders as they present in children. The ADHD sub-section of the K-SADS was used to determine presence of specific ADHD symptoms in each participant and was not the primary diagnostic tool. Individuals were screened for stimulant medication use. All participants, with the exception of one, were medication-naïve.

Symptom Severity

Attention-deficit/hyperactivity symptom severity was determined using the Conners-3 Self-assessment. The Conners-3 is a standardized method of assessing both the hyperactive-impulsive and inattentive symptomatology of ADHD and, therefore, is a tool through which one can compare symptom severity across subjects. The Conners questionnaires are used to generate *T-Scores* (Conners, 2011). By providing a translation from behavioral presentation to a standardized, quantitative measure of symptom severity, it is an invaluable tool for performing the type of between-subject analysis we were aiming for.

Conners-3 scores are quantified so that a score of 70 or above denotes a degree of symptom presentation severity typical of diagnosable ADHD. By means of this threshold, one can use the Conners diagnostic tool to separate individuals into groups that are above or below the “clinical

limit" for the disorder. However, rather than using these prescribed cutoffs, we chose to use the continuous, standard scale of symptom severity measurement that the Conners provides for the purposes of this investigation. By doing so, we could better regress symptom severity onto different, continuous measures of MSIT performance. Additionally, according to the third edition of the Conners manual, there is "no reason to believe that there is a perceptible difference [in symptom presentation] between a *T*-score of 69 and a *T*-score of 70" (Conners, 2011). Therefore, it seems unproductive to place these individuals in completely separate, opposite groupings. We did not want the effect of variation in symptom severity to be lost in analysis, therefore, we opted for continuous coding of ADHD symptomatology.

Nights

Participants were all asked to keep a stabilization schedule prior to completing the in-lab nights of the study. This required all subjects to keep a sleep schedule where they went to bed at 9:00PM every night and woke up at 6:30AM every morning for seven days prior to completing the overnight portion of the study. They were also asked to leave a voicemail message to the lab every evening before bed and every morning right after waking up in order to assure compliance with prescribed schedule. Actigraphs were also used for the same purpose. During this time, participants were also asked to refrain from ingesting caffeine, eating chocolate, and napping during the day.

All participants also came into the lab for an evening of Adaptation. On Adaptation day, the participants familiarized themselves with the lab environment, the lab staff, and the polysomnography (PSG) equipment that they would be required to wear overnight. All individuals underwent a simulated bedtime procedure in order to better understand what the overnight portion

of the study would be like. The purpose of Adaptation is for all the children to become acquainted with the space and the equipment they would be sleeping in for the subsequent two nights.

On the following day, participants completed their baseline (BSLN) sleep night at the lab. On BSLN night, participants were allowed a total of 9.5 hours of time in bed. This schedule was directly matched with the stabilization schedule (9:00PM bedtime followed by a 6:30 rise time) that they were asked to maintain at home prior to coming into the lab. At 8:30AM the following morning, participants were taken to the fMRI facility where they completed the MSIT as part of a scanning protocol. Following the fMRI scan, all subjects went home and were asked to refrain from napping before returning to the Bradley Sleep Lab later that day for their short night of sleep.

The following night, participants returned to the lab in order to complete the sleep restriction (SR) portion of the study. On this night, the subjects were only allowed a total of 4 hours time in bed as a means of restricting sleep. This was achieved through a wake-extension protocol in which participants were kept awake until 2:30AM. Rise times remained the same, at 6:30AM. Thus, the sleep opportunity was reduced from 9.5 hours to 4 hours. The following morning, participants were taken to the fMRI facility at the same time as the day before (8:30AM) to once again complete the fMRI scanning protocol during which the MSIT was administered.

On both nights in the laboratory, participants were monitored using polysomnography. All individuals wore electroencephalography caps, as well as EKG, electrooculography, and electromyography leads overnight. These devices were used to monitor their brainwaves, heart rate, eye movements, and chin muscle tone, respectively, for sleep staging.

MSIT

The Multi-Source Interference Task was administered as part of an fMRI protocol which all participants included in this analysis underwent. The task was presented on a BOLD screen to the individual in the scanner. As detailed above, each trial consisted of a stimulus containing three numbers printed centrally in white atop a solid black background. For each trial the participant is asked to select which of the three numbers on the display is different. On congruent trials, the identity of the number matches its position on the screen (for example, in the stimulus 020, the different number is two and it is in the second position). On incongruent trials, the identity of the number does not match its position on the screen, (for example, in the stimulus 311, the different number is three, but it is in the first position). While the identity of the flanker numbers in incongruent trials can be 1, 2, or 3, in all congruent trials, the numbers flaking the target stimulus are always 0.

Trials were presented across three blocks in each experimental condition (three following baseline night and three following the short night). Each block contained a total of 80 trials (40 congruent trials and 40 incongruent trials, presented in pseudo-random order) as well as null events. Each trial consisted of 500ms of stimulus display and 2500ms of a fixation cross. Intervening null events extended the fixation cross for a random interval for purposes of ensuring an adequate jitter of stimulus onsets. Null events were included in order to bring the total block length to 5 minutes and 6 seconds.

MSIT responses were entered by a button press on a hand-held keypad. All participants were right-handed and held the button box in their dominant hand. They used their index, middle, and ring fingers to press buttons one, two, and three, respectively. Responses were collected beginning with stimulus onset and extending into the inter-trial interval (not including null events),

creating a total response window of 3 seconds. Failure to make a response within this time would result in the trial being counted as "No Response." If multiple buttons were pressed in response to the same trial, only the identity of the first press was recorded.

Before starting the first scanning session following baseline night, participants took part in an individual training session. This session consisted of first familiarizing themselves with the environment of the fMRI scanner. The children were placed in a mock scanner with no magnetic field and were played the different sounds they could expect to hear during the scan so they would not be startled during the protocol. They were also thoroughly taught the rules of the MSIT and we ensured they had properly understood them by running a practice run outside of the scanner. All participants were also given the chance to ask questions before entering the fMRI machine and were asked to verbally repeat the rules of the MSIT to the experimenter.

Performance on the MSIT was quantified using a combination of reaction time (RT) and accuracy, as suggested by Mullane (2009). This was done by using the reaction times for accurate trials only, excluding any trials in which the subjects provided either an incorrect or a lack of response. By doing so, we avoided placing unequal importance on either reaction time or accuracy, recognizing that both hold important information regarding task performance. Instead of raw reaction times, we also chose to use reciprocal reaction time (that is, the original value raised to the power of -1 or 1/RT). This transformation was done in order to better satisfy the assumption of normality behind the statistical tests used in this investigation.

Statistical Analysis

With our first aim in mind, we performed a two-way within-subject ANOVA to assess whether shortened sleep duration was affecting performance on the MSIT and if this was

happening differentially based on interference (that is, whether a trial is congruent or incongruent). This analysis of variance assessed performance (1/RT) across the factors of sleep conditions (either baseline night or shortened night) and task interference (congruent or incongruent). The reciprocal reaction times used were averaged across each block of 80 runs (exploratory analyses confirmed no presence of time-on-task effects across blocks).

In order to assess whether symptoms were indexing performance differences, we also performed a linear regression of symptom severity (both for hyperactive-impulsive and inattentive symptoms) on both mean 1/RT at baseline, to assess general performance, and on the difference in mean 1/RT between congruent and incongruent trials. We performed this second analysis in order to determine whether children with more severe symptom presentation were more vulnerable to congruence effects.

The final part of the analysis joined both the sleep and symptom severity pieces in order to better understand the interactions between the two. In this combined analysis, we first performed a multi-factor ANOVA that included study condition, task condition, symptom severity (for both symptom subgroups), and once again 1/RT as the dependent variable. This analysis allowed us to better understand the individual effect of each of these factors on task performance as well as their interactions. In order to complement this analysis of variance with an even more detailed look at these relationships we also performed another linear regression. In this part of the investigation, we regressed symptom severity for both inattentive and hyperactive-impulsive symptoms onto the difference in congruence effect (performance between congruent and incongruent trials) between baseline and short nights. By doing so, we aimed to answer the question of whether children with more severe symptoms were indeed more vulnerable to sleep loss, as indexed by the difference in

magnitude of the congruence effect (a greater congruence effect is caused by greater cognitive interference in incongruent trials).

Results

Sample

Participants in the sample showed typical to moderate presentation of ADHD symptoms, with one individual showing severe inattentive presentation, as determined by self-report responses on the Conners-3. Conners-3 *T-scores* spanned a large range for both groups of symptoms. There was both a greater range and greater variation in inattentive symptom severity, although the average *T-score* for this symptom subgroup was lower (inattention range: 38 - 79, mean: 56.8 ± 10.3). The average hyperactive-impulsive symptom Conners *T-score* was higher in this participant pool, although these scores showed a lower range and less variation than the inattention scores (hyperactivity-impulsivity range: 53 - 70, mean: 59.5 ± 5.7). Conners scores are a dimensional measure of symptom severity. Individuals scoring below 60 are considered to have typical presentation of the respective symptom, scores above 60 denote subclinical presentation, and those with scores equal to or above 70 are considered to have clinical presentation of ADHD. The maximum symptom *T-score* that one can receive using the Conners- 3 is 90 (Conners, 2011). See **Figure 3** below for *T-score* distributions of this sample.

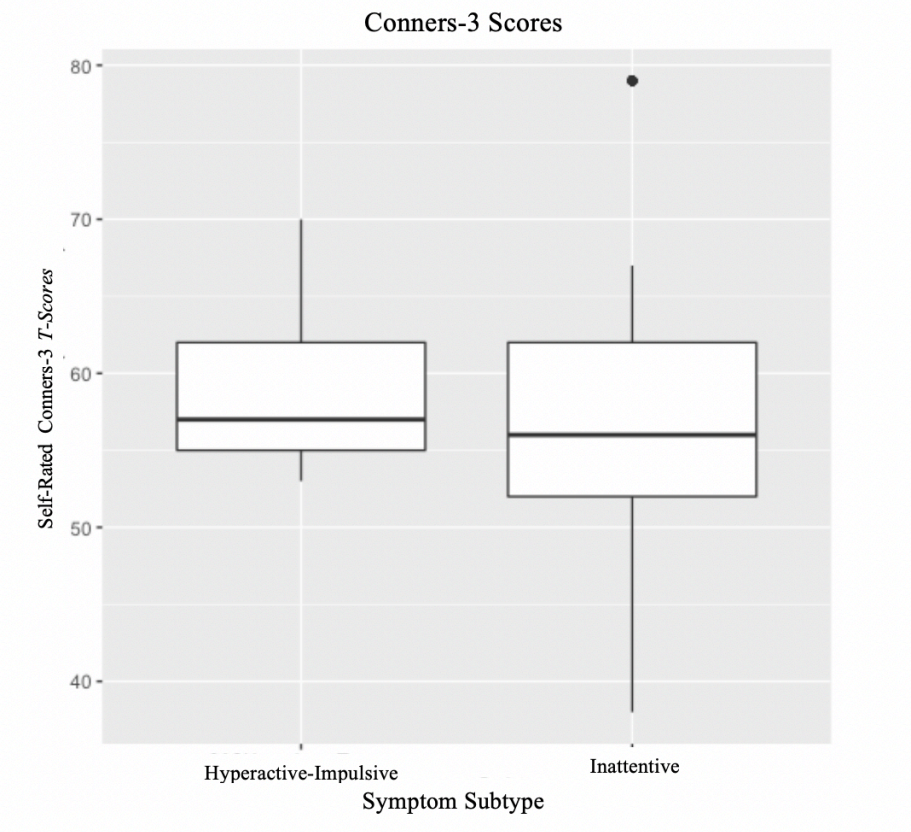

Figure 3: Box-and-whisker plot of self-rated Conners-3 *T- scores* for all participants for each of the two ADHD symptom subgroups: hyperactivity-impulsivity and inattention. The black line indicates the median *T- score* for each set of data (hyperactivity median: 57, inattention median: 56).

Sleep and Interference

According to our analysis of variance, reaction time did not show a main effect of sleep loss (BSLN vs. SR: $F(1,148)=2.070$; $p=0.15$; $\eta^2=0.010$). However, as we hypothesized, performance on the MSIT did demonstrate a congruence effect (Congruent vs. Incongruent: $F(1,148)=29.592$; $p<0.0001$;$\eta^2=0.137$). More specifically, reaction times were significantly slower on incongruent trials (mean RT: 886.7ms) versus congruent trials (mean RT: 686.8ms). There was no statistically significant interaction between the effects of interference and sleep condition on

performance on the MSIT (Sleep and Interference: $F(1,148)=0.043$; $p=0.836$; $\eta^2=0.000$). A complete summary of participant performance across trial type and sleep condition can be found in *Appendix 1.*

	Performance (1/RT)			F -Value	*p*
	df	SS	Mean Sq.		
Sleep	1	2.89E-07	2.89E-07	2.070	0.152
Interference	1	4.13E-06	4.13E-06	29.592	**<.001**
Sleep:Interference	1	6.00E-09	6.00E-09	0.043	0.836
Residuals	148	2.07E-05	1.40E-07		

Table 2: ANOVA results for analysis of variance in 1/RT ($msec^{-1}$) as an effect of sleep, interference, and their interaction.

Symptom Severity and Baseline Performance

Multiple linear regression analysis of symptom severity and performance on the MSIT at baseline revealed no statistically significant relationships between the two. This was true for both inattentive ($b= -7031.4$; $t=-0.801$; $p=0.440$) as well as hyperactive-impulsive ($b= -6634.4$; $t=-1.45$; $p=0.174$) symptoms. There seems to be no clear pattern of how Conners-3 *T-scores* relate to performance at baseline (see **Figure 4**).

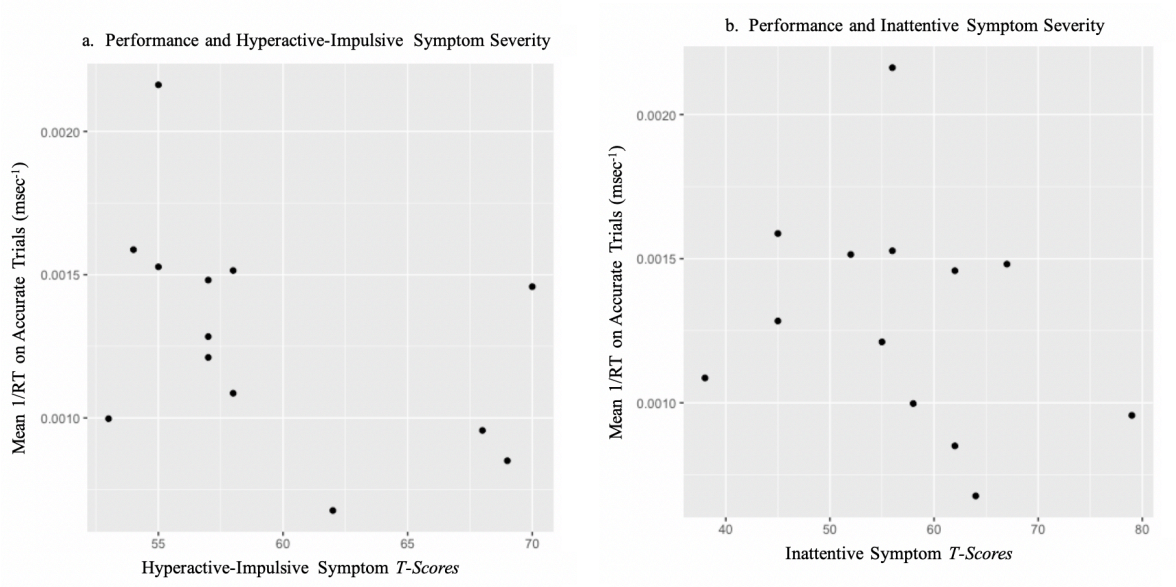

Figure 4: Scatter plots of each subjects' performance (mean 1/RT on accurate trials) on the MSIT based on hyperactive-impulsive (a) and inattentive (b) symptom severity.

Congruence Effects and Symptom Severity

Multiple linear regression analysis of symptom severity and difference in 1/RT between congruent and incongruent trials of the MSIT revealed no statistically significant relationship between hyperactive-impulsive symptom severity and difference in performance based on stimulus congruence (b= -8382.5; t=-0.90; p=0.388). Results are displayed in panel *a* of **Figure 5** below. There was, however, a significant relationship between inattentive symptom severity and the congruence effect (b=-34816; t= -2.49; p<0.05). As seen in panel *b*, children showing more inattentive symptoms appear to be showing a decrease in the difference between their reaction times on congruent and incongruent trials of MSIT. These results prompted further, *post-hoc* analysis into what was driving this effect. As shown in panel *c* of the same graph, children are performing similarly on incongruent trials, but those presenting with more inattention show decreased performance on congruent ones. Thus, performance on congruent trials approached that

of incongruent trials for children with more severe symptom presentations. These findings will be further discussed in the subsequent section.

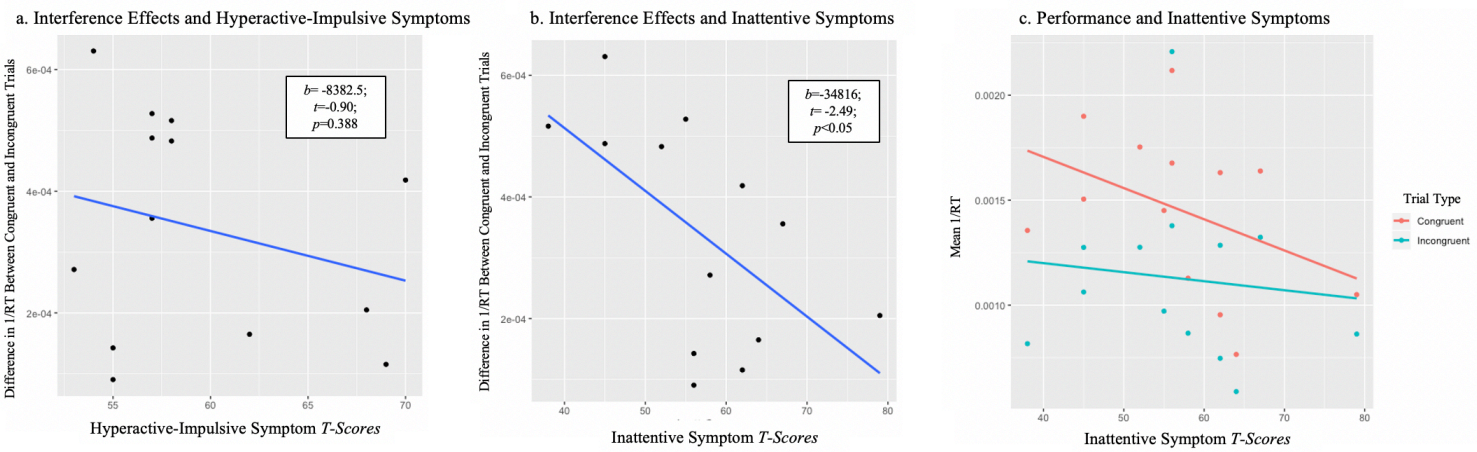

Figure 5: Scatter plots of each subjects' difference in performance based on interference (mean 1/RT on accurate congruent trials minus that on incongruent trials) and hyperactive-impulsive (a) and inattentive (b) symptom severity. (c) Scatter plot of performance (mean 1/RT in $msec^{-1}$) on both congruent and incongruent trials and inattentive symptom severity.

Sleep, Interference, and Symptom Severity

The multi-factor within-subject ANOVA assessing the main and interactive effects of sleep, interference, and symptom severity of either symptom subgroup on MSIT performance revealed some significant results. In the analysis of inattentive symptoms, we found no main effects of sleep (BSLN vs. SR: $F(1,140)=2.352$; $p=0.13$; $\eta^2=0.011$), symptom severity ($F(1,140)=1.073$; $p=0.30$; $\eta^2=0.005$), or any interactions of the variables of interest on performance as measured by 1/RT (all p's > 0.05). There was however, once again, an effect of task condition (Congruent vs Incongruent: $F(1,140)=11.381$; $p<0.001$; $\eta^2=0.052$), further confirming that indeed participants had significantly worse performance on incongruent trials. This main effect of interference was also seen in the analysis of hyperactive-impulsive symptoms (Congruent vs. Incongruent: $F(1,140)=27.111$; $p<0.0001$; $\eta^2=0.101$). Although this analysis also failed to reveal

an effect of sleep (BSLN vs. SR: $F(1,140)=2.352$; $p=0.13$; $\eta^2=0.012$), it did reveal a main effect of symptom severity ($F(1,140)=14.710$; $p<0.001$; $\eta^2=0.055$). According to this analysis, children with more severe presentation of hyperactive-impulsive symptoms showed worse performance on the MSIT, regardless of sleep or interference.

	Performance (1/RT)			F -Value	*p*
	df	SS	Mean Sq		
Sleep	1	3.26E-07	3.26E-07	2.352	0.127
Interference	1	1.58E-06	1.58E-06	11.381	**<0.001**
Inatt. Score	1	1.49E-07	1.49E-07	1.073	0.302
Sleep:Interference	1	6.00E-09	5.80E-09	0.042	0.839
Sleep: Inatt. Score	1	1.50E-08	1.54E-08	0.111	0.739
Interference:Inatt. Score	1	5.00E-09	4.90E-09	0.035	0.946
Sleep:Interference:Inatt. Score	1	1.00E-09	6.00E-10	0.005	
Residuals	140	1.94E-05	1.39E-07		

Table 3: ANOVA results for analysis of variance in 1/RT ($msec^{-1}$) as an effect of sleep, interference, inattentive symptom severity, and their interaction.

	Performance (1/RT)			F -Value	*p*
	df	SS	Mean Sq		
Sleep	1	3.76E-07	3.76E-07	3.333	0.070
Interference	1	3.06E-06	3.06E-06	27.111	**<0.0001**
Hyper-Imp. Score	1	1.66E-06	1.66E-06	14.710	**<0.0001**
Sleep:Interference	1	3.00E-09	2.90E-09	0.026	0.872
Sleep: Hyper-Imp. Score	1	7.90E-08	7.94E-08	0.704	0.403
Interference:Hyper-Imp. Score	1	1.50E-08	1.49E-08	0.132	0.717
Sleep:Interference:Hyper-Imp. Score	1	0.00E+00	1.00E-10	0.001	0.978
Residuals	140	1.58E-05	1.13E-07		

Table 4: ANOVA results for analysis of variance in 1/RT ($msec^{-1}$) as an effect of sleep, interference, hyperactive-impulsive symptom severity, and their interaction.

Further multiple linear regression analysis was also conducted in order to better understand the relationships between interference, sleep, and symptom severity. A regression of the difference between congruence effects on baseline and short night on hyperactive-impulsive symptom severity revealed no statistically significant relationship (b=-3324; t= -0.30; p=0.77). The same

was true for inattentive symptoms (b=1966; t= 0.098; p=0.92). These analyses reveal that children with more severe presentation of symptoms indeed do not show a differential effect of sleep loss on interference effects.

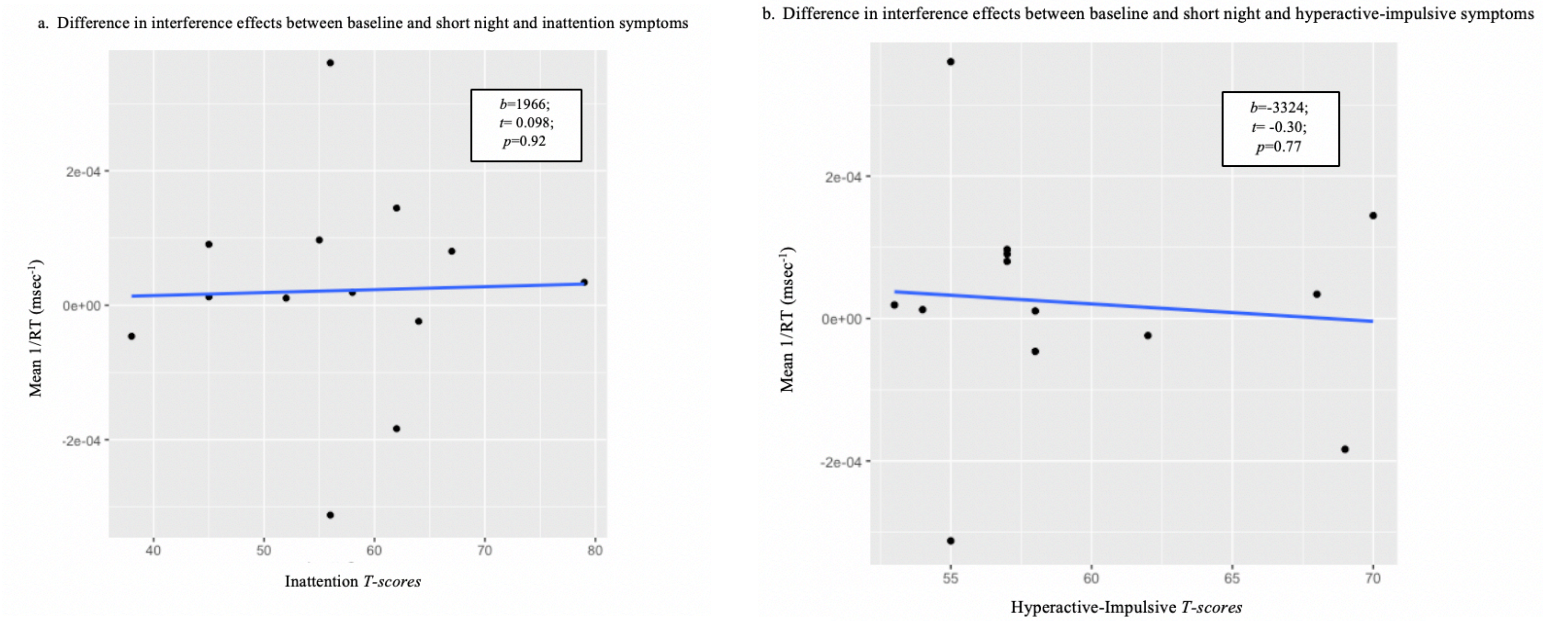

Figure 6: Scatter plots of each subjects' difference in interference effects based on sleep condition (difference between mean 1/RT on accurate congruent trials minus that on incongruent trials on baseline night minus that on short night) and (a) inattentive and (b) hyperactive-impulsive symptom severity.

Discussion

Overview

This exploration examined the effects of sleep loss on performance on an interference task in children with varying degrees of attention-deficit/hyperactivity disorder. Since sleep problems have been particularly implicated in the presentation of ADHD (Conners, 2011), we used direct manipulation of sleep duration to further elucidate the directional aspects of this relationship. By using a task that directly probes resolving of cognitive interference, which seems to be impaired in ADHD (Bush, 2010; Hart et al., 2013), this protocol gave us further insight on whether children

with more severe symptom presentation show more increased vulnerability to sleep loss as measured by performance on this task.

The Multi-Source Interference Task showed consistent interference effects throughout all analyses: participants were slower on accurate incongruent trials than congruent ones, regardless of symptom severity or sleep condition. This finding supports the assertion that the interference task condition is in fact more cognitively demanding (Donders, 1969). However, according to our analyses and unlike we hypothesized, sleep was not significantly interacting with performance on the task. Participants are performing statistically similarly regardless of being given 9.5 hours or 4 hours time in bed prior to completion of the task.

According to our regression analysis, more hyperactive-impulsive children showed decreased performance as evidenced by slowed reaction time on accurate trials. However, children with more severe hyperactive impulsive symptoms did not show a greater difference in performance between congruent and incongruent trials. On the other hand, while children with more severe inattention did not perform statistically differently as a function of their symptom severity, they did show decreased difference in performance between congruent and incongruent trials. This will be discussed further in the following section. No interactions were found between symptom severity, sleep, and interference, which leads us to suggest that individuals with more severe ADHD presentation might not show increased vulnerability to acute sleep loss.

Interference

In this investigation, the Multi-Source Interference Task consistently showed effects of interference. On average, across both sleep conditions, participants showed greater mean reaction times for accurate responses on incongruent trials as compared to congruent ones. These slowed

responses lay bare the more cognitively taxing nature of the interference condition, which requires a lengthier cognitive process to be resolved (Donders, 1969). These findings are important to highlight as not only do they corroborate Bush's original results but, in doing so, they confirm that the MSIT is creating cognitive interference, as was intended (Bush et al., 2003; Bush & Shin, 2006). By confirming that the participants are behaving as expected, these results assuage any concerns regarding the suitability of the MSIT for this investigation and provide important guidance for result interpretation. Any significant findings or lack thereof, therefore, will not be attributable to the task not generating interference, but rather to other factors.

Sleep

We did not identify a significant main effect of sleep duration on performance on the MSIT. Children's performance after 4 hours of time in bed did not differ statistically from their performance after 9.5 hours in bed. Past studies have shown that sleep deprivation increases sleepiness and negatively affects cognitive performance (Cunningham et al., 2018; Khullar et al., 2020; Sagaspe et al., 2006), but, according to our results, we suggest that one night of acute sleep deprivation might not be enough to see this effect on a task like the MSIT. In Molfese's study (2013), for example, children were chronically deprived of a single hour of sleep every night for an entire week. Following this consistent sleep deprivation, they showed decreased event-related potential amplitude on cognitive interference tasks, which they attributed to a marked decrease in cognitive performance in response to high processing demands. It is unclear whether this effect would still be observed had their participants only experienced one night of restriction. Further investigation needs to be done and can be supplemented with our fMRI data when it is analyzed.

Another study on the effects of sleep loss on cognitive presentation and performance on attentional tasks specifically following acute deprivation, however, revealed results that would suggest the contrary (Cunningham 2018). The sleep protocol used in this study was quite similar to our own, as it tested performance after 9 hours of time in bed and after 3 hours of time in bed. These researchers found that participants did in fact show effects of only one night of sleep restriction on task performance (as measured by reaction time on accurate trials) on the Eriksen flanker task. These findings suggest that one night of sleep curtailment can be enough to see detrimental performance effects on tasks that are similar to the MSIT. It is possible that our sample of thirteen kids was too small and, therefore, underpowered for us to observe the same effect.

As evidenced, the field of sleep research currently fails to reach a consensus on the precise effects of sleep loss on the same cognitive processes measured by different tasks (Sagaspe et al., 2006). Some authors suggest that this heterogeneity of results should be attributed to the fact that sleep loss affects different cognitive processes in different ways and the distributed nature of cognition is not accounted for in these analyses (Cain et al., 2011; Cunningham et al., 2018). It is not possible to properly reflect these nuances when comparing performance across studies that rely on slightly different tasks, which is why answers to these questions might seem disjointed. In order to properly assess how our results compare with information in the literature, it would be beneficial for future sleep restriction studies to also employ on the MSIT as their designated cognitive interference task. This would clear "task impurity problem," which may arise from the components from other cognitive domains that influence performance uniquely in different tasks (Cain et al., 2011).

Our analysis also revealed a lack of interaction between sleep condition and trial interference on participants' performance. This lack of interaction, although it initially might seem

counterintuitive, was expected (Cain et al., 2011; Dixit & Mittal, 2015; Mullins et al., 2019; Sagaspe et al., 2006). In a study conducted by Cain and colleagues (2011), the experimenters found that, following just one night of sleep deprivation, participants did not show an increase in interference effects. In other words, in their study, the difference in performance between congruent and incongruent trials remained the same regardless of sleep duration preceding the task (Cain et al., 2011). The same lack of effect of shortened sleep on congruence effects was found in another study in which subjects were kept awake throughout a single night (Sagaspe et al., 2006). These authors suggest that the lack of interference effects is due to acute sleep restriction for just one night, as opposed to a chronic curtailment approach over a few days, not being enough to cause a change in ability to resolve interference. This is likely the case for our sample, as well.

ADHD Symptom Severity

According to our analyses, ADHD symptom severity on both inattentive and hyperactive-impulsive symptom scales does not affect performance on the MSIT as measured by average reaction time on accurate trials at baseline. More symptomatic youth are performing statistically the same as individuals presenting with less symptoms. We suggested that symptom severity would index a decrease in performance, therefore, these effects do not support our hypothesis and contradict current studies in the field (Bush, 2008; Kóbor et al., 2015). This raises an important issue: in the event that our investigation is not in fact underpowered, the Multi-Source Interference Task might not be as effective in detecting the presence of ADHD as George Bush originally suggested in his original proposals of the task (Bush, 2008). Although children presenting with more hyperactive-impulsive symptoms did show decreased performance when short night results

were also included in the analysis, the lack of a main effect at baseline still raises questions about the validity of the chosen interference task.

While our results did not show a relationship between hyperactive-impulsive symptom severity and the congruence effect (that is, the difference in performance between congruent trials and incongruent trials), we did find this association for inattentive symptoms. Contrary to our hypothesis, we conclude from the results that children with more severe inattentive presentation show a decrease in the congruence effect. Further exploration of the data uncovered that these individuals are performing increasingly worse on congruent trials with increasing symptom severity, but maintaining a relatively constant performance on incongruent trials, therefore minimizing the difference between the two.

This decrease in difference may be attributed to floor effects. According to a meta-analysis of studies on ADHD and the Stroop Task, children with the disorder have been found to perform poorly on incongruent trials of interference tasks (Lansbergen et al., 2007). Due to the even greater number of sources of interference on the MSIT, it is possible that the participants' performance could not get worse on incongruent trials, showing a floor effect. However, since incongruence cannot be a reason for error on congruent trials, we suggest that inattention is driving an overall decrease in performance—most prominently demonstrated on congruent trials— and therefore minimizing the performance difference between congruent and incongruent trials. Trouble holding attention on tasks, avoiding doing tasks that require mental effort for extended periods of time, and thinking about unrelated subjects when completing a task are all inattention symptoms that can affect performance on the MSIT (American Psychiatric Association & American Psychiatric Association, 2013). This is an important nuance to highlight, because initially it might seem as the effect of interference is decreasing as inattentive symptom severity increases, which is somewhat

misleading. It is most likely that increased inattention is driving worse performance: this constitutes not a decrease in interference, but rather a decrease in facilitation as symptom presentation becomes more severe.

Sleep, Interference, and Symptom Severity

There was also a lack of interaction between sleep, interference, and symptom severity. This is an important finding as it challenges our original proposition. This lack of interaction might be an indication that more symptomatic youth are not more vulnerable to sleep loss as assessed by performance on a cognitive interference task. However, different interpretations might also explain these results.

One possible explanation is that this lack of effect is again being driven by sleep restriction being contained to just one night. Several studies suggest that individuals might have compensatory mechanisms at play that counter the effects of just one night of sleep restriction or complete deprivation (Cain et al., 2011; Cunningham et al., 2018; Dixit & Mittal, 2015). The identity and function of these mechanisms is not yet completely known or understood in this context. The functional imaging data that we collected throughout the MSIT protocol can be an important tool through which the neural correlates of these compensatory mechanisms can be uncovered in future analyses.

Regardless of the factor that is driving the lack of interaction between sleep, interference, and symptom severity, it is important to highlight that one night of sleep restriction does not accurately reflect the reality of children living with ADHD (Baddam et al., 2018; Kothare & Kotagal, 2011). Attention-deficit/hyperactivity is a chronic condition and, given the prevalence of sleep disturbances in this population, the sleep curtailment that is seen in this population is not

limited to one night (Corkum et al., 2001; Kothare & Kotagal, 2011). Future experimental studies should aim to incorporate more nights of directly manipulated, mild sleep curtailment in order to better mimic the reality of children with varying ADHD severity and determine how multiple nights of restriction affects performance on the MSIT. Future observational studies could employ mid- to long-term objective monitoring of naturalistic sleep in this population to use as a predictor of task performance alongside symptom severity (Campos et al., 2019).

Limitations

The particularly small size of the participant sample in this investigation is noteworthy. Given that the MSIT was administered, as intended, as part of an fMRI protocol, only children who were MRI-eligible could complete that portion of the study. A total of 10 participants from an original pool of 23 who completed the overnight portion of the investigation were excluded from this investigation for not meeting the criteria for being in the MRI scanner (e.g. having non-removable dental metal). Having a final total of thirteen participants resulted in being underpowered for some of the analyses that were conducted in this investigation. For example, the main effect of sleep on MSIT performance which trended toward significance in our sample might have been more evident in a larger sample that was more appropriately powered for the ANOVA that we conducted.

Our sample was also not representative of a wide range of symptom severity. Participants in the sample showed typical to moderate presentation of the disorder. Only one individual for either symptom camp had a Conners-3 *T-score* corresponding to clinical presentation of ADHD. Future analyses should include a wider range of symptom presentations in order to allow for more robust analyses of how these associations behave at all severity levels of the disorder and,

consequently, better and clearer understanding of said associations. This would also minimize model extrapolation to points that are not represented in the current sample, providing more reliable results from which to base conclusions. A more symptomatic, representative sample could be recruited with the help of other local research laboratories that work specifically with children with ADHD or through local academic or afterschool programs that target children with the disorder.

Conclusions and Future Analyses

This current investigation provides an important exploration of how ADHD symptom severity and direct manipulation of sleep duration affect performance on a cognitive interference task. While our results suggest that one night of sleep restriction might not be affecting performance on this task for youth of varying degrees of ADHD severity, we suggest that more analyses are required in order to reach well-founded conclusions. Future manipulations should investigate the effects of multiple nights of restriction, employ fMRI to identify the functional neural correlates of behavior during the task, and continue to use the MSIT in order to create more points of comparison for performance. It is also important to highlight that we had a particularly small sample size. Future analyses will ideally include a larger group of children with a wider range of ADHD symptom severity as assessed by the Conners-3.

Understanding the factors involved in the etiology and manifestation of ADHD symptoms can have clinical implications which render this line of study critically important, especially given the prevalence of the disorder (NIMH, 2016). The more we understand about how sleep interacts with the disorder and about the behavioral presentation of ADHD on the MSIT, the better we will be able to rely on these factors when designing future clinical interventions, accommodations, and

therapies for these children. More research is required and will be done in order to determine what these will look like.

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Appendix

Appendix 1

Summary of Task Performance

		Mean Reaction Time (msec)	
		Accurate Trials	Overall
Sleep Condition	Baseline	746.27	719.42
	Short Night	800.00	781.25
Trial Type	Congruent	684.93	675.68
	Incongruent	884.96	847.46

Table 5: Summary of participants' mean reaction times in msec. across both study and task condition for both accurate trials and across all trials for which they provided a response regardless of accuracy.

		Trial Response (%)		
		Total Accurate	No Response	Accurate/ Responded
Sleep Condition	Baseline	0.763	0.064	0.801
	Short Night	0.797	0.077	0.855
Trial Type	Congruent	0.875	0.054	0.922
	Incongruent	0.685	0.087	0.735

Table 6: Mean percentages of total correct trials, no response trials, and accurate trials out of all responded trials across all runs for all participants across both study and task conditions.